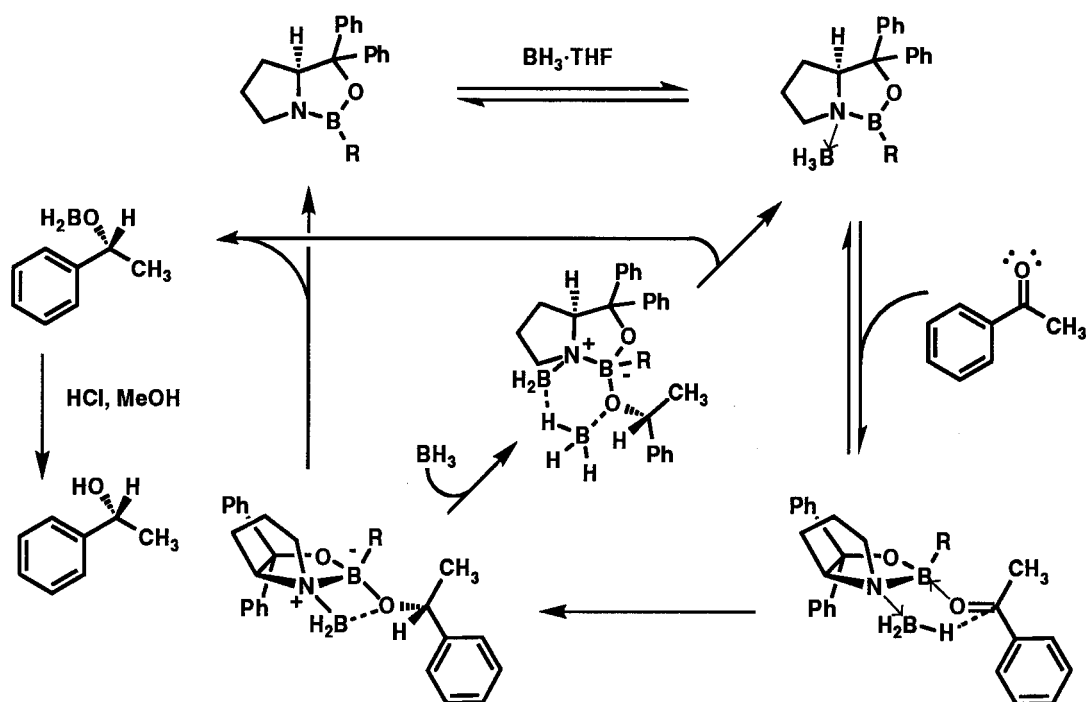
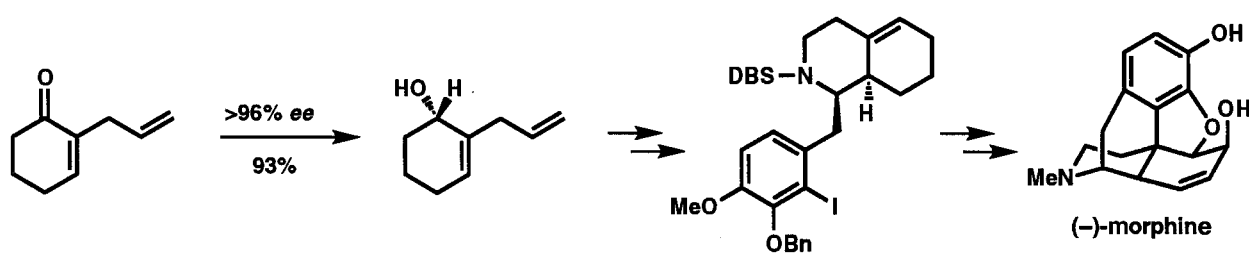
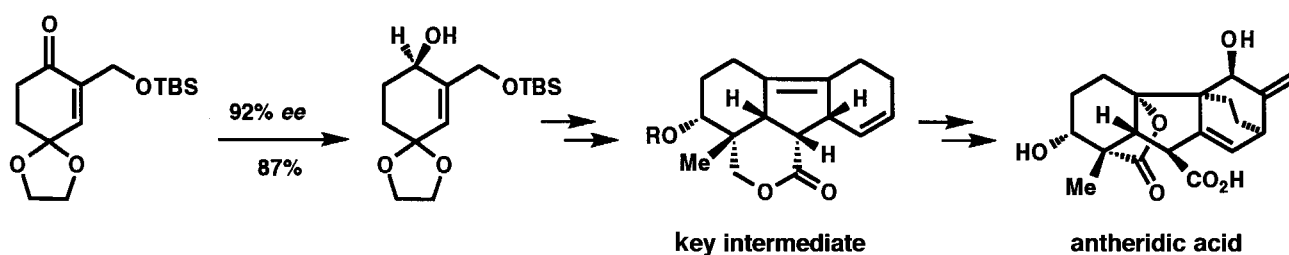




Remarkable advances in catalytic methods for enantioselective synthesis of chiral organic molecules have made the past decade truly momentous for organic chemistry. Great progress has been made not only in the discovery of useful new reactions, but also in our understanding of the fundamental mechanistic principles underlying enantioselective catalysis.



Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method**

Elias J. Corey* and Christopher J. Helal

The introduction of complex metal hydrides such as lithium aluminum hydride and sodium borohydride into synthetic organic chemistry half a century ago greatly accelerated progress in this field. For many years, efforts to combine these reducing agents with various chiral ligands for the purpose of achieving efficient asymmetric synthesis proved disappointing. However, promising results obtained by Itsuno and his collaborators in the 1980s with

mixtures of chiral 1,2-amino alcohols and borane paved the way for the discovery of oxazaborolidines as chiral catalysts for the borane-mediated enantioselective reduction of a wide variety of achiral ketones (CBS reduction). The well-defined structure of the catalyst and the straightforward reaction pathway have allowed the rapid expansion of the scope of the CBS reduction and the rational modification of catalyst structure to achieve

optimal enantioselectivity for a particular type of substrate. This enantioselective catalytic reduction is now established as a major synthetic method for the asymmetric synthesis of chiral medicinals, catalytic ligands, complex natural products, and synthetic intermediates.

Keywords: asymmetric catalysis • boron • ketones • reductions • total synthesis

1. Introduction

The introduction of aluminum and boron hydrides for the reduction of carbonyl groups half a century ago had an enormous impact on the field of synthetic chemistry, and helped to usher in a golden age for the rationally planned multistep construction of complex organic molecules.^[1] These reagents not only provided predictable site selectivity in multifunctional substrates, but often predictable diastereoselectivity as well. The versatile parent compounds LiAlH_4 ,^[2] AlH_3 ,^[3] NaBH_4 ,^[4] and $\text{BH}_3 \cdot \text{THF}$ ^[5] have been modified in almost every conceivable way to generate a large collection of derivatives, each of which has a special reactivity and utility, for example $\text{NaBH}(\text{OMe})_3$, $\text{NaBH}(\text{OAc})_3$, NaBH_3CN , $\text{LiBH}(\text{sBu})_3$, Cl_2BH , $(\text{cyclohexyl})_2\text{BH}$, catecholborane, $(\text{RS})_2\text{BH}$, $\text{NaBH}_4 \cdot \text{CeCl}_3$, $\text{LiAlH}(\text{OtBu})_3$, $\text{LiAlH}(\text{OMe})_3$, $\text{NaAlH}_2(\text{OR})_2$, and $i\text{Bu}_2\text{AlH}$.^[6] The literature on carbonyl reduction by this extensive family of hydride/hydrogen donors is so vast that a comprehensive review would require several large volumes. However, despite five decades of research and countless

thousands of applications of hydride donors, much remains to be learned regarding detailed reaction mechanisms and transition-state structures.^[6,7] One consequence of this primitive understanding of transition-state structure is that it is difficult to predict how a new reagent will behave.

In view of the enormous utility of Al-H and B-H reagents for the reduction of carbonyl groups, it is natural that the modification of these structures by the emplacement of chiral ligands would be investigated for the purpose of achieving absolute stereochemical control (*re-* or *si-*face selectivity) in the synthesis of chiral alcohols. For more than thirty years there have been numerous studies of mixtures of LiAlH_4 , NaBH_4 , or $\text{BH}_3 \cdot \text{THF}$ with chiral 1,2-diols, 1,2-amino alcohols, or 1,2-diamines as reagents for enantioselective carbonyl reduction.^[8] Specific examples of such "mixture reagents" include *cis*-2,3-pinenediol and LiAlH_4 ,^[9a] (2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (Darvon alcohol) and LiAlH_4 ,^[9b, c, d] (–)-*N*-methyl-*N*-(1-phenylethyl)amine $\cdot$ HCl and LiAlH_4 ,^[9e] hydroxymethyl oxazolines and LiAlH_4 ,^[9f] (–)-*N*-methylephedrine, various phenols, and LiAlH_4 ,^[9g, h, i] (*S*)-leucine methyl ester $\cdot$ BH_3 and BF_3 ,^[9j] 2,2'-dihydroxy-1,1'-binaphthol, ethanol, and LiAlH_4 (BINAL-H),^[9k, l] (*S*)-2-(*N*-arylaminoethyl)pyrrolidines and LiAlH_4 ,^[9m] (*S*)-4-aniliny-3-methylamino-1-butanol and LiAlH_4 ,^[9n, o] 2,2'-dihydroxy-6,6'-dimethylbiphenyl, $\text{BH}_3 \cdot \text{THF}$, and various amines,^[9p] (–)-*N*-methylephedrine, 2-alkylaminopyridines, and LiAlH_4 ,^[9q] *N*-

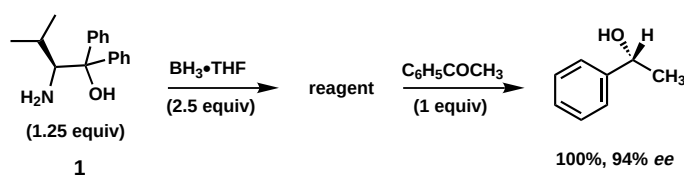
[*] Prof. E. J. Corey, Dr. C. J. Helal
Department of Chemistry and Chemical Biology
Harvard University
12 Oxford Street, Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-0376
E-mail: corey@chemistry.harvard.edu

[**] A list of abbreviations used is provided in the Appendix.

benzoylcysteine, LiBH_4 , and *tert*-butyl alcohol;^[9r] and (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol and $\text{BH}_3 \cdot \text{Me}_2\text{S}$.^[9s]

While good levels of enantioselectivity have been reported for some of these early empirical studies, these reducing systems have seen very limited use in synthesis. In addition, because the reactive species are generally unknown, and in many cases insoluble as well, there has been no reliable information on the mechanistic basis for enantioselectivity. This is the situation for the Darvon alcohol– LiAlH_4 complex, introduced by Mosher and Yamaguchi,^[9b] and used with some success by others.^[9c, d] It is probably the best known of these mixture reagents. The Noyori reagent BINAL-H ^[9k, l]—which is made from (*S*)- or (*R*)-BINOL, LiAlH_4 , and ethanol, and seems to be structurally better defined—also has seen very little use although it reacts with very high enantioselectivity with certain substrates; clearly high cost and marginal practicality are factors which detract from the usefulness of this reducing system.

After a survey of the extensive literature of these mixture reagents for hydride reduction and in an attempt to rationalize the basis for the observed enantioselectivities, we became very interested in a system introduced by Itsuno et al. in 1981.^[10] In this initial work, the authors reported the novel finding that mixtures of chiral amino alcohols such as (*S*)-valinol and $\text{BH}_3 \cdot \text{THF}$ in a ratio of 1:2 in THF at 30 °C effected the enantioselective reduction of a number of achiral ketones to chiral secondary alcohols in nearly 100% yield with enantiomeric excesses in the range of 10–73% *ee*.^[11] The most thoroughly studied substrate, butyrophenone, was reduced by this reagent to (*R*)-1-phenylbutan-1-ol with 69% enantiomeric purity. Upon screening numerous amino alcohols, it was discovered that the tertiary amino alcohol **1** derived from (*S*)-valine together with two equivalents of $\text{BH}_3 \cdot \text{THF}$ at –78 to 0 °C over several hours converted acetophenone into (*R*)-1-phenylethanol with a much improved enantiomeric excess (94%, Scheme 1).^[12] The dependence of the enantioselectivity of this process on the ratio of BH_3 to amino alcohol, the quantity of hydride present in the



Scheme 1. Highly enantioselective ketone reduction reported by Itsuno.

reagent, and the steric bulk of the ketone substituents was studied. However, no mechanistic rationale was proposed by Itsuno et al. for either the sense or magnitude of this surprisingly good enantioselectivity. No applications were reported by other groups. Studies of this intriguing reaction were initiated by our group on the basis of mechanistic insights which were subsequently confirmed and which led to a new and powerful catalytic version of the original stoichiometric Itsuno reduction.

2. Development of the CBS Catalytic Enantioselective Reduction^[13]

From the outset it appeared reasonable that the primary reaction product of the tertiary amino alcohol **1** would be an oxazaborolidine of structure **2**. This was confirmed in 1986–1987 by Bakshi and Shibata of our laboratories. They found that the reaction of amino alcohol **1** with two equivalents of BH_3 in THF at 35 °C produced two equivalents of hydrogen gas and the oxazaborolidine **2**, which was obtained in pure form upon sublimation (105–130 °C, 0.05 Torr) after removal of the solvent and excess BH_3 in vacuo (see Scheme 2). Its structure was demonstrated by FT-IR and ^1H and ^{11}B NMR spectroscopy and mass spectrometry (EI). Although solutions of **2** in THF did not reduce acetophenone after several hours at 23 °C, mixtures of **2** and $\text{BH}_3 \cdot \text{THF}$ (0.6 equiv) effected the rapid reduction of acetophenone in less than one minute at 23 °C to afford (*R*)-1-phenylethanol in 94.7% *ee*, which is

Elias J. Corey, born in 1928 in Methuen, 30 miles north of Boston, MA, studied chemistry from 1945 to 1950 at the Massachusetts Institute of Technology, where he gained his doctorate for work on synthetic penicillins under the supervision of John C. Sheehan. In 1951 he joined the University of Illinois at Urbana-Champaign as an Instructor in Chemistry and was promoted in 1956 to full Professor. Since 1959 he has been at Harvard University. For as long as he can remember he has enjoyed study, adventure, and discovery.

Christopher J. Helal, born in 1969 in Columbus, OH, received his Bachelor of Science degree in chemistry in 1991 from the Ohio State University. He enrolled in the graduate program at Harvard University, where he was a National Science Foundation Graduate Fellowship recipient. He earned his doctorate in 1997 under the direction of Professor E. J. Corey on the investigation of novel electronic and steric effects in the enantioselective oxazaborolidine-catalyzed reduction of ketones, and is currently employed at Pfizer Central Research, Groton, CT, where he is involved in drug discovery.

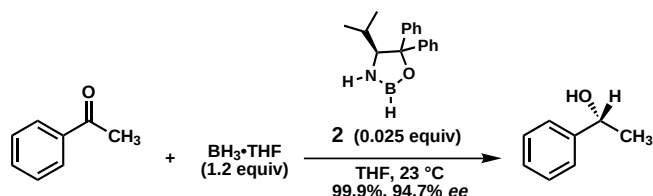


E. J. Corey



C. J. Helal

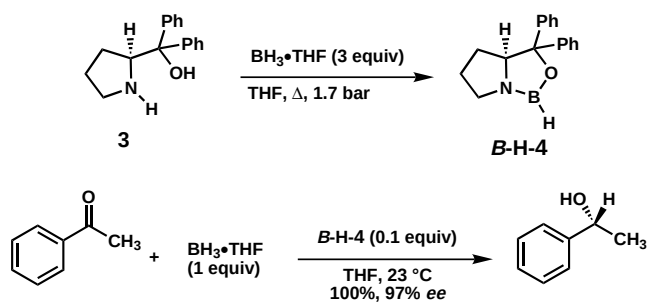
comparable to the results reported by Itsuno.^[12] In the absence of **2**, acetophenone was reduced relatively slowly with $\text{BH}_3 \cdot \text{THF}$ at 23 °C. The rate acceleration with **2** immediately suggested that substoichiometric quantities of **2** could effect an asymmetric reduction of a ketone. This was readily verified by an experiment with 2.5–5 mol % of **2** and 1.2 equivalents of $\text{BH}_3 \cdot \text{THF}$, which produced (*R*)-1-phenylethanol with 94.7% *ee* (Scheme 2). Thus, the careful inves-



Scheme 2. Oxazaborolidine-catalyzed reduction with borane.

tigation of an impressive yet, in the original report, poorly understood reaction led to the discovery of a highly enantioselective *catalytic* reduction of ketones mediated by an *isolable* and *structurally defined* catalyst.

The demonstration of the catalytic activity of oxazaborolidine **2** and mechanistic considerations (see Section 3) led to the expectation that oxazaborolidine **4** should be a superior reagent (Scheme 3). Treatment of amino alcohol **3**^[14a, b] with

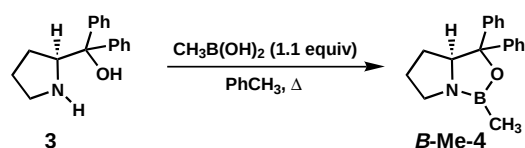


Scheme 3. A superior oxazaborolidine catalyst for the enantioselective reduction of ketones.

$\text{BH}_3 \cdot \text{THF}$ gave oxazaborolidine *B-H-4* (CBS catalyst named after Corey, Bakshi, and Shibata), which was characterized by ^1H and ^{11}B NMR spectroscopy and mass spectrometry (EI).

Oxazaborolidine **4** was indeed found to be generally superior to **2** as an enantioselective reduction catalyst. For example, the reduction of acetophenone with 1.2 equivalents of $\text{BH}_3 \cdot \text{THF}$ and 0.1 equivalents of *B-H-4* in THF at 25 °C gave (*R*)-1-phenylethanol with 97% *ee* and in quantitative yield.

The methyl-substituted oxazaborolidine *B-Me-4* was prepared as shown in Scheme 4 and characterized by ^1H and ^{11}B



Scheme 4. A more stable and enantioselective catalyst.

NMR spectroscopy and mass spectrometry (EI). An improvement in the selectivity and practicality of the CBS reduction was realized with this catalyst relative to the *B-H* analogue. The reduction of ketones with *B-Me-4* as the catalyst frequently resulted in appreciably higher enantioselectivity than with *B-H-4*. Additionally, *B-H-4* is extremely air- and moisture-sensitive, and its formation requires extended heating with BH_3 under increased pressure. On the other hand, *B-Me-4* is less sensitive and can be stored in closed containers, weighed or transferred in air, and is readily formed by heating **3** and methanboronic acid at reflux in toluene for 4 h with removal of water.

Table 1 summarizes the results for the reduction of a variety of different ketones with *B-Me-4* as the catalyst.^[13b] These data show that the CBS reduction process results in excellent enantioselectivities, near quantitative yields, and short reaction times, and leads to a product whose absolute configuration can be predicted from the relative effective steric bulk of the two carbonyl appendages. Another notable attribute of

Table 1. CBS reduction of ketones catalyzed by *B-Me-4*.^[13b]

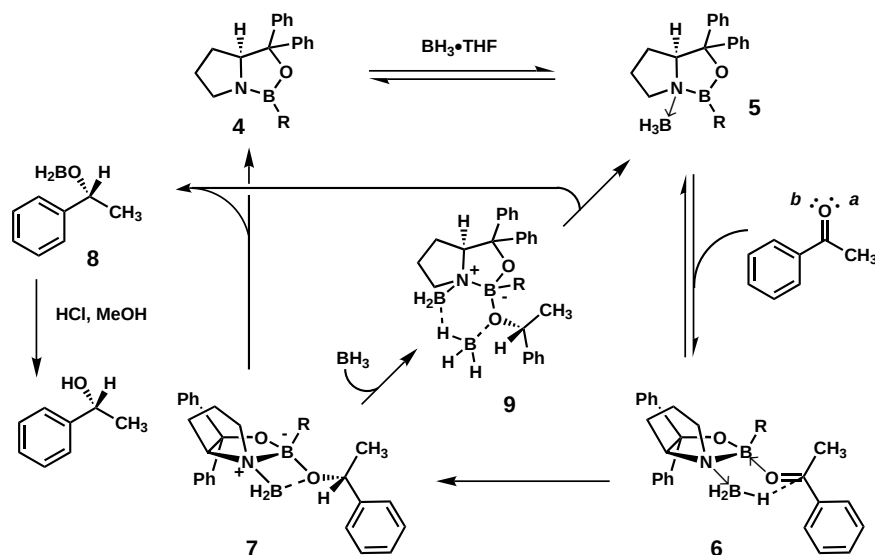
Ketone	Config. (<i>ee</i> [%])	<i>T</i> [°C]
	<i>R</i> (96.5)	2
	<i>R</i> (96.7)	–10
	<i>S</i> (95.3)	32
	<i>R</i> (97.3)	–10
	<i>R</i> (86) ^[a]	–15
	<i>R</i> (84)	–10
	<i>R</i> (91)	23
	<i>R</i> (97.6)	23
	<i>R</i> (94) for <i>n</i> = 2 <i>R</i> (96.7) for <i>n</i> = 3	0 ^[b]

[a] 0.25 equiv of *B-Me-4*. [b] The reaction time was 25 min.

this methodology is the easy recovery of the catalyst precursor **3** by precipitation from organic solvent as the hydrochloride salt and efficient recycling.^[14c]

3. Mechanistic Rationale^[13, 15]

The general mechanistic model which was developed for reduction of ketones with oxazaborolidine catalyst **4** (and analogous catalysts such as **2**) is outlined in Scheme 5. The



Scheme 5. Proposed mechanism for the catalytic enantioselective reduction of ketones by oxazaborolidines **4**.

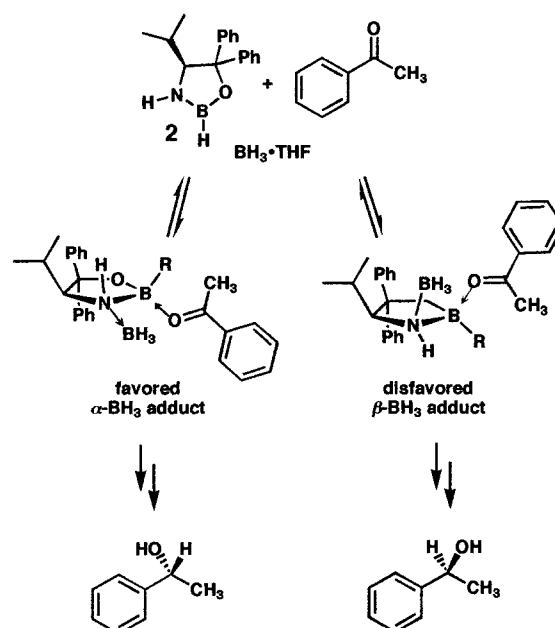
mechanistic model explains 1) the absolute stereochemistry of the reduction, 2) the outstanding enantioselectivity obtained for the reduction, 3) the exceptional rate enhancement of the reduction, and 4) the turnover of the catalyst.

The initial step in the pathway is the rapid (and probably reversible) coordination of BH_3 to the Lewis basic nitrogen atom on the α face of oxazaborolidine **4** to form the *cis*-fused oxazaborolidine· BH_3 complex **5**. Unambiguous support for the initial step comes from the observation by ^{11}B NMR spectroscopy^[16] that **4** and $\text{BH}_3\cdot\text{THF}$ form the 1:1 complex *B*-*H*-**5** and the fact that crystalline *B*-*Me*-**5** (**5**, $\text{R} = \text{Me}$) can be isolated and structurally defined by single-crystal X-ray diffraction analysis.^[17] The coordination of the electrophilic BH_3 to the nitrogen atom of **4** serves to activate BH_3 as a hydride donor and also to increase strongly the Lewis acidity of the endocyclic boron atom. The strongly Lewis acidic complex **5** then readily binds to the ketone substrate, for example acetophenone, at the more sterically accessible electron lone pair (*a* in the case of acetophenone) and *cis* to the vicinal BH_3 group ($\rightarrow$ **6**). This manner of binding minimizes unfavorable steric interactions between the oxazaborolidine and the ketone, and aligns the electronically deficient carbonyl carbon atom and the coordinated BH_3 for stereoelectronically favorable, face-selective hydride transfer via a six-membered transition state to form the reduction product **7**. Thus, the rate enhancement for the

oxazaborolidine-catalyzed reduction is due to the activation of the stoichiometric reducing agent BH_3 by coordination with the Lewis basic nitrogen atom of **4** with simultaneous intensification of the Lewis acidity of the boron atom in the heterocycle for coordination to the ketone. This leads to subsequent enthalpically and entropically favorable face-selective intramolecular hydride transfer.^[18]

Dissociation of the reduction product from **7** to regenerate the oxazaborolidine catalyst may occur by two different pathways: 1) reaction of the alkoxide ligand attached to the endocyclic boron atom with the adjacent boron atom of **7** to regenerate **4** and form the borinate **8** by cycloelimination;^[13d, 15] or 2) by the addition of BH_3 to **7** to form a six-membered BH_3 -bridged species **9**, which decomposes to produce the catalyst- BH_3 complex **5** and borinate **8**.^[19, 20] The facile disproportionation of **8** to afford dialkoxyborane $(\text{RO})_2\text{BH}$ and BH_3 allows the efficient use of the three hydrogen atoms of the stoichiometric reductant.^[21]

The mechanism proposed in Scheme 5 provides a simple explanation for the superior effectiveness of oxazaborolidine **4** relative to **2**. As shown in Scheme 6, the selective binding of BH_3 to one face of **2** is the result of a steric preference for a *trans* relationship between the isopropyl substituent and BH_3 . Competing formation of the *cis* adduct leads to lower enantioselectivity of the reduction. The rigid [3.3.0] ring system of **4**, however, strictly requires the α coordination



Scheme 6. A possible reduction pathway for catalyst **2** with low enantioselectivity.

of BH_3 to the Lewis basic nitrogen atom (see **6**); β coordination would result in a very strained (by ca. 10 kcal mol^{-1}) *trans*-fused [3.3.0]pentalane. Thus, production of the undesired alcohol enantiomer through a diastereomeric BH_3 coordination mode is energetically precluded with CBS catalyst **4**.

A final issue posed by the mechanistic model in Scheme 5 is whether the complexation of the ketone by **5** or the subsequent hydride transfer to form **7** is the rate-limiting step of the reduction. To answer this question, the rates of reduction of acetophenone and the *p*- NO_2 and *p*-MeO derivatives catalyzed by *B*-Me-**4** were measured.^[22a] The relative rates of reduction were 3.4 (*p*- NO_2), 1.8 (*p*-MeO), and 1.0 (*p*-H).^[22b] This implies that the coordination of the ketone to **5** is not strictly rate-limiting for these substrates. Additional information was obtained from the ^1H – ^2H kinetic isotope effect ($k_{\text{H}}/k_{\text{D}}$) for hydride transfer, which was measured with an excess of a 1:1 mixture of B^1H_3 and B^2H_3 (6 equiv of each) in THF with two equivalents of oxazaborolidine *B*-Me-**4** and one equivalent of acetophenone. The ratio of ^1H to ^2H in the reduction product 1-phenylethanol at low conversion was determined by mass spectrometry to be 1.7, which is then the approximate value of $k_{\text{H}}/k_{\text{D}}$.^[22a] This low value is indicative of an early transition state for highly exothermic transfer of hydride from the boron atom to the carbonyl group. Thus, both association to the carbonyl compound and hydride transfer are probably fast and comparably rate-limiting. In agreement with these experimental results, semiempirical molecular orbital calculations with the AM1 Hamiltonian provided similar transition state enthalpies for ketone complexation and hydride transfer.^[18c] The calculated kinetic isotope effect for the oxazaborolidine-catalyzed reduction of 2-propanone was 1.8 at 23°C , which is in agreement with the experimentally determined value of 1.7.^[23]

4. Further Studies in the Optimization of the CBS Reduction

The high enantioselectivity, generality, and profound mechanistic understanding of the CBS reduction have led to a number of other studies aimed at further elucidating in ever increasing detail the effect of five variations in the structure of the oxazaborolidine catalyst on enantioselectivity over a wide range of substrates. Described in the following are results from investigations of varying 1) the oxazaborolidine ring system, 2) the *gem*-diphenyl substituents, 3) the group on the endocyclic boron atom, 4) the stoichiometric reducing agent, and 5) the mode of catalyst preparation.

4.1. Variations in the Oxazaborolidine Ring System

Subsequent to the discovery of the high enantioselectivity imparted by the proline-derived oxazaborolidine catalyst **4** in the reduction of ketones with BH_3 , many other fused bicyclic oxazaborolidines have been prepared by other research groups and by our own to demonstrate the relationship between catalyst structure and enantioselectivity. The effectiveness of the various oxazaborolidine catalysts for the

enantioselective reduction of acetophenone is summarized in Table 2. For example, the aziridine (entries 1 and 2),^[24] azetidine (entry 3),^[25] and pyrrolidine catalysts (entry 4, **4**)^[13] afford (*R*)-1-phenylethanol in very high enantiomeric excess (94–97%). The structurally constrained tricyclic oxazaborolidine in entry 5 is among the most effective of all the oxazaborolidines synthesized, as it has demonstrated exceptional enantioselectivity for the reduction of acetophenone (98% *ee*) as well as numerous other substrates.^[26] The use of a catalyst with a more flexible [4.3.0] ring system (entry 6) resulted in lower enantioselectivity.^[27] Entry 7 reveals that the

Table 2. Fused bicyclic oxazaborolidine catalysts for the enantioselective reduction of acetophenone.

Entry	Catalyst	R	<i>ee</i> [%]	Solvent, <i>T</i> [°C]
1		H	94	THF, 23
2		H	94	PhCH_3 , 23
3		H Me	97 75	THF, 23 PhCH_3 , 23
4		H Me	97 97	THF, 23 THF, 23
5		Me	98	THF, 0
6		H	87	THF, 0
7		H Me	96 92	THF, 23 PhCH_3 , 27
8		Me	86	THF, 0
9		H Me	94 93	THF, 25–30 THF, 0–5

enantioselectivity of the reduction is not strongly affected by decreased Lewis basicity of the endocyclic nitrogen atom of the catalyst owing to conjugation with the fused aromatic ring (up to 96 % *ee* for the reduction of acetophenone).^[28] Industrial interest in the large-scale application of CBS reductions has led to the search for other inexpensive and readily available enantiopure amino alcohols as precursors to chiral oxazaborolidines. Towards this end, enantiopure *cis*-1-amino-2-indanol (entry 8, prepared in four steps from indene)^[29] and an amino alcohol derived from α -pinene (entry 9, prepared from α -pinene)^[30] have been used to generate bicyclic oxazaborolidine catalysts which mediate the reduction of acetophenone with high enantioselectivity (86 and 94 % *ee*, respectively).

4.2. Variation of the Carbinol Substituents

The effects of the *gem*-diphenyl substituents of the carbinol center (R') on the enantioselectivity of acetophenone reduction are summarized in Table 3. Replacing the phenyl group (entry 1, *B*-Me-4) by the somewhat bulkier β -naphthyl group (entry 2) leads to a slight increase in enantioselectivity (98 % *ee*) in this and some other cases.^[31] The use of still bulkier *ortho*-substituted aromatic groups such as α -naphthyl (entry 3),^[25c] *ortho*-tolyl (entry 4),^[32] or *ortho*-anisyl (entry 5),^[32] however, results in considerably lower enantioselectivity, as does the use of the smaller 2-thienyl group (entry 6).^[32] Substitution with straight-chain alkyl (*n*-butyl, entry 7)^[25c] and spiroalkyl groups (entries 8 and 9),^[33] did not provide useful catalysts. However, a catalyst containing the rigid spiro-2-indanyl substituent (entry 10) afforded the reduction product with high enantioselectivity (96 % *ee*).^[34] Emplacement of two strongly electron-withdrawing trifluoromethyl groups on the oxazaborolidine ring system (entry 11), which should inductively increase the Lewis acidity of the heterocyclic boron atom, led to a catalyst which provided relatively poor enantioselectivity.^[35, 36]

4.3. Variation of the Substituent on the Heterocyclic Boron Atom

The group *R* on the heterocyclic boron atom can play an important role in determining the selectivity of complexation by the catalyst to the two possible ketone electron lone pairs. Because of differential steric interactions between *R* and the carbonyl substituents (see 6, Scheme 5), a discrimination is crucial to the enantioselectivity of the reduction. Table 4 lists several groups which have been studied as boron substituents in our laboratory^[37] for the CBS reduction of a range of ketonic substrates. Besides the compounds *B*-H-4 (entry 1) and *B*-Me-4 (entry 2) previously discussed, a variety of other catalysts containing *n*-alkyl (entries 3,^[38] 4,^[39] 5^[35]), 3-phenyl-propyl (entry 6),^[40] allyl (entry 7),^[37] *s*-alkyl (entry 8),^[40] and β -branched attachments both with chiral centers (entry 9)^[41] and without (entries 10^[40] and 11^[42]) have been synthesized

Table 3. Influence of the substituents R' at the carbinol center.

Reaction scheme: Acetophenone + CBS catalyst (R') $\xrightarrow{BH_3 \cdot THF (0.6-1.0 \text{ equiv}), 23^\circ C}$ (R)-1-phenylethanol

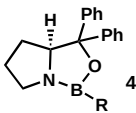
Entry	R'	<i>ee</i> [%]
1		97
2		98
3		62
4		76
5		28
6		82
7	$CH_3CH_2CH_2CH_2$	55
8 ^[a]		67
9 ^[a]		71
10 ^[a]		96
11 ^[b]	CF_3	60

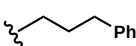
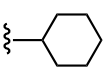
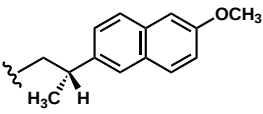
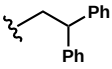
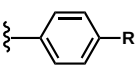
[a] The oxazaborolidine (0.15 equiv) was formed from the corresponding precursor by reaction with $BH_3 \cdot THF$ and contains a hydrogen atom on boron instead of the methyl group. The reduction was carried out at 0 °C.

[b] The group on the oxazaborolidine boron atom was *n*-pentyl.

and tested in the enantioselective reduction. In general, the *R* group exerts a steric effect in proximity to the boron atom to which it is attached that can influence the selectivity of binding at one of the oxygen lone pairs. In addition, it has been possible to design substituents, such as trialkylsilylmethyl (entry 12)^[43] and *p*-substituted aryl groups (entry 13),^[44] which interact sterically with more remote sites on the coordinated ketone and thus influence dramatically the enantioselectivity of reduction (see Sections 5, 6.3, and 6.4). The optimal *R* group for enantioselective reduction can be expected to depend on the structure of the substrate, as discussed in Section 5.

Table 4. Boron substituents in CBS catalysts.



Entry	R
1	H
2	CH ₃
3	CH ₂ CH ₃
4	CH ₂ CH ₂ CH ₂ CH ₃
5	CH ₂ CH ₂ CH ₂ CH ₂ CH ₃
6	
7	
8	
9	
10	
11	
12	
13	

4.4. Variation of the Stoichiometric Reducing Agent

Since the initial use of $\text{BH}_3 \cdot \text{THF}$ as the stoichiometric reductant in the CBS reduction, a number of other BH_3 complexes have been employed—including $\text{BH}_3 \cdot \text{Me}_2\text{S}$,^[44b] $\text{BH}_3 \cdot 1,4\text{-thioxane}$,^[45] and $\text{BH}_3 \cdot \text{diethylaniline}$ ^[46]—all of which lead to comparable enantioselectivity. An advantage of these reagents over $\text{BH}_3 \cdot \text{THF}$ is lower sensitivity to moisture and oxygen. The coordination of Me_2S , THF, etc. to BH_3 generally does not effect the level of enantioselection except at temperatures below -30°C .^[47] At this temperature the equilibria between BH_3 , the coordinated ligand, the oxazaborolidine catalyst, and the ketone are sufficiently altered to allow the intervention of competing reduction pathways; this then results in diminished enantioselectivity. The use of catecholborane,^[48] a less reactive monohydridic reagent that requires no ancillary ligand for stabilization, permits CBS reductions to occur at temperatures as low as -126°C in noncoordinating solvents (CH_2Cl_2 or toluene) with excellent enantioselectivity.^[31, 47] Furthermore, the decreased reactivity of catecholborane as compared to BH_3 , especially at lower temperatures, minimizes both uncatalyzed ketone reduction and hydroboration of sensitive functional groups (e.g., $\text{C}=\text{C}$, $\text{C}\equiv\text{C}$, $\text{C}=\text{O}$) within the ketonic substrate.

4.5. Variations in Oxazaborolidine Formation

The preparation of chiral oxazaborolidines in pure form was vital to the discovery of the CBS catalyst *B*-H-4 and the demonstration of the mechanism outlined in Scheme 5. Catalyst purity is essential for the attainment of high enantioselectivity and reproducibility in the reduction of ketones. As a result, considerable effort has been extended towards the development of effective procedures for the generation of pure oxazaborolidines without the need for a purification step. The first-generation CBS catalyst *B*-H-4 was originally prepared by the extended heating of amino alcohol **3** with three equivalents of $\text{BH}_3 \cdot \text{THF}$ under argon (1.7 bar) followed by sublimation.^[13a] Subsequently, a more convenient procedure was developed for the synthesis of *B*-H-4 that consists of heating **3** and $\text{BH}_3 \cdot \text{Me}_2\text{S}$ in toluene at reflux for 17 h and then removing solvent in vacuo without further purification.^[49, 50] The alkyl- and aryl-substituted oxazaborolidines (Section 4.3) are easily prepared by heating a solution of **3** and the corresponding boronic acid $\text{RB}(\text{OH})_2$ or boroxine $(\text{RBO})_3$ at reflux in toluene for 12–24 h with removal of water with molecular sieves.^[51] To shorten the time required for complete catalyst formation, the more reactive boronic acid equivalents bis(trifluoroethyl)alkyl boronates $(\text{RB}(\text{OCH}_2\text{CF}_3)_2)$ have been developed; they allow for quantitative oxazaborolidine formation in less than one hour.^[52]

5. Scope of Oxazaborolidine-Catalyzed Reductions

The well-defined mechanistic pathway of the enantioselective reduction of ketones mediated by chiral oxazaborolidine **4** greatly simplified application of this reaction to the enantioselective reduction of many different types of ketones and to the expansion of its scope and generality. As shown in Table 5, many conjugated aryl ketones of varying structure undergo highly enantioselective reduction with BH_3 or catecholborane in the presence of the proline-derived oxazaborolidine **4**. For example, acetophenone^[46] and derivatives with functional groups on the alkyl side chain such as $\text{P}(\text{O})(\text{O}i\text{Pr})_2$ ^[53] or Cl ^[44a] are reduced with high enantioselectivity, as are the *para*-,^[17b] *meta*-,^[13b, 54] and *ortho*-substituted^[55] aryl ketones and the cyclic aryl ketones 1-tetralone,^[46] 1-indanone,^[17b] and 1-benzosuberone.^[17b] The presence of nitrogen and other heteroatoms in the ketonic substrate is tolerated in the oxazaborolidine-catalyzed reduction, but often requires the use of an additional equivalent of the stoichiometric reductant L_2BH to coordinate to the Lewis basic site.^[50a, 56] Representative procedures for the CBS reduction of acetophenone and α -chloroacetophenone are detailed in reference [57].

Recently, the oxazaborolidine-catalyzed reduction of essentially isosteric electronically biased benzophenones^[58, 59] as well as *ortho*-substituted benzophenones^[59] and 2-benzoyl pyridinium triflates^[59] has been shown to be strikingly selective as a result of gearing effects between the aromatic rings. This reaction provides an efficient route to optically active benzhydrols (Table 6).^[60] The presence of an *ortho*-substituent on the aromatic ring also proved to be very

Table 5. Oxazaborolidine-catalyzed reduction of aryl ketones.

Ketone	ee [%]	Catalyst	L ₂ BH	T [°C]	Ketone	ee [%]	Catalyst	L ₂ BH	T [°C]
	99 ^[46]	<i>B</i> -Me-4	BDEA	30		91 ^[53]	<i>B</i> -nBu-4	CB	−20
	98 ^[44a]	<i>B</i> -Me-4	BDEA	31		99,7 ^[55a]	<i>B</i> -nBu-4	CB	−78
	97 (X = F) ^[17b] 99 (X = OMe) ^[17b]	<i>B</i> -Me-4 · BH ₃	BMS	−20		96 (X = Br) ^[54] 97 (X = OMe) ^[54]	<i>B</i> -Me-4	BTHF	23
	97 (X = OMe) ^[55b] 94 (X = H) ^[55b]	<i>B</i> -Me-4	BMS	23		96 (X = H) ^[54] 98 (X = OMe) ^[13b]	<i>B</i> -Me-4	BTHF	23
	≥ 99 ^[46]	<i>B</i> -Me-4	BDEA	20		98 ^[17b]	<i>B</i> -Me-4 · BH ₃	BMS	−20
	99 ^[17b]	<i>B</i> -Me-4 · BH ₃	BMS	−20		94 ^[56]	<i>B</i> -Me-4	BMS	25
	94 ^[56]	<i>B</i> -Me-4	BMS	25		99 ^[50a]	3 + (MeO) ₃ B	BMS	23

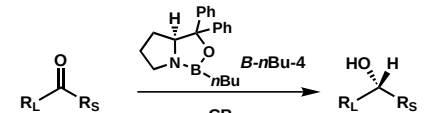
important for the enantioselective reduction of aryl diisopropylphosphono ketones.^[53]

α,β -Enones have been extensively investigated as CBS reduction substrates since enantiopure allyl alcohols are extremely versatile intermediates which can participate in many useful synthetic elaborations, for example the Claisen rearrangement or S_N2' displacement reactions with organometallic reagents that allow transfer of chirality by cleavage of C–O bonds and formation of C–C bonds to new chiral centers. It is interesting to note that in the case of acyclic enones (Table 7) the olefinic portion generally behaves as the large group R_L, especially in the presence of a β substituent such as aryl,^[58] trimethylsilyl, tri-*n*-butylstannyl,^[61] or alkyl groups.^[62b–f] Even an α substituent^[62a, f] (see below) can serve to reinforce the intrinsic preference for lone pair coordination. For cyclic α,β -enones with endocyclic unsaturation, α substitution of the C–C double bond with alkyl^[47, 63] or halogen^[64] is crucial for effective steric differentiation of the carbonyl oxygen electron lone pairs (Table 8). The reduction of cyclic α,β -enones with an exocyclic double bond has not

been extensively studied. However, it can be expected that β substitution is not crucial for high enantioselectivity, but helps to minimize reduction of the conjugated double bond.^[65, 66]

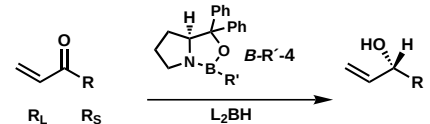
The oxazaborolidine-catalyzed reduction of α,β -ynones to afford propargyl alcohols of high optical purity has recently been accomplished by two different reaction protocols (Table 9). The use of (*S*)-*B*-Me-4 as catalyst and BH₃ · Me₂S as reductant in THF leads to (*S*)-alcohols, with ethynyl behaving as the small group R_S.^[67] In contrast, the use of (*S*)-*B*-CH₂SiMe₃-4^[43] or (*S*)-*B*-*p*-tBuC₆H₄-4^[44a] and catecholborane in CH₂Cl₂ for the reduction of triisopropylsilyl or trimethylsilylacetylene ketones furnishes (*R*)-propargyl alcohols, with ethynyl behaving as the large group R_L.^[68] This intriguing reversal in the enantioselectivity of the reduction is the consequence of repulsive interactions between the remotely situated bulky substituents on the triple bond and the heterocyclic boron atom of the catalyst.^[43]

Ketones with two sp³-hybridized carbon atoms attached to the carbonyl center can also be reduced with high enantio-

Table 6. Oxazaborolidine-catalyzed reduction of diaryl- and aryl diisopropylphosphono ketones.^[a]


Ketone	ee [%]	T [°C]
	95 ^[58]	− 78
	93 ^[59]	− 78
	97 (X = Br, Me) ^[59]	− 40
	> 90 (X = Me) ^[59] 99 (X = allyl) ^[59]	− 40
	91–97 (X = F, Cl, Br, I, Me) ^[53]	− 20

[a] A procedure for the CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)-pyridinium triflate is provided in reference [60].

Table 7. Oxazaborolidine-catalyzed reduction of acyclic α,β -enones.^[a]


Enone	ee [%]	Catalyst	L ₂ BH	T [°C]
	97 (Ar = Ph) ^[58] 95 (Ar = 4-MeOC ₄ H ₄) ^[58]	<i>B</i> - <i>n</i> Bu-4	CB	− 78
	94 (M = SiMe ₃) ^[61] 88 (M = SnBu ₃) ^[61]	<i>B</i> -CH ₂ SiMe ₃ -4	CB	− 78 − 60
	94 ^[62a]	<i>B</i> - <i>n</i> Bu-4	CB	− 78
	85 ^[62b,c]	<i>B</i> -Me-4	CB	− 30
	95 ^[62d,e]	<i>B</i> - <i>n</i> Bu-4	BMS	23
	92–97 ^[62f]	<i>B</i> -Me-4	BMS	− 30

[a] A procedure for the CBS reduction of (*E*)-4-(4'-methoxyphenyl)-3-buten-2-one is provided in reference [66].

Table 8. Oxazaborolidine-catalyzed reduction of cyclic α,β -enones.


Enone	ee [%]	Catalyst	L ₂ BH	T [°C]
	93 ^[47]	<i>B</i> - <i>n</i> Bu-4	CB	− 78
	92 ^[63a]	<i>B</i> - <i>n</i> Bu-4	BTHF	37
	93 ^[63b]	<i>B</i> -Me-4	BTHF	10
	96 ^[64a]	<i>B</i> -Me-4	BMS	− 15
	90 ^[64b]	<i>B</i> -Me-4	BTHF	23
	96 ^[65]	<i>B</i> -Me-4 · BH ₃	BMS	− 20

Table 9. Oxazaborolidine-catalyzed reduction of α,β -ynones.

Ynone	ee [%]	Catalyst	L ₂ BH	T [°C]
	71–88 (R = <i>n</i> -alkyl) ^[67] 94–96 (R = <i>s</i> -alkyl) ^[67]	<i>B</i> -Me-4 ^[a]	BMS	–30
	95 (R = <i>n</i> -alkyl) ^[67] 98 (R = <i>c</i> -Hexyl) ^[67]	<i>B</i> -Me-4 ^[a]	BMS	–30
	90–97 (R = <i>n</i> -, <i>s</i> -alkyl) ^[43]	<i>B</i> -CH ₂ SiMe ₃ -4	CB	–78
	91–97 (R = CH ₃ , <i>n</i> -alkyl) ^[44a]	<i>B</i> - <i>p</i> -tBuC ₆ H ₄ -4	CB	–40

[a] 2 equiv of *B*-Me-4.

Table 10. Oxazaborolidine-catalyzed reduction of dialkyl ketones.

Ketone	ee [%]	Catalyst	L ₂ BH	T [°C]	Ketone	ee [%]	Catalyst	L ₂ BH	T [°C]
	97.4 ^[46]	<i>B</i> -Me-4	BDEA	20		97 ^[44a]	<i>B</i> - <i>n</i> Bu-4	BMS	23
	97 ^[55a]	<i>B</i> -Me-4	BTHF	120		92 ^[69a]	<i>B</i> -Me-4	BMS	40
	93 ^[70]	<i>B</i> - <i>n</i> Bu-4	CB	25		≥ 99 ^[46]	<i>B</i> -Me-4	BDEA	20
	91 ^[46]	<i>B</i> -Me-4	BDEA	20		91 ^[58]	<i>B</i> - <i>n</i> Bu-4	CB	–78
	82 ^[71]	<i>B</i> -Me-4	BMS	–15		— ^[a]	<i>B</i> -Me-4	BTHF	23

[a] 70 % *de*.^[70]

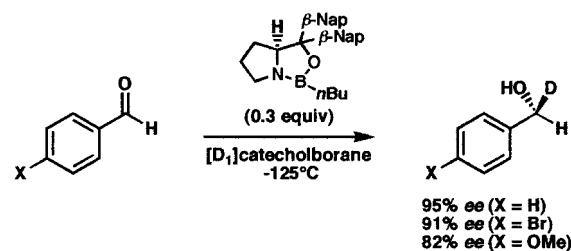
selectivity whenever there are substantial differences in the accessibility of the two oxygen electron lone pairs for coordination (Table 10). For example, ketones having a *tert*-alkyl group and a primary or *n*-alkyl-type group as carbonyl appendages can be reduced with high enantioselectivity.^[44a, 46] The reduction of some ketones, especially those in which the carbonyl group is quite hindered, often proceeds with better stereoselectivity at higher temperatures (30–120 °C), possibly due to accelerated removal of the bulky boronate product from the oxazaborolidine.^[55a, 69a, b] The highly enantioselective reduction of *s*-alkyl ketones such as cyclohexyl methyl ketone and isopropyl methyl ketone was recently accomplished by the use of BH₃·diethylaniline as stoichiometric reductant.^[46] In the CBS reduction of cyclopropyl isopropyl ketone, the strong influence of electronic factors is clearly evidenced, as the π electron rich cyclopropyl group behaves as R_L in comparison to the sterically similar isopropyl group.^[58] Methyl *n*-alkyl ketones are reduced with modest selectivity with *n*-alkyl as R_L,^[70] but the factors responsible for enantiodifferentiation of di-*n*-alkyl ketones can be quite subtle;^[71] further study of the reduction of such challenging substrates represents an attractive area for future research.

Transition metal π complexes of achiral ketones can often be reduced with high enantioselectivity. Thus, the CBS reduction of a variety of ketones π -complexed with chromium,^[72] cobalt,^[58] iron,^[73] or ruthenium^[73b] has been investigated with outstanding results (Table 11). The resulting optically active products are useful for the synthesis of pharmaceutically important compounds^[72] and chiral ligands for asymmetric catalysis.^[73]

The study of trihalomethyl ketones has provided deep insights into the connection between ketone conformation and reactivity.^[22, 74] The electron-withdrawing nature of the trihalomethyl group results in a stereoelectronically favorable deformation of the carbonyl group towards CX_3 . Together with the steric bulk of the trihalomethyl group, this leads to highly selective catalyst binding *anti* to CX_3 and subsequent fast hydride transfer^[22] to furnish trihalomethyl carbinols of high enantiopurity across a wide range of ketonic structures (Table 12).^[75]

Primary alcohols deuterated in the 1-position have been prepared by the reduction of the corresponding aldehydes

with $[D_1]$ catecholborane at low temperature (Scheme 7).^[31] 1-Octanal (90 % *ee*) and cyclohexanecarbaldehyde (92 % *ee*) also undergo highly selective reduction under these conditions.



Scheme 7. Preparation of primary alcohols deuterated in the 1-position.

6. Applications of the Oxazaborolidine-Catalyzed Reduction of Ketones

The ever-increasing need for absolute stereochemical control in the construction of organic molecules has resulted

Table 11. Oxazaborolidine-catalyzed reduction of ketones in ligands of metal complexes.

Complex	<i>ee</i> [%]	Catalyst	L_2BH	<i>T</i> [°C]
 Cr(CO) ₃	98 ^[72]	<i>B</i> - <i>n</i> Bu-4	CB	− 40
 (OC) ₃ Co	97 ^[58]	<i>B</i> -CH ₂ SiMe ₃ -4	CB	− 78
 Fe	> 95 (R = Me, Et, Ph, <i>i</i> Pr) ^[73a]	<i>B</i> -Me-4	BTHF	0
 Fe	> 99 (R = <i>n</i> -, <i>s</i> -alkyl, Ph) ^{[a][73b]}	<i>B</i> -Me-4	BTHF	0
 Ru	> 98 ^{[b][73c]}	<i>B</i> -Me-4	BTHF	0
 Ru	> 99 (R = Me, <i>n</i> -pentyl) ^{[c][73b]}	<i>B</i> -Me-4	BTHF	0

[a] 74–94 % *de*. [b] 74 % *de*. [c] 68–78 % *de*.

Table 12. Oxazaborolidine-catalyzed reduction of trihalomethyl ketones.

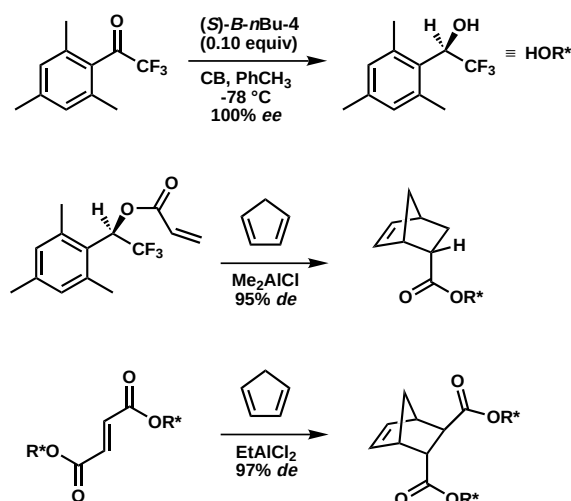
Ketone	ee [%]	T [°C]
	90 ^[47]	− 78
	96 ^[22]	− 23
	98 ^[22]	− 23
	94 ^[47]	− 78
	100 ^[55a]	− 78
	92–98 (R = <i>n</i> -, <i>s</i> -, <i>t</i> -alkyl) ^[75]	− 23 bis − 78

in a large number of applications of the CBS reduction to asymmetric synthesis. These applications include the preparation of 1) chiral ligands for enantioselective synthesis, 2) highly useful chiral intermediates, 3) synthetic bioactive compounds, and 4) natural products.

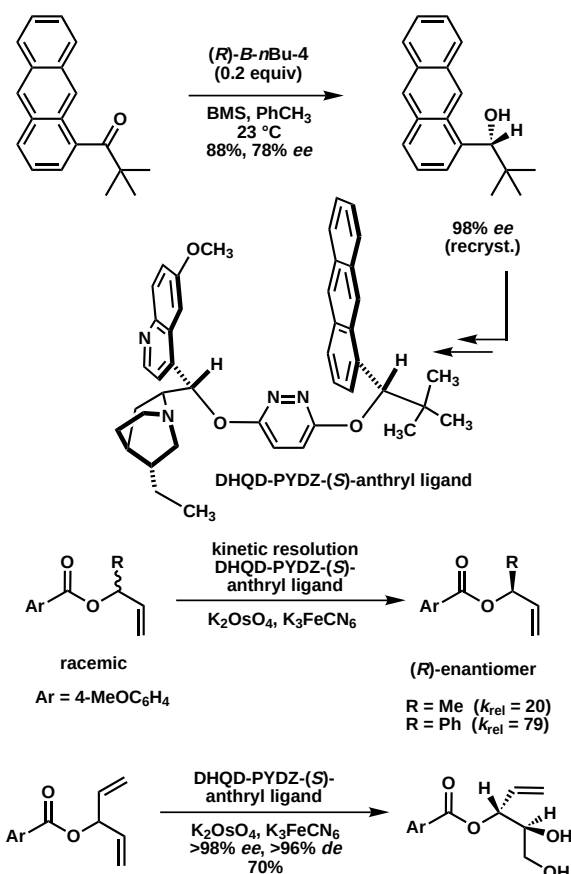
6.1. Preparation of Enantiopure Ligands for Asymmetric Synthesis

The CBS reduction of 1-mesityl trifluoromethyl ketone provided the corresponding (*R*)-alcohol with greater than 99.8% ee (Scheme 8).^[55a] This product served as a useful chiral controller in Lewis acid catalyzed Diels–Alder reactions. The corresponding acrylate and fumarate esters react with cyclopentadiene to form Diels–Alder adducts with excellent diastereoselectivity.^[76]

The Sharpless asymmetric dihydroxylation (AD) of olefins is broadly useful in organic synthesis. To increase the scope of this reaction, the DHQD-PYDZ-(*S*)-anthryl ligand (designed under guidance from the dihydroxylation mechanism) was prepared from enantioenriched *tert*-butyl anthryl alcohol (Scheme 9).^[77] This catalyst has a deep binding pocket that can accommodate olefinic substrates with remote binding



Scheme 8. Synthesis of (*R*)-(-)-mesityl-2,2,2-trifluoroethanol, an outstanding chiral auxiliary for the Lewis acid catalyzed Diels–Alder reaction.

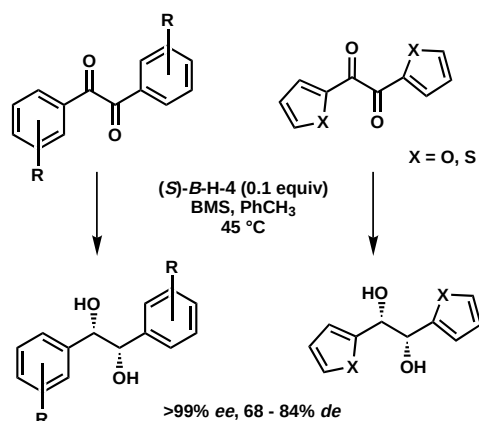


Scheme 9. Highly selective kinetic resolution of allyl alcohol derivatives with a catalyst for asymmetric dihydroxylation.

groups, such as allyl 4-methoxybenzoates.^[78] It is highly effective for kinetic resolution of racemic allyl 4-methoxybenzoate (Scheme 9).

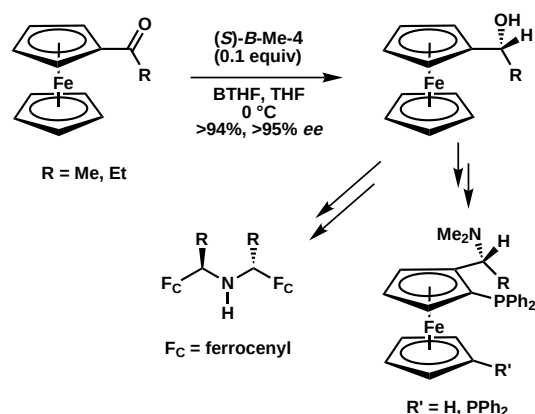
Chiral 1,2-diols have been extensively utilized as ligands and chiral controllers for the asymmetric preparation of C–X and C–C stereocenters. The CBS reduction of 1,2-diketones, in particular benzil derivatives and heterocyclic analogues, with $\text{BH}_3 \cdot \text{Me}_2\text{S}$ in the presence of (*S*)-*B*-H-4 furnishes

the optically active (*S,S*)-hydrobenzoins with outstanding enantiomeric excess and good diastereomeric excess (Scheme 10).^[79]



Scheme 10. Enantioselective reduction of 1,2-diketones to valuable chiral 1,2-diols.

The oxazaborolidine-catalyzed reduction of ferrocenyl ketones, F_cCOR , proceeds with excellent enantioselectivity ($>95\%$ *ee*, Scheme 11 and Table 11).^[76] The resultant opti-

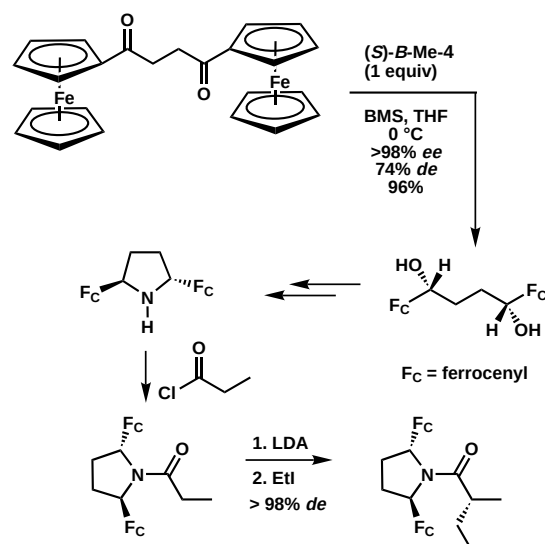


Scheme 11. CBS reduction of acylferrocenes to useful chiral ligands.

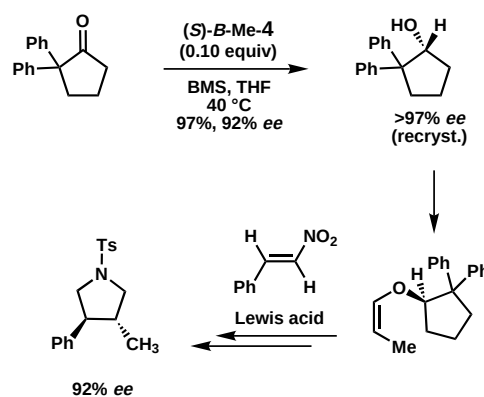
cally active ferrocenyl carbinols can be converted into chiral ferrocenylamines with complete retention of configuration. This affords useful chiral bases for asymmetric deprotonation or chiral ligands for transition metal catalyzed reactions.

The asymmetric reduction of 1,2-bis(ferrocenyl)ethane occurs with high enantioselectivity ($>98\%$ *ee*) and diastereoselectivity (74% *de*) to form a diol which was converted into a chiral C_2 -symmetric pyrrolidine. This is a useful chiral auxiliary for diastereoselective alkylation (Scheme 12).^[73c]

(*R*)-2,2-Diphenylcyclopentanol was obtained by oxazaborolidine-catalyzed reduction (92% *ee*) and converted into vinyl ethers for Lewis acid promoted [4 + 2] cycloaddition with 2-substituted 1-nitroalkenes. Hydrogenation of the resulting cycloadducts affords a route to chiral 3,4-disubstituted pyrrolidines (Scheme 13).^[69a, 80]



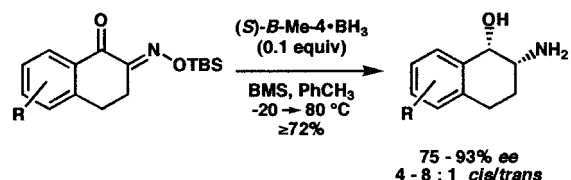
Scheme 12. A C_2 -symmetric ferrocenylpyrrolidine is an effective chiral auxiliary.



Scheme 13. Preparation of a useful auxiliary for nitroalkene–vinyl ether cycloadditions.

6.2. Preparation of Useful Chiral Building Blocks

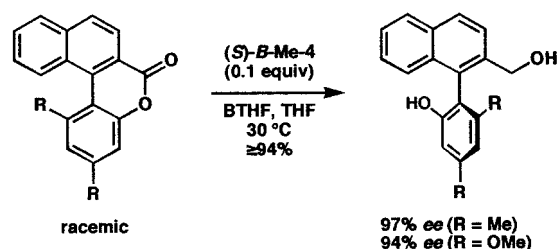
Enantiopure amino alcohols are of interest because of their biological activity and value as chiral ligands in metal-catalyzed organic reactions. The catalytic oxazaborolidine-mediated reduction of α -keto oximes results in reduction of $C=O$ followed by $C=N$ to give primarily the *cis*-amino alcohol (Scheme 14).^[81]



Scheme 14. One-step synthesis of optically active *cis*-amino alcohols.

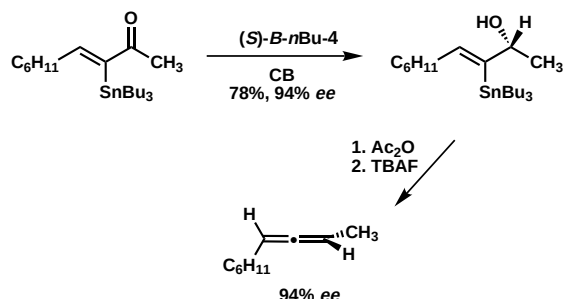
In a particularly striking example of the broad applicability of the CBS methodology, the enantioselective reduction of axially prostereogenic biaryl lactones affords one atropisomer

in a ratio of 97:3 or higher (Scheme 15).^[82] It was proposed that the product-determining step is the selective reduction of an equilibrating mixture of enantiomeric hydroxy aldehydes.



Scheme 15. Selective ring opening to an atropisomer of axially chiral biaryl compounds.

The chiral stannylated allyl alcohol shown in Scheme 16 was readily obtained by CBS reduction and transformed into a chiral allene by fluoride-catalyzed elimination.^[62a]

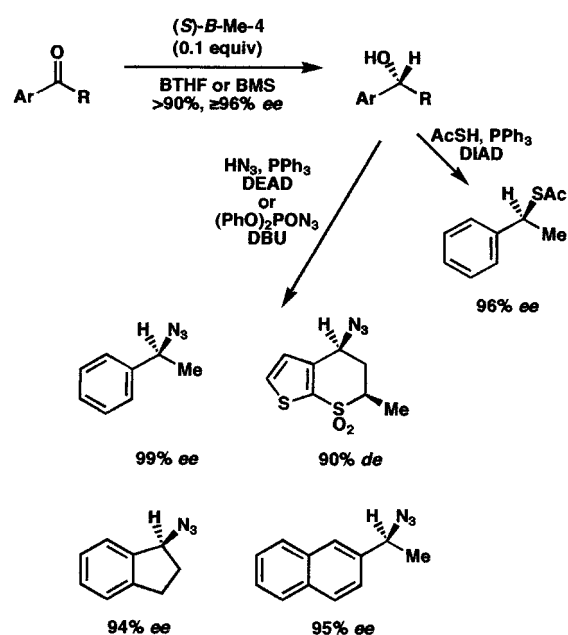


Scheme 16. A different route to optically active allenes.

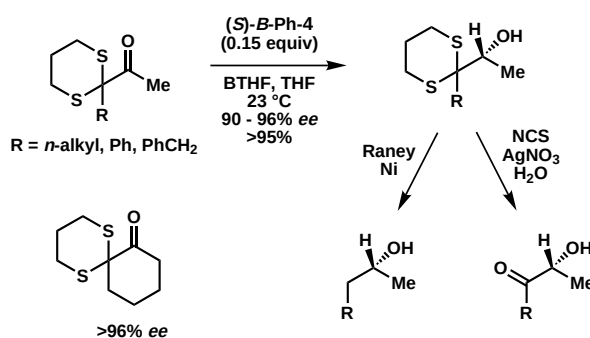
Whereas chiral C–O stereocenters can be readily accessed by oxazaborolidine-catalyzed reduction of ketones, the asymmetric reductions of other heteroatom–carbon double bonds are not as efficient. To overcome these limitations, the displacement of the hydroxyl group of chiral secondary alcohols from the CBS reduction with either nitrogen or sulfur nucleophiles under Mitsunobu-type conditions has been investigated and found to occur by S_N2 inversion; this yields optically active nitrogen^[54, 83] and sulfur compounds^[86] (Scheme 17). These results are especially noteworthy considering the tendency of benzyl substrates to undergo S_N1 displacement with loss of configuration.

The dithiane protecting group for ketones has been utilized as a steric control element in the CBS reduction to differentiate the carbonyl oxygen lone pairs (Scheme 18).^[85] The reductions were highly enantioselective for both acyclic and cyclic compounds. Subsequent desulfurization (with Raney Ni) gave aliphatic carbinols, whereas hydrolysis gave α -hydroxy ketones.

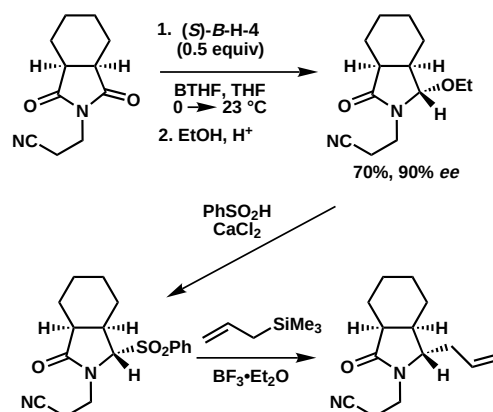
The desymmetrization of a *meso*-imide by the selective reaction of one of the two prochiral carbonyl groups is extremely powerful as three new chiral centers result. As shown in Scheme 19, oxazaborolidine-catalyzed reduction accomplishes this transformation with good enantiomeric excess (90% ee). This provides a route to enantioenriched starting materials for *N*-acyliminium ion chemistry.^[86]



Scheme 17. The Mitsunobu route to chiral nitrogen and sulfur compounds.

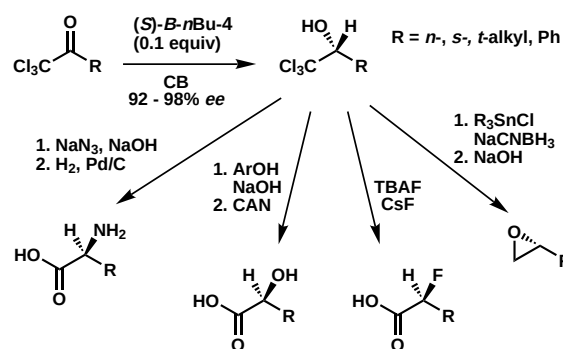


Scheme 18. Dithiane as the large group R_L in the CBS reduction.



Scheme 19. CBS reduction of *meso*-imides yields chiral pyrrolidinones.

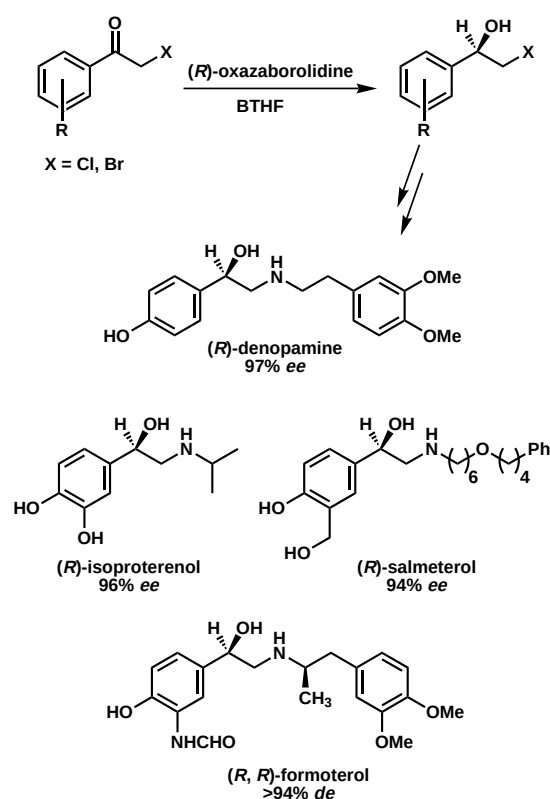
Trichloromethyl carbinols, which are available with very high levels of enantioselectivity by the asymmetric reduction of achiral trichloromethyl ketones,^[87] are readily converted into α -amino,^[75] α -hydroxy,^[88] and α -fluoro acids^[89] under basic conditions via a highly reactive 1,1-dichloro epoxide (Scheme 20). The selective dechlorination of trichloromethyl carbinols to chlorohydrins followed by ring closure provides a straightforward route to optically active terminal oxiranes.^[90]



Scheme 20. Trichloromethyl alcohols give access to many useful chiral intermediates.

6.3. Synthesis of Bioactive Compounds

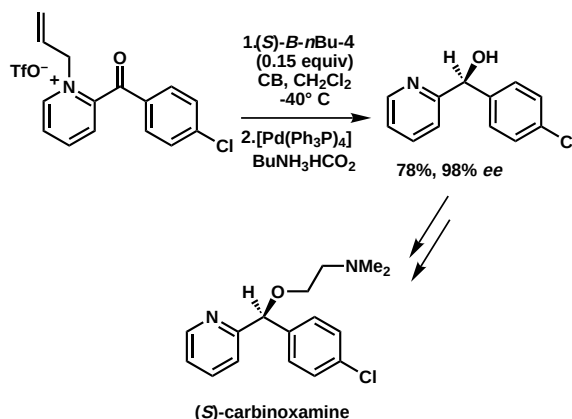
Many β -agonists, which are useful in the treatment of asthma and bronchitis, are currently sold as racemates despite the demonstration of enhanced efficacy of the *R* isomers. The oxazaborolidine-catalyzed reduction of α -haloacetophenones has permitted the highly efficient preparation of a number of β -agonists in enantiomerically pure form by amination of the corresponding optically active styrene oxide or O-silyl halohydrin (Scheme 21).^[91]



Scheme 21. Enantioselective synthesis of β -agonists.

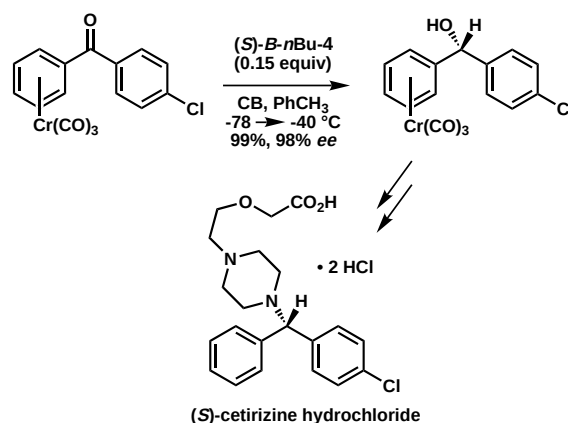
The commercial histamine antagonist carbinoxamine has been prepared as essentially a single enantiomer (98% ee); the key steps are a CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate followed by in situ deallyl-

ation (Scheme 22).^[59, 60] The allyl group serves both to prevent coordination of the pyridine nitrogen atom to the stoichiometric reductant catecholborane and/or the oxazaborolidine catalyst, and to provide the necessary steric bias for the selective binding of one of the carbonyl oxygen electron lone pairs to the catalyst.



Scheme 22. Enantioselective synthesis of (S) -carbinoxamine.

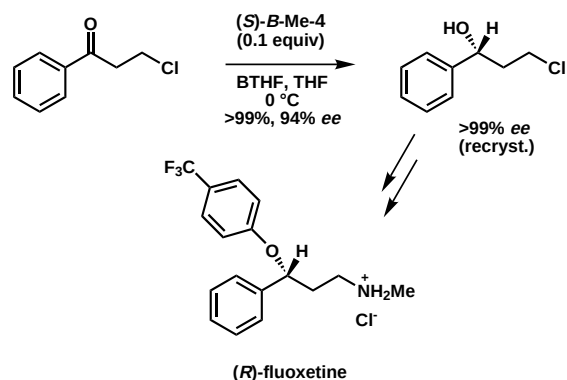
Cetirizine hydrochloride (zyrtec), an antihistamine that is notable for its nonsedating properties and potency, contains an amino-substituted benzhydryl stereocenter. This stereocenter has been established by a highly selective CBS reduction of a benzophenone– $\text{Cr}(\text{CO})_3$ π complex (Scheme 23).^[75] The complexed $\text{Cr}(\text{CO})_3$ group behaves as R_L both for steric and electronic reasons, and functions as a controller for the enantiospecific displacement of the hydroxyl group by amine with retention of configuration.



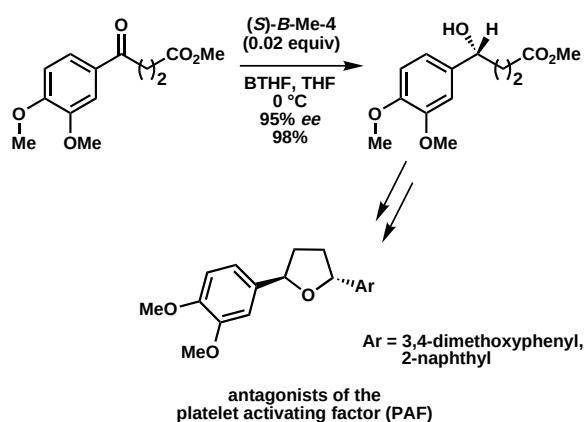
Scheme 23. Enantioselective synthesis of (S) -cetirizine hydrochloride.

The antidepressant fluoxetine hydrochloride (prozac, Eli Lilly) has been synthesized in enantiomerically pure form by the oxazaborolidine-catalyzed reduction of β -chloropropiophenone as a key step (Scheme 24).^[92] This four-step synthesis proceeds in high overall yield (77–82%) and does not require chromatographic purification.

Chiral *trans*-2,5-diaryltetrahydrofurans, inhibitors of the platelet activating factor, have been prepared by CBS


 Scheme 24. Enantioselective synthesis of (*R*)-fluoxetine.

reduction of a γ -ketoester followed by lactonization, reduction, and stereoselective arylation (Scheme 25).^[93]



Scheme 25. Enantioselective synthesis of antagonists of the platelet activating factor (PAF).

The chiral thioether L-691,698, an antagonist of leukotriene D₄, has also been synthesized by the oxazaborolidine-catalyzed reduction (Scheme 26).^[94]

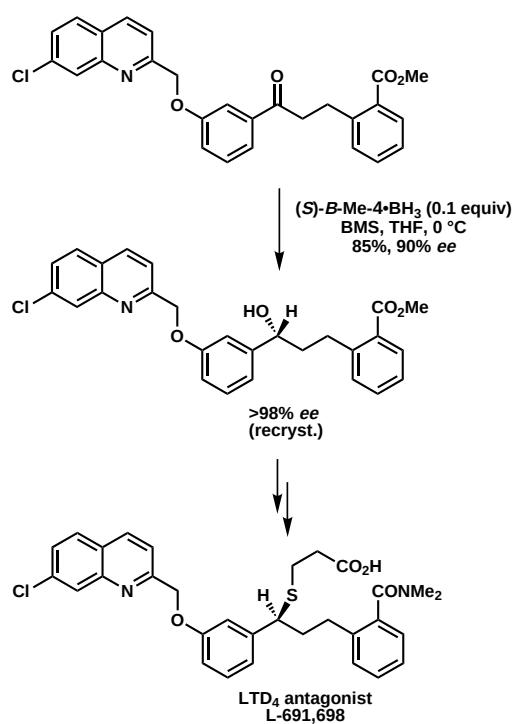
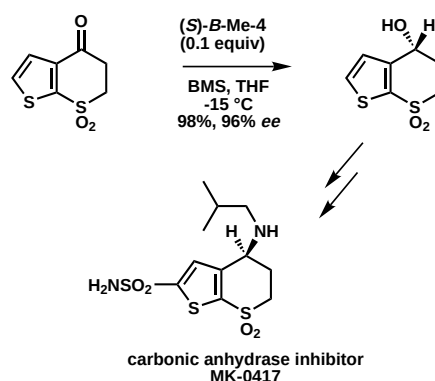
The carbonic anhydrase inhibitor MK-0417 has been prepared on a large scale by the oxazaborolidine-catalyzed reduction of the heterocyclic ketone shown in Scheme 27.^[44b]

The synthesis of the potassium channel blocker MK-0499 utilized a variant of the CBS reduction in which one equivalent of 2-propanol was added prior to BH₃·SMe₂ (Scheme 28).^[21] The use of 2-propanol as additive increased the diastereoselectivity from 93 to 98 %.

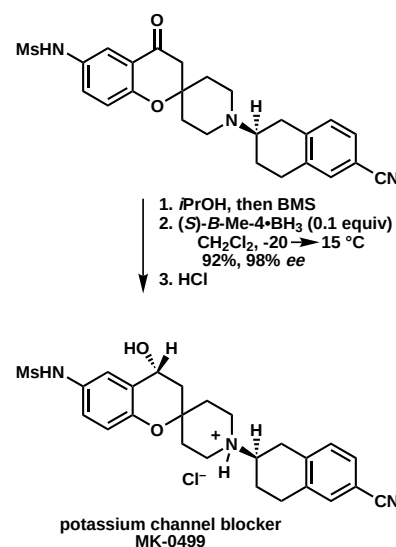
The CBS reduction of the acyclic α,β -enone shown in Scheme 29 proceeded diastereoselectively to form the corresponding allyl alcohol, which was used for the synthesis of an isomer of colletalol.^[62d, e]

Oxazaborolidine-catalyzed reduction of the α,β -enone in Scheme 30 to the optically pure allyl alcohol provided the first chiral center in the synthesis of the antiinflammatory and immunosuppressive agent RS-97613.^[62f] Subsequent stereoselective orthoester Johnson–Claisen rearrangement, diastereoselective α -methylation, and hydrolysis completed the synthesis of this analogue of mycophenolic acid.

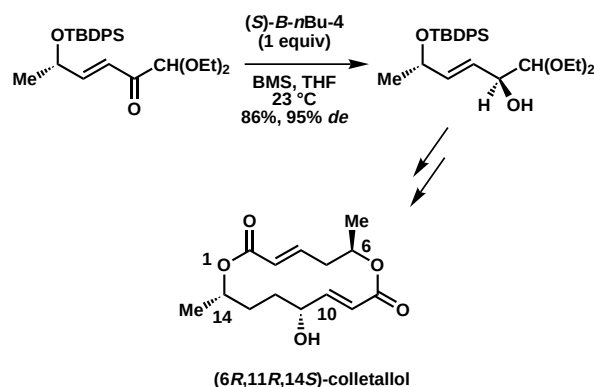
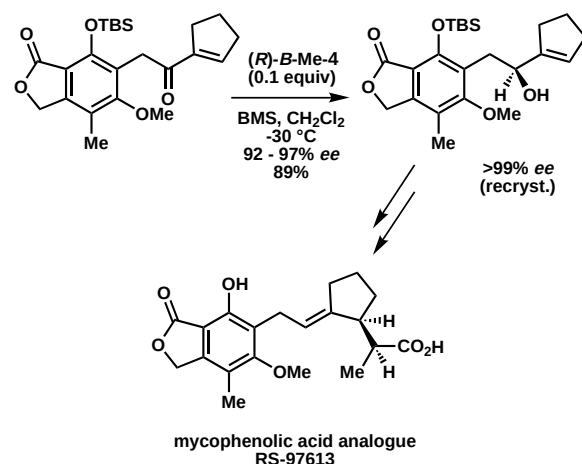
The 3-deoxy-3-thia analogue of vitamin D was synthesized by CBS reduction of the cyclic α,β -enone shown in Scheme 31.


 Scheme 26. Enantioselective synthesis of a leukotriene D₄ antagonist.


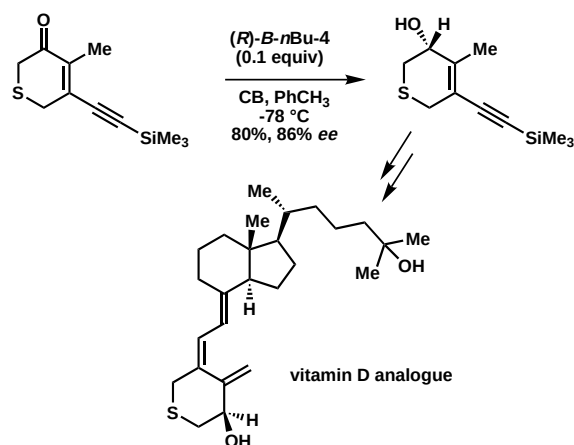
Scheme 27. Enantioselective synthesis of a carbonic anhydrase inhibitor.



Scheme 28. Enantioselective synthesis of a potassium channel blocker.

Scheme 29. Asymmetric synthesis of (6*R*,11*R*,14*S*)-colletalol.

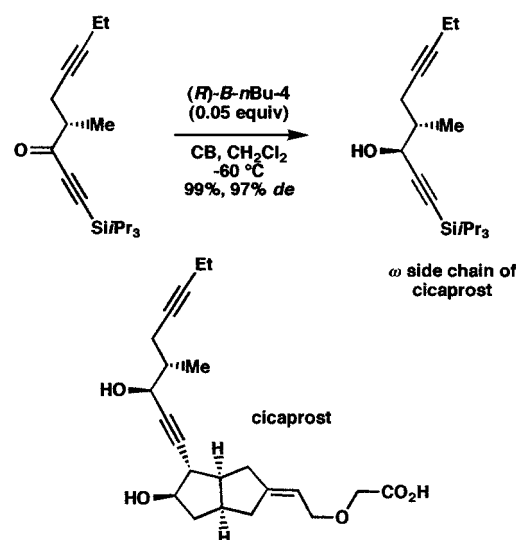
Scheme 30. Enantioselective synthesis of an immunosuppressive and antiinflammatory agent.



Scheme 31. Asymmetric synthesis of a vitamin D analogue.

This provided a chiral allyl alcohol corresponding to the A ring.^[95]

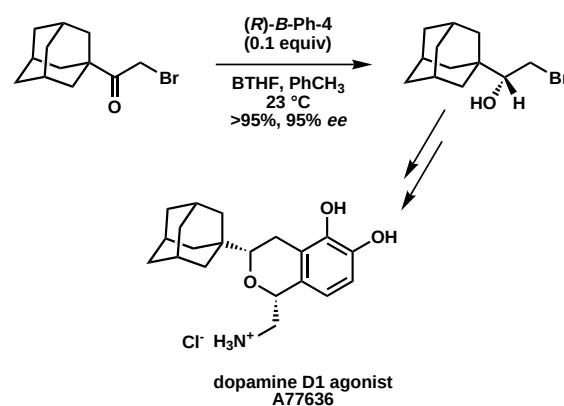
Cicaprost, an orally active, metabolically stable prostaglandin I₂ (PGI₂) analogue, contains a complex side chain which was constructed by oxazaborolidine-catalyzed reduction (Scheme 32).^[96] Long-range steric interactions between *n*-butyl group on the boron atom of the catalyst and the triisopropylsilyl group of the ketonic substrate cause ethynyl to behave as the large group R_L. The chirality of the starting ketone does not affect the selectivity of the reduction since



Scheme 32. Asymmetric synthesis of the ω side chain of cicaprost.

the use of the enantiomeric (*S*)-oxazaborolidine catalyst gave the other diastereomer with high diastereomeric excess (96 %).

The dopamine D1 agonist A77636 was recently prepared in optically pure form by oxazaborolidine-catalyzed reduction of adamantyl bromomethyl ketone (Scheme 33).^[97] Conversion of the chiral bromohydrin into the corresponding epoxide, ring opening with an aryllithium reagent, intramolecular acetal cyclization, and deprotection gave the desired product in very good yield.

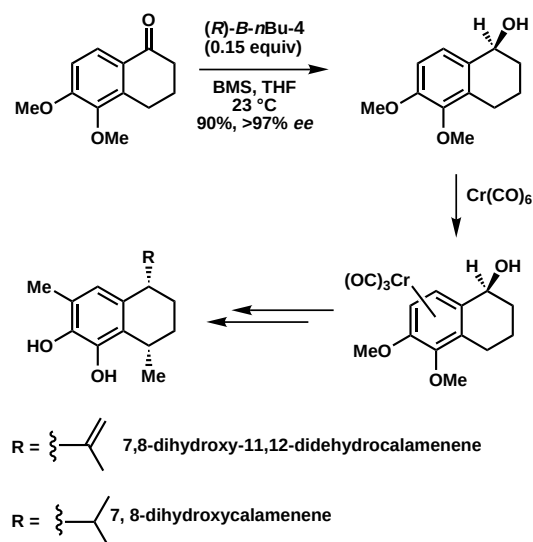


Scheme 33. Asymmetric synthesis of A77636.

6.4. Synthesis of Natural Products

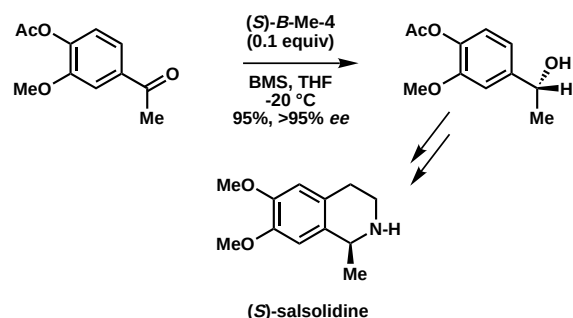
The antiinfective compounds 7,8-dihydroxycalamenene and 7,8-dihydroxy-11,12-didehydrocalamenene were synthesized by CBS reduction of 5,6-dimethoxy-1-tetralone, hydroxyl-directed face-selective complexation of a Cr(CO)₃ moiety, and subsequent hydrogenolysis, metalation/alkylation, and decomplexation (Scheme 34).^[98]

The tetrahydroisoquinoline (*S*)-salsolidine was prepared efficiently by oxazaborolidine-catalyzed reduction of a substituted acetophenone followed by Mitsunobu displacement



Scheme 34. Enantio- and stereocontrolled synthesis of chiralen anti-infective tetralins.

of the hydroxyl group with a sulfonamide and intramolecular cyclization (Scheme 35).^[99] This approach should be applicable to the synthesis of a number of enantiopure tetrahydro-isoquinoline derivatives.

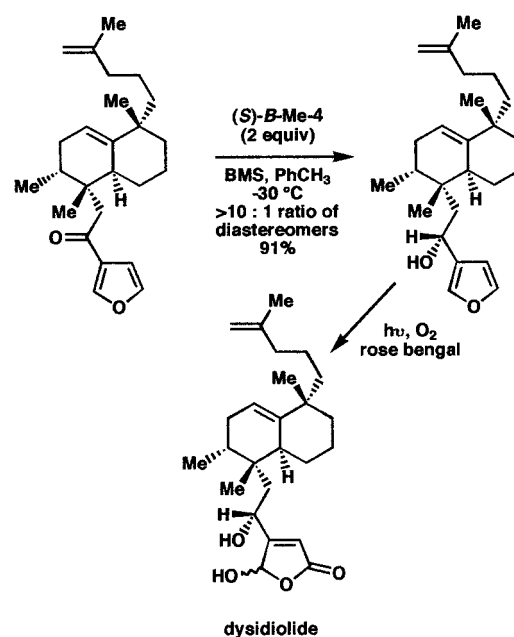


Scheme 35. Enantioselective synthesis of (*S*)-salsolidine.

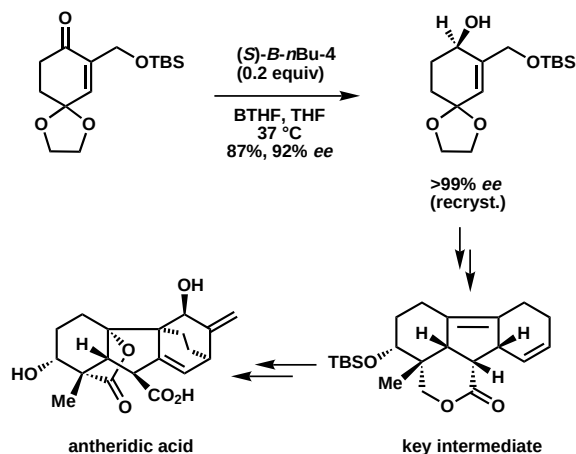
In a recent total synthesis of the sesterterpene dysidiolide, a marine sponge metabolite that has been shown to exhibit antitumor activity, oxazaborolidine-catalyzed reduction afforded greater than 10:1 selectivity for the required alcohol; the 3-furyl group acted effectively as R_L , and the bicyclic ring system as R_S (Scheme 36).^[100] Importantly, this route permitted conversion of the *S* diastereomer into the desired *R* isomer by oxidation and subsequent asymmetric reduction. Mitsunobu displacement of the hydroxyl group of the *S* diastereomer was nonstereoselective.

The fern hormone antheridic acid was initially synthesized in racemic form. An enantioselective synthesis of a key intermediate was achieved by the oxazaborolidine-catalyzed reduction and subsequent conversions depicted in Scheme 37.^[63a]

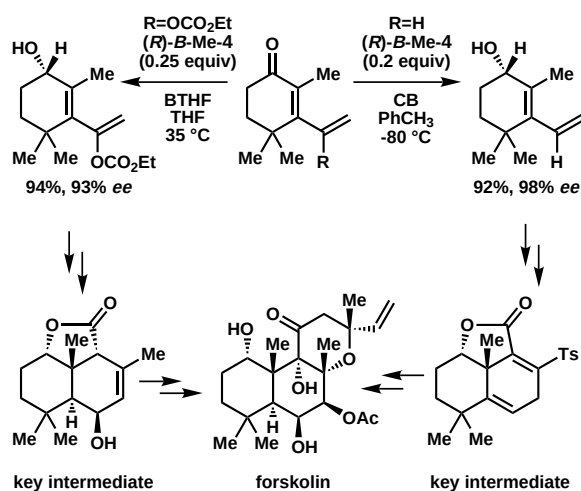
Two different routes to optically active intermediates for the synthesis of forskolin, a potent activator of adenylate cyclase, have been devised utilizing CBS reduction of the dieneones shown in Scheme 38.^[101, 102]



Scheme 36. Enantioselective synthesis of dysidiolide.

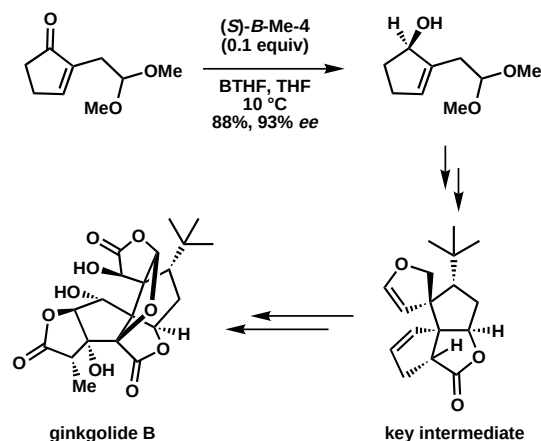


Scheme 37. Enantioselective synthesis of antheridic acid.



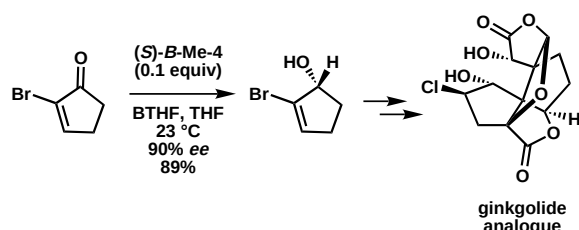
Scheme 38. Enantioselective synthesis of forskolin.

Ginkgolide B, a potent antagonist of the platelet activating factor, has been synthesized enantioselectively by CBS reduction of a α -functionalized cyclopentenone to introduce chirality (Scheme 39).^[63b] The resulting optically active allyl



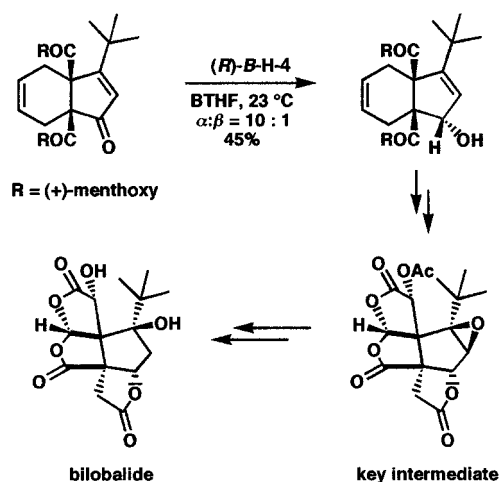
Scheme 39. Enantioselective synthesis of ginkgolide B.

alcohol was then elaborated in a stereocontrolled fashion via a tetracyclic lactone to ginkgolide B. The CBS reduction of 2-bromo-2-cyclopentenone served as a key step in the synthesis of a truncated analogue of ginkgolide B (Scheme 40).^[64b]



Scheme 40. Enantioselective synthesis of a ginkgolide analogue.

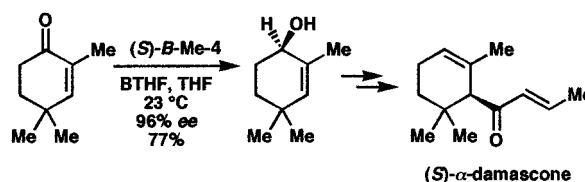
An asymmetric synthesis of bilobalide, an unusual substance produced by the ginkgo tree *Ginkgo biloba*, has been carried out starting from the bicyclic enone depicted in Scheme 41.^[103] Attempts to reduce this chiral ketone to the α -



Scheme 41. Enantioselective synthesis of bilobalide.

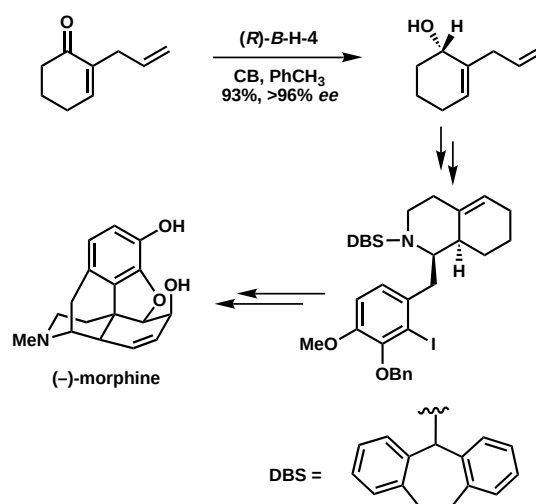
epimer with a number of reagents (NaBH_4 , $\text{Zn}(\text{BH}_4)_2$, SmI_2 in THF/MeOH, $\text{BH}_3 \cdot \text{THF}$, Na powder in 2-propanol/toluene) gave unsatisfactory results. The oxazaborolidine-mediated reduction of this substrate, however, provided greater than 10:1 selectivity for the α -epimer, which was then transformed into bilobalide via the tetracyclic trilactone shown.

The important fragrance (*S*)- α -damascone could be prepared by a sequence involving CBS reduction of the cyclic α -methyl- α,β -enone shown in Scheme 42, transfer of chirality from C–O to C–C by the Still variant of the [2,3] Wittig rearrangement to set the tertiary chiral center, oxidation, and introduction of the side chain.^[104]



Scheme 42. Enantioselective synthesis of (*S*)- α -damascone.

A recent elegant synthesis of (–)-morphine also employed a highly enantioselective CBS reduction (Scheme 43).^[105] Stereospecific conversion of the hydroxyl group into dimethylphenylsilyl and the terminal vinyl moiety into an amino



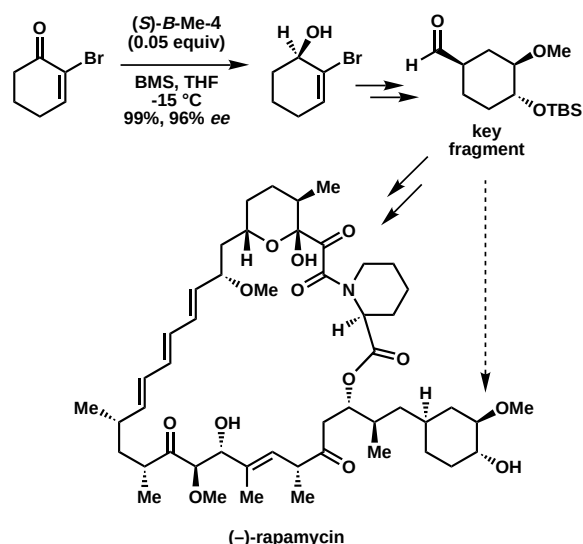
Scheme 43. Enantioselective synthesis of (–)-morphine.

substituent (*N*-DBS) set the stage for an intramolecular iminium ion – allylsilane cyclization to give the bicyclic system shown in Scheme 43. The bridgehead ring system was established by an intramolecular Heck reaction.

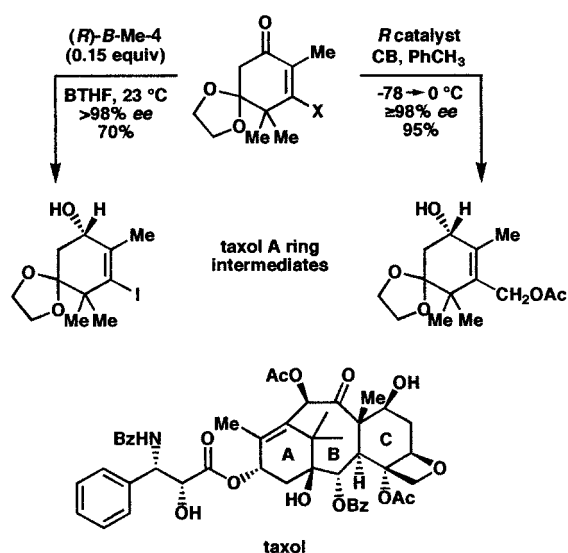
In the synthesis of the powerful immunosuppressive agent (–)-rapamycin, oxazaborolidine-catalyzed reduction of 2-bromo-2-cyclohexen-1-one was used to generate the functionalized cyclohexyl subunit (Scheme 44).^[64a, 106]

Two conceptually similar routes to the A ring of taxol have been developed by CBS reduction of functionalized cyclohexenones (Scheme 45).^[107]

While many conjugated cyclic α,β -enones with *endocyclic* (*s-trans*) unsaturation have been reduced to allyl alcohols in



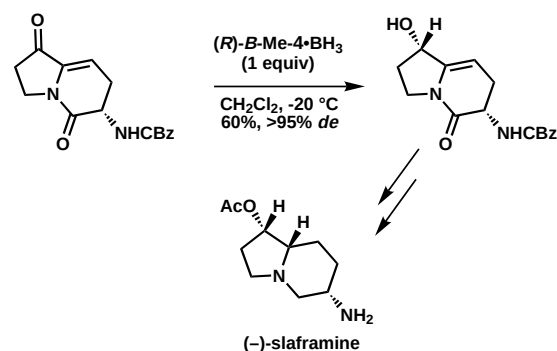
Scheme 44. Asymmetric synthesis of the cyclohexyl moiety of (-)-rapamycin.



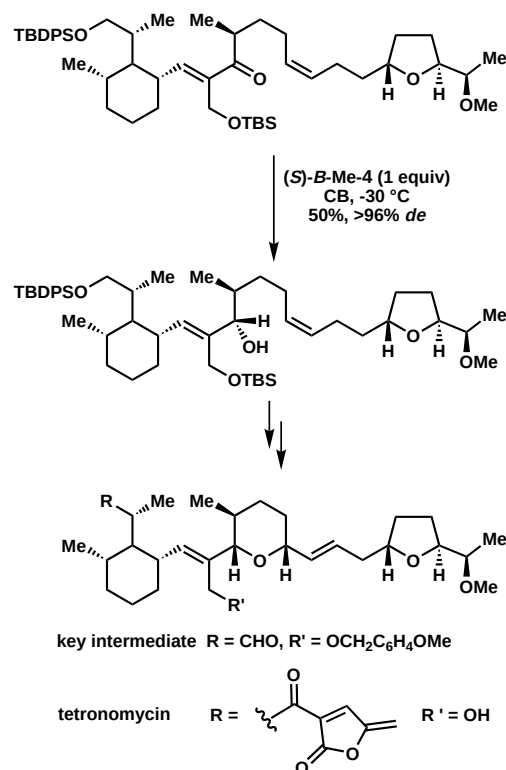
Scheme 45. Enantioselective synthesis of taxol A ring intermediates.

the presence of chiral oxazaborolidines, the reduction of such compounds with *exocyclic (s-cis)* double bonds has been reported only recently in connection with the synthesis of the alkaloid (-)-slaframine.^[108] The chiral α,β -enone shown in Scheme 46 was reduced with one equivalent of the (*R*)-*B*-Me-4·BH₃ complex (*B*-Me-5) to provide the required allyl alcohol with excellent diastereomeric purity. In contrast, the use of the enantiomeric oxazaborolidine–BH₃ complex afforded the other diastereomer with high selectivity.

An approach to the synthesis of the ionophore antibiotic tetronomycin utilized the CBS reduction outlined in Scheme 47^[109] (>96% *de*) followed by an intramolecular Pd^{II}-mediated cyclization to establish the central *cis*-substituted tetrahydropyran ring. Attempts to prepare the same allyl alcohol by addition of vinyl lithium to an aldehyde yielded a 1:2 ratio of desired to undesired diastereomeric alcohols.



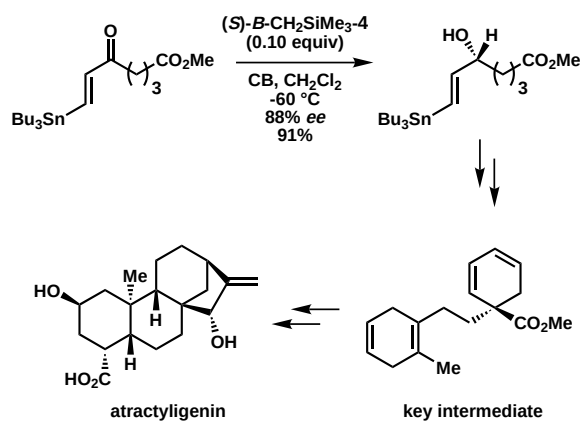
Scheme 46. Asymmetric synthesis of (-)-slaframine.



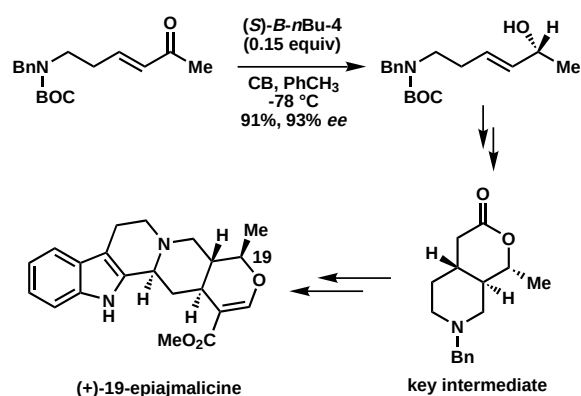
Scheme 47. Diastereoselective CBS reduction of a chiral ketone on the way to tetronomycin.

The naturally occurring adenosine diphosphate transport inhibitor atractyligenin was originally synthesized as the racemate; the first key chiral intermediate in the enantioselective CBS reduction is the substituted 1,3-cyclohexadiene shown in Scheme 48.^[61] The use of the β -trialkylstannyl substituent on the enone to provide temporary steric bulk and the CH₂SiMe₃ group on the boron atom of the catalyst to maximize long-range steric interactions were crucial for high enantioselectivity in the oxazaborolidine-catalyzed reduction. Subsequent steps including a Claisen rearrangement effected the transfer of chirality from C–O to C–C to form the quaternary carbon stereocenter of the key intermediate.

A recent study on the synthesis of heteroyohimbine alkaloids utilized a CBS reduction of the acyclic α,β -enone shown in Scheme 49 to the allyl alcohol; the *B*-*n*Bu-oxazaborolidine catalyst (93% *ee*) was superior to the *B*-Me-oxazaborolidine catalyst (81% *ee*).^[110] Orthoester Johnson –



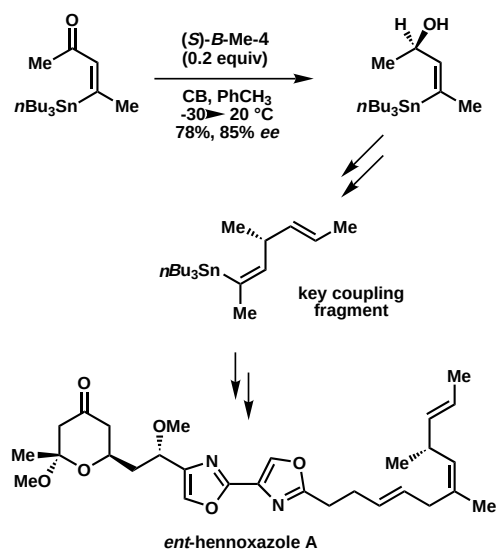
Scheme 48. Enantioselective synthesis of atractyligenin.



Scheme 49. Asymmetric synthesis of a key intermediate on the way to (+)-19-epiajmalicine.

Claisen rearrangement and iminium ion bicyclization provided the bicyclic amino lactone.

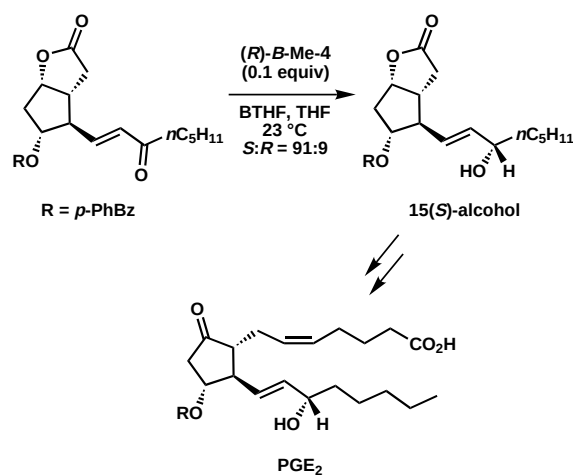
The relative and absolute configurations of the marine alkaloid hennoxazole A, which actively inhibits the herpes simplex virus, were unambiguously determined by enantioselective total synthesis. CBS reduction of the *cis*- β -stannyl-enone as depicted in Scheme 50 followed by hydroxyl activa-



Scheme 50. Enantioselective synthesis of *ent*-hennoxazole A.

tion and stereospecific displacement with a propenyl cuprate gave the indicated chiral 1,4-diene fragment.^[62b, c] Transmetalation of this key coupling fragment from the tin to the zinc derivative facilitated a palladium-mediated coupling with an allyl bromide to afford the carbon framework of the natural product.

A long-standing challenge in the synthesis of prostanoids has been the selective introduction of the C(15) hydroxyl-bearing stereocenter by reduction of the α,β -enone. While a number of reagents and reaction conditions have been designed to effect this transformation, the CBS reduction provides a pleasing catalytic solution, and furnishes a 10:1 ratio of the diastereomeric alcohols under exceedingly mild conditions (Scheme 51).^[13b]

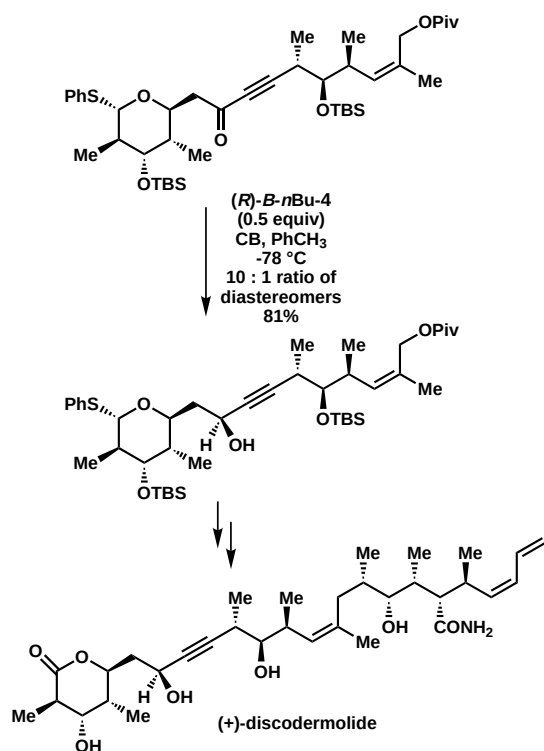


Scheme 51. Asymmetric synthesis of prostaglandins.

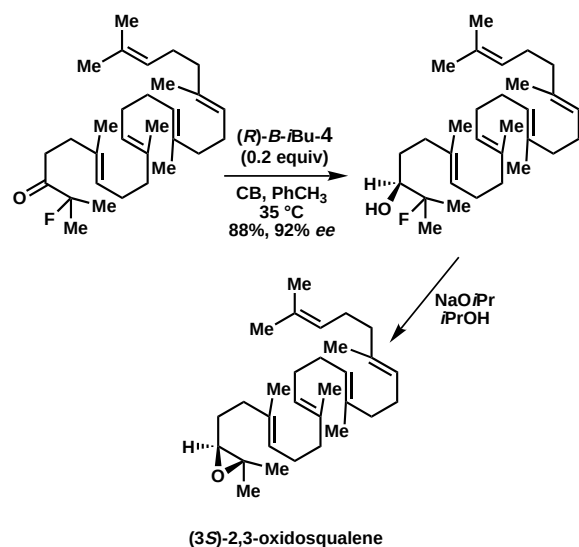
The scarce marine natural product (+)-discodermolide has been observed to possess impressive immunosuppressive activity and, as a result, has been the object of total synthesis. Oxazaborolidine-catalyzed reduction of the propargylic ketone shown in Scheme 52 gave a 10:1 mixture of isomers with the desired antipode predominating.^[111] The alkynyl group behaved as R_L in this CBS reduction in a nonpolar solvent and with catecholborane as stoichiometric reductant, which is in agreement with other studies (see Table 9).^[43]

(3*S*)-2,3-Oxidosqualene is the biosynthetic precursor to numerous steroids and polycyclic triterpenoids. Asymmetric reduction of the α -fluoro ketone shown in Scheme 53 followed by oxirane ring closure gave (3*S*)-2,3-oxidosqualene with 92 % *ee*.^[42] The choice of α -fluoro ketone was crucial for high enantioselectivity in the reduction, since the use of the α -chloro or β -bromo ketone resulted in slow reaction rates and only modest enantioselectivities. The magnitude and sense of enantioselectivity were highly dependent on temperature: The enantiomeric ratio *S*:*R* is 96:4 at 35 °C, 93:7 at 23 °C, and 20:80 at –23 °C.

In a recent improved synthesis of the right half of halichondrin B, a potent antitumor agent, a Nozaki–Kishi coupling of vinyl iodide with aldehyde afforded a 4:1 ratio of diastereomers favoring the desired alcohol.^[112] Dess–Martin oxidation of the mixture of alcohols to the α -substituted α,β -



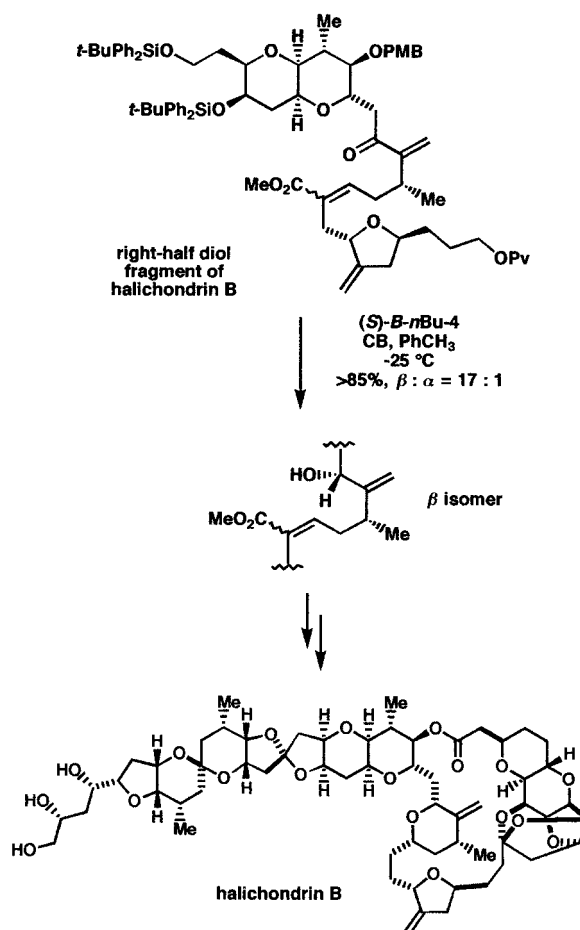
Scheme 52. Enantioselective synthesis of discodermolide.

Scheme 53. Enantioselective synthesis of (*3S*)-2,3-oxidosqualene.

enone followed by CBS reduction gave a much improved 17:1 ratio of diastereomers at the carbinol center and permitted the efficient stereoselective construction of the central pyran unit of the right-half diol fragment (Scheme 54).

7. Summary and Outlook

Chiral oxazaborolidine-catalyzed reduction of ketones with coordinated borane or catecholborane as stoichiometric reductant provides access to a broad range of chiral secondary alcohols. These products, in turn, can serve as key intermedi-



Scheme 54. Asymmetric synthesis of halichondrin B.

ates for the synthesis of an enormous range of compounds with regard to functionality, size, and topological complexity. Thus, many types of chiral natural products and bioactive molecules can be synthesized efficiently without the need for optical resolution. The applications of this methodology continue to increase rapidly in number and could become commercially important.

Appendix: Abbreviations Used

BDEA = BH₃ · diethylaniline, BMS = BH₃ · Me₂S, Bn = benzyl, BOC = *tert*-butoxycarbonyl, BTHF = BH₃ · THF, Bz = benzoyl, CAN = cerammonium nitrate, CB = catecholborane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DEAD = diethyl azodicarboxylate, DIAD = diisopropyl azodicarboxylate, Ms = methanesulfonyl, Nap = naphthyl, NCS = *N*-chlorosuccinimide, Piv = pivaloyl, PMB = *p*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl.

We are grateful to the National Institutes of Health and the National Science Foundation for generous financial support.

Received: October 28, 1997 [A258IE]
German version: *Angew. Chem.* **1998**, *110*, 2092–2118

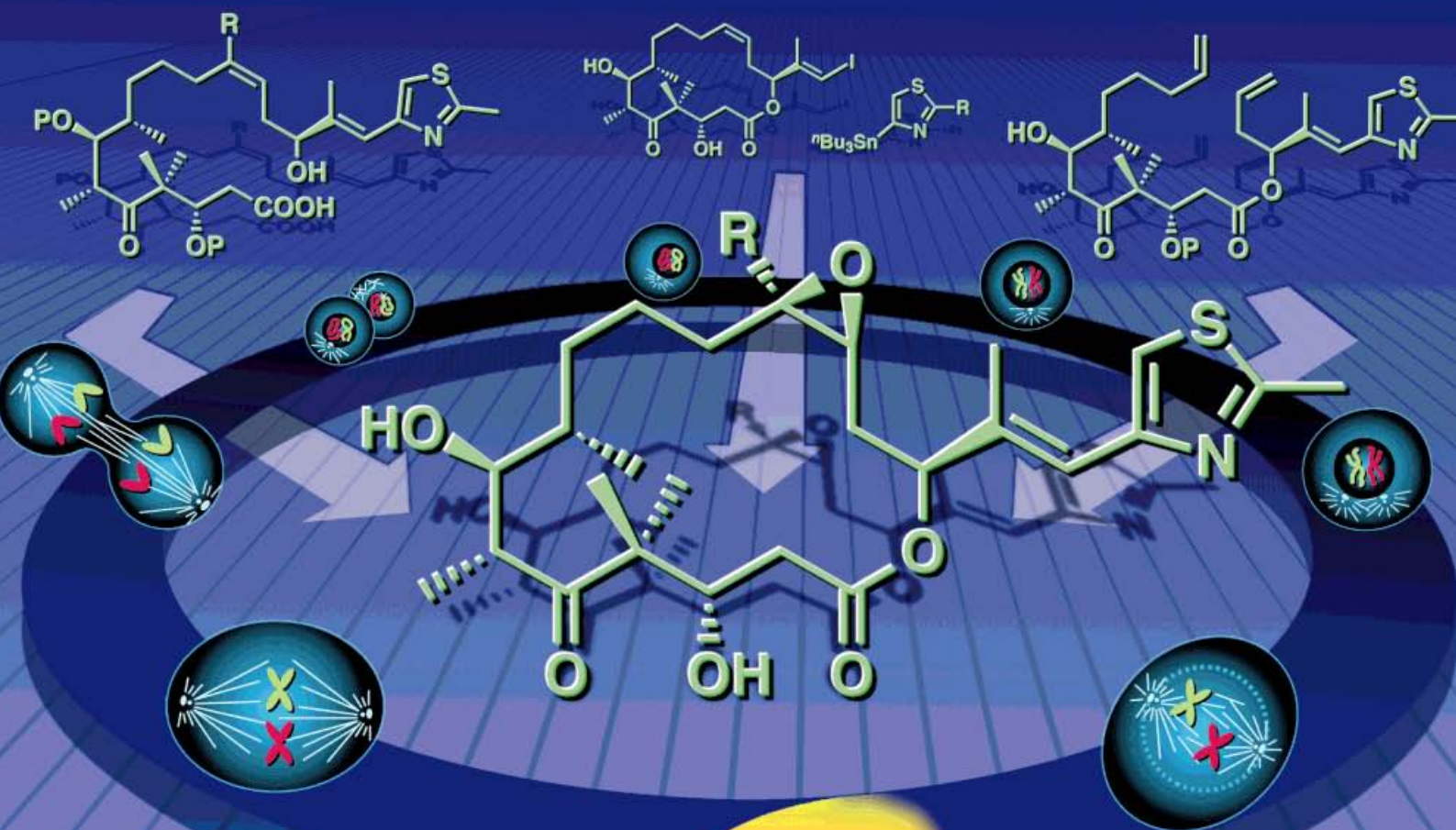
- [1] General reviews: a) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, New York, **1956**; b) *Reduction Techniques and Applications in Organic Synthesis* (Ed.: R. L. Augustine), Marcel Dekker, New York, **1968**; c) A. Hajos, *Complex Hydrides in Organic Synthesis*, Elsevier, New York, **1979**; d) M. Hudlicky, *Reductions in Organic Chemistry, Vols. 1 and 2*, Ellis Harwood, Chichester, **1984**.
- [2] a) W. G. Brown, *Organic Reactions*, **1951**, 6, 469–509; b) *Encyclopedia of Reagents for Organic Synthesis, Vol. 5* (Ed.: L. A. Paquette), Wiley, New York, **1995**, pp. 3009–3014.
- [3] a) K. N. Semenko, B. M. Bulychev, E. A. Shevlyagina, *Russ. Chem. Rev.* **1966**, 35, 649–658; b) H. C. Brown, S. T. Krishnamurthy, *Tetrahedron* **1979**, 35, 567–607.
- [4] a) E. Schenker, *Angew. Chem.* **1961**, 73, 81–106; b) reference [3b].
- [5] H. C. Brown, *Boranes in Organic Synthesis*, Cornell University Press, Ithaca, NY, **1972**.
- [6] For a brief summary of the uses of such reagents in synthesis, see M. Greeves in *Comprehensive Organic Synthesis, Vol. 8* (Ed.: B. M. Trost), Pergamon Press, Oxford, **1991**, pp. 1–24.
- [7] D. C. Wigfield, *Tetrahedron* **1979**, 35, 449–462.
- [8] Reviews: a) E. R. Grandbois, S. I. Howard, J. D. Morrison, *Asymmetric Synthesis, Vol. 2*, Academic Press, New York, **1983**, pp. 71–90; b) J. W. ApSimon, T. L. Collier, *Tetrahedron* **1986**, 42, 5157–5254; c) H. Haubenstock, *Topics in Stereochemistry, Vol. 14* (Eds.: N. L. Allinger, E. L. Eliel, S. H. Wilen), Wiley, New York, **1983**, pp. 231–300; d) T. Mukaiyama, M. Asami in *Topics in Current Chemistry, Organic Chemistry, No. 127* (Ed.: F. L. Boschke), Springer, Berlin, **1985**, pp. 133–167.
- [9] a) R. Haller, H. J. Schneider, *Chem. Ber.* **1973**, 106, 1312–1318; b) S. Yamaguchi, H. S. Mosher, *J. Org. Chem.* **1973**, 38, 1870–1877; c) R. S. Brinkmeyer, V. M. Kapoor, *J. Am. Chem. Soc.* **1977**, 99, 8339–8341; d) N. Cohen, R. J. Lopresti, C. Neukom, G. Saucy, *J. Org. Chem.* **1980**, 45, 582–588; e) G. M. Giongo, F. Di Gregorio, N. Palladino, W. Marconi, *Tetrahedron Lett.* **1973**, 14, 3195–3198; f) A. I. Meyers, P. M. Kendall, *Tetrahedron Lett.* **1974**, 15, 1337–1340; g) I. Jacquet, J. P. Vigneron, *ibid.* **1974**, 15, 2065–2068; h) J. P. Vigneron, I. Jacquet, *Tetrahedron* **1976**, 32, 939–944; i) J. P. Vigneron, V. Bloy, *Tetrahedron Lett.* **1980**, 21, 1735–1738; j) M. F. Grundon, D. G. McCleery, J. W. Wilson, *ibid.* **1976**, 17, 295–296; k) R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, 106, 6709–6716; l) R. Noyori, I. Tomino, M. Yamada, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, 106, 6717–6725; m) M. Asami, H. Ohno, S. Kobayashi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1978**, 51, 1869–1873; n) T. Sato, Y. Goto, T. Fujisawa, *Tetrahedron Lett.* **1982**, 23, 4111–4112; o) T. Sato, Y. Gotoh, Y. Wakabayashi, T. Fujisawa, *ibid.* **1983**, 24, 4123–4126; p) H. Suda, S. Kanoh, N. Umeda, T. Nakajo, M. Motoi, *ibid.* **1983**, 24, 1513–1516; q) M. Kawasaki, Y. Suzuki, S. Terashima, *Chem. Lett.* **1984**, 239–242; r) K. Soai, T. Yamanoi, H. Oyamada, *ibid.* **1984**, 251–254; s) A. K. Mandal, T. G. Kasar, S. W. Mahajan, D. G. Jawalkar, *Synth. Commun.* **1987**, 17, 563–574.
- [10] A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, *J. Chem. Soc. Chem. Commun.* **1981**, 315–317.
- [11] S. Itsuno, A. Hirao, S. Nakahama, N. Yamazaki, *J. Chem. Soc. Perkin Trans. I* **1983**, 1673–1676.
- [12] a) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Chem. Commun.* **1983**, 469–470; b) S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Perkin Trans. I* **1985**, 2039–2044.
- [13] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, 109, 5551–5553; b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, 109, 7925–7926; c) E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, 53, 2861–2863; d) E. J. Corey, *Pure Appl. Chem.* **1990**, 62, 1209–1216.
- [14] For improved preparations of amino alcohol **3**, see a) D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. Turner Jones, K. Hoogsteen, M. W. Baum, E. J. J. Grabowski, *J. Org. Chem.* **1991**, 56, 751–762; b) J. V. B. Kanth, M. Periasamy, *Tetrahedron* **1993**, 49, 5127–5132; c) for an earlier review of oxazaborolidine-catalyzed reduction of ketones, see V. K. Singh, *Synthesis* **1992**, 605–616.
- [15] J. O. Link, Ph.D. thesis, Harvard University (USA), **1992**.
- [16] Interestingly, the treatment of oxazaborolidine **2** with $\text{BH}_3 \cdot \text{THF}$ under the same conditions reveals only a small proportion of the $\text{BH}_3 \cdot \text{2}$ complex relative to free **2**.^[13a]
- [17] a) E. J. Corey, M. Azimioara, S. Sarshar, *Tetrahedron Lett.* **1992**, 33, 3429–3430. Researchers at Merck have used *B*-Me-**5** as a stoichiometric reagent and as a catalyst with stoichiometric amounts of $\text{BH}_3 \cdot \text{Me}_2\text{S}$ to effect the enantioselective reduction of ketones: b) D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, E. J. J. Grabowski, *J. Org. Chem.* **1993**, 58, 2880–2888.
- [18] It has not been proven if the hydride transfer occurs via a boat or a chair transition state. Both conformations, however, are consistent with the mechanistic model in Scheme 5: a) D. A. Evans, *Science* **1988**, 240, 420–426; for computational studies, see b) D. K. Jones, D. C. Liotta, I. Shinkai, D. J. Mathre, *J. Org. Chem.* **1993**, 58, 799–801; c) L. P. Linney, C. R. Self, I. H. Williams, *J. Chem. Soc. Chem. Commun.* **1994**, 1651–1652; for computational studies concerning different oxazaborolidines, see d) G. J. Quallich, J. F. Blake, T. M. Woodall, *J. Am. Chem. Soc.* **1994**, 116, 8516–8525.
- [19] For the initial report proposing the direct conversion of **7** into **5**, see a) reference [13a]; for computational studies, see b) V. Nevalainen, *Tetrahedron: Asymmetry* **1994**, 5, 289–296; c) reference [18c].
- [20] A recent low-temperature NMR study was inconclusive in determining the detailed mechanism by which **7** is recycled to the active catalytic species: A. W. Douglas, D. M. Tschaen, R. A. Reamer, Y.-J. Shi, *Tetrahedron: Asymmetry* **1996**, 7, 1303–1308.
- [21] For studies detailing the role of the borinate **8** in effecting product enantioselectivity, see a) D. M. Tschaen, L. Abramson, D. Cai, R. Desmond, U.-H. Dolling, L. Frey, S. Karady, Y.-J. Shi, T. R. Verhoeven, *J. Org. Chem.* **1995**, 60, 4324–4330; b) Y.-J. Shi, D. Cai, U.-H. Dolling, A. W. Douglas, D. M. Tschaen, T. R. Verhoeven, *Tetrahedron Lett.* **1994**, 35, 6409–6412.
- [22] a) E. J. Corey, J. O. Link, R. K. Bakshi, *Tetrahedron Lett.* **1992**, 33, 7107–7110. b) If ketone complexation was the rate-limiting step, then the relative rates of reduction should have been $p\text{-MeO} > p\text{-H} > p\text{-NO}_2$; if hydride transfer was the rate-limiting step, then the relative rates should have been $p\text{-NO}_2 > p\text{-H} > p\text{-MeO}$.
- [23] The calculated kinetic isotope effect for the direct reduction of 2-propanone with $\text{BH}_3 \cdot \text{THF}$ was 1.3.^[18c]
- [24] J. G. H. Willems, F. J. Dommerholt, J. B. Hammink, A. M. Vaarhorst, L. Thijs, B. Zwaneburg, *Tetrahedron Lett.* **1995**, 36, 603–606.
- [25] R = H: a) A. V. Rama Rao, M. K. Gurjar, V. Kaiwar, *Tetrahedron: Asymmetry* **1992**, 3, 859–862; b) W. Behnen, C. Dauelsberg, S. Wallbaum, J. Martens, *Synth. Commun.* **1992**, 22, 2143–2153; R = Me: c) E. J. Corey, V. K. Singh, unpublished results.
- [26] E. J. Corey, C.-P. Chen, G. A. Reichard, *Tetrahedron Lett.* **1989**, 30, 5547–5550.
- [27] A. V. Rama Rao, M. K. Gurjar, P. A. Sharma, V. Kaiwar, *Tetrahedron Lett.* **1990**, 31, 2341–2344.
- [28] R = H: a) Y. H. Kim, D. H. Park, I. S. Byun, I. K. Yoon, C. S. Park, *J. Org. Chem.* **1993**, 58, 4511–4512; b) J. Martens, C. Dauelsberg, W. Behnen, S. Wallbaum, *Tetrahedron: Asymmetry* **1992**, 3, 347–350. R = Me: c) reference [25c].
- [29] a) Y. Hong, Y. Gao, X. Nie, C. M. Zepp, *Tetrahedron Lett.* **1994**, 35, 6631–6634; b) B. Di Simone, D. Savoia, E. Tagliavini, A. Umani-Ronchi, *Tetrahedron: Asymmetry* **1995**, 6, 301–306; c) C. M. Bellucci, A. Bergamini, P. G. Cozzi, A. Papa, E. Tagliavini, A. Umani-Ronchi, *Tetrahedron: Asymmetry* **1997**, 8, 895–902.
- [30] M. Masui, T. Shioiri, *Synlett* **1996**, 49–50.
- [31] E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1989**, 30, 6275–6278.
- [32] E. J. Corey, S. Shibata, unpublished results.
- [33] A. S. Demir, E. Mecitoglu, C. Tanyeli, V. Gülbeyaz, *Tetrahedron: Asymmetry* **1996**, 7, 3359–3364.
- [34] The spectral characterization of the spiro-2-indanyl catalyst (entry 10) has not been published.^[33]
- [35] E. J. Corey, J. O. Link, unpublished results.
- [36] Heating a mixture of (*S*)-prolinol ($\text{R}' = \text{H}$) and $\text{BH}_3 \cdot \text{THF}$ in toluene at reflux effected the enantiocontrolled reduction of acetophenone in moderate yield (95% *ee*, 59% yield). The exact nature of the reducing agent as well as the precise mode of reduction under these conditions is not clear, however, as the treatment of (*S*)-prolinol with $\text{BH}_3 \cdot \text{THF}$ results in the formation of dimeric species: a) J. M. Brunel, M. Maffei, G. Buono, *Tetrahedron: Asymmetry* **1993**, 4, 2255–2260; b) A. Lang, H. Nöth, M. Schmidt, *Chem. Ber.* **1997**, 130, 241–246.
- [37] Upon treatment with $\text{BH}_3 \cdot \text{Me}_2\text{S}$, the allyl group (entry 7) undergoes hydroboration to afford a novel internally bound reducing agent: R.

- Berenguer, J. Garcia, J. Vilarrasa, *Tetrahedron: Asymmetry* **1994**, *5*, 165–168.
- [38] E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1992**, *33*, 4141–4144.
- [39] E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1990**, *31*, 601–604.
- [40] E. J. Corey, R. K. Bakshi, S. Shibata, unpublished results.
- [41] E. J. Corey, C.-P. Chen, R. K. Bakshi, S. Shibata, unpublished results.
- [42] E. J. Corey, K. Y. Yi, S. P. T. Matsuda, *Tetrahedron Lett.* **1992**, *33*, 2319–2322.
- [43] C. J. Helal, P. A. Magriotis, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 10938–10939.
- [44] a) E. J. Corey, C. J. Helal, unpublished results; b) a number of oxazaborolidine catalysts with *p*-substituted aryl groups on the boron atom of the catalyst have been prepared: T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. Turner Jones, R. A. Reamer, F. E. Roberts, E. J. J. Grabowski, *J. Org. Chem.* **1991**, *56*, 763–769.
- [45] G. B. Stone, *Tetrahedron: Asymmetry* **1994**, *5*, 465–472.
- [46] A. M. Salunkhe, E. R. Burkhardt, *Tetrahedron Lett.* **1997**, *38*, 1523–1526.
- [47] E. J. Corey, R. K. Bakshi, *Tetrahedron Lett.* **1990**, *31*, 611–614.
- [48] For a recent in situ preparation of catecholborane, see Y. Suseela, M. Periasamy, *J. Organomet. Chem.* **1993**, *450*, 47–52.
- [49] Preparation of *B*-H-4: A solution of amino alcohol **3** (126 mg, 0.5 mmol, azeotropically dried with toluene (2×2 mL)) in dry toluene (3 mL) at 0°C was treated dropwise with $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (110 μL , 1.1 mmol, 10M, neat) to afford a white precipitate. After the mixture was stirred for 20 min, the solvent was removed in vacuo. Dry toluene (3 mL) was added to the white solid, and the mixture was heated at reflux, which resulted in dissolution of the solid. After 17 h the solution was allowed to cool to 23°C, and the solvent was removed in vacuo to afford a glassy oil. The addition of dry toluene (5 mL) provided a 0.1M solution of *B*-H-4 (>95% conversion as determined by ^1H NMR spectroscopy); ^{11}B NMR (96 MHz, CDCl_3): $\delta = 28.3$; E. J. Corey, K. A. Cimprich, C. J. Helal, unpublished results.
- [50] Numerous in situ preparations of *B*-H-4 have recently been reported which result in excellent enantioselectivity for the reduction of a number of different ketones, but which do not provide physical characterization of the catalyst system: a) M. Masui, T. Shioiri, *Synlett* **1997**, 273–274; b) K. R. K. Prasad, N. N. Joshi, *Tetrahedron: Asymmetry* **1996**, *7*, 3147–3152; c) M. Periasamy, J. V. B. Kanth, A. S. B. Prasad, *Tetrahedron* **1994**, *50*, 6411–6416; d) G. J. Quallich, T. M. Woodall, *Synlett* **1993**, 929–930.
- [51] a) Preparation of (*S*)-*B*-*n*Bu-4: Toluene (15–20 mL) was added to amino alcohol **3** (253 mg, 1 mmol) and *n*BuB(OH) $_2 \cdot n\text{H}_2\text{O}$ (164 mg) in a 25-mL round-bottom flask fitted with a Dean–Stark apparatus (sidearm filled with 4-Å molecular sieves) and a reflux condenser. The mixture was vigorously heated at reflux for 12 h. The toluene was removed by distillation through the Dean–Stark sidearm until about 3 mL were left. After the reaction mixture was cooled to 23°C, the Dean–Stark apparatus was replaced by a rubber septum and the remaining toluene was removed in vacuo at 40°C. Toluene (5.0 mL) was added to provide a 0.20M solution of (*S*)-*B*-*n*Bu-4 (>95% conversion as determined by ^1H NMR spectroscopy). Spectral data were identical to that reported in the literature.^[14a] The catalyst was stored by placing an additional rubber septum on the flask followed by cooling the solution to –78°C under a positive pressure of nitrogen. The nitrogen source was removed, and the catalyst solution was stored in a jar containing Drierite at –20°C. This precooling procedure prevents possible introduction of air into the flask due to a pressure difference. b) *n*BuB(OH) $_2$ was prepared by a known method (H. C. Brown, T. E. Cole, *Organometallics* **1983**, *2*, 1316–1319) except that aqueous 1N HCl was used instead of anhydrous HCl in the workup. The amount of water in the *n*BuB(OH) $_2$ prepared by this method varies. Therefore, ^1H NMR analysis of the catalyst formation is required to ascertain the exact amount of the boronic acid necessary for complete catalyst formation. Once this is known for a specific batch of *n*BuB(OH) $_2$, however, the proper amount of boronic acid (1.05 equiv) can be added at the start of the reaction. c) Preparation of *B*-Me-4: The catalyst was prepared from amino alcohol **3** (253 mg, 1 mmol) and MeB(OH) $_2$ (72 mg, 1.2 mmol) as described above for (*S*)-*B*-*n*Bu-4, except that 1) the reaction mixture was heated at 60°C for 1 h before heating at reflux temperature and 2) heating at reflux was maintained for 5 h. The material so obtained showed identical spectral properties with those reported.^[14a]
- [52] a) Reference [38]; for a related procedure with alkyl boronic amides $\text{RB}(\text{NR}_2)_2$, see b) P. Y. Chavant, M. Vaultier, *J. Organomet. Chem.* **1993**, *455*, 37–46.
- [53] C. Meier, W. H. G. Laux, *Tetrahedron: Asymmetry* **1995**, *6*, 1089–1092.
- [54] C.-P. Chen, K. Prasad, O. Repic, *Tetrahedron Lett.* **1991**, *32*, 7175–7178.
- [55] a) E. J. Corey, X.-M. Cheng, K. A. Cimprich, S. Sarshar, *Tetrahedron Lett.* **1991**, *32*, 6835–6838; b) T. S. Kaufman, *ibid.* **1996**, *37*, 5329–5332.
- [56] G. J. Quallich, T. M. Woodall, *Tetrahedron Lett.* **1993**, *34*, 785–788.
- [57] a) Reduction of acetophenone with *B*-Me-4 as catalyst and $\text{BH}_3 \cdot \text{diethylaniline}$ (BDEA) as stoichiometric reductant (from reference [46]): A dry 100-mL two-necked flask equipped with an addition funnel, magnetic stirring bar, thermocouple, and septum inlet was charged with a solution of (*R*)-*B*-Me-4 (0.84 mmol, 0.084 M in toluene, 10 mL) followed by BDEA (2.74 g, 16.8 mmol). The reaction vessel was immersed in a water bath, and acetophenone (2.0 mL, 16.6 mmol) in toluene (5 mL) was added through the addition funnel over 1–1.5 h. After ketone addition was complete, the reaction mixture was stirred for an additional hour. MeOH (5 mL) was then slowly added (hydrogen evolution) followed by aqueous 1N HCl (10 mL). After 15–20 min the organic and aqueous layers were separated, and the aqueous layer was extracted with toluene or Et_2O (3×10 mL). The combined organic layers were washed with aqueous 1N HCl (2×10 mL), water, and brine, and then dried (MgSO_4). Analysis of the organic layer by gas chromatography (CDX-B column, 30 m $\times$ 0.25 mm, J&W Scientific) showed the product to be (*S*)-1-phenylethanol with 94.7% *ee*. Removal of the solvent in vacuo followed by distillation gave (*S*)-1-phenylethanol that was spectroscopically identical with an authentic sample. b) Reduction of α -chloroacetophenone with *B*-*n*Bu-4 as catalyst and $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (BMS) as stoichiometric reductant: This protocol requires the *simultaneous* addition of ketone and BMS to a solution of the catalyst (0.01 equiv) in order to suppress uncatalyzed reduction pathways and is practical on multigram scale. Dry THF (10 mL) was added to (*S*)-*B*-*n*Bu-4 (0.647 mmol, 0.2 M in toluene, 3.2 mL) and BMS (65 μL , 0.65 mmol, 10M (neat)) under nitrogen. Separate solutions of α -chloroacetophenone (10 g, 64.7 mmol, azeotropically dried with benzene) in dry THF (40 mL) and BMS (4.5 mL, 45 mmol, 10M (neat)) in dry THF (40 mL) were then added simultaneously to the solution of the oxazaborolidine catalyst over 1 h. After addition of ketone and BMS was complete no starting material remained, as determined by thin-layer chromatography. A solution of HCl in MeOH (0.5 M, 1.5 mL, 1.2 equiv; prepared by adding acetyl chloride to MeOH at 0°C) was then slowly added (hydrogen evolution), and the solution was stirred for 30 min. THF was removed in vacuo, Et_2O (75 mL) added, and the HCl salt of the amino alcohol that precipitated as a white solid removed by filtration. The Et_2O layer was washed with saturated aqueous NaHCO_3 (2×10 mL) and brine (2×10 mL), dried (MgSO_4), filtered, and concentrated in vacuo. HPLC analysis (Chiralcel OD, 2-propanol/hexane 2.5/97.5, 1 mL min $^{-1}$, $\lambda = 254$ nm) showed the product to be of 98.5% *ee*; t_R : 17.2 min, major; 22.5 min, minor isomer. Purification by filtration through a small plug of silica gel with hexanes/EtOAc (4/1) afforded 10 g (99%) of (*S*)-2-chloro-1-phenylethanol. See reference [13c] for the first report of this procedure with (*S*)-*B*-Me-4 as catalyst and $\text{BH}_3 \cdot \text{THF}$ (BTHF).
- [58] E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1995**, *36*, 9153–9156.
- [59] E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 5675–5678.
- [60] CBS reduction of *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate and in situ deallylation: A flame-dried flask was charged with a solution of (*S*)-*B*-*n*Bu-4 (370 μL , 0.074 mmol, 0.20 M in toluene), and the toluene was removed in vacuo. CH_2Cl_2 (370 μL) was added followed by catecholborane (104 μL , 0.98 mmol). The solution was cooled to –78°C, and *N*-allyl-2-(4-chlorobenzoyl)pyridinium triflate (200 mg, 0.49 mmol, azeotropically dried with CH_2Cl_2) in CH_2Cl_2 (2 mL) was added. After 5 min the heterogeneous mixture was warmed to –40°C and vigorously stirred for 36 h, over which period the mixture became homogeneous. MeOH (300 μL) was added, the solution was warmed to 23°C, and $[\text{Pd}(\text{PPh}_3)_4]$ (30 mg, 0.025 mmol) and *n*-butylammonium

- formate (300 μL) were added. The solution was stirred for 3 h at 23 °C, and Et_2O (60 mL) was then added. The organic layer was washed with buffer (pH = 13) until the aqueous washings were colorless. The solution was then washed with brine (2×10 mL), dried (MgSO_4), filtered, and concentrated in vacuo. Purification by chromatography (silica gel, hexane/ EtOAc 4/1 $\rightarrow$ 2/1) provided 84 mg (78 %) of (*S*)-(4-chlorophenyl)-2-pyridylmethanol as a colorless oil. $[\alpha]_D^{25} = +119$ ($c = 0.50$ in CHCl_3 , literature value for the *R* isomer: $[\alpha]_D^{25} = -132.5$ ($c = 0.7$ in CHCl_3)); ^1H NMR (400 MHz, CDCl_3): $\delta = 8.55$ (d, $J = 4.8$ Hz, 1H), 7.63 (td, $J = 1.7, 7.7$ Hz, 1H), 7.33–7.28 (m, 4H), 7.20 (dd, $J = 5.0, 7.5$ Hz, 1H), 7.12 (dd, $J = 0.4, 7.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 160.426, 147.987, 141.789, 137.023, 133.666, 128.774, 128.457, 122.678, 121.283, 74.338$. HPLC analysis (Chiralpak AD, 2-propanol/hexane 5/95, 1 mL min^{-1} , $\lambda = 254$ nm) showed the product to be of 98 % *ee*; t_R : 17.7 min, major; 23 min, minor isomer.
- [61] E. J. Corey, A. Guzman-Perez, S. E. Lazerwith, *J. Am. Chem. Soc.*, in press.
- [62] a) T. Konoike, Y. Araki, *Tetrahedron Lett.* **1992**, 33, 5093–5096; b) P. Wipf, S. Lim, *Chimia* **1996**, 50, 157–167; c) P. Wipf, S. Lim, *J. Am. Chem. Soc.* **1995**, 117, 558–559; d) S. J. Amigoni, L. J. Toupet, Y. J. Le Floch, *J. Org. Chem.* **1997**, 62, 6374–6378; e) H. Dumartin, Y. Le Floch, R. Grée, *Tetrahedron Lett.* **1994**, 35, 6681–6684; f) D. B. Smith, A. M. Waltos, D. G. Loughhead, R. J. Weikert, D. J. Morgans, Jr., J. C. Rohloff, J. O. Link, R. Zhu, *J. Org. Chem.* **1996**, 61, 2236–2241.
- [63] a) E. J. Corey, H. Kigoshi, *Tetrahedron Lett.* **1991**, 32, 5025–5028; b) E. J. Corey, A. V. Gavai, *ibid.* **1988**, 29, 3201–3204.
- [64] a) K. C. Nicolaou, P. Bertinato, A. D. Piscopio, T. K. Chakraborty, N. Minowa, *J. Chem. Soc. Chem. Commun.* **1993**, 619–622; b) E. J. Corey, K. S. Rao, *Tetrahedron Lett.* **1991**, 32, 4623–4626.
- [65] A. F. Simpson, P. Szeto, D. C. Lathbury, T. Gallagher, *Tetrahedron: Asymmetry* **1997**, 8, 673–676.
- [66] CBS reduction of *E*-4-(4'-methoxyphenyl)-3-buten-2-one: (*E*)-4-(4'-methoxyphenyl)-3-buten-2-one (50 mg, 0.28 mmol, azeotropically dried with toluene) was treated with (*S*)-*B*-*n*Bu-4 (86 μL , 0.043 mmol, 0.20 M in toluene) and toluene (900 μL). Upon being cooled to -78°C the solution became heterogeneous. Catecholborane (51 mg, 46 μL , 0.43 mmol) in toluene (138 μL) was added directly into the rapidly stirred reaction mixture, and the color immediately turned dark red (this is unique for 4-aryl-3-buten-2-ones). After the mixture was stirred for 20 h at -78°C the dark red color had faded to light pink. MeOH (200 μL) was added down the side of the flask, and the solution was warmed to 23 °C, diluted with Et_2O (40 mL), and washed with buffer (pH = 13, 1N NaOH/saturated NaHCO_3 2/1) until the aqueous washings were colorless. The dark aqueous washes were extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (2×5 mL), dried (MgSO_4), filtered, and concentrated in vacuo to a volume of about 10 mL. A solution of HCl in MeOH (0.5 M, 86 μL , 0.043 mmol) was added, the HCl salt of the amino alcohol removed by filtration, and the solution concentrated in vacuo. Purification by chromatography (silica gel, hexane/ EtOAc 4/1) provided 44 mg (88 %) of the alcohol as a white solid. $[\alpha]_D^{25} = +36.9$ ($c = 1.15$ in CHCl_3); m.p. 96–97 °C; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.30$ (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 6.50 (d, $J = 15.9$ Hz, 1H), 6.12 (dd, $J = 6.6, 15.9$ Hz, 1H), 4.46 (m, 1H), 3.80 (s, 3H), 1.78 (brs, 1H), 1.36 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 159.25, 131.43, 129.44, 129.01, 127.65, 114.01, 69.11, 55.31, 23.48$. HPLC analysis (Chiralcel OD, 2-propanol/hexane 2.5/97.5, 1 mL min^{-1} , $\lambda = 254$ nm) showed the product to be of 95 % *ee*; t_R : 42.2 min, major; 49.3 min, minor isomer.
- [67] K. A. Parker, M. W. Ledebor, *J. Org. Chem.* **1996**, 61, 3214–3217.
- [68] CBS reduction of 1-trimethylsilyl-1-octyn-3-one: A flame-dried flask was charged with (*S*)-*B*-4-*t*Bu C_6H_4 -4 (0.128 mmol, 1.28 mL, 0.1 M in toluene), the solvent was removed in vacuo, and a solution of 1-trimethylsilyl-1-octyn-3-one (500 mg, 2.55 mmol, azeotropically dried with benzene) in CH_2Cl_2 (5 mL) was added. The solution was cooled to -40°C , and catecholborane (364 mg, 324 μL , 3.06 mmol) in CH_2Cl_2 (2.2 mL) was added down the side of the flask over 30 min. After 1 h MeOH (2 mL) was added, and the solution was warmed to 23 °C. The reaction solution was diluted with Et_2O (150 mL), washed with buffer (pH = 13) until the aqueous washings were colorless and then with brine (10 mL), dried (MgSO_4), filtered, and concentrated in vacuo.
- The addition of Et_2O (10 mL) followed by HCl in MeOH (0.5 M, 256 μL , 0.128 mmol) resulted in precipitation of the HCl salt of the amino alcohol as a fine powder, which was removed by filtration. The Et_2O was removed in vacuo, and the residue was passed through a short column of silica gel (hexane/ Et_2O 10/1) to provide 480 mg (96 %) of (*R*)-trimethylsilyl-1-octyn-3-ol as a colorless oil. $[\alpha]_D^{25} = +12$ ($c = 0.15$ in benzene); ^1H NMR (400 MHz, CDCl_3): $\delta = 4.34$ (t, $J = 6.4$ Hz, 1H), 2.05–2.00 (brs, 1H), 1.73–1.62 (m, 2H), 1.50–1.40 (m, 2H), 1.35–1.25 (m, 4H), 0.88 (t, $J = 6.8$ Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 107.08, 89.28, 62.94, 37.71, 31.45, 24.82, 22.56, 13.99, -0.08$. Conversion of the alcohol into the *p*-nitrobenzoate (*p*-nitrobenzoyl chloride, dimethylaminopyridine, CH_2Cl_2 , 23 °C) and HPCL analysis (Whelk-O1, 2-propanol/hexane 0.5/99.5, 1 mL min^{-1} , $\lambda = 254$ nm) showed the product to be of 94 % *ee*; t_R : 21.3, major; 25.8 min, minor isomer. The absolute configuration of the product was determined by desilylation (1.1 equiv of tetrabutylammonium fluoride, THF, 0 °C, 5 min, >95 %) and comparison of the optical rotation ($[\alpha]_D^{25} = +6.0$ ($c = 2.25$ in CH_2Cl_2)) with the literature value ($[\alpha]_D^{25} = +6.5$ ($c = 2.0$ in CH_2Cl_2)). b) (*S*)-*B*-4-*t*Bu C_6H_4 -4 was prepared from **3** (1 equiv) and *p*-tert-butylphenylboroxine ((ArBO) $_3$, 0.35 equiv) according to the literature procedure.^[51]
- [69] a) S. E. Denmark, M. E. Schnute, L. R. Marcin, A. Thorarensen, *J. Org. Chem.* **1995**, 60, 3205–3220; b) E. J. Corey, A. Huang, unpublished results; c) for a study of the effect of temperature on the enantioselectivity of the oxazaborolidine-catalyzed reduction of acetophenone and cyclohexylmethyl ketone, see reference [45].
- [70] M. Morr, C. Proppe, V. Wray, *Leibigs Ann.* **1995**, 2001–2004.
- [71] O. W. Gooding, R. P. Bansal, *Synth. Commun.* **1995**, 25, 1155–1166.
- [72] E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, 37, 4837–4840.
- [73] a) J. Wright, L. Frambes, P. Reeves, *J. Organomet. Chem.* **1994**, 476, 215–217; b) L. Schwink, P. Knochel, *Tetrahedron Lett.* **1996**, 37, 25–28; c) *ibid.* **1997**, 38, 3711–3714; d) M. Woltersdorf, R. Kranich, H.-G. Schmalz, *Tetrahedron* **1997**, 53, 7219–7230; e) A. Ohno, M. Yamane, T. Hayashi, N. Oguni, M. Hayashi, *Tetrahedron: Asymmetry* **1995**, 6, 2495–2502.
- [74] E. J. Corey, J. O. Link, S. Sarshar, Y. Shao, *Tetrahedron Lett.* **1992**, 33, 7103–7106.
- [75] E. J. Corey, J. O. Link, *J. Am. Chem. Soc.* **1992**, 114, 1906–1908.
- [76] E. J. Corey, X.-M. Cheng, K. A. Cimprich, *Tetrahedron Lett.* **1991**, 32, 6839–6842.
- [77] E. J. Corey, M. C. Noe, M. J. Grogan, *Tetrahedron Lett.* **1994**, 35, 6427–6430.
- [78] E. J. Corey, M. C. Noe, A. Guzman-Perez, *J. Am. Chem. Soc.* **1995**, 117, 10817–10824.
- [79] K. R. K. Prasad, N. N. Joshi, *J. Org. Chem.* **1996**, 61, 3888–3889.
- [80] S. E. Denmark, L. R. Marcin, *J. Org. Chem.* **1995**, 60, 3221–3235.
- [81] R. D. Tillyer, C. Boudreau, D. Tschäen, U.-H. Dolling, P. J. Reider, *Tetrahedron Lett.* **1995**, 36, 4337–4340.
- [82] a) G. Bringmann, D. Vitt, *J. Org. Chem.* **1995**, 60, 7674–7681; b) G. Bringmann, T. Hartung, *Tetrahedron* **1993**, 49, 7891–7902; c) *Angew. Chem.* **1992**, 104, 782–783; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 761–762.
- [83] A. S. Thompson, G. R. Humphrey, A. M. Demarco, D. J. Mathre, E. J. Grabowski, *J. Org. Chem.* **1993**, 58, 5886–5888.
- [84] E. J. Corey, K. A. Cimprich, *Tetrahedron Lett.* **1992**, 33, 4099–4102.
- [85] a) M. P. DeNinno, R. J. Perner, L. Lijewski, *Tetrahedron Lett.* **1990**, 31, 7415–7418; b) K. Kanematsu, A. Nishizaki, Y. Sato, M. Shiro, *Tetrahedron Lett.* **1992**, 33, 4967–4970.
- [86] a) M. Ostendorf, R. Romagnoli, I. Cabeza Pereiro, E. C. Roos, M. J. Moolenaar, W. N. Speckamp, H. Hiemstra, *Tetrahedron: Asymmetry* **1997**, 8, 1773–1789; b) R. Romagnoli, E. C. Roos, H. Hiemstra, M. J. Moolenaar, W. N. Speckamp, *Tetrahedron Lett.* **1994**, 35, 1087–1090.
- [87] For the preparation of trichloromethyl ketones, see E. J. Corey, J. O. Link, Y. Shao, *Tetrahedron Lett.* **1992**, 33, 3435–3438.
- [88] E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1992**, 33, 3431–3434.
- [89] A. P. Khirmian, J. E. Oliver, R. M. Waters, S. Panicker, J. M. Nicholson, J. A. Klun, *Tetrahedron: Asymmetry* **1996**, 7, 37–40.
- [90] E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1993**, 34, 5227–5230.

- [91] Denopamine: a) E. J. Corey, J. O. Link, *J. Org. Chem.* **1991**, *56*, 442–444; isoproterenol: b) reference [39]; salmeterol: c) R. Hett, R. Stare, P. Helquist, *Tetrahedron Lett.* **1994**, *35*, 9375–9378; formoterol (the oxazaborolidine derived from *cis*-(1*R*, 2*S*)-aminoindanol (Table 2, entry 8) was used): d) R. Hett, Q. K. Fang, Y. Gao, Y. Hong, H. T. Butler, X. Nie, S. A. Wald, *ibid.* **1997**, *38*, 1125–1128.
- [92] E. J. Corey, G. A. Reichard, *Tetrahedron Lett.* **1989**, *30*, 5207–5210.
- [93] a) E. J. Corey, C.-P. Chen, M. J. Parry, *Tetrahedron Lett.* **1988**, *29*, 2899–2902; b) reference [13].
- [94] R. D. Larsen, E. G. Corley, A. O. King, J. D. Carroll, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang, R. J. Zamboni, *J. Org. Chem.* **1996**, *61*, 3398–3405.
- [95] A. S. Lee, A. W. Norman, W. H. Okamura, *J. Org. Chem.* **1992**, *57*, 3846–3854.
- [96] E. J. Corey, C. J. Helal, *Tetrahedron Lett.*, in press.
- [97] M. P. DeNinno, R. J. Perner, H. E. Morton, S. DiDomenico, Jr., *J. Org. Chem.* **1992**, *57*, 7115–7118.
- [98] a) H.-G. Schmalz, J. Hollander, M. Arnold, G. Dürner, *Tetrahedron Lett.* **1993**, *34*, 6259–6262; b) H.-G. Schmalz, M. Arnold, J. Hollander, J. W. Bats, *Angew. Chem.* **1994**, *106*, 77–79; *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 109–111.
- [99] V. L. Ponzo, T. S. Kaufman, *Tetrahedron Lett.* **1995**, *36*, 9105–9108.
- [100] E. J. Corey, B. E. Roberts, *J. Am. Chem. Soc.*, in press.
- [101] a) E. J. Corey, P. Da Silva Jardine, T. Mohri, *Tetrahedron Lett.* **1988**, *29*, 6409–6412; b) D. Calvo, M. Port, B. Delpéch, R. Lett, *ibid.* **1996**, *37*, 1023–1024.
- [102] E. J. Corey, P. Da Silva Jardine, *Tetrahedron Lett.* **1989**, *30*, 7297–7300.
- [103] E. J. Corey, W.-g. Su, *Tetrahedron Lett.* **1988**, *29*, 3423–3426.
- [104] K. Mori, M. Amaike, M. Itou, *Tetrahedron*, **1993**, *49*, 1871–1878.
- [105] C. Y. Hong, N. Kado, L. E. Overman, *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029.
- [106] K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, **1996**, pp. 616–617.
- [107] a) M. J. DiGrandi, D. K. Jung, W. J. Krol, S. J. Danishefsky, *J. Org. Chem.* **1993**, *58*, 4989–4992; b) K. C. Nicolaou, C.-K. Hwang, E. J. Sorenson, C. F. Clairborne, *J. Chem. Soc. Chem. Commun.* **1992**, 1117–1118.
- [108] P. Szeto, D. C. Lathbury, T. Gallagher, *Tetrahedron Lett.* **1995**, *36*, 6957–6960.
- [109] M. F. Semmelhack, W. R. Epa, A. W.-H. Cheung, Y. Gu, C. Kim, N. Zhang, W. Lew, *J. Am. Chem. Soc.* **1994**, *116*, 7455–7456.
- [110] M. Lögers, L. E. Overman, G. S. Welmaker, *J. Am. Chem. Soc.* **1995**, *117*, 9139–9150.
- [111] a) D. T. Hung, J. B. Nerenberg, S. L. Schreiber, *J. Am. Chem. Soc.* **1996**, *118*, 11054–11080; b) J. B. Nerenberg, D. T. Hung, P. K. Sommers, S. L. Schreiber, *ibid.* **1993**, *115*, 12621–12622.
- [112] D. P. Stamos, S. S. Chen, Y. Kishi, *J. Org. Chem.*, in press.

EPOTHILONES



CELL DEATH

Chemical Biology of Epothilones**

K. C. Nicolaou*, Frank Roschangar, and Dionisios Vourloumis

Dedicated to Professor E. J. Corey on the occasion of his 70th birthday

In July of 1996 a paper appeared in *Angewandte Chemie* revealing the structures of a remarkable new class of antitumor agents represented by epothilones A and B. This publication became a milestone in the epothilone story, which began in the late 1980s with their isolation from a species of myxobacteria and gathered momentum in the early 1990s when their taxol-

like mechanism of action against tumor cells was discovered. The realization of their unique potential as anticancer agents marked an intense race for their total synthesis, structural modification, and biological investigation. A number of epothilones have now been recognized as superior to taxol in terms of potency and effectiveness against drug-resistant tumor cells, including taxol-

resistant cell lines. In this article we describe the fascinating saga of these substances and discuss their total synthesis, chemical biology, and potential in cancer chemotherapy.

Keywords: antitumor agents • epothilones • natural products • structure–activity relationships • total synthesis

1. Introduction

Earlier this century, the word “cancer” was not even mentioned in “polite” company. We have made great strides since then, and today we do not only talk about cancer openly, but can actually find answers to questions about many aspects of cancer prevention, detection, treatment, and recovery. Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells that invade and disrupt other tissues and spread to other areas of the body. If the spread is not controlled, it can result in death. Both external factors (for example, chemicals, radiation, and viruses) and internal factors (for example, hormones, immune conditions, and inherited genes) can be responsible for the development of cancer. Causal factors may act together, or in sequence, to initiate or promote carcinogenesis. Ten or more years often pass between exposures or mutations and detectable cancer.^[1]

Cancer is a growing public health problem whose estimated worldwide new incidences are over six million cases per

year.^[2] In the USA it is estimated that one in two men and one in three women will develop cancer during their lifetime. According to American Cancer Society (ACS) statistics, around 1382400 new cancer cases are expected to be diagnosed in 1997 in the USA alone, and around 560000 Americans are expected to die of cancer—that is more than 1500 people a day, averaging approximately one death per minute. This rate makes it the second leading cause of death in the USA, exceeded only by cardiovascular disease that accounts for one of every four deaths. The financial costs of cancer are immense, both to the individual and to society as a whole. The National Cancer Institute (NCI) estimates overall costs for cancer at \$104 billion in 1997: \$35 billion for direct medical costs, \$12 billion for morbidity costs (cost of lost productivity), and \$57 billion for mortality costs. Treatment of breast, lung, and prostate cancers account for over half of the direct medical costs.^[2]

Breast cancer is the second most common cancer, after skin cancers, among women. The ACS estimates that in 1997 approximately 180200 new cases of invasive breast cancer will be diagnosed in women, and an estimated 1400 cases will be diagnosed in men in the USA.^[2] Breast cancer related deaths will top 44190 (43900 women, 290 men) in 1997, making this type of cancer the second major cause of cancer death in women after lung cancer. Ovarian cancer, termed “the silent disease” due to the lack of obvious signs or symptoms until late in its development, accounts for 4% of all cancers in women, and is predicted to cause about 14200 deaths in the USA in 1997. It ranks fifth as a cause of cancer deaths among women, causing more deaths than any other cancer of the female reproductive system. Prostate cancer, aside from skin

[*] Prof. Dr. K. C. Nicolaou, Dr. F. Roschangar, Dr. D. Vourloumis
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 619-784-2469
E-mail: kcn@scripps.edu
and

Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

[**] Abbreviations are given in the appendix.

cancer, is the most common cancer in American males, and is developed in approximately one out of every five American men during their lifetime. The ACS estimates that in 1997, around 209 900 new cases of prostate cancer will be diagnosed in the United States and 41 800 men will die of this disease, thus making it the second leading cause of cancer death in men, exceeded only by lung cancer, and accounting for 14 % of male cancer-related deaths. Prostate cancer is most common in North America and northwestern Europe, although it is more rare in Asia, Africa, Central America, and South America.^[2]

A major share of the anticancer drug market is commanded by the complex diterpene taxol (paclitaxel), whose discovery from the Pacific Yew Tree in 1971^[3] and culmination into a billion dollar drug today represents a remarkable story. Developed and sold by Bristol-Myers Squibb in the 1990s, taxol is currently available in more than 60 countries. It is mainly used for the treatment of a variety of solid tumors commonly encountered with ovarian and breast cancers.^[4] Taxotere (docetaxel), developed by Rhone-Poulenc Rorer (France), has more recently been approved for the treatment of similar indications.^[5] As seen in Table 1, major drugs used today in the treatment of cancer patients include, in addition to taxol, the hormones Lupron (leuprolide acetate) and Zoladex (goserelin), the nonsteroidal anti-estrogen Nolvadex (tamoxifen), and the cytotoxic agents Paraplatin (carboplatin), as well as the biological-response modifiers Neupogen (filgrastim) and Intron A (interferon alpha-2b).^[6]

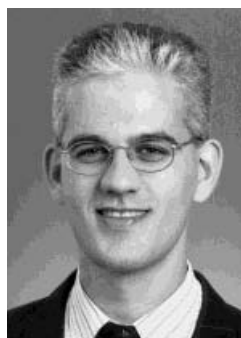
The success story of taxol^[7] demonstrated once again the wealth of mother nature in terms of biologically active molecules as cures for disease.^[8] Aspirin^[9] and penicillin^[10] are two additional classic examples of such discoveries. These stories will certainly not be the last. In the late 1980s, a new

tale of cytotoxic natural products began to unfold. The epothilones A and B (Figure 1) were discovered by Höfle, Reichenbach, and their coworkers at the Gesellschaft für Biotechnologische Forschung (GBF) in Germany.^[11] These compounds were isolated from culture extracts of the cellulose-degrading myxobacterium *Sorangium cellulosum* (Myxococcales) strain So ce90, first found in soil collected from the banks of the Zambesi River in South Africa, and were initially found to exhibit a narrow antifungal spectrum against the fungus *Mucor hiemalis* only.^[12] Figure 2 shows growing cells of *Sorangium cellulosum* So ce90 (left) and spore capsules (sporangioles, diameter approximately 15–20 μm) of the same organism (right). The latter are formed within the swarm colonies of many yellowish-orange to brown-black fruiting bodies.^[13] In this state, the spores survive in dry soil for more than 10–20 years. Due to their activity against *Mucor hiemalis*, the epothilones and spirangienes (compounds isolated from the same organism) were first tested as potential antifungal and pesticide agents,^[11, 14] but field experiments proved the epothilones to be too toxic (see Section 2). In the meantime, scientists at Merck in the USA had independently isolated epothilones A and B and made the remarkable discovery that these substances kill tumor cells through a mechanism of action similar to that of taxol, namely through induction of tubulin polymerization to microtubules and microtubule stabilization.^[15] This observation was later confirmed by the GBF scientists.^[12] Furthermore, the Merck scientists found in displacement experiments that epothilones A and B were competitive inhibitors of [^3H]taxol binding, with almost identical IC_{50} values to that of taxol, and that these new compounds retained a much greater toxicity against Pgp-expressing multiple drug resistant (MDR) cells (Pgp = P-glycoprotein).^[15]

K. C. Nicolaou is the Chairman of the Department of Chemistry at The Scripps Research Institute, La Jolla, California where he holds the Darlene Shiley Chair in Chemistry and the Skaggs Professorship of Chemical Biology. He is also Professor of Chemistry at the University of California, San Diego.



K. C. Nicolaou



F. Roschangar



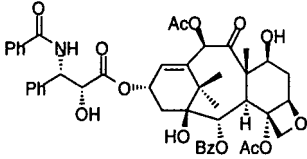
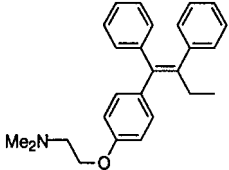
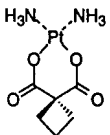
D. Vourloumis

Frank Roschangar, born in 1969 in Hannover, Germany, received his B.Sc. degree from the University of

Cologne in 1991 and his Ph.D. degree from Rice University, Texas, in 1996 under the supervision of Prof. M. A. Ciufolini where he accomplished an enantiomerically pure total synthesis of camptothecin. He joined the Nicolaou group in 1996 and has been involved in the synthesis of various epothilones. Currently, he holds a position as a research scientist at Glaxo-Wellcome, North Carolina.

Dionisios Vourloumis, born in 1966 in Greece, received his B.Sc. degree from the University of Athens and his Ph.D. from West Virginia University under the direction of Professor P. A. Magriotis, in 1994, working on the synthesis of novel enediyne antibiotics. Since joining Professor Nicolaou's group in 1996, he has been involved in the total syntheses of epothilones A and B, eleutherobin, sarcodictyins A and B, and analogues thereof.

Table 1. The biggest-selling agents for cancer and cancer-related treatments in 1996.^[6]

Active substance group	Trade name (chemical name)	Structure/description	Marketer (worldwide sales [US-Dollar])	Indication
Antineoplastics				
Taxoid	Taxol (Paclitaxel)		Bristol-Meyers Squibb (813×10^6)	treatment of primary ovarian cancer in combination with cisplatin, and for metastatic ovarian cancer where standard platinum- or anthracycline-containing therapy has failed
Hormone	Lupron (Leuprolide acetate)	an agonist of the naturally occurring decapeptide gonadorelin	TAP Pharmaceuticals (810×10^6)	treatment of advanced prostate cancer as an alternative to castration, of endometriosis and central precocious puberty, and for the presurgical management of patients with anaemia caused by benign fibroid tumours
	Zoladex (Goserelin)	a synthetic analogue of gonadorelin	Zeneca Pharmaceuticals (563×10^6)	treatment of prostate carcinoma advanced breast cancer, endometriosis, and endometrial thinning
Anti-Oestrogens	Nolvadex (Tamoxifen)		Zeneca Pharmaceuticals (561×10^6)	treatment of hormonally responsive breast cancer; can consistently extend survival rates for up to 5 years ^[b]
Cytotoxic agent	Paraplatin (carboplatin)		Bristol-Myers Squibb (373×10^6)	treatment of ovarian cancer
Biological Response Modifiers				
	Neupogen (Filgrastim)	a 175 amino acid protein manufactured by recombinant DNA technology and produced by <i>Escherichia coli</i> bacteria	Amgen (1.02×10^9)	regulation and control of bacteria-fighting white blood cells called neutrophils; prevents drop in white blood cells during chemotherapy and radiotherapy
	Intron A (Interferon alpha-2b)	an interferon, which belongs to a group of naturally occurring proteins that were first discovered as a result of their ability to prevent viral replication	Schering-Plough Corporation (524×10^6)	treatment of chronic hepatitis C, basal cell carcinoma, AIDS-related Kaposi's sarcoma, carcinoids, genital warts, and multiple myeloma; adjuvant treatment for malignant melanoma

[a] Also called the luteinizing hormone-releasing hormone. [b] The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as the breast.

These observations gave rise to a great deal of excitement, anticipating the possible development of these compounds as anticancer agents, particularly in view of their effectiveness

against a number of taxol-resistant tumor cell lines. A series of miscalculations, however, prompted the major players in the epothilone business from pursuing patent applications for

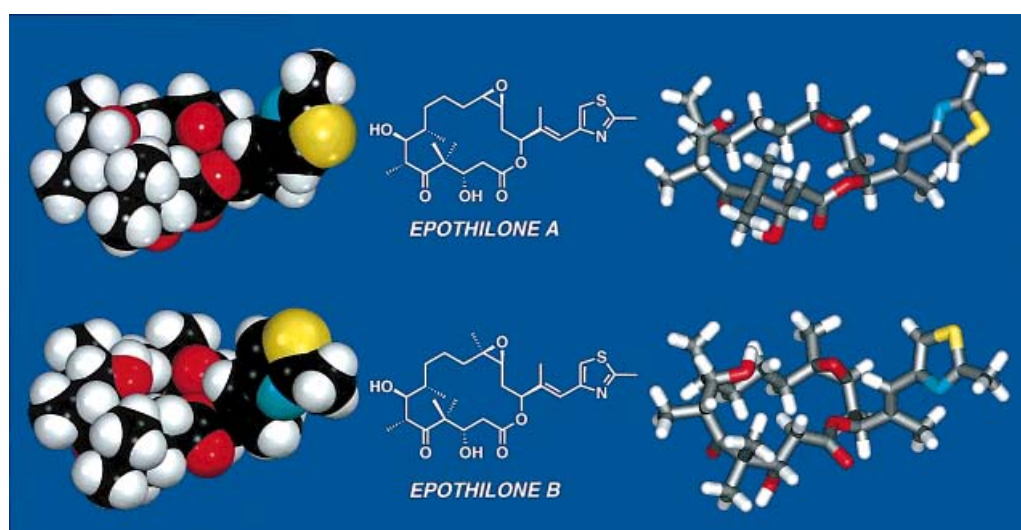


Figure 1. Computer-generated space-filling, ChemDraw, and stick models of epothilones A and B. Carbon: black; oxygen: red; nitrogen: blue; sulfur: yellow; hydrogen: white (we thank C. N. C. Boddy for the computer graphics).

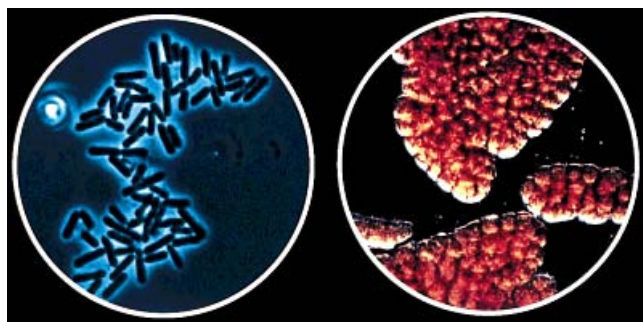


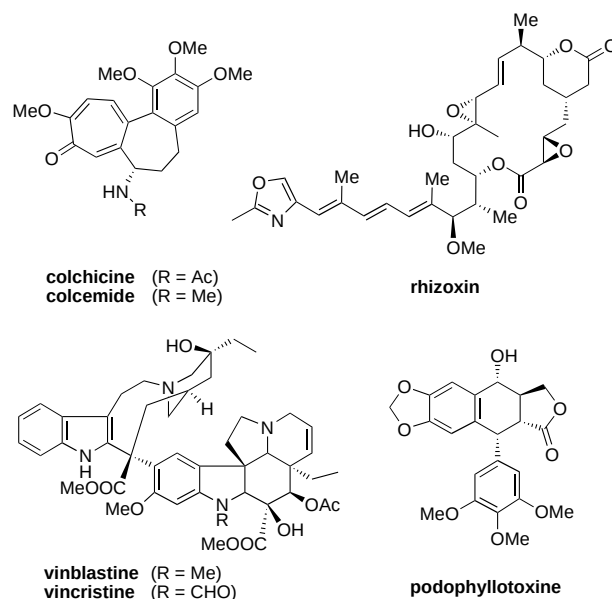
Figure 2. The epothilone-producing myxobacterium *Sorangium cellulosum*: growing cells (left) and spore capsules (right) (courtesy of Dr. H. Reichenbach).

of the epothilones A and B was reported by the German scientists.^[12] The structural assignments were made on the basis of spectroscopic^[12, 16] and X-ray crystallographic data,^[12] and the compounds were named *epothilones* after their structural subunits, *epoxide*, *thiazole* and *ketone*. Seemingly, the carbon backbone of the macrocycle is largely flat, and the side-chain with the thiazole moiety adopts an equatorial position. Apparent structural similarities with taxol are a) a main framework; b) considerable lipophilicity, partly in the form of several methyl groups, including a geminal dimethyl functionality; and c) a side chain. The release of the absolute stereochemical structures of the epothilones^[12] marked the beginning of a new era in their destiny, with efforts to synthesize them assuming top priority in several laboratories around the world. A number of groups had a head start, by learning of their structures prior to publication, and within a short span of time, three research groups had dispatched manuscripts for publication describing their total syntheses. A spate of subsequent reports elaborated on the synthesis and biological evaluation of numerous analogues. In this article, we will review the chemical biology of these fascinating compounds, and discuss their potential in cancer chemotherapy.

2. Biological Properties of Epothilones

Initial investigations by the GBF group focused on the action of the epothilones against fungi, bacteria, and a variety of animal cell lines.^[11] These studies revealed only a narrow spectrum of antifungal activity but a rather dramatic effect against oomycetes such as *Phytophthora infestans*, the causative species of the dreaded potato-blight disease.^[11] Although greenhouse experiments were encouraging regarding their potential applications in agriculture,^[17] the early interest in the epothilones soon subsided due to their failure in field experiments and their apparent phytotoxicity. Soon it was discovered that the compounds also had powerful activity against mouse fibroblast and leukemia cells (2 ng mL⁻¹)^[13, 18] and strong immunosuppressive action as revealed by their cytotoxicity against human T-cells.^[18, 19] The compounds were also tested at the NCI in the USA and proved to be highly active against a panel of cells, including breast and colon cancer cell lines.^[20] But it was not until 1995, when a team

from Merck in the USA reported their findings on the mode of action of epothilones,^[15] that interest in these compounds resurfaced again, this time with much more excitement and momentum. During a high-throughput screening program to discover taxol-like tubulin polymerization agents, the Merck group subjected tens of thousands of compounds to biological assays.^[15] Their only hits were epothilones A and B. An investigation of compounds with homology to the epothilones, such as the 16-membered macrocyclic substances erythromycin,^[21] chalcomycin,^[22] carbomycin,^[23] and rosamycin,^[24] revealed no active compounds (the 16-membered macrocyclic natural product rhizoxin (Scheme 1),^[25] however, is a known



Scheme 1. Selected compounds promoting depolymerization of tubulin.

microtubule-destabilizing agent^[26, 27]).^[15] The uniqueness of the epothilones immediately placed them in the same class as taxol, whose tubulin-binding mechanism of action was discovered by Horwitz in 1979.^[28] The Merck group compared the effects of the epothilones and taxol on tubulin and microtubules and reported higher potencies for both epothilones A and B as tubulin polymerization agents (epothilone B > epothilone A > taxol). Most significantly, all three compounds were shown to compete for the same binding site within their target protein.^[15, 29] Furthermore, the epothilones were found to exhibit similar kinetics in their induction of tubulin polymerization, and gave rise to microscopic pictures of stabilized microtubules and damaged cells that were essentially identical to those obtained with taxol.^[15] Perhaps the most exciting property of the epothilones is their superiority over taxol as a killer of tumor cells, particularly MDR cell lines, including a number resistant to taxol.^[15, 29] In some of the cytotoxicity experiments, epothilone B demonstrated a 2000–5000-fold higher potency than taxol, a striking enough observation to awaken and stimulate the interest of many in the academic community and the pharmaceutical industry. Moreover, in vivo experiments, carried out recently at Sloan Kettering in New York involving subcutaneous

implantations of tumor tissues to SCID mice, proved the superiority of epothilone B over taxol.^[30] Before we proceed to the next phase of research within the epothilone field, however, it will be instructive to discuss further the molecular and cellular biology of tubulin and tubulin binding agents, and how epothilones relate to them.

2.1. Epothilones, Tubulin, Microtubules, and the Cytoskeleton

Tubulin polymerization–depolymerization^[31] plays an important role in the cell cycle (Figure 3), particularly during mitosis. Tubulin is a heterodimeric protein composed of globular α - and β -tubulin subunits (which are amongst the most highly conserved proteins known),^[32, 33] and represents the monomeric building block of microtubules. Microtubules, in turn, are one of the fundamental structural components of the cytoskeleton in all eukaryotic cells. They serve both as structural beams and conveyor belts within cells.^[27, 34–37] Microtubules rigidify the cell^[38] and translocate vesicles, granules, organelles,^[39] and chromosomes through special attachment proteins.^[38–40] As part of the cytoskeleton, microtubules help develop and maintain the shape and structure of the cell as needed. They may operate alone, or in conjunction with other proteins to form more complex structures, such as cilia, centrioles, or flagella, which are used for cellular movement. The cytoskeleton is the “nanolevel web” made out of filamentous protein networks that dynamically organize the interior of living cells; it is usually transparent and, therefore, invisible under the microscope. Despite its importance to the functioning of the cell, the cytoskeleton is usually left out of cell drawings, so it is crucial to remember its existence and dynamic role.

Structurally, microtubules are regular internetworked linear polymers (protofilaments) of highly dynamic assemblies

of heterodimers of α - and β -tubulin. When thirteen of these protofilaments are arranged parallel to a cylindrical axis they self-assemble to form microtubules. These polymers form tubes of approximately 24 nm in diameter and up to several μm in length.^[41] Figures 4 and 5 display such microtubules and

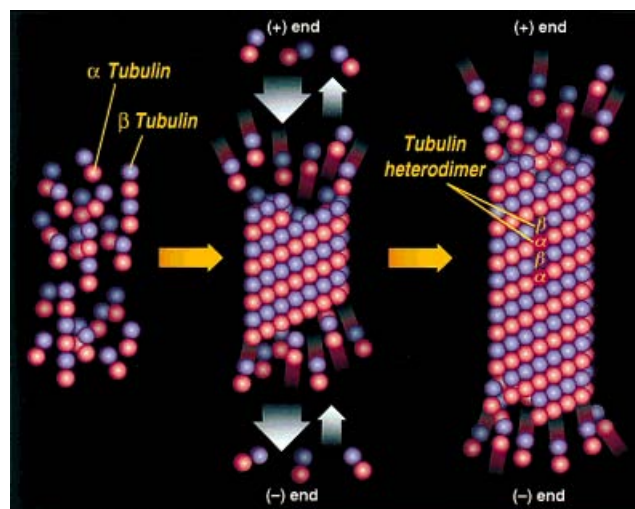


Figure 4. Polymerization of tubulin to microtubules.

demonstrate their assembly from tubulin. Formation of microtubules proceeds by a nucleation-elongation mechanism.^[42, 43] Nucleation is the initial phase of the process in which preformed heterodimers of α - and β -tubulin assemble in the presence of Mg^{2+} , guanosine triphosphate (GTP), and microtubule-associated proteins (MAPs). This process is relatively slow until a short microtubule is formed, triggering the much faster elongation phase. The elongation phase involves extension of the microtubule nucleus at both ends by a reversible, noncovalent addition of tubulin heterodimers to

form growing oligomers which become linear rows of tubulin beads. The tubulin units within the protofilaments are held together by stronger bonds within the α/β tubulin dimers, and weaker and reversible bonds formed during microtubule assembly between the α/β -dimers. The microtubules are formed within the cell in an area called the “aster”. Their dipolar structures consist of a (+)-end, which is kinetically more dynamic, and a (–)-end, which is less dynamic (Figures 4 and 5). Although both ends can either grow or dissociate, it is the (+)-end that usually grows faster than the (–)-end, and net growth occurs at the (+)-end, while net shortening takes place at the (–)-end.^[44] When both of these dynamic processes occur at once, the microtubule is said to be treadmilling.^[45]

The growth and dissolution of microtubules is regulated by bound GTP molecules. Each tubulin dimer carries two

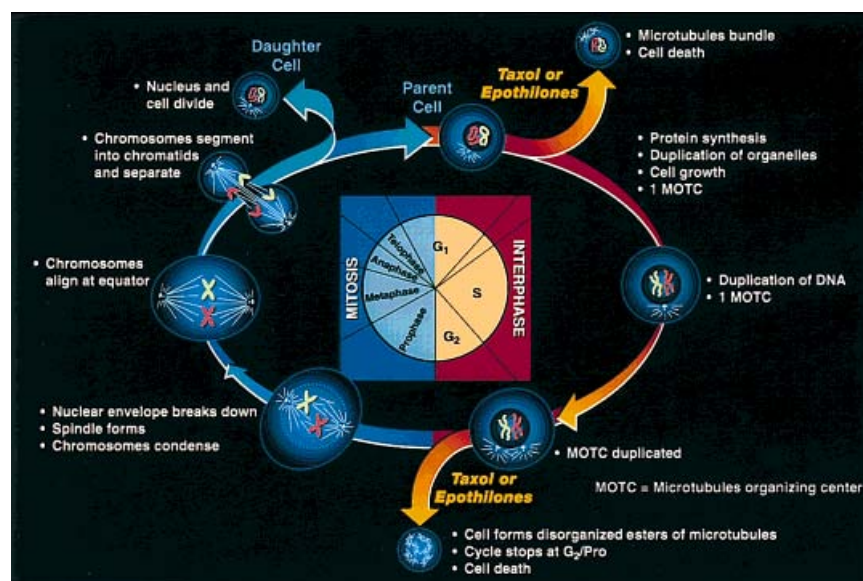


Figure 3. Schematic diagram of the cell cycle showing the inhibition of mitosis by taxol and the epothilones. MOTC = Microtubular organizing center.

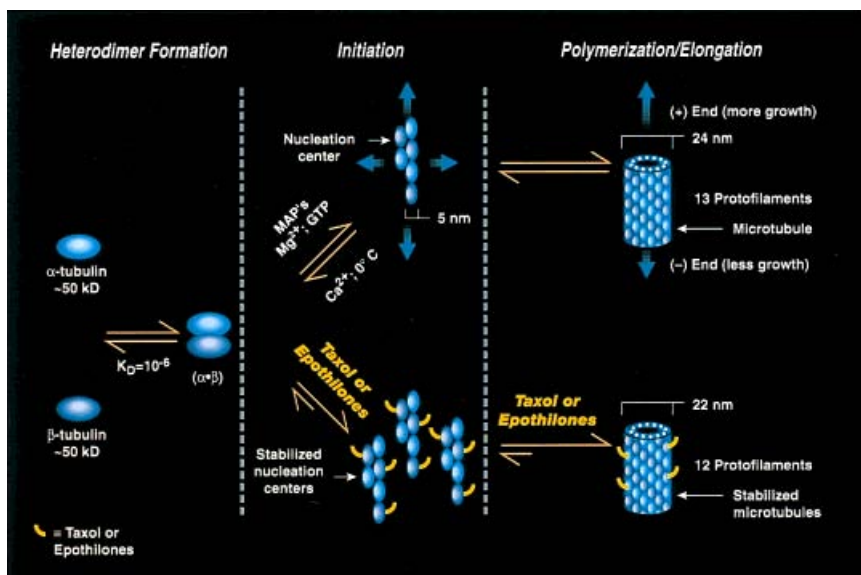


Figure 5. Dynamic equilibria of tubulin-microtubules.

GTP molecules, but only the one on the β subunit of the tubulin dimers appears to function.^[46] During polymerization, the GTP molecule hydrolyzes to guanosine diphosphate (GDP) and orthophosphate (P_i). The presence of the GTP, GDP, and P_i forming a “cap” on the ends of the microtubules facilitates further growth due to their higher affinity for additional tubulin subunits.^[47] While the half-life of tubulin at 37 °C is nearly a full day, that of a given microtubule may be only about 10 min. Consequently, microtubules are in a constant state of flux responding to the needs of the cell. This state is called “dynamic instability”^[42, 48] and is controlled by regulatory processes within the cell. Thus, microtubule growth is promoted in a dividing or moving cell, but more controlled in a stable polarized cell. The regulatory control is exerted by adding (for growth) or hydrolyzing (for shrinkage) GTP on the ends of the microtubule.

As major components of the cellular apparatus known as the mitotic spindle, the microtubules also play a crucial role in mitosis, which is the process during cell replication in which the duplicated genetic material in the form of chromosomes is partitioned equally between the two daughter cells.^[49] When cells enter mitosis, the cytoskeletal microtubule network (mitotic spindle) is dismantled by melting at the center, and two dipolar spindle-shaped arrays of microtubules are formed outwards from the centrosome. In vertebrate cells, the centrosome acts as the major site of microtubule nucleation (microtubule-organizing center or MTOC) by lowering the critical concentration of tubulin required for polymerization and anchoring the (–)-ends of the resulting microtubules.^[50] At metaphase, the chromosomes are assembled to an equatorial position on the mitotic spindle by the dynamic action of microtubules.^[51] At anaphase the microtubule dynamics change and the chromosomes partition and move to the new spindle poles on the dynamic microtubules, where the new cells are being formed.^[52] In this process, the parent cell duplicates its chromosomes to provide each of the two daughter cells with a complete set of genes. When it is time for a eukaryotic cell to divide, the microtubules literally pull its

chromosomes apart pushing them into the compartments of the two emerging daughter cells. The rate by which microtubules change their length increases by 20- to 100-fold during mitosis relative to the rate during interphase. These rapid dynamics are extremely sensitive to tubulin-interactive agents which exert their antimitotic action at the metaphase to anaphase transition (Figure 6).^[48, 53] Compounds displaying considerable structural diversity, such as vinblastine,^[42, 54, 55] colchicine,^[55, 56] taxol, and the epothilones, block mitosis by intervening at this important juncture in the cell cycle (see Section 2.2 for more on tubulin binding agents). These and other similar drugs may exert their antiproliferative and cytotoxic effects at this cell cycle checkpoint by suppressing spindle microtubule dynamics.^[57]

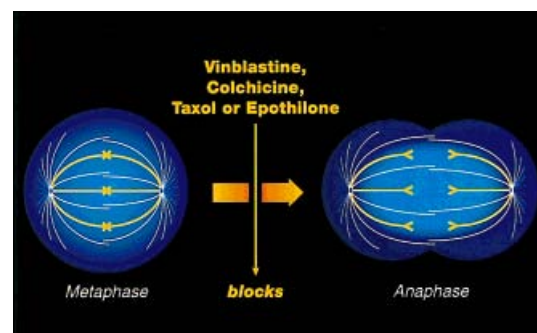


Figure 6. Blocking of mitotic spindle division by antimitotic agents.

Microtubule dynamics can also be suppressed both in vitro and in vivo by MAPs,^[58] the cell- and tissue-type specific cellular proteins.^[27, 34] MAPs are high molecular weight proteins (200–300 kDa) or tau proteins (20–60 kDa).^[27, 59] One end of the MAP binds monomeric or polymerized tubulin, thus speeding up polymerization and facilitating assembly and stabilization of the microtubules. The other end of the MAP binds to vesicles or granules. It is believed that some of these MAPs may bind to special sites on α -tubulin after it is incorporated into the microtubule. Such sites include points of acetylation or removal of tyrosine residues from the carboxyl terminus of tubulin and are important markers for stabilized microtubules because they disappear upon depolymerization. Interestingly, a tau protein suppresses steady-state dynamic instability of microtubules in vitro in a manner which is qualitatively indistinguishable from that of taxol.^[60] This observation is consistent with the notion that antimitotic drugs may mimic the actions of naturally occurring regulatory ligands. The MAPs include kinensin and dynein which “walk” along the microtubules in opposite directions. A number of MAPs have head domains that bind to microtubules and ATP,

thus acting as ATPase motors. Their tail domains may bind to the organelle to be moved, but the mechanism by which energy, generated by the ATP breakdown, is converted into vectorial transport is not known. In summary, MAPs are auxiliary “machines” that accelerate tubulin polymerization, serve as motors for vesicles and granules, and essentially control cell compartmentalization.

2.2. Epothilones, Tubulin Binding Agents, and Cell Death

A number of anticancer drugs possessing diverse molecular structures exert their cytotoxicity by disrupting microtubule dynamics.^[27, 34, 35, 61] Most of these compounds, including the well-established chemotherapeutic agents colchicine,^[55, 56] colcemid,^[62] podophyllotoxin,^[63, 64] vinblastine,^[42, 54, 55] and vincristine^[42, 54, 55] (see Scheme 1), operate by interfering with the formation and growth of microtubules and preventing polymerization of microtubules by diversion of tubulin into other types of aggregates,^[56, 65] thereby promoting net depolymerization and inhibition of cell proliferation at mitosis. This class of antimitotic compounds further includes combretastatin,^[64] maytansine,^[66, 67] rhizoxin (Scheme 1),^[25] phomopsin,^[67] the dolastatins,^[66–68] cryptophycins,^[69] benzimidazoles (such as nocadazol),^[42, 48, 70] and the curacins.^[71] At appropriate concentrations, these drugs inhibit the formation of spindle microtubules or depolymerize existing ones.^[42, 48]

Figure 7 depicts graphically the different complex formations of vinblastine, colchicine, and taxol (see also Figure 5) with microtubules. Vinblastine binds to the ends of microtubules with high affinity, and its potent cytotoxicity appears

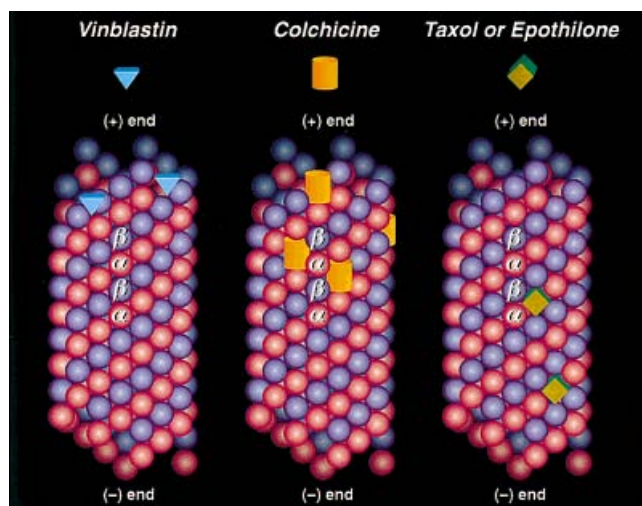
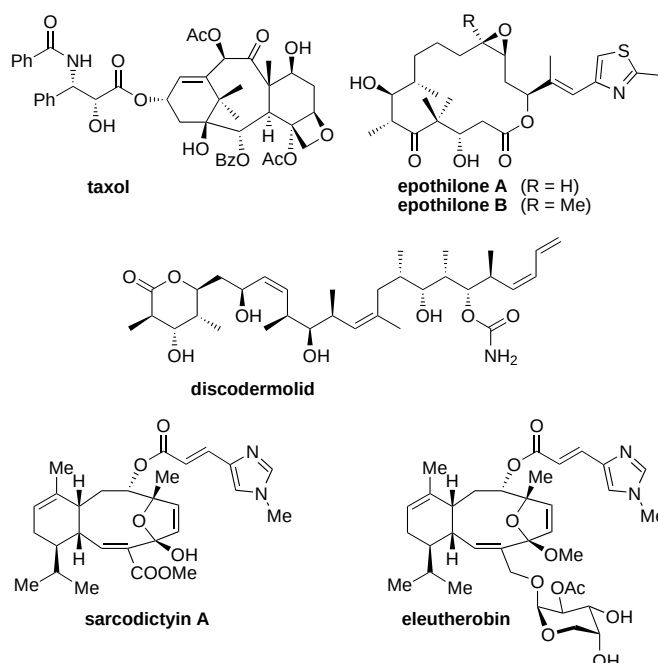


Figure 7. Microtubule–ligand complexes.

to be due to a relatively small number of end-binding molecules.^[42] Colchicine, on the other hand, first binds to free tubulin, and the formed complexes are incorporated into the microtubules at the growing ends in relatively low concentrations, but show profound effects on the microtubule dynamics.^[56] In contrast to the antimitotic drugs described above, taxol disturbs the polymerization–depolymerization

dynamics of microtubules in vitro, with cell death as the net result, by binding to the polymeric microtubules and stabilizing them against depolymerization (see Scheme 2 for examples of tubulin-polymerizing natural products).^[72] Despite



Scheme 2. Selected natural products with tubulin polymerization and microtubule stabilization properties.

their seemingly little structural similarities to taxol, the epothilones appear to act by the same mechanism and bind to the same general regions as taxol does.^[15, 29] Although the epothilones displace taxol from its receptor, they must bind in a slightly different manner to microtubules as suggested by their action against taxol-resistant tumor cells, which contain mutated tubulin. Each tubulin molecule (α/β -tubulin heterodimer) on the microtubules contains a taxol binding site. High-resolution electron microscopy revealed that the taxol binding site is located between the protofilaments formed from α - and β -tubulin units.^[29] Taxol and epothilone binding markedly reduces the rate of α/β -tubulin dissociation. Therefore, taxoids and epothilones act as a bracket to augment and stabilize the pool of tubulin polymers.^[73]

Taxol has also been shown to nucleate tubulin polymerization in vitro without the presence of the GTP that is required for normal polymerization.^[28, 74] Figure 8 demonstrates the cellular effects of epothilone B with cultures of PtK₂ cells of *Potorous tridactylis*. The top picture (control) shows the PtK₂ cells with their nuclei (blue) surrounded by tubulin (red). One of the cells (center) is in the anaphase showing the chromosomes (bright color) being pulled apart towards the poles. On treatment with epothilone B (bottom), however, the cells appear to be in disarray with their nuclei (blue) fragmented in irregular shapes and the tubulin (red) aggregated in distinct wedge-shaped bundles. Thus, by interacting with tubulin, the epothilones block nuclear division and kill the cell by initiating apoptosis (“gene-

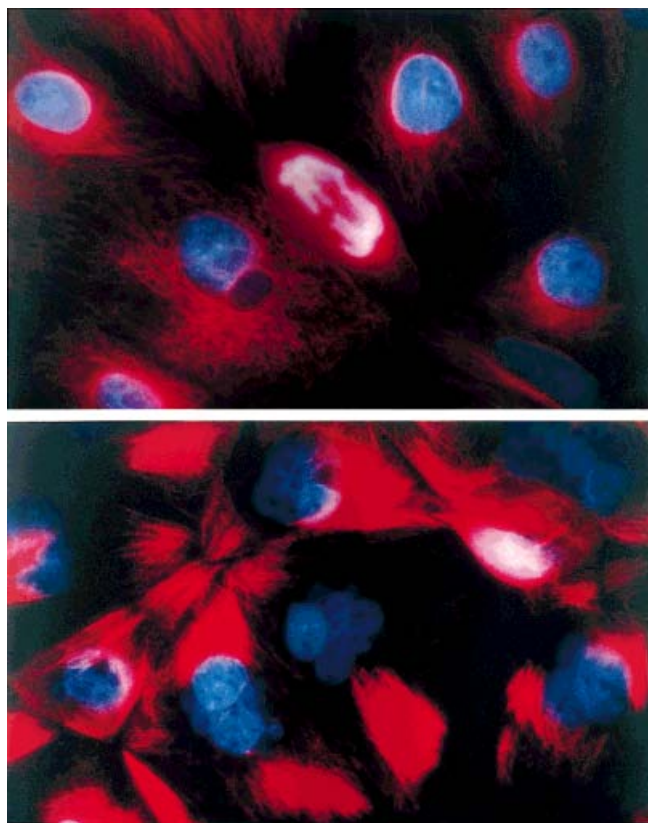


Figure 8. Effect of epothilones on PtK2 cells. See text for explanation (picture courtesy of Drs. F. Sasse and H. Reichenbach).

directed cellular self-destruction” or programmed cell death). Recently, Hamel and co-workers examined the actions of epothilones A and B with additional colon and ovarian carcinoma cell lines and compared them with the action of taxol.^[29] Thus, the Pgp-overexpressing MDR colon carcinoma line SW620 and the taxol-resistant ovarian tumor cell line KBV-1 retained susceptibility to the epothilones, whereas taxol revealed its weakness. With *Potorous tridactylis* kidney epithelial (PtK₂) cells, examined by indirect immunofluorescence, epothilone B proved to be the most active, inducing extensive formation of microtubule bundles. Furthermore, it was confirmed that the epothilones are not substrates for Pgp (as originally reported by Bollag et al.^[15]) and that subtle differences between taxol and the epothilones exist in terms of their mechanism of action on microtubules. This observation was revealed by differences in microtubule morphology. Researchers at the University of Freiburg, Germany, have recently demonstrated that epothilone A initiates apoptosis in neuroblastoma cells just as taxol does.^[75] However, unlike taxol, epothilone A was active against a constitutively Pgp-expressing MDR neuroblastoma cell line (SK-N-SH),^[76] and moreover, its efficacy was not diminished despite the increase of the Pgp level during administration of the drug.^[15] While taxol’s ability to polymerize tubulin is associated with nearly stoichiometric binding to its target,^[77] its stabilization effect on microtubules depends on a relatively small number of molecules binding to the microtubules. When taxol molecules bind to microtubules, they render them extremely stable and static,^[73] making cell division impossible, and killing the cells

as they begin to divide. Since cancer cells divide more frequently than healthy cells, taxol damages tumors where runaway cell division occurs most profoundly. But other rapidly dividing cells such as white blood cells and hair cells can also be attacked, and consequently side effects are experienced by patients taking the drug. Chemotherapy with taxol, therefore, is frequently accompanied by suppression of the immune system, deadening of sensory nerves, nausea, and hair loss (neutropenia, peripheral neuropathy, and alopecia).^[78]

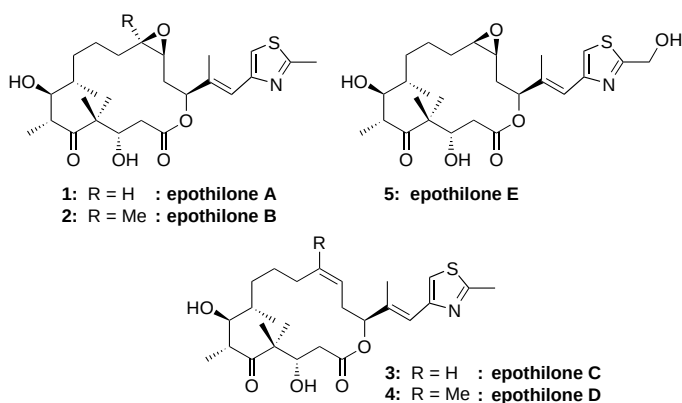
Taxol exhibits endotoxin-like properties by activating macrophages,^[79–81] which in turn synthesize proinflammatory cytokines^[82] and nitric oxide.^[83] It was recently found that epothilone B, despite its similarities to taxol in its effects on microtubules, lacked any IFN- γ -treated murine macrophage stimulatory activity as measured by nitric oxide release (nor did it inhibit nitric oxide production).^[84] It was concluded that epothilone-mediated microtubule stabilization does not trigger endotoxin-signalling pathways, which may translate in clinical advantages for the epothilones over taxol in terms of side effects.^[85] Like taxol and the epothilones, the polyketide marine natural product discodermolide,^[86] and the recently discovered eleutherobin^[87] and sarcodictyin A^[88] (see Scheme 2) also exhibited cytotoxic properties against tumor cells by interfering with tubulin-microtubule dynamics.

3. Chemistry of the Epothilones

Soon after the recognition of the importance of the epothilones, a number of groups around the world began to pursue strategies for their total synthesis. Several groups rushed into the synthesis and it was a very close finish among three groups.^[19] The structures of epothilones are considerably less complex than that of taxol. Nevertheless, the epothilones posed a considerable challenge to synthetic chemists and, most importantly, offered opportunities for the discovery and development of new synthetic technologies and strategies. Of particular interest were the 16-membered macrolide ring, the seven stereocenters, and the thiazole side-chain, whose nitrogen and sulfur atoms held potential complications. While the splendor of the molecular architecture and the highly congested nature of epothilones A and B can be seen in Figure 1, Scheme 3 presents the five naturally occurring epothilones (A–E) identified to date. The topical nature of the field has already elicited highlight reviews from Wessjohann,^[89] Kalesse,^[90] and Finlay.^[91] In the sections below we will first describe the various total syntheses of epothilones A (1) and B (2) and then discuss the design, synthesis and biological evaluation of the many analogues reported. It should be noted at this point that the Danishefsky group was the first to accomplish total syntheses of epothilones A and B.

3.1. The Nicolaou Strategies to Epothilones

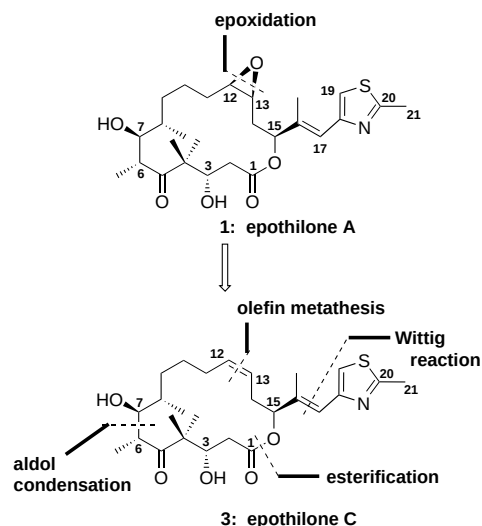
It was on a visit to the Gesellschaft für Biotechnologische Forschung (GBF) in Germany on April 18, 1996, that one of us (KCN) met Professor G. Höfle. Listening to his epothilone



Scheme 3. Structures of the naturally occurring epothilones A (**1**)–E (**5**).

story was both fascinating and stimulating, and quite sufficient to convince one interested in chemistry, biology, and medicine that a research program in the field was warranted. But there was one problem: no stereochemical assignments had been revealed up to that time, and Höfle was not ready to release them yet. Nevertheless, as he had promised, on May 15, 1996, Höfle dispatched a manuscript to us (later to appear in *Angewandte Chemie*^[12]), fully assigning the proper stereochemistries of epothilones A (**1**) and B (**2**). The relocation of our group into the newly constructed Arnold and Mabel Beckmann Center for Chemical Sciences on May 28, 1996, marked the official embarkation date of our epothilone project at Scripps.

Amongst the many strategies we considered, the olefin metathesis approach^[92] shown in Scheme 4 was, perhaps, the



Scheme 4. Nicolaou's olefin metathesis strategy to epothilones A (**1**) and C (**3**): retrosynthetic analysis and strategic bond disconnections (Nicolaou et al.)^[96, 97]

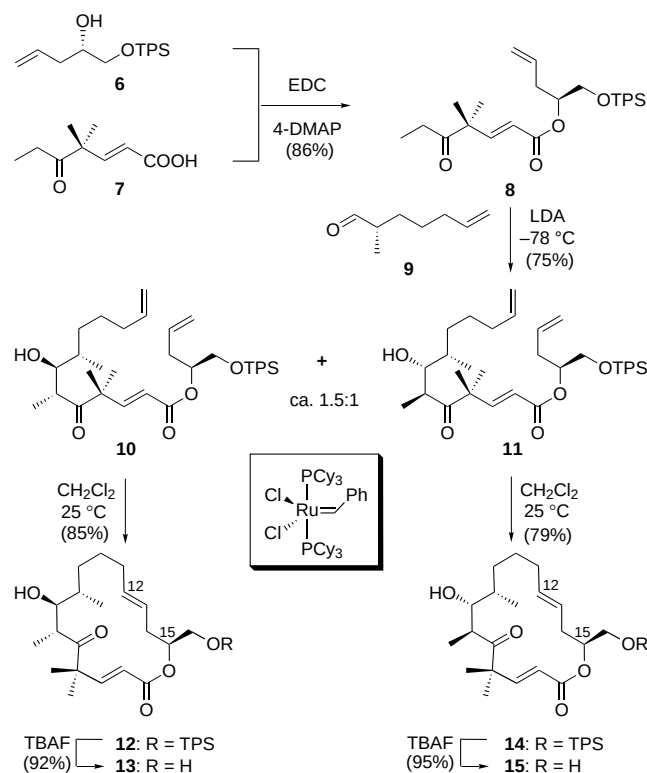
most intriguing. Despite the elegant precedents for such reactions from the groups of Schrock,^[93] Grubbs,^[94] and Hoveyda,^[95] we were faced with a number of dilemmas and questions:

- Will the macrocycle be formed under the metathesis conditions?

- Will the stereochemical outcome of this reaction favor the *Z*-olefin geometry as required, or the *E* geometry?
- Will the thiazole moiety interfere with the catalyst?
- Will an epoxidation be possible in the presence of the α,β -unsaturated thiazole side-chain, and if so, which of the two diastereomeric epoxides will be formed?

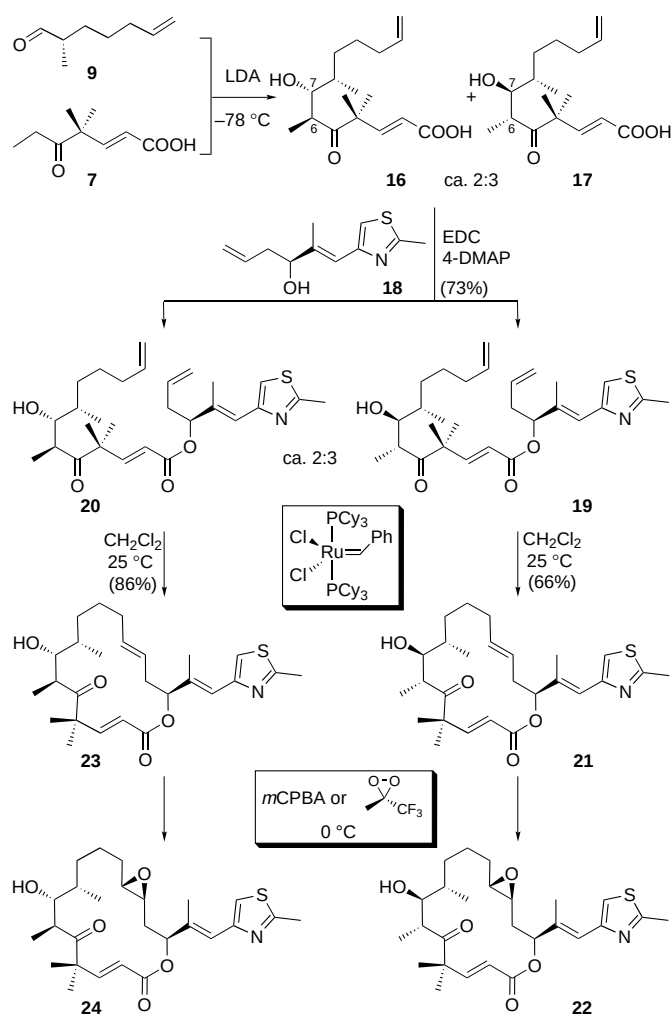
While there were no guaranteed answers to these questions, we immediately recognized that those were the ingredients for an exciting and challenging synthetic adventure, and hence we hesitated no more. In addition to the olefin metathesis, this strategy would require a Wittig olefination, an esterification, and an aldol reaction (Scheme 4). Furthermore, the strategy appeared flexible and convergent enough to deliver both epothilones A and B and, most significantly, a series of analogues for biological screening.

The first generation studies^[96, 97] summarized in Scheme 5 were designed and carried out in order to test the olefin metathesis concept with substrates of minimal functionality. A “fortunate” misassignment of the newly generated double bond geometry in products **13** and **15** as *Z* (later we proved by X-ray crystallographic analysis that the stereochemistry of this olefin was in fact *E*,^[97] as shown in Scheme 5) encouraged us to proceed to the next stage.



Scheme 5. Nicolaou's olefin metathesis strategy to epothilone A: testing the concept with first generation model studies (Nicolaou et al.).^[96, 97]

The second generation model studies (Scheme 6)^[97] were designed to test the feasibility of the olefin metathesis strategy in the presence of the thiazole side-chain, and whether a selective epoxidation was viable. As seen in Scheme 6, the experiments were encouraging and both concerns could be dismissed, even though the stereochemistry of the C12–C13 double bond was incorrect.



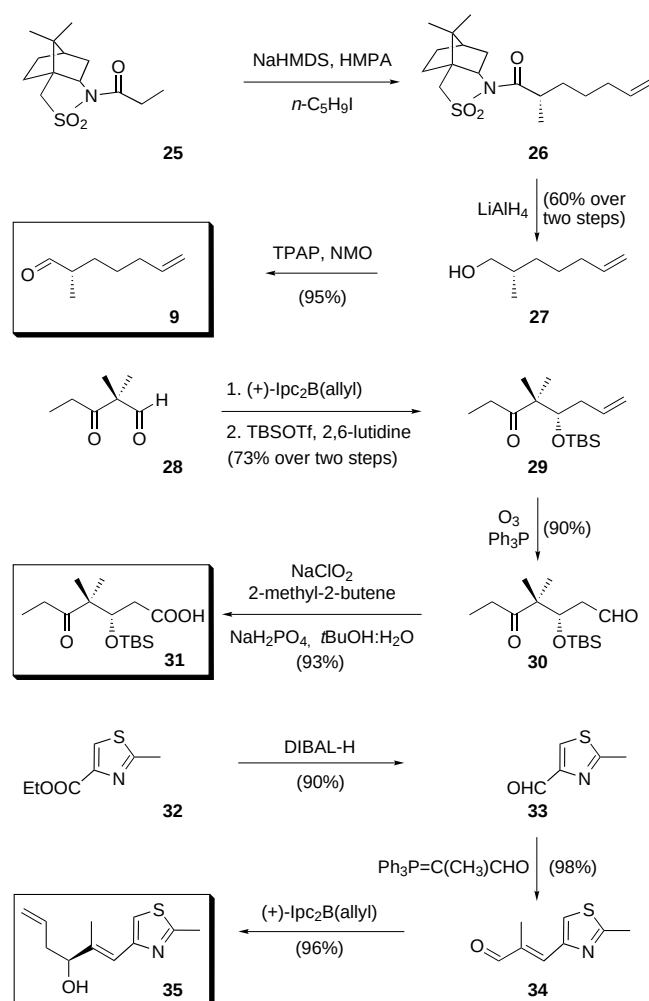
Scheme 6. Nicolaou's olefin metathesis strategy to epothilone A: second generation model studies for testing the feasibility of the concept in the presence of the thiazole moiety (Nicolaou et al.).^[97]

Comforted by the information obtained thus far regarding a possible total synthesis of epothilones by the designed olefin metathesis approach, we embarked on the construction of the requisite building blocks. Scheme 7 summarizes these constructions leading to enantiomerically enriched fragments **9**, **31**, and **35**.^[97–99] These fragments were assembled sequentially, as shown in Scheme 8,^[97, 98] affording the olefin metathesis precursors **38** and **39**. To our delight, the desired precursor **38** entered smoothly into the olefin metathesis reaction forming a mixture of *Z* and *E* macrocyclic olefins **40** (46%) and **41** (39%). Furthermore, the correct geometrical isomer, epothilone C (**3**), underwent selective epoxidation at the C12–C13 double bond to afford epothilone A (**1**) and its diastereomer **43**. The degree of diastereoselectivity in the final step depended upon the epoxidizing agent used [**1**:**43** ≈ 3:1^[97, 98] (*m*CPBA, 0 °C); 3:1^[98] (dimethyldioxirane, 0 °C); 5:1^[98] (methyl(trifluoromethyl)dioxirane, 0 °C); 13:1^[100] (methyl peroxydicarboximide, 25 °C)]. Our first total synthesis of epothilone A (**1**) was accomplished in November 1996.

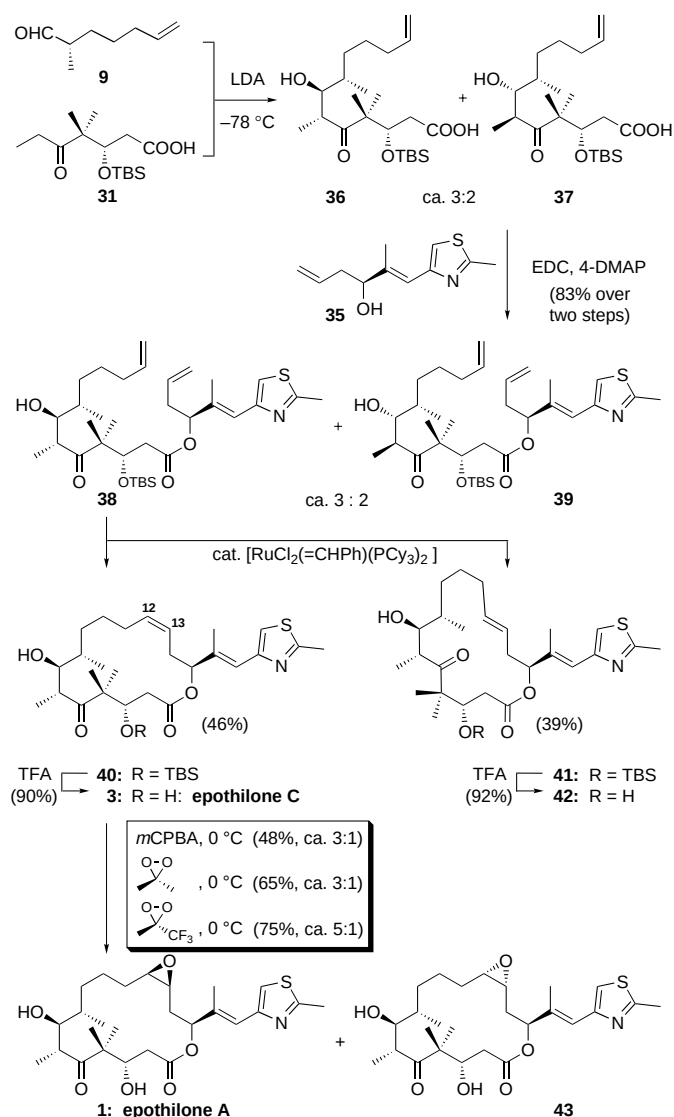
Our explorations of the olefin metathesis reaction within the epothilone field would not end here. Prompted by our

desire to produce a large epothilone library for chemical biology studies, we sought to develop a solid phase synthesis of epothilone A, which—we projected—would be amenable to powerful split-pool combinatorial methods for constructing compound libraries.^[101–103] Thus, the solid phase synthesis of epothilones A (**1**) and C (**3**) was pursued and accomplished as outlined in Scheme 9. The highlight of this assembly is the simultaneous formation and release of the macrocycle from the resin. A further noteworthy feature of this synthesis is the delivery of four isomers of epothilone C (two C6–C7 aldol and two C12–C13 olefinic isomers), which could be chromatographically separated and further reacted to afford the corresponding epoxides. Application of this technology to the construction of combinatorial epothilone libraries will be presented in Section 4.2.

Simultaneously, as the olefin metathesis campaign was proceeding, a second strategy based on a macrolactonization approach (Scheme 10) had been initiated.^[99, 101, 104] The objective of this strategy was to avoid the geometric mixtures of macrocyclic olefins of the metathesis-based synthesis, which, wonderful as it was for the purpose of library construction, suffered from low efficiency when applied to a specific target. Another reason for the macrolactonization alternative was

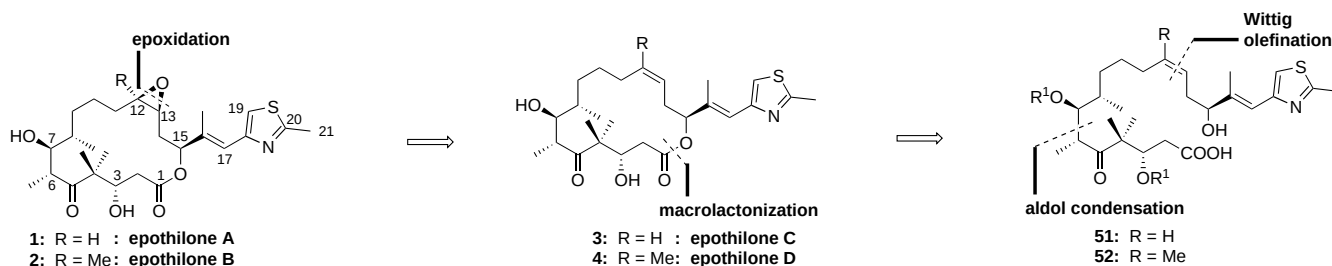


Scheme 7. Nicolaou's synthesis of key intermediates **9**, **31**, and **35** (Nicolaou et al.).^[97, 99]

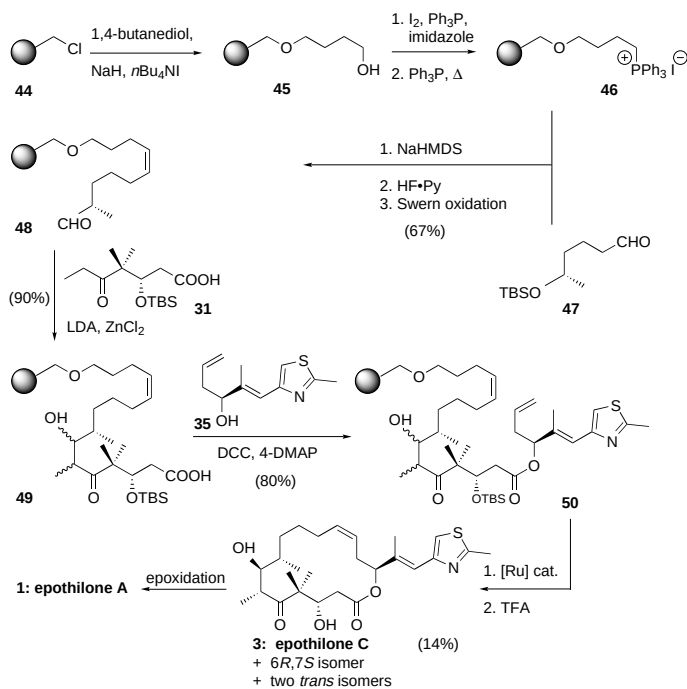


Scheme 8. Nicolaou's olefin metathesis strategy to epothilones A (**1**) and C (**3**): total synthesis in solution (Nicolaou et al. and Yang et al.).^[97, 98]

the perception of a more convenient and efficient synthesis of epothilones B (**2**) and D (**4**), for which the metathesis approach would surely encounter a more severe challenge due to the trisubstituted C12–C13 double bond. As delineated in Schemes 11 and 12, the macrolactonization strategy to epothilones A (**1**) and C (**3**),^[99, 104] and B (**2**) and D (**4**)^[99, 101] proceeded smoothly and with a high degree of stereoselectivity at C12–C13 (**53** + **47** → **54**; *Z*:*E* ≈ 9:1). A further improvement in the aldol diastereoselectivity was also



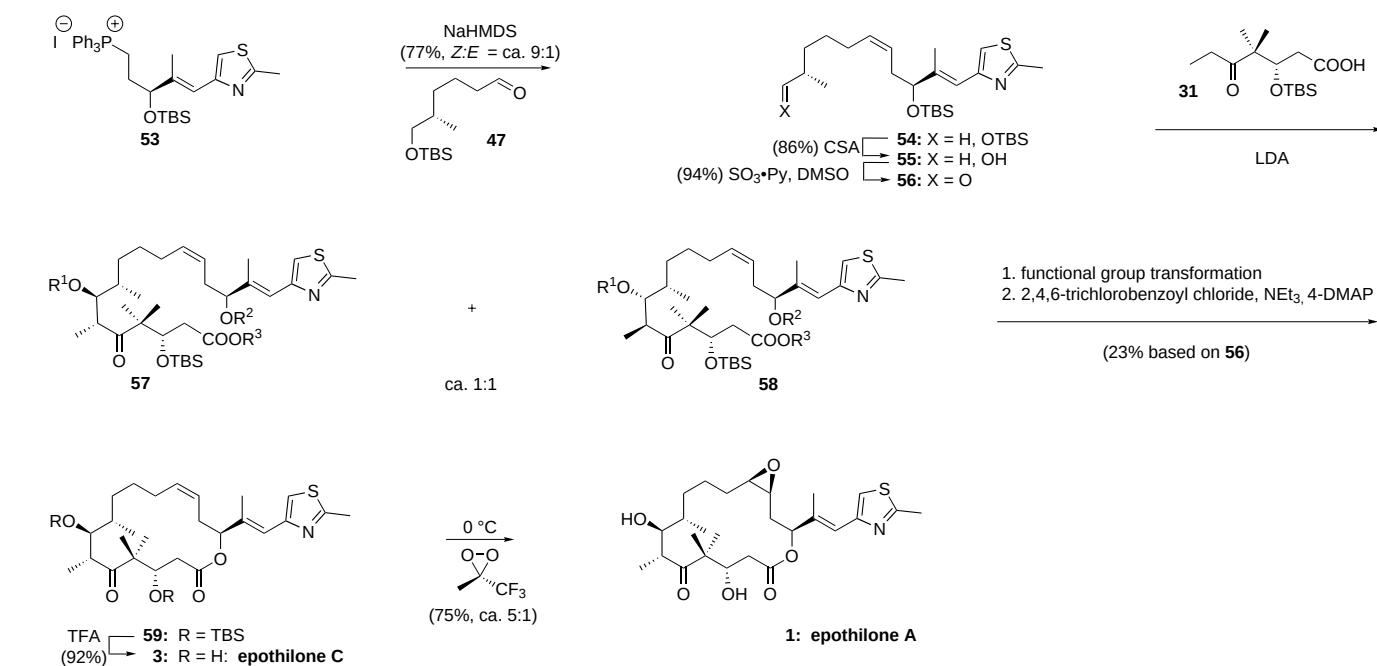
Scheme 10. Nicolaou's macrolactonization strategy to epothilones A–D: retrosynthetic analysis and strategic bond disconnections (Nicolaou et al.).^[99, 104]



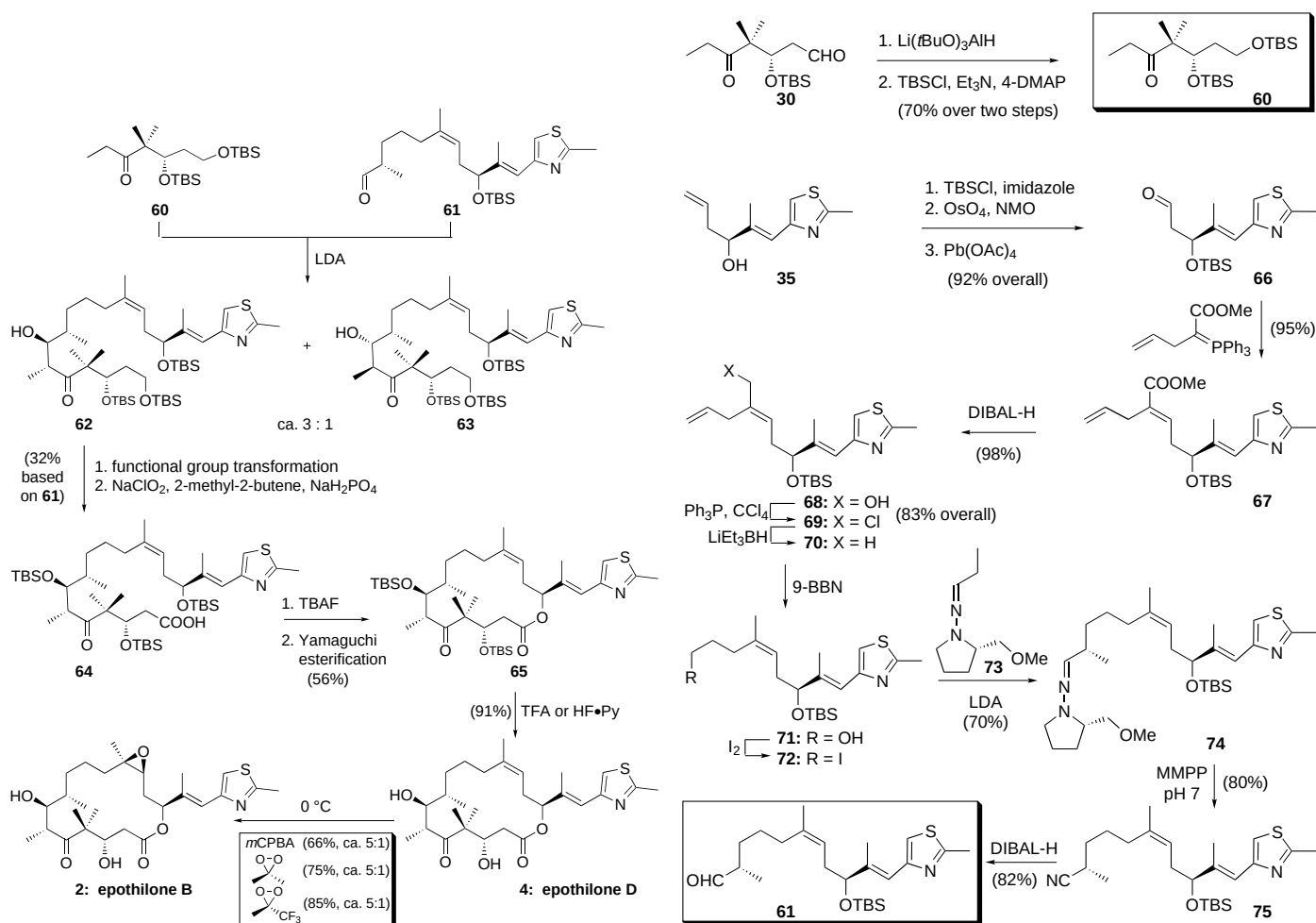
Scheme 9. Nicolaou's olefin metathesis strategy to epothilones A (**1**) and C (**3**): solid phase synthesis. [Ru] = [RuCl₂(=CHPh)(PCy₃)₂] (Nicolaou et al.).^[101]

achieved (6*S*,7*R*:6*R*,7*S* ≈ 3.5:1) by the use of the reduced fragment **60** in the aldol step (**60** + **61** → **62** + **63**, Scheme 12).^[99] The epoxidation of epothilone D (**4**) to epothilone B (**2**) with methyl(trifluoromethyl)dioxirane proceeded in 85 % yield and approximately 5:1 diastereoselectivity. The stereocontrolled construction of the requisite fragments **60** and **61** for this approach was carried out as summarized in Scheme 13.

The emergence of epothilone E (**5**)^[105] as a naturally occurring substance with important biological activity, coupled with our desire to develop yet another approach to epothilones, prompted our next excursion within the field. The olefin metathesis/Stille coupling strategy shown in Scheme 14 would serve particularly well in a projected synthesis of side-chain analogues of epothilone A,^[106] and, potentially, of analogues of epothilone B. A demonstration of the power of this strategy is summarized in Scheme 15, with the first total synthesis of epothilone E (**5**). The methods described above were utilized to construct not only the natural epothilones (A–E), but most importantly, allowed the generation of a series of interesting analogues for biological screening, as shown in Section 4.

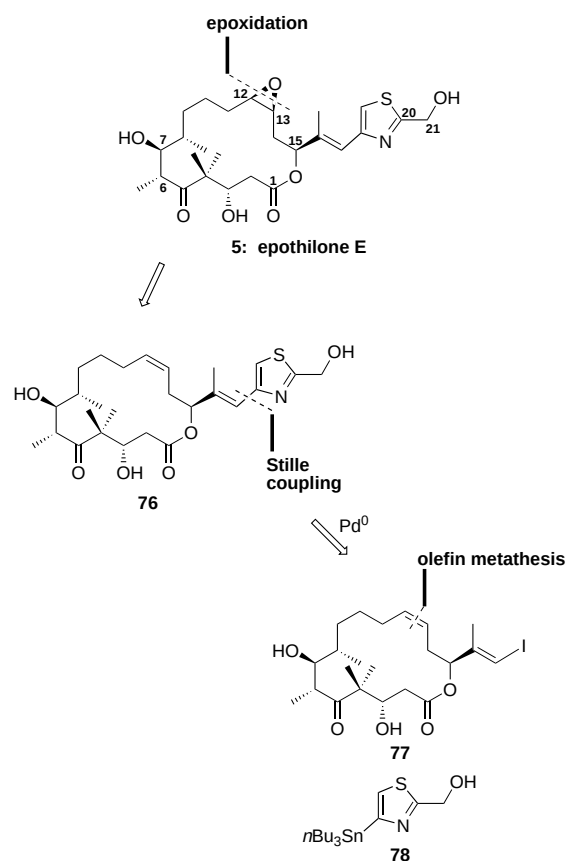


Scheme 11. Nicolaou's total synthesis of epothilones A (**1**) and C (**3**) based on the macrolactonization approach (Nicolaou et al.).^[99, 104]

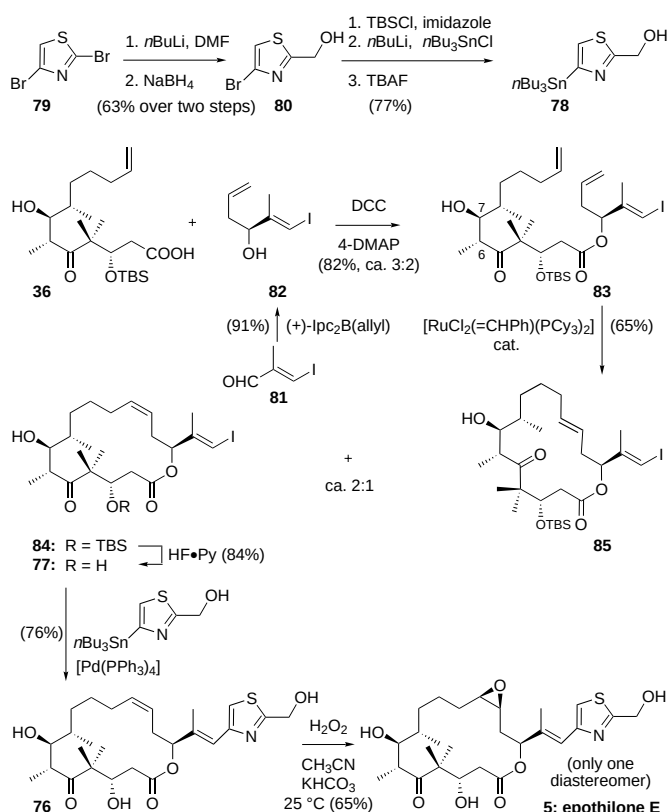


Scheme 12. Nicolaou's macrolactonization approach: stereoselective total syntheses of epothilones B (**2**) and D (**4**) (Nicolaou et al.).^[99, 101]

Scheme 13. Nicolaou's synthesis of key intermediates **60** and **61** (Nicolaou et al.).^[99]



Scheme 14. Nicolaou's olefin metathesis/Stille coupling strategy to epothilone E (**5**): retrosynthetic analysis and strategic bond disconnections (Nicolaou et al.).^[106]

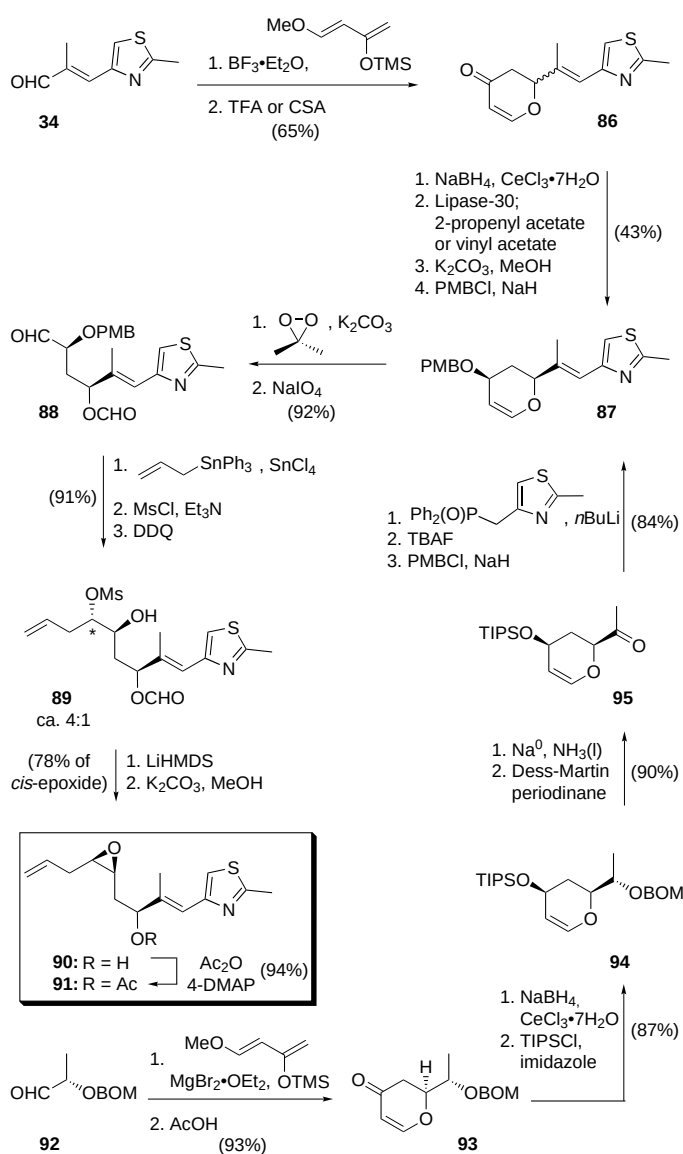


Scheme 15. Nicolaou's olefin metathesis/Stille coupling strategy to epothilone E (**5**): total synthesis (Nicolaou et al.).^[106]

3.2. The Danishefsky Strategies to the Synthesis of Epothilones

The Danishefsky group made major contributions to the epothilone field, being the first to accomplish a total synthesis of both epothilones A (**1**)^[107] and B (**2**)^[108] and their desoxy precursors (epothilones C (**3**) and D (**4**), respectively).^[107, 108] Their strategies included an elegant macroaldolization reaction,^[107–109] an olefin metathesis approach,^[109, 110] and a macro-lactonization-based process^[109] for the construction of the macrocycle. In addition, a number of interesting reactions and sequences were applied, including Suzuki-type couplings and dihydropyran formation and rupture, as means to install functionality and control stereochemistry.

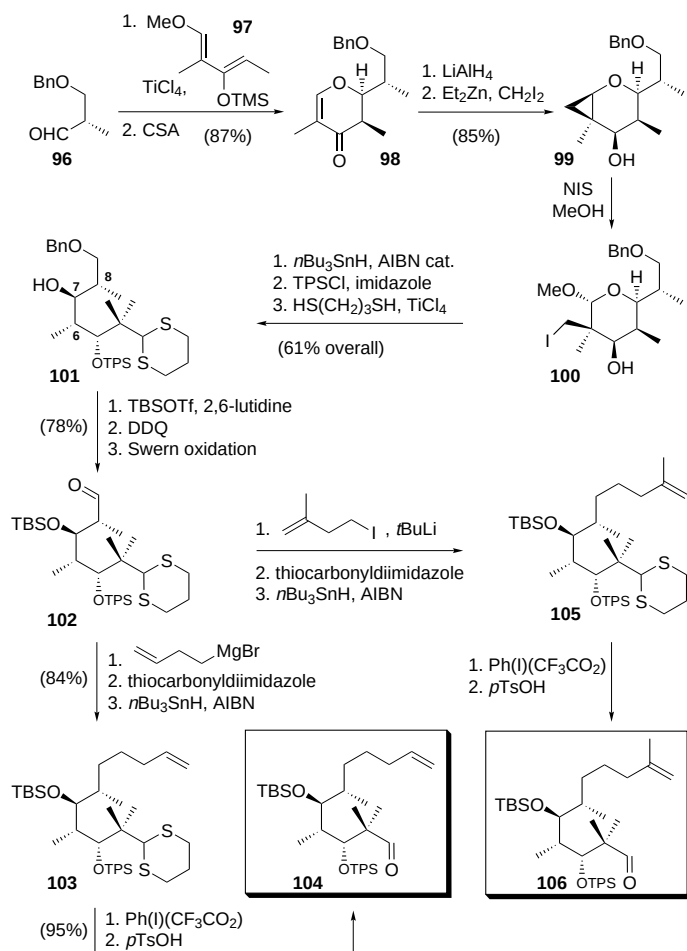
Thus, the group was able to demonstrate the use of dihydropyran templates synthesized from the Danishefsky diene,^[111] for the stereocontrolled constructions of their required fragments **90** and **91** as shown in Scheme 16.^[109, 112]



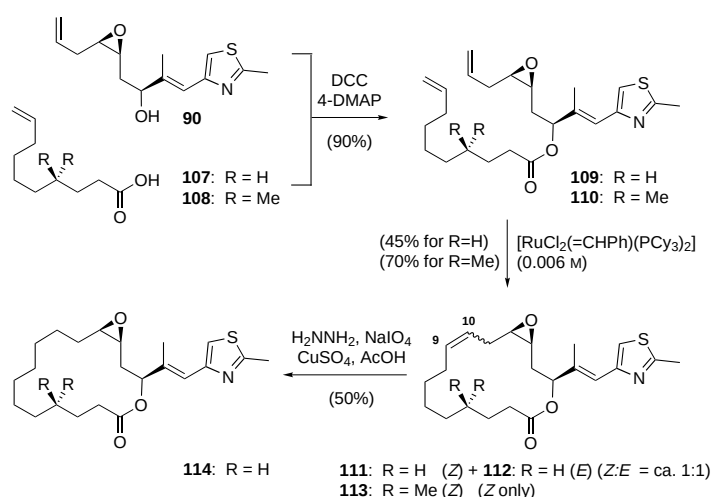
Scheme 16. Danishefsky's utilization of dihydropyran templates as controlling elements in the diastereosynthesis of epothilone fragments **90** and **91** (Meng et al.).^[109, 112]

Further elaboration along similar lines allowed the synthesis of the C3–C12 segments **104** and **106** (Scheme 17) necessary for the synthesis of epothilones A (**1**) and B (**2**), respectively.^[109, 110] In both schemes, sequential formation and opening of the dihydro- and tetrahydropyran systems was the key tactic for introduction of the stereochemistry onto the final open-chain intermediates. An early model study by the Danishefsky group for the elaboration of the epothilone macrocycle through olefin metathesis, targeting the C9–C10 bond, was encouraging (Scheme 18), but unfortunately proved less fruitful in the real case.^[109, 113]

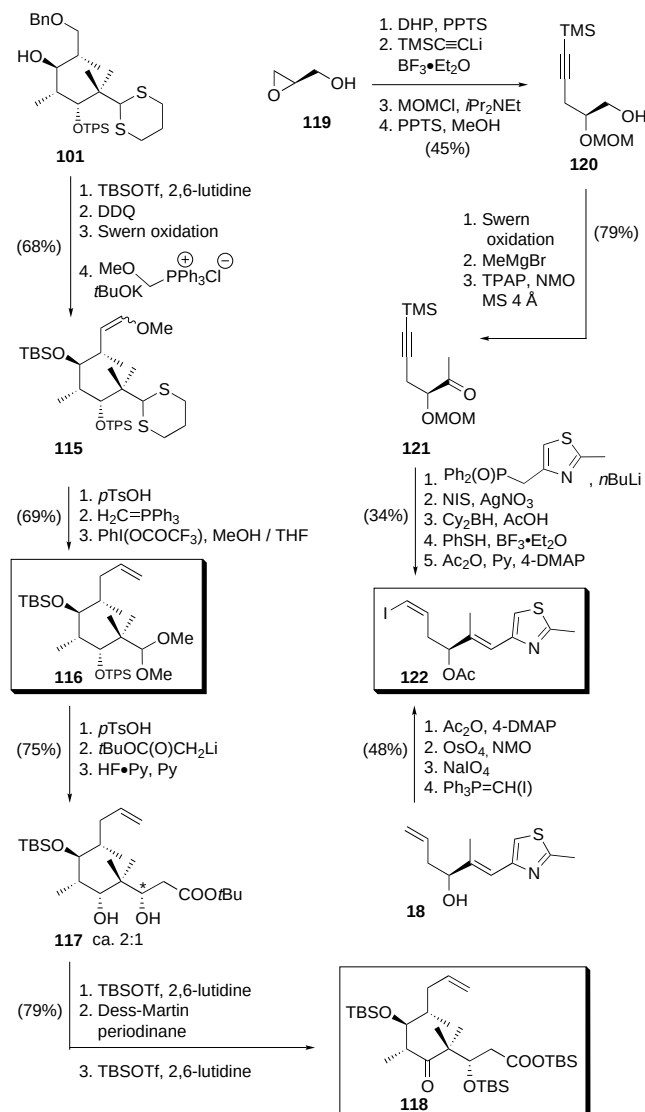
The first breakthrough in the Danishefsky group came with the employment of the macroaldolization strategy for the construction of epothilones A (**1**) and C (**3**) (Schemes 19 and 20).^[108, 109] First, the advanced intermediates **116** and **122** were constructed in a stereocontrolled fashion as outlined in Scheme 19. In assembling the fragments (Scheme 20), a stereospecific Suzuki coupling allowed the union of intermediates **116** and **122** to form compound **123**, which underwent a stereoselective ring closure under basic conditions, leading to the desired macrocycle **59**. Subsequent functional group manipulations and epoxidation led to epothilones C (**3**) and A (**1**) in good overall yield and stereoselectivity (Scheme 20). Danishefsky's second approach to epothilone A (**1**) proceeded through intermediates **118** and **122**



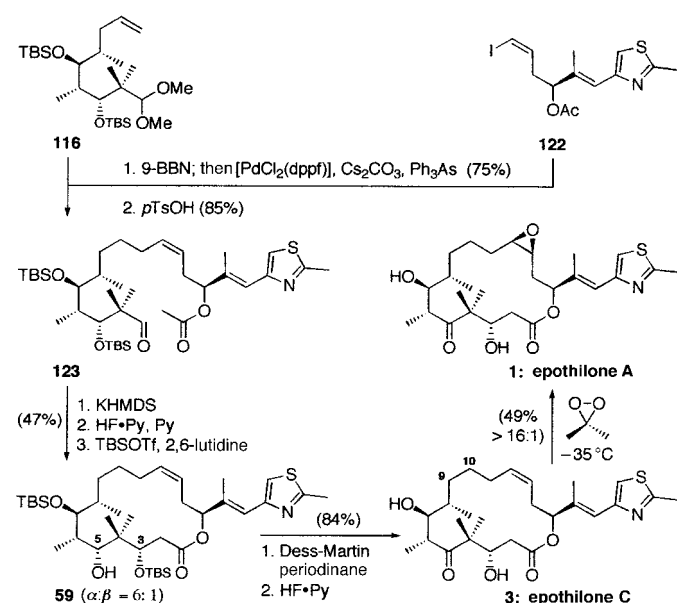
Scheme 17. Danishefsky's stereoselective synthesis of the epothilone C3–C12 fragments **104** and **106** (Meng et al. and Bertinato et al.).^[109, 110]



Scheme 18. Danishefsky's model study targeting the C9–C10 double bond through olefin metathesis (Meng et al. and Bertinato et al.).^[109, 113]



Scheme 19. Danishefsky's synthesis of advanced intermediates **116**, **118**, and **122** for the macroaldolization and macrolactonization strategies towards epothilone A (Balog et al. and Su et al.).^[107, 108]

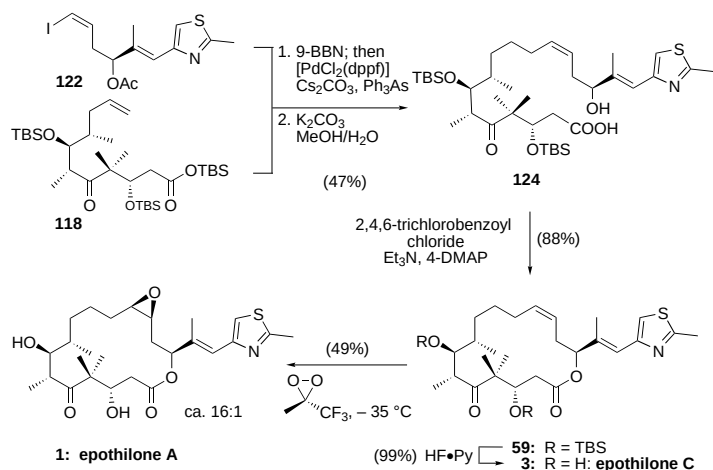


Scheme 20. Danishefsky's total syntheses of epothilones A (**1**) and C (**3**) through the macroaldolization strategy (Su et al. and Balog et al.).^[108, 109]

(Scheme 21), and involved a stereospecific Suzuki coupling to join them, as well as a macrolactonization reaction to form the macrocyclic framework.^[109]

Employing the olefin metathesis approach, but now targeting the C12–C13 double bond, the Danishefsky group carried out an interesting and revealing study (Scheme 22).^[110] By varying the substituents on the open-chain precursor **128**, they observed different ratios for the *Z*:*E* cyclic olefins ranging from around 5:3 to 1:9. Using their macroaldolization strategy, the group has also synthesized epothilones B (**2**) and D (**4**) as shown in Scheme 23.^[108] Again, a stereospecific Suzuki coupling (**116** + **130** → **131**), followed by base treatment and functional group manipulation resulted in ring closure (**131** → **65**), to afford the desired framework, which served admirably as a precursor to both epothilones D (**4**) and B (**2**).

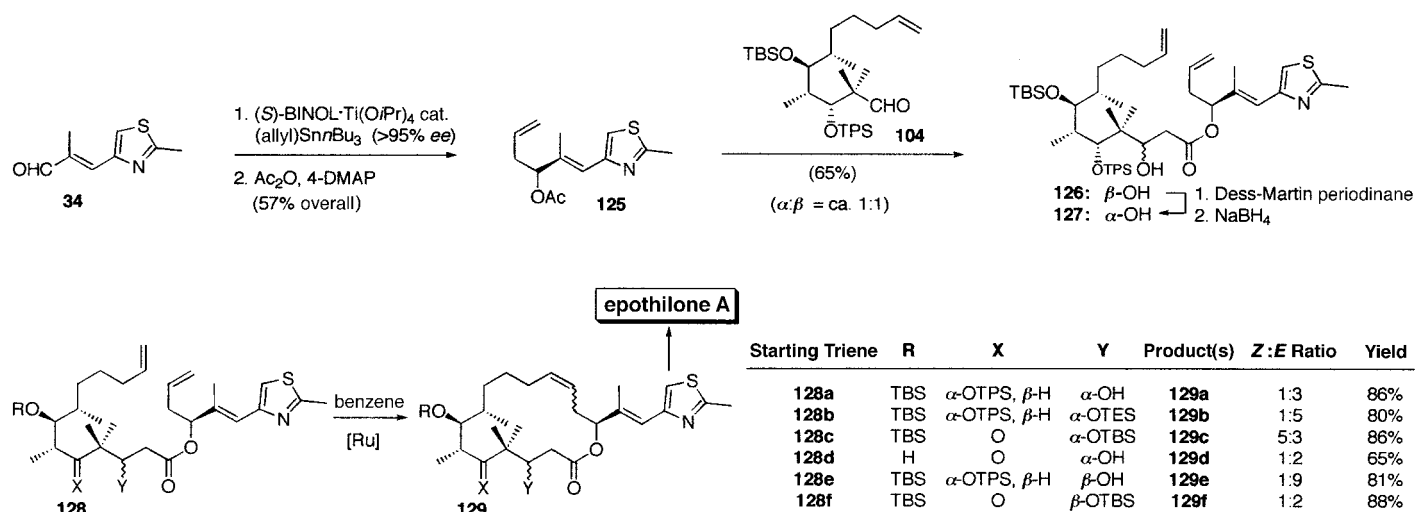
Finally, a remarkable olefin metathesis reaction (Scheme 24) involving a trisubstituted olefin and the molybdenum-based Schrock catalyst^[93] served as the basis for a conceptually different total synthesis of epothilones D (**4**) and B (**2**).^[109] In this case, however, the C12–C13 double bond was formed as a mixture of *Z:E* isomers in an approximately 1:1 ratio.



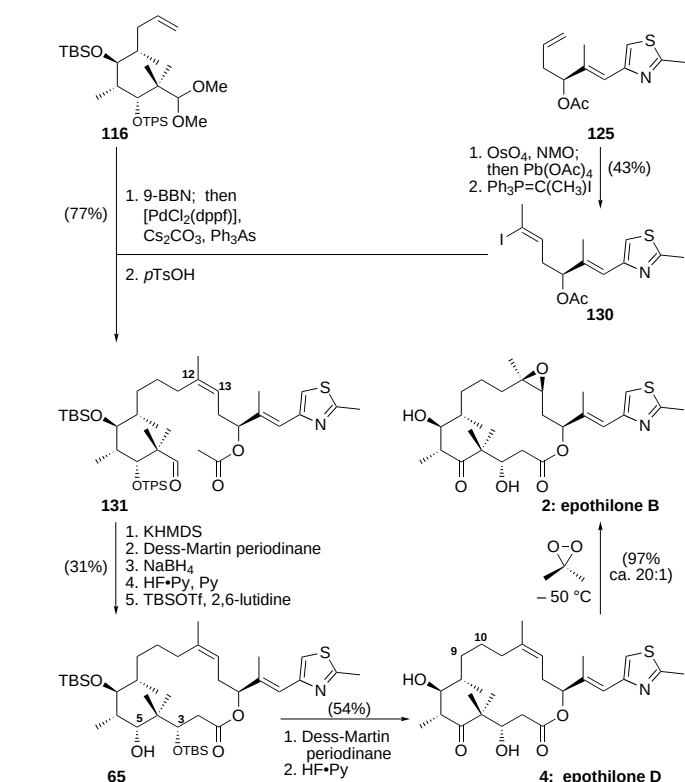
Scheme 21. Danishefsky's synthesis of epothilones A (**1**) and C (**3**) by the macrolactonization approach (Meng et al.).^[109]

3.3. The Schinzer Strategy to the Synthesis of Epothilones A and C

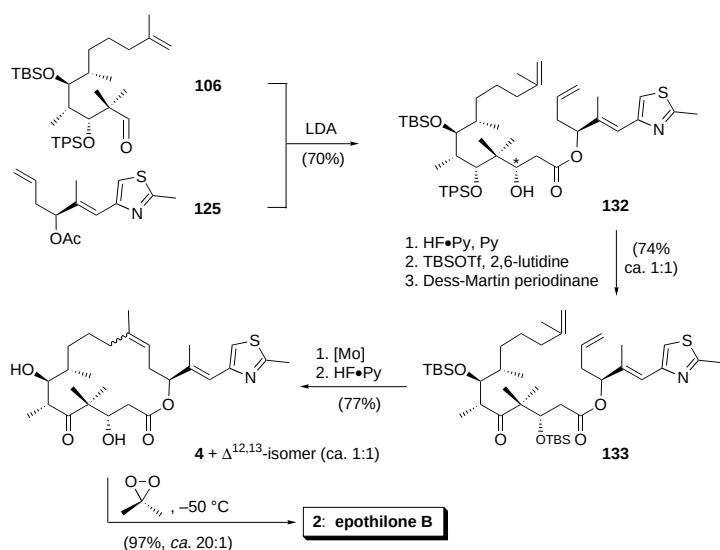
The Schinzer group, working in Braunschweig (not far from the GBF where the epothilones were first discovered) independently developed an olefin metathesis approach to epothilones A (**1**) and C (**3**) as shown in Schemes 25 and 26.^[114, 115] Their design required the key intermediates **137**, **141**, and **146**, which were obtained by asymmetric synthesis according to the sequences depicted in Scheme 25.^[114] The formation of a single (*6R,7S*) diastereoisomer in the aldol condensation of ethyl ketone **137** with aldehyde **9** under the influence of LDA was most impressive, and was attributed to the influence of the acetonide moiety (Scheme 26).^[115] Attachment of the side-chain by esterification, ring closure through olefin metathesis, and epoxidation with dimethyldioxirane, then led to epothilones (**3**) and A (**1**).



Scheme 22. Danishefsky's olefin metathesis studies towards the total synthesis of epothilones A and C [Ru] = RuCl₂(=CHPh)(PCy₃)₂] (Meng et al.).^[109, 110]



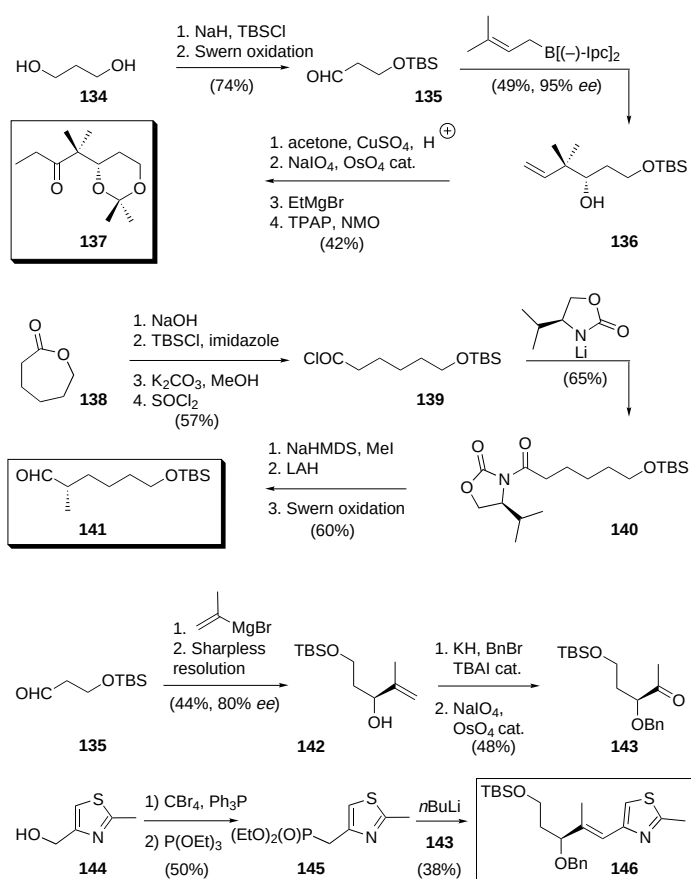
Scheme 23. Danishefsky's total synthesis of epothilones B (2) and D (4) by macroaldolization (Su et al. and Meng et al.).^[108, 109]



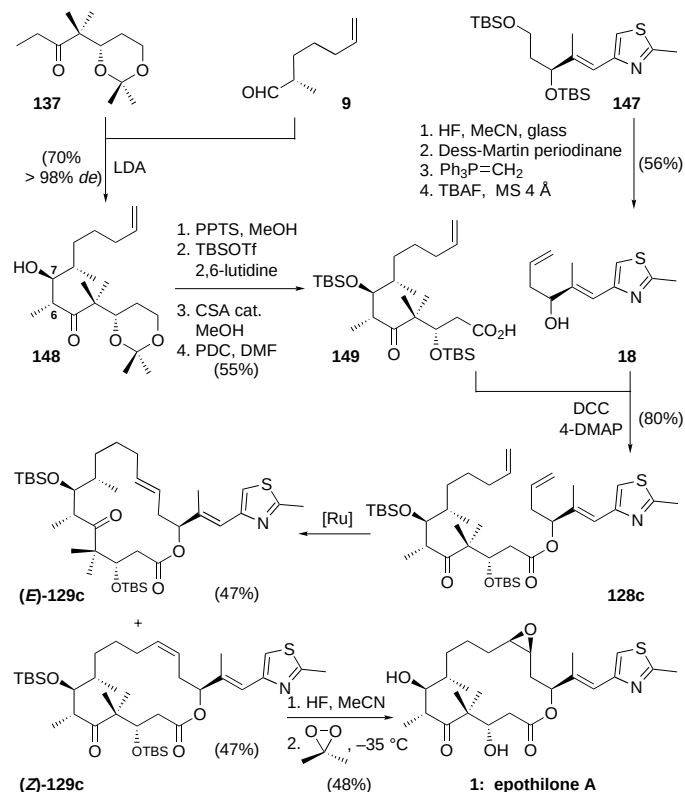
Scheme 24. Danishefsky's total synthesis of epothilones B (2) and D (4) by ring-closing olefin metathesis. [Mo] = [Mo(=CHMe₂Ph){N(2,6-(iPr)₂C₆H₃)}(OCMe(CF₃)₂)₂] (Meng et al.).^[109]

3.4. Miscellaneous Other Approaches to Epothilones

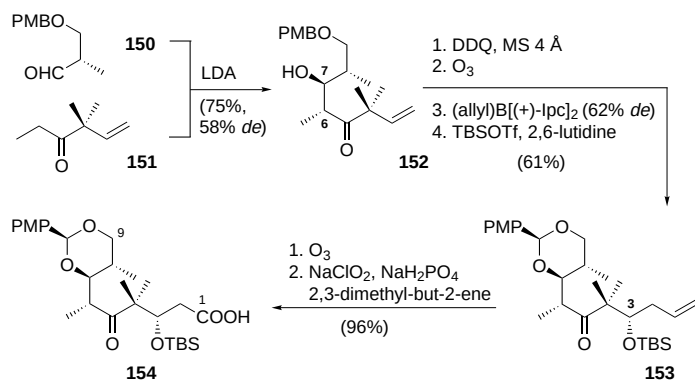
A number of other groups also made important contributions to the epothilone field, in terms of model studies and synthesis of key intermediates. Amongst them are those of Mulzer,^[116, 117] Kalesse–Meyer,^[118] Wessjohann,^[119] Taylor,^[120] and De Brabander.^[121] Thus, by using elegant sequences, Mulzer et al.^[116, 117] synthesized the C1–C9 and C11–C21 epothilone fragments **154** and **161** as shown in Schemes 27 and



Scheme 25. Schinzer's asymmetric synthesis of intermediates **137**, **141**, and **146** for the total synthesis of epothilone A (1) (Schinzer et al.).^[112]

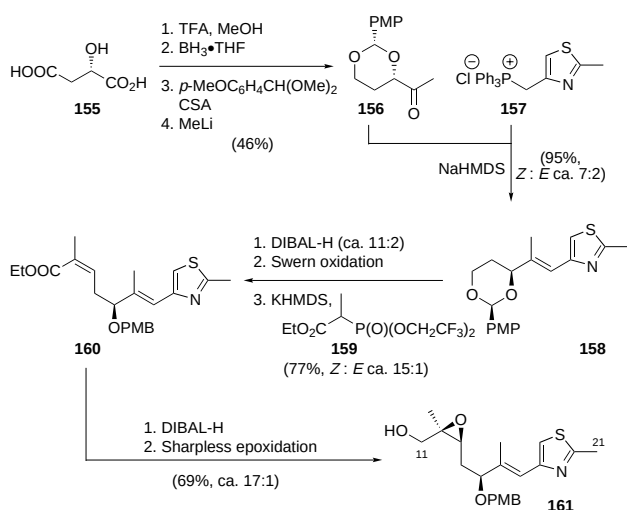


Scheme 26. Schinzer's total synthesis of epothilones A (1) and C (3) by olefin metathesis. [Ru] = [RuCl₂(=CHPh)(PCy₃)₂] (Schinzer et al.).^[115]



Scheme 27. Mulzer's synthesis of the C1–C9 epothilone fragment **154** (Mulzer et al.).^[116]

28, respectively. The Kalesse–Meyer contribution^[118] resulting in the asymmetric synthesis of building block **166** is shown

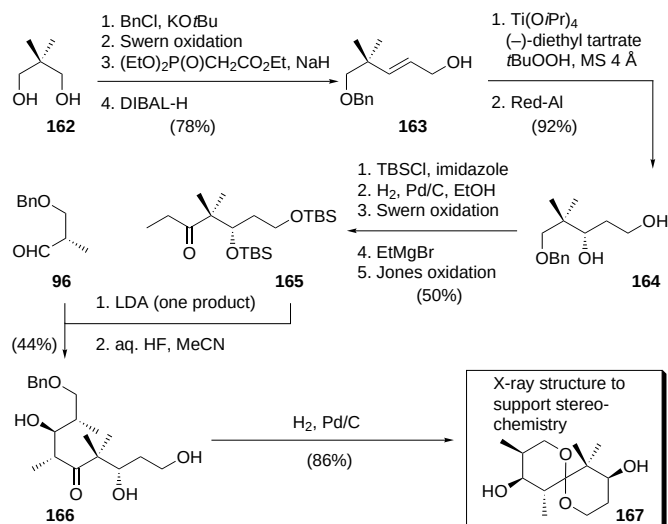


Scheme 28. Mulzer's synthesis of the C11–C21 epothilone fragment **161** (Mulzer et al.).^[117]

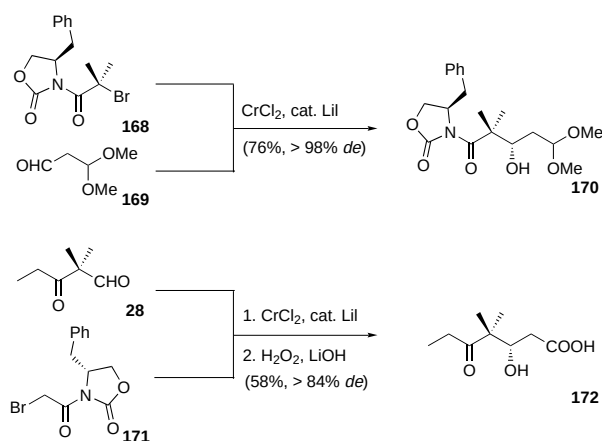
in Scheme 29. Based on their recently developed chromium(II)-mediated Reformatsky reaction, Gabriel and Wessjohann^[119] devised routes to two different C1–C5 fragments (**170** and **172**) of epothilones as outlined in Scheme 30. The work of Taylor and Haley^[120] involved the asymmetric construction of the key thiazole-containing intermediate **35** and an olefin metathesis model study as summarized in Scheme 31. Asymmetric routes to key intermediates **9** (C7–C11) and **31** (C1–C6) were developed by De Brabander et al.^[121] as depicted in Scheme 32.

4. Chemical Synthesis and Biological Properties of the Designed Epothilones

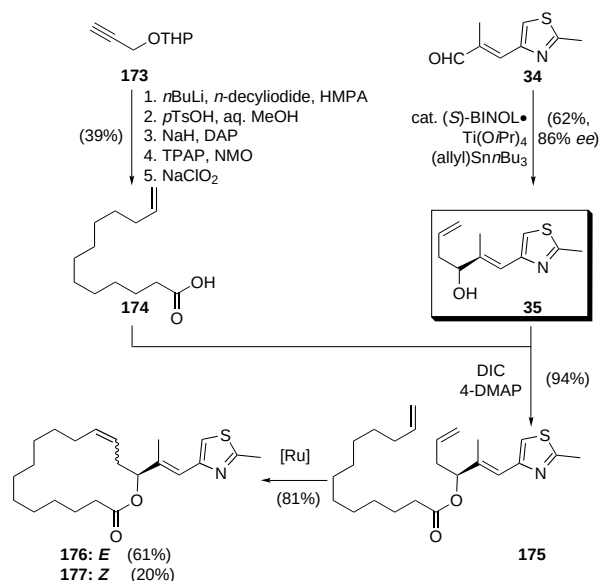
The successful crusade for the total synthesis of the natural epothilones paved the way for the chemical synthesis of a large number of designed epothilones for chemical biology studies. Thus, a new campaign began for the design, synthesis, and biological evaluation of epothilone libraries. Tables 2–6 list the analogues synthesized by the two principal groups



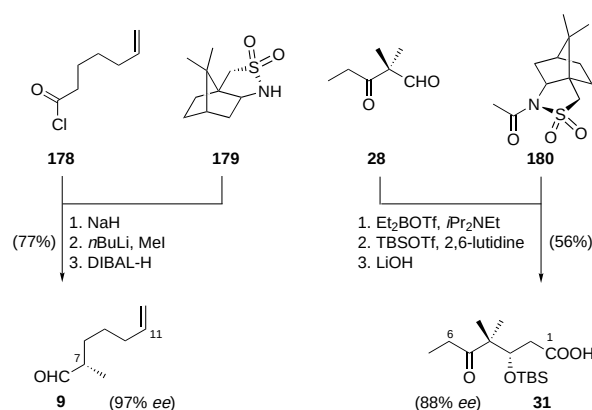
Scheme 29. The Kalesse–Meyer synthesis of the C1–C9 epothilone fragment **166** (Claus et al.).^[118]



Scheme 30. Wessjohann's application of the chromium-Reformatsky reaction for the asymmetric synthesis of C1–C6 epothilone fragments **170** and **172** (Gabriel et al.).^[119]

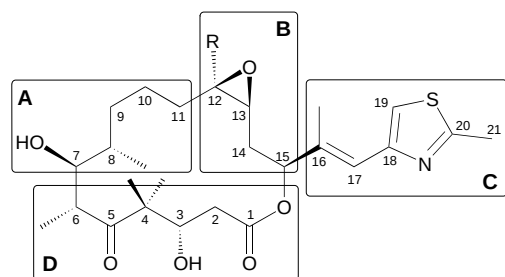


Scheme 31. Taylor's enantioselective synthesis of thiazole side chain **35** and olefin metathesis model studies. [Ru] = [RuCl₂(=CHPh)(PCy₃)₂] (Taylor et al.).^[120]



Scheme 32. De Brabander's enantioselective synthesis of Nicolaou's key intermediates **9** and **31** (De Brabander et al.).^[121]

involved in this campaign, namely ours and the Danishefsky group. The Höfle and Schinzer teams also made contributions to this area, even though their results remain, for the most part, unreported. For discussion purposes, the epothilone structure is divided into four regions, A–D, as shown in Scheme 33. The design of analogues was directed primarily at simplifying the molecular structure for purposes of gaining more-facile access to the target molecules and at answering

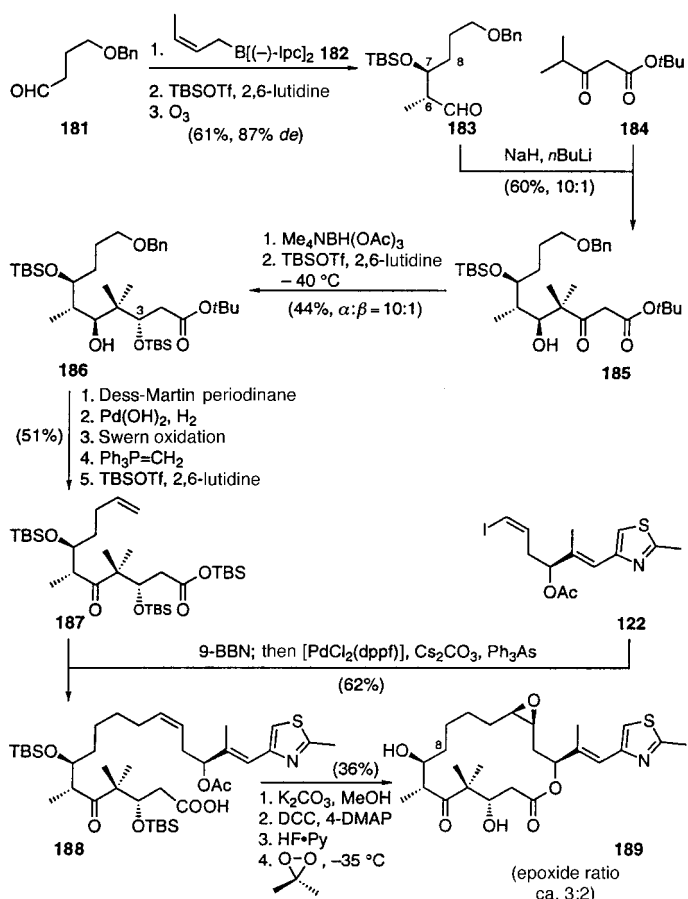


Scheme 33. Regions A–D of the epothilone molecule where structural variations were performed.

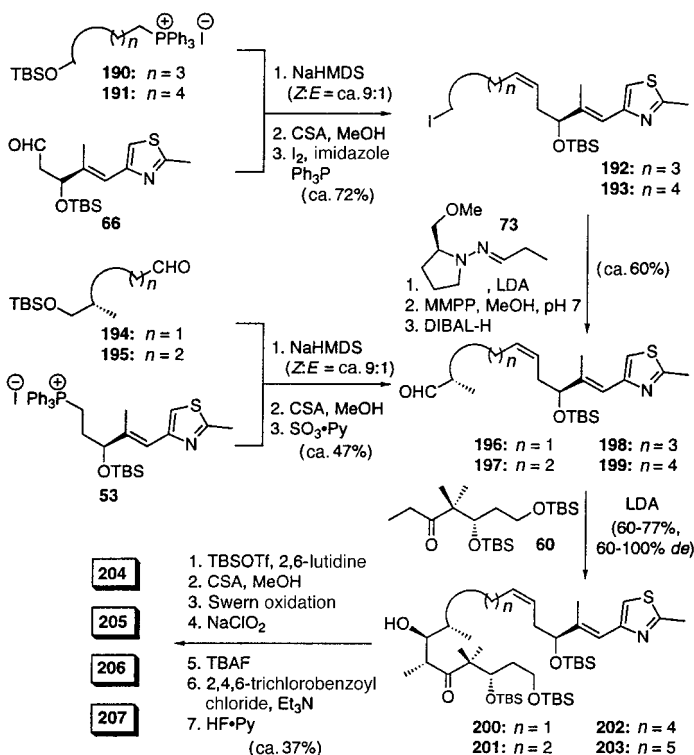
questions regarding the requirement of certain functionalities and stereochemical elements for activity, as well as the introduction of novel structural elements. To achieve the synthesis of these analogues, a number of novel methods and strategies were developed, as we will briefly discuss. The compounds shown in Tables 2–6 were constructed by applying the previously discussed methods, or by implementing the sequences demonstrated in Schemes 34–38.

4.1. Solution-Phase Synthesis of Epothilone Analogues

The solution-phase synthesis of 8-desmethylepothilone A (**189**); (region **A** modification) was accomplished by both Danishefsky et al. (macrolactonization approach)^[122] and Nicolaou et al. (olefin metathesis approach).^[102] The Danishefsky synthesis is summarized in Scheme 34. The 14-, 15-, 16-, and 17-membered ring desoxyepothilones (**204**–**207**) were synthesized by the Nicolaou group using the macro-



Scheme 34. Danishefsky's synthesis of 8-desmethylepothilone A (region A modification; see Table 2; Ballog et al.).^[122]



Scheme 35. Synthesis of 14-, 15-, 17-, and 18-membered epothilones A by the macrolactonization strategy (Region A modifications; see Table 2; Nicolaou et al.).^[123]

Table 2. Structures and tubulin polymerization properties of region A-modified epothilone analogues.

Ref.	Structure	Tubulin poly- merization [%] ^[a]	Ref.	Structure	Tubulin poly- merization [%] ^[a]	Ref.	Structure	Tubulin poly- merization [%] ^[a]
Nicolaou								
[102] [102] [102]		239: R ¹ = R ² = H 23 240: R ¹ = Me, R ² = H 11 241: R ¹ = R ² = Me 2	[102] [102] [102]		246: R ¹ = R ² = H 23 247: R ¹ = Me, R ² = H 8 248: R ¹ = R ² = Me 5	[123] [123] [123] [123]		204: n = 1 6 205: n = 2 9 206: n = 4 12 207: n = 5 41
[102] [102] [102]		242: R ¹ = R ² = H 24 243: R ¹ = Me, R ² = H 11 244: R ¹ = R ² = Me 3	[102] [102] [102]		249: R ¹ = R ² = H 21 250: R ¹ = Me, R ² = H 11 251: R ¹ = R ² = Me 4	[123] [123] [123] [123]		254: n = 1 4 255: n = 2 5 256: n = 4 7 257: n = 5 21
[102]		245 21	[102]		252 27	[123] [123] [123]		258: n = 2 3 259: n = 4 5 260: n = 5 29
Danishefsky								
[30]		205: n = 2 –	[122]		239 –	[30]		189 –

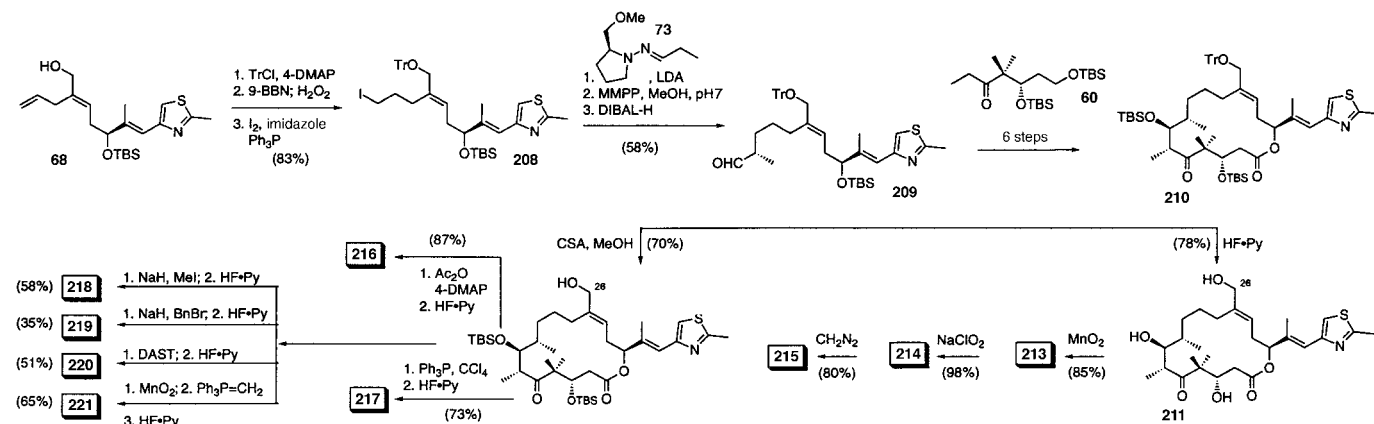
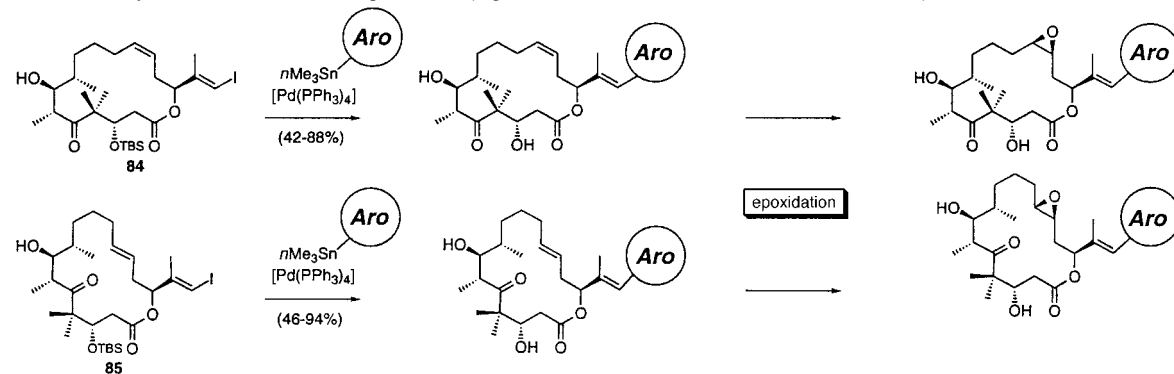
[a] Tubulin polymerization was determined by the filtration-colorimetric assay following the procedure of Bollag et al.^[15] and Nicolaou et al.^[102]Scheme 36. Synthesis of C26-modified epothilones (region B modifications; see Table 3; Nicolaou et al.).^[124]Scheme 37. Synthesis of side-chain modified epothilones by Stille coupling (region C modifications; see Table 4; Nicolaou et al.).^[106] Aro = aromatic group.

Table 3. Structures and tubulin polymerization properties of region B-modified epothilone analogues.

Ref.	Structure	Tubulin poly- merization [%] ^[a]	Ref.	Structure	Tubulin poly- merization [%] ^[a]	Ref.	Structure	Tubulin poly- merization [%] ^[a]	
Nicolaou									
[102]		261	18	[102]		10	[97,99,101] [99,101]	 42: R = H 289: R = Me	76 72
[124] [124] [128] [128] [124] [124] [124] [128] [128] [128] [128] [128] [124] [124] [124]	 211: R = CH ₂ OH 216: R = CH ₂ OAc 262: R = CH ₂ OC(O) <i>t</i> Bu 263: R = CH ₂ OC(O)Ph 218: R = CH ₂ OMe 219: R = CH ₂ OBn 220: R = CH ₂ F 217: R = CH ₂ Cl 264: R = CH ₂ I 265: R = CH ₂ CH ₃ 266: R = CH ₂ NHAc 221: R = CH=CH ₂ 267: R = C≡CH 213: R = CHO 214: R = CO ₂ H 215: R = CO ₂ Me	52 66 43 69 47 62 83 88 11 66 10 95 81 64 12 12	[102]		10	[97,99,101] [99,101]	 290: R = H 291: R = Me	92 84	
[128]		268: R = CH ₂ OH 269: R = CH ₂ OAc 270: R = CH ₂ OC(O) <i>t</i> Bu 271: R = CH ₂ OC(O)Ph 272: R = CH ₂ OMe 273: R = CH ₂ OBn 274: R = CH ₂ F 275: R = CH ₂ Cl 276: R = CH ₂ I 277: R = CH ₂ CH ₃ 278: R = CH=CH ₂ 279: R = CHO 280: R = CO ₂ Me	29 51 6 5 6 12 93 69 41 79 94 87 19	[97]		13	[128]		29
[128] [128]	 281: R = Me 282: R = Ac	2 25	[97]		19	[128]		31	
[97,99]		43	17	[97]		16	[102]		12
						[97]		297	20
Danishefsky									
[30] [30] [30]	 265: R = CH ₂ CH ₃ 298: R = <i>n</i> Pr 299: R = <i>n</i> Pr	— — —	[107,108] [30] [30]	 42: R = H 300: R = Me 301: R = <i>n</i> Pr	— — —	[30] [30] [30]	 303: R = CH ₂ CH ₃ 304: R = <i>n</i> Pr 305: R = <i>n</i> Hex	— — —	
[108]		289	—			[30]		302	—

[a] Tubulin polymerization was determined by the filtration-colorimetric assay following the procedure of Bollag et al.^[15] and Nicolaou et al.^[102]

Table 4. Structures and tubulin polymerization properties of region C-modified epothilone analogues.

Ref.	Structure	Tubulin polymeri- zation [%] ^[a]	Ref.	Structure	Tubulin polymeri- zation [%] ^[a]	Ref.	Structure	Tubulin polymer- ization [%] ^[a]	
Nicolaou									
[102]		306	34		320: R = H 76: R = CH ₂ OH 321: R = CH ₂ OAc 322: R = CH ₂ F 323: R = (CH ₂) ₅ OAc 324: R = Piperidyl 325: R = SMe 326: R = Ph 327: R = OEt	31 34 2 57 3 18 92 25 3		343: R = H 344: R = CH ₂ OH 345: R = CH ₂ OAc 346: R = (CH ₂) ₅ OAc 347: R = Piperidyl 348: R = SMe 349: R = Ph 350: R = OEt	41 40 1 2 5 71 16 2
[102]		307	48		328: R =	51		351: R =	61
[100] [125]		308: R = H 309: R = Me	75 93	[106]	329: R =	13	[106]	352: R =	2
[128]		310	62	[106]	330: R =	16	[106]	353: R =	26
[128]		311	18	[106]	331: R =	34	[106]	354: R =	2
[100]		312: R = H 313: R = Me	43 54	[106]	332: R =	63	[106]	355: R =	57
[100]		314	20	[106]	333: R =	4	[106]	356: R =	1
[100] [125]		315: R = H 316: R = Me	58 93	[106]	334: R =	6	[106]	357: R =	2
[128]		317	21	[128]	335: R =	1	[128]	358: R =	1
[100] [125]		318: R = H 319: R = Me	64 95	[106]	77: R = I	26	[106]	359: R = I	2
[128]		365	6	[102] [128]	336: R = Ph, R ¹ = H 337: R = Me, R ¹ = Me	12 39	[128] [128]	360: R = 361: R = I	8 21
				[100] [125]	338: R = H 339: R = Me	24 71	[128]	362:	8
				[128]	340:	14	[97,98]	363:	20
				[100] [128]	341: R = H 342: R = Me	46 71	[97,98]	364:	9
				[128]	369:	8	[97]	371:	22

[a] Tubulin polymerization was determined by the filtration-colorimetric assay following the procedure of Bollag et al.^[15] and Nicolaou et al.^[102]

Table 4. (Continued).

Ref.	Structure	Tubulin polymerization [%] ^[a]	Ref.	Structure	Tubulin polymerization [%] ^[a]	Ref.	Structure	Tubulin polymerization [%] ^[a]
[97]		12	[97]		7	[97]		16
[97]		23	[97]			[97]		14
[97]		22				[97]		26
Danishefsky								
[30]		–	[30]		–	[30]		–
[30]		–				[30]		–

[a] Tubulin polymerization was determined by the filtration-colorimetric assay following the procedure of Bollag et al.^[15] and Nicolaou et al.^[102]

lactonization strategy as outlined in Scheme 35,^[123] while the Danishefsky group reported the 15-membered desoxyepothilone B (**205'**).^[30] These compounds and their epoxidized counterparts are represented in Table 2.

A stereoselective entry into a series of desoxyepothilones substituted in position 26 (region **B**) were synthesized in our group utilizing the macrolactonization strategy as demonstrated in Scheme 36 for compounds **213–221**.^[124] Most of

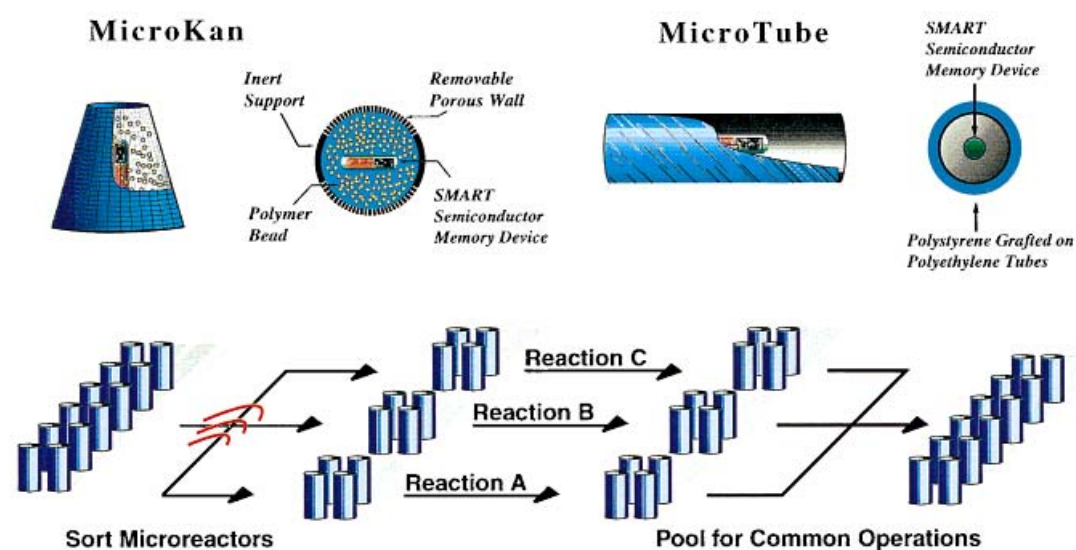
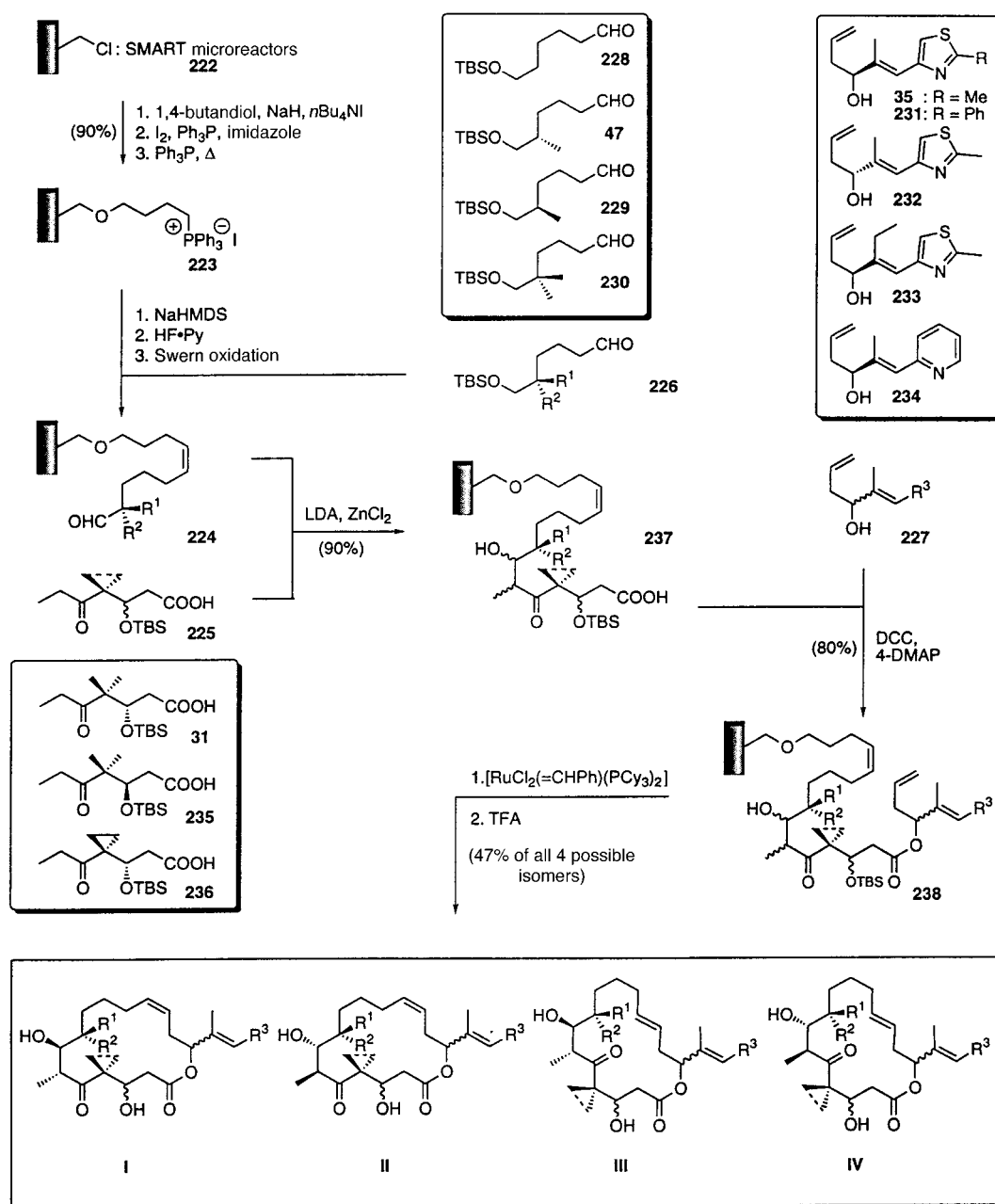


Figure 9. Top: SMART microreactores. Bottom: general strategy for the radiofrequency encoded pool-split combinatorial synthesis of epothilones (Nicolaou et al.).^[102, 103]



Scheme 38. Synthesis of epothilone libraries by split-pool-REC (modifications in regions A–D (seen Tables 2–6; Nicolaou et al.).^[102]

these materials were further elaborated to the corresponding epoxides and are listed in Table 3. The olefin metathesis/Stille coupling strategy developed for epothilone E (see Scheme 15 above) was applied to the synthesis of a number of side-chain epothilone analogues (region C) as generalized in Scheme 37.^[106] The use of a late-stage Stille coupling in this strategy allowed convergent and rapid access to several interesting compounds of this family (Table 4).

4.2. Solid-Phase Synthesis of Combinatorial Libraries of Epothilones

Our group applied the solid-phase radiofrequency-encoded chemistry (REC)^[103] pool-split strategy to combinatorial

synthesis for the construction of an epothilone library using both Microkans and Microtubes (Figure 9).^[102] This approach resulted in the rapid assembly of several epothilone analogues with modifications in regions A–D (Scheme 38). Furthermore, this chemistry demonstrated a new concept for natural product synthesis and library generation. Particularly appealing was the ability to employ the olefin metathesis reaction to form and simultaneously cleave the macrocycle (desoxyepothilones I–IV) from the solid support. The epothilones so generated were chromatographically separated and epoxidized to yield a total of eight final epothilones (two diastereomeric *syn* aldol products times the two olefin diastereoisomers (*Z* and *E*) times two diastereomeric epoxides) from each microreactor, as discrete compounds and in milligram quantities.

Table 5. Structures and tubulin polymerization properties of region D-modified epothilone analogues.

Ref.	Structure	Tubulin polymerization [%] ^[a]	Ref.	Structure	Tubulin polymerization [%] ^[a]	Ref.	Structure	Tubulin polymerization [%] ^[a]	
Nicolaou									
[102]		379	16		388: R = H 389: R = Me	17		400	34
[102]		380	23		390: R = H 391: R = Me	13		401	58
[102]		381	21		392	25		402	20
[102]		382	24		393	18		22	46
[102]		383	25		394: R = H 395: R = Me	10		403	28
[100] [125]		384: R = H 385: R = Me	20		396: R = H 397: R = Me	9		404	3
[100] [125]		386: R = H 387: R = Me	6		398	31		405	1
		18			399	18			
Danishefsky									
		379	[107,110]						

[a] Tubulin polymerization was determined by the filtration-colorimetric assay following the procedure of Bollag et al.^[15] and Nicolaou et al.^[102]

Table 6. Structures and tubulin polymerization properties of multiple regions-modified epothilone analogues.

Ref.	Structure	Tubulin polymerization [%] ^[a]	Ref.	Structure	Tubulin polymerization [%] ^[a]	Ref.	Structure	Tubulin polymerization [%] ^[a]		
Nicolaou										
[102] [102]		406: R ¹ = Me, R ² = H 407: R ¹ = R ² = Me	5 4	[102]		3	[128] [128]		430: R = OMe 431: R = OBn	20 8
[102] [102]		408: R ¹ = Me, R ² = H 409: R ¹ = R ² = Me	1 5	[102] [102]		5 1	[128]		432	4
[102] [102]		410: R ¹ = Me, R ² = H 411: R ¹ = R ² = Me	9 5	[102] [102]		3 4	[128]		13	17
[100] [102]		412: R ¹ = Me, R ² = H 413: R ¹ = R ² = Me	5 4	[102] [102]		7 5	[128]		433	1
[128] [128]		414: R = CH ₂ F 415: R = OMe	11 25	[128]		18	[128]		434	1
[128] [128]		416: R = OH 417: R = F	9 91	[128]		17	[102]		435	13
[128] [128]		418: R = CH ₂ OH 419: R = CHO	16 5	[102]		7	[128]		436	17

[a] Tubulin polymerization was determined by the filtration-colorimetric assay following the procedure of Bollag et al.^[15] and Nicolaou et al.^[102]

4.3. Structure–Activity Relationships of Epothilones

As we have seen, chemical synthesis allowed the preparation of a large number of designed epothilones. Selected libraries of these compounds are given in Tables 2–6, together with tubulin polymerization data. Tables 7 and 8 list cytotoxicity results for a number of highly active compounds identified from screening of these libraries. Figure 10 summarizes the conclusions of these investigations regarding the structural requirements for biological activity within the epothilone structure.

Inspection of Tables 2–6 reveals the effect on biological activity of structural changes by region (A–D, Scheme 33). Thus, as seen from Table 2, modifications in region A

(C8–C11), such as ring size (with the exception of the 18-membered epothilone A (**206**) that exhibited significant tubulin polymerization activity), change of the C8 stereochemistry, and addition or removal of a methyl group at C8 resulted in considerable loss of biological action.

In contrast, changes in region B (C12–C15) are well tolerated (see Table 3). With regards to the C12–C13 functionality, it was of interest to find that:

- Both the olefin and the epoxide were active.
- Both epoxide stereoisomers exhibited high activity.
- Changing the geometry of the double bond had little effect on the activity of the desoxyepothilones or their epoxide counterparts.

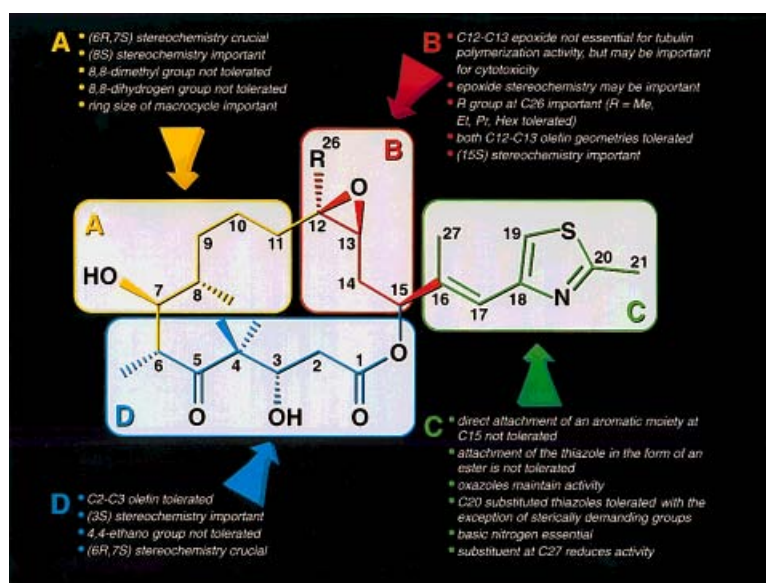


Figure 10. Structure–activity relationship of the epothilones.

Since epothilone B was more active than A, the role of the C12 substituent was studied extensively. The majority of C12 analogues synthesized were very active—some rivaling epothilone B—demonstrating the potential of such modifications in finding a suitable drug candidate. Finally, inversion of the C15 configuration led to a significant decrease of tubulin polymerization activity.

Region C modified compounds are exhibited in Table 4 and reveal less tolerance than region B analogues. Specifically, depletion or direct attachment of the aromatic moiety at C15, as well as replacement of the C20 methyl group with bulkier alkyl or aryl substituents, resulted in a loss of tubulin binding and cytotoxic properties. Hydrogen atom or thiomethyl substitution at C19 was, however, well tolerated. Furthermore, replacement of the C16 methyl with an ethyl group, and of the thiazole by a number of structurally diverse aromatic moieties turned out to be, in general, detrimental to biological activity. Notable exceptions were the corresponding oxazoles,^[100, 125] 2-pyridyl,^[102] and 2-thiazyl-containing^[106] compounds, which exhibited properties comparable to the natural epothilones.

Modification in region D led to interesting findings as presented in Table 5. For example, inversion of the C3 stereochemistry resulted in significantly reduced potency, as did substitution of the C4 *gem* dimethyl group with a 4,4-ethano moiety. Similar loss of activity was observed, when the C5 ketone was reduced, or when the C5, C6 and C7 substituents were removed. Interestingly, however, when an *E* olefin was introduced at C2–C3, the resulting compound retained considerable potency. Table 6 lists a series of compounds in which modifications were attempted simultaneously in more than one region (A–D) of the epothilone structure. Thus far, results from such concurrent changes have not yielded any breakthroughs in term of bioactive compounds.

The cytotoxicity data shown in Tables 7 and 8 (next page) for a number of potent epothilone analogues compare well with those of the natural epothilones and hold considerable promise as lead compounds and drug candidates. As in the

case of epothilones A and B, the exciting aspect of these designed analogues resides in their ability to act against drug-resistant tumor cells, including taxol-, vinblastine- and etoposide-resistant cell lines. The idea of *in vivo* epoxidation of desoxyepothilones is an intriguing hypothesis, which may explain the observation that some of these compounds exhibited strong cytotoxic properties, while others were less active, despite their potent tubulin-polymerizing properties.

Since it was suggested that epothilones and taxol share a common pharmacophore,^[12, 16] Winkler and Axelsen proposed a model for the active sites common to these structurally dissimilar substances in 1996.^[126] They based their molecular mechanics calculations on structure-activity relationship data of taxol, indicating which parts of this material appear to be essential for biological activity. More recently, Ojima reported similar molecular modeling studies attempting to correlate conformations of taxol analogues, epothilones, and discodermolide.^[127]

Using the naturally derived epothilones A–D, the Höfle group in Germany constructed approximately 100 derivatives and studied their biological action.^[134] Figure 10 summarizes a number of conclusions on the structure–activity relationships (SARs) drawn on the basis of the chemical biology studies, carried out so far on the epothilones. New designs can now be directed towards those modifications that look most promising in the quest for suitable candidates for drug development.

5. Summary and Future Perspectives

Coming at the heels of the taxol era, whose development as a billion dollar drug was accompanied by a wealth of new scientific knowledge, the epothilones burst onto the scene as the most promising new candidates for cancer chemotherapy of the 1990s. Particularly attractive is their taxol-like mechanism of action and their superiority over taxol in causing death to taxol-resistant tumor cells. Their novel, but in comparison to taxol, less complex molecular structure

Table 7. Biological properties^[a] of taxol, the natural epothilones, and selected synthetic epothilone analogues. (Nicolaou et al.).^[102,128]

Screening	Induction of tubulin polymerization			Inhibition of carcinoma cell growth ^[b]		
	Quant. assay ^[a] polymer formed [%] ^[f]	Glutamate assay ^[c] EC ₅₀ [μM]	Ovarian ^[d] Parental 1A9 IC ₅₀ [nM]	Breast ^[e] β-tubulin mutations 1A9PTX10 IC ₅₀ [nM]	1A9PTX22 IC ₅₀ [nM]	MCF7
taxol	50	4.7	1.4	32	38	4.2
epothilone A (1)	76	4.6	2.2	20	5.9	5.1
epothilone B (2)	98	3.4	0.13	1.0	0.31	1.0
epothilone C (3)	72	8.3	32	> 100	100	38
epothilone D (4)	94	3.9	6.5	23	9.0	9.3
epothilone E (5)	95	–	> 100	50	20	–
22	46	–	32	> 100	> 100	–
42	76	9.8	60	> 100	100	> 100
211	52	–	40	80	> 100	–
217	88	–	80	> 100	> 100	–
218	47	–	30	> 100	65	–
219	62	–	18	65	> 100	–
220	83	–	0.5	7.5	6	–
221	95	–	5	30	20	–
263	69	–	40	> 100	> 100	–
268	29	–	50	30	90	–
269	51	–	20	7	40	–
270	6	–	80	20	95	–
274	93	–	0.2	0.4	0.2	–
275	69	–	0.4	0.6	0.25	–
276	41	–	10	50	10	–
278	94	–	0.05	1.0	0.05	–
279	87	–	5	30	5	–
289	84	7.5	61	> 100	85	75
290	92	6.2	2.0	18	3.0	5.4
291	84	5.6	1.0	8.5	1.0	1.8
293	63	13	6.0	30	6.5	14
295	31	–	50	50	> 100	–
308	75	6.1	68	> 100	90	74
309	93	3.3	8.0	30	12	> 100
313	54	6.0	32	> 100	> 100	68
315	58	5.3	3.0	25	8.0	6.1
316	93	–	0.12	1.1	–	–
318	64	7.8	3.5	32	9.5	> 100
325	92	–	9	22	28	–
328	51	7.6	32	> 100	70	57
332	63	–	10	28	25	–
339	71	6.1	1.5	11	3.0	6.2
341	46	8.1	4.8	34	9.0	5.7
342	71	–	8	65	17	–
343	41	–	20	> 100	45	–
348	71	–	15	> 100	20	–
351	61	11	82	> 100	> 100	78

[a] See Table 1. [b] Cell growth was evaluated by measurement of the increase in cellular protein.^[129] [c] Assay performed according to literature procedures.^[102, 130] The EC₅₀ value is defined as the drug concentration resulting from a 50% reduction in supernatant protein relative to control values. [d] The parental ovarian line, derived as a clone of line A2780,^[131] was used to generate taxol-resistant cell lines by incubating the cells with increasing concentrations of taxol with verapamil;^[132] the cells were grown in the presence of drug for 96 h. [e] The MCF7 cells were obtained from the National Cancer Institute drug screening program;^[133] cells were grown in the presence of the drug for 48 h. [f] Polymer formed relative to that formed with GTP.

prompted intense research activities with the intention of developing practical synthetic routes for their production, and of synthesizing analogues for biological evaluation. Both objectives were met to a large extent by a number of laboratories, even though much remains to be done. Amongst the challenges remaining are:

- Synthetic routes even more efficient than the ones so far developed, which can be adapted for large scale production.
- Determination of the pharmacological and toxicological profiles of the natural epothilones and selected synthetic

analogues in a variety of animal models for choosing suitable drug candidates.

- Clinical evaluation of such candidate compounds for the treatment of a variety of cancers.

In addition to their prospects as new weapons against cancer, these naturally occurring substances have already stimulated new inventions and discoveries in the areas of chemistry and biology. If epothilone B elicited our admiration by virtue of its novel structure and biological action, our failure thus far to surpass its potency against tumor cells left us

Table 8. Biological properties^[a] of taxol, the natural epothilones, and selected synthetic epothilone analogues (Danishefsky et al.).^[30]

Compound	parental CCRF-CEM IC ₅₀ [nM]	CCRF-CEM/VBL IC ₅₀ [nM]	CCRF-CEM/VM ₁ IC ₅₀ [nM]
taxol	2.0	4140	2.0
epothilone A (1)	3.0	20	3.0
epothilone B (2)	0.2	1.0	2.0
epothilone C (3)	22	12	13
epothilone D (4)	9.0	17	14
42	52	35	111
265	21	77	–
298	39	67	–
299	3.0	9.0	–
300	90	262	94
301	90	254	–
302	55	197	–
303	1.0	7.0	–
304	4.0	6.0	–
305	27	49	–
308	30	49	–
375	98	146	–

[a] The cytotoxicities of the tested compounds were determined by the growth of human lymphoblastic leukemic cells CCRF-CEM, or their sublines resistant to vinblastine and taxol (CCRF-CEM/VBL) or resistant to etoposide (CCRF-CEM/VM-1).

in awe of nature's exquisite molecular engineering abilities. While natural evolution through combinatorial chemistry took nature millions of years to reach this lethal weapon, synthetic chemists should be able to accelerate this process by imagination and logical design and arrive at even more appropriate candidates for selective medical intervention. It is expected that by summarizing the results in the field, this review article will encourage and facilitate further research and development. Our hope is that the chapter on the chemistry and biology of epothilones will soon expand to include medicine as well. Since the submission of this review the following relevant articles appeared in the literature (up to February 28, 1998).^[135–137]

Appendix: List of Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
BINOL	1,1-bi-2-naphthol
Bn	benzyl
BOM	benzyloxymethyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
DAP	1,3-diaminopropane
DAST	(diethylamino)sulfur trifluoride
DCC	1,3-dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	3,4-dihydro-2H-pyran
DIBAL-H	diisobutylaluminum hydride
4-DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide

dppf	1,1'-bis(diphenylphosphanyl)ferrocene
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
Ipc	isopinocampheyl
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
mCPBA	m-chloroperoxybenzoic acid
MMPP	monoperoxyphthalic acid, magnesium salt
MOM	methoxymethyl
Ms	methanesulfonyl
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMO	4-methylmorpholine N-oxide
OTf	trifluoromethanesulfonate
PDC	pyridinium dichromate
PMB	p-methoxybenzyl
PMB-Cl	p-methoxybenzylchloride
PPTS	pyridinium p-toluenesulfonate
Py	pyridine
TBAF	tetra-n-butylammonium fluoride
TBAI	tetra-n-butylammonium iodide
TBS	tert-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-n-propylammonium perruthenate
Tr	triphenylmethyl
TsOH	p-toluenesulfonic acid

We are pleased to acknowledge the important contribution of our collaborators on this project, whose names appear in the original publications. We are grateful to Prof. Höfle for bringing the epothilone story to our attention and for his encouragement, and to Professor S. J. Danishefsky for helpful discussions. This work was supported by The Skaggs Institute for Chemical Biology, the CaPCURE Foundation, Novartis, the National Institutes of Health, USA, and the Deutsche Forschungsgemeinschaft (fellowship to F.R.). We also wish to thank our friends from industry (Merck Sharp & Dohme, Dupont-Merck, Pfizer, Schering-Plough, Amgen, and Glaxo Wellcome) for their support of our programs.

Received: January 8, 1998 [ZA269IE]
German version: *Angew. Chem.* **1998**, *110*, 2120–2153

- [1] a) C. S. Muir, *Cancer Res.* **1990**, *50*, 6441–6448; b) B. N. Ames, L. S. Gold, *Angew. Chem.* **1990**, *102*, 1233–1246; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1197–1208; c) *Intermediate Biomarkers of Precancer and their Application in Chemoprevention* (Eds.: M. Lipkin, B. Levin, Y. S. Kim, G. J. Kelloff), Wiley-Liss, New York, NY, **1992**, p 196 (*J. Cell Biochem. (Suppl. 16G)*); d) J. M. Bishop, *Science* **1987**, *235*, 305–311; e) H. M. Schüller, *Biochem. Pharmacol.* **1991**, *42*, 1511–1523; f) I. R. Hart, A. Saini, *Lancet* **1992**, *339*, 1453–1457; g) D. G. Brodland, J. A. Zitelli, *J. Am. Acad. Dermatol.* **1992**, *27*, 1–8.
- [2] Information retrieved from the Internet Homepages of the American Cancer Society (ACS; <http://www.cancer.org>) and of the National Cancer Institute (NCI; <http://www.nci.nih.gov>).

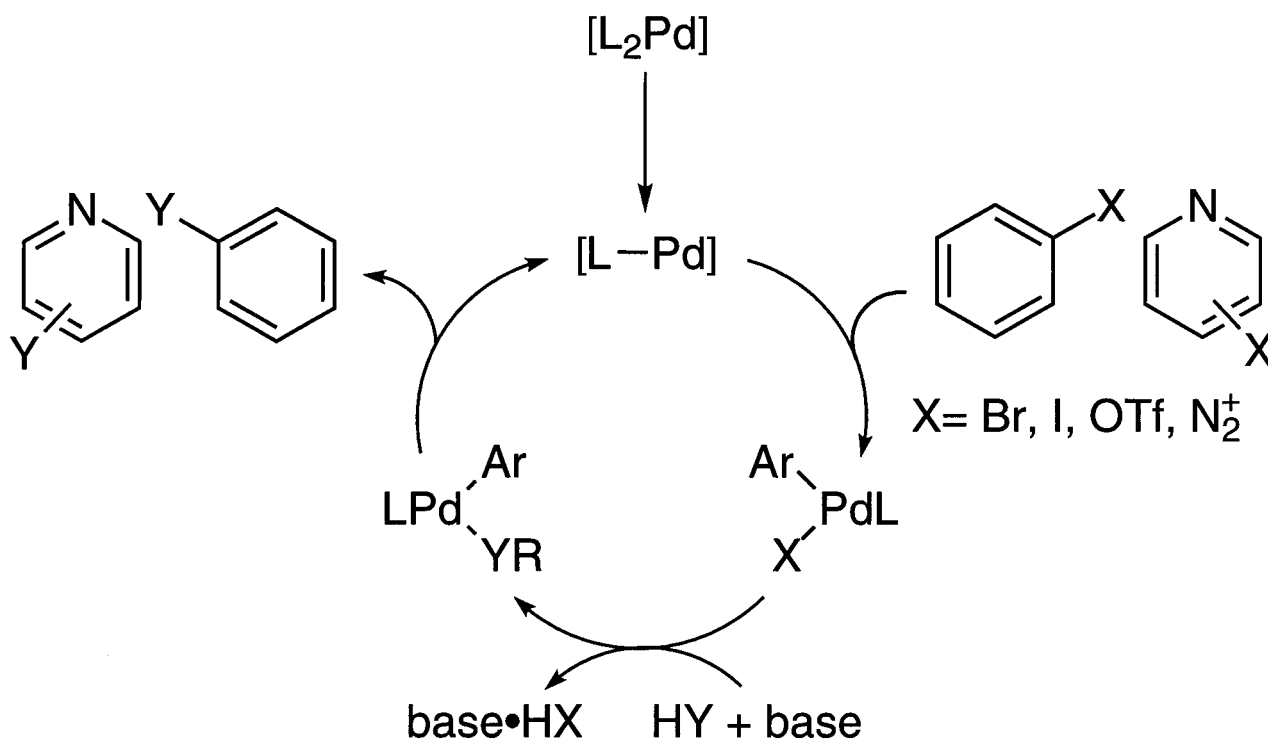
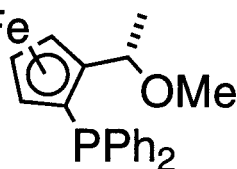
- [3] a) M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, 93, 2325–2327; b) T. Junod, *Life* **1992**, 15, 71–76; c) “Taxane Anticancer Agents: Basic Science and Current Status”: G. I. Georg, T. T. Chen, I. Ojima, D. M. Vyas, ACS Symposium Series **1995**, 583, 35.
- [4] a) E. K. Rowinsky, R. C. Donehower, *New Engl. J. Med.* **1995**, 332, 1004–1014; b) J. E. Cortes, R. Pazdur, *J. Clin. Oncol.* **1995**, 13, 2643–2655.
- [5] a) J. N. Denis, A. E. Greene, D. Guénard, F. Gueritte-Voegelein, L. Mangatal, P. Potier, *J. Am. Chem. Soc.* **1988**, 110, 5917–5919; b) L. Mangatal, M. T. Adeline, D. Guénard, F. Gueritte-Voegelein, P. Potier, *Tetrahedron* **1989**, 45, 4177–4190; c) I. Barasoain, C. De Ines, F. Duz, J. M. Andreia, V. Peyrot, D. Leynadier, P. Garcia, C. Briand, G. De Suusa, R. Rahmani, *Proc. Am. Assoc. Cancer Res.* **1991**, 32, 329; d) I. Ringel, S. B. Horwitz, *J. Natl. Cancer Inst.* **1991**, 83, 288–291; e) J. F. Diaz, J. M. Andreu, *Biochemistry* **1993**, 32, 2747–2755; f) V. Fromes, P. Guonon, M. C. Bissery, A. Fellous, *Proc. Am. Assoc. Cancer Res.* **1992**, 33, 511.
- [6] “Annual Report: Top 100 drugs” anonymous, *MedAdNews* **1997**, 16, 11–91.
- [7] K. C. Nicolaou, W.-M. Dai, R. K. Guy *Angew. Chem.* **1994**, 33, 15–44.
- [8] K. C. Nicolaou, R. K. Guy, J. L. Gunzer, *MedChem News* **1997**, 7, 12–18.
- [9] a) K. D. Rainsford, *Aspirin and the Salicylates*, Thetford Press, Thetford, England, **1984**; b) G. Weissmann, *Sci. Amer.* **1991**, 268(1), 84–90.
- [10] a) *The beta-Lactam Antibiotics: Penicillins and Cephalosporins in Perspective* (Ed.: S. Selwyn), Hodder and Stoughton, London, **1980**; b) *Murder, Magic, and Medicine* (Ed.: J. Mann), Oxford University Press, London, **1994**, pp. 124–140.
- [11] G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-B 4138042, **1993** [*Chem. Abstr.* **1993**, 120, 52841].
- [12] G. Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, 108, 1671–1673; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1567–1569.
- [13] b) K. Gerth, N. Bedorf, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1996**, 49, 560–563.
- [14] G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-B 4211055, **1993** [*Chem. Abstr.* **1993**, 119, 180598].
- [15] a) D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Res.* **1995**, 55, 2325–2333; for a recent review on the biology of epothilones, see b) D. M. Bollag, *Exp. Opin. Invest. Drugs* **1997**, 6, 867–873.
- [16] S. F. Victory, D. G. Vander Velde, R. K. Jalluri, G. L. Grunewald, G. I. Georg, *Bioorg. Med. Chem. Lett.* **1996**, 6, 893–898.
- [17] J. P. Pachlatko, Novartis, Personal communication.
- [18] D. Schinzer, *Eur. Chem. Cron.* **1997**, 7–10.
- [19] S. Borman, *Chem. Eng. News* **1996**, 74(52), 24–26.
- [20] a) Developmental Therapeutics Program of the National Cancer Institute (NCI), USA: M. R. Grever, S. A. Schepartz, B. A. Chabner, *Semin. Oncol.* **1992**, 19, 622–638.
- [21] P. B. Fernandes, *Antimicrob. Newsl.* **1987**, 4, 25–34.
- [22] D. C. Jordan, *Antibiotics (USSR)* **1967**, 1, 446–450.
- [23] a) A. Abou-Zeid, A. I. El-Dewany, *Indian Chem. Manuf.* **1978**, 16, 17–25; b) E. E. Schmid, *Antibiot. Chemother. (Basel)* **1971**, 17, 52–66.
- [24] A. Baumüller, U. Hoyme, P. O. Madsen, *Antimicrob. Agents Chemo-ther.* **1977**, 12, 240–242.
- [25] a) S. B. Kaye, P. Workman, M. A. Graham, J. Cassidy, D. Jodrell, *Cancer Surv.* **1993**, 17, 371–396; b) E. Hamel, *Pharmacol. Ther.* **1992**, 51, 31–51; c) D. R. Budman, *Semin. Oncol.* **1992**, 19, 639–645.
- [26] M. Takahashi, S. Iwasaki, H. Kobayashi, S. Okuda, T. Murai, Y. Sato, *Biochim. Biophys. Acta* **1987**, 926, 215–223.
- [27] *Microtubules* (Eds.: J. S. Hyams, C. W. Lloyd), Wiley-Liss, New York, **1994**.
- [28] P. B. Schiff, J. Fant, S. B. Horwitz, *Nature* **1979**, 277, 665–667.
- [29] R. J. Kowalski, P. Giannakakou, E. Hamel, *J. Biol. Chem.* **1997**, 272, 2534–2541.
- [30] D.-S. Su, A. Ballog, D. Meng, P. Bertinato, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, 109, 2178–2181; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2093–2096.
- [31] For an excellent review in this field, see J. Avila, J. D. Nido, in *Cytoskeleton Vol. 1* (Eds.: J. E. Hesketh, I. F. Pryme), JAI, Greenwich, CT, **1995**, pp. 47–85.
- [32] K. F. Sullivan, *Annu. Rev. Cell Biol.* **1988**, 687–716.
- [33] R. G. Burns, *Cell Motil. Cytoskeleton* **1991**, 20, 181–189.
- [34] *Microtubules* (Ed.: P. Dustin), Springer, Berlin, **1984**, pp. 482 ff.
- [35] M. A. Jordan, R. J. Toso, D. Thrower, L. Wilson, *Proc. Natl. Acad. Sci. U.S.A.* **1993**, 90, 9552–9556.
- [36] For a recent review on microtubule structures and dynamics, see R. H. Wade, A. A. Hyman, *Curr. Opin. Cell Biol.* **1997**, 9, 12–17.
- [37] L. Wilson, M. A. Jordan, *Chem. Biol.* **1995**, 2, 569–573.
- [38] B. R. Brinkley, *Cold Spring Harbor Symp. Quant. Biol.* **1982**, 46, 1029–1040.
- [39] a) E. H. Ball, J. J. Singer, *Proc. Natl. Acad. Sci. USA* **1982**, 79, 123–126; b) M. S. Cooper, A. H. Cornell-Bell, A. Chernjowsky, J. W. Dani, S. J. Smith, *Cell* **1990**, 61, 135–145.
- [40] a) M. M. Rasenick, N. Wang, K. Yan, *Adv. Second Messenger Phosphoprotein Res.* **1990**, 24, 381–386; b) J. M. Scholey, *Nature* **1990**, 343, 118–120.
- [41] L. A. Amos in *Microtubules* (Eds.: K. Roberts, J. Hyams), Academic Press, New York, **1979**, 129, pp. 135–148.
- [42] a) T. Mitchison, M. W. Kirschner, *Nature* **1984**, 312, 237–242; b) M. W. Kirschner, T. Mitchison, *Cell* **1986**, 45, 329–342; c) M. W. Kirschner, T. Mitchison, *Nature* **1986**, 324, 621–622; d) J. Avila, *FASEB J.* **1990**, 4, 3284–3290.
- [43] a) E. Schulze, M. Kirschner, *J. Cell Biol.* **1986**, 102, 1020–1031; b) L. Cassimeris, N. K. Pryer, E. D. Salmon, *J. Cell Biol.* **1988**, 107, 2223–2231.
- [44] a) L. T. Haimo, *Methods Cell Biol.* **1982**, 24, 189–206; b) P. R. Burton, R. H. Himes, *J. Cell Biol.* **1978**, 77, 120–133; c) E.-M. Mandelkow, E. Mandelkow, *J. Mol. Biol.* **1979**, 129, 135–148.
- [45] R. L. Margolis, L. Wilson, *Cell* **1978**, 13, 1–8.
- [46] a) L. U. Cassimeris, R. A. Walker, N. K. Pryer, E. D. Salmon, *Bioessays* **1987**, 7, 149–154; b) H. P. Erickson, E. T. O'Brien, *Annu. Rev. Biophys. Biomol. Struct.* **1992**, 21, 145–146; c) V. I. Gelfand, A. D. Bershadsky, *Annu. Rev. Cell Biol.* **1991**, 7, 93–116; d) E. D. Salmon in *Mitosis* (Eds.: J. S. Hyams, B. R. Brinkley), Academic Press, New York, **1989**, pp. 119–181.
- [47] L. Wilson, M. A. Jordan, *Chem. Biol.* **1995**, 2, 569–573.
- [48] M. Kirschner, T. J. Mitchison, *Cell* **1986**, 45, 329–342.
- [49] a) J. R. McIntosh, *Trends Biochem. Sci.* **1984**, 9, 195–198; b) C. Mazia in *The Cell, Vol. III* (Eds.: J. Brachet, A. E. Mirsky), Academic Press, London, **1961**, pp. 77–412.
- [50] a) B. R. Brinkley, *Annu. Rev. Cell Biol.* **1985**, 1, 145–172; b) M. DeBrabander, *Cell Biol. Int. Rep.* **1982**, 6, 901–915.
- [51] J. R. McIntosh, C. M. Pfarr, *J. Cell Biol.* **1991**, 115, 577–585.
- [52] G. Gorbisky, *Bioassays* **1992**, 14, 73–80.
- [53] a) R. Li, A. W. Murray, *Cell*, **1991**, 66, 519–531; b) M. A. Hoyt, L. Totis, B. T. Roberts, *Cell* **1991**, 66, 507–517.
- [54] B. A. Boggs, M. L. Gonzales-Garay, W. E. O'Brien, S. B. Barlow, F. Cabral, *Cell. Pharmacol.* **1993**, 1, S95–S101.
- [55] S. Timashiff, J. Andreu, M. Gorbunoff, F. Medranot, V. Prakash, *Cell. Pharmacol.* **1993**, 1, S27–S33.
- [56] a) R. J. Toso, M. A. Jordan, K. W. Farrell, B. Matsumoto, L. Wilson, *Biochemistry* **1993**, 32, 1285–1293; b) S. B. Hastie, *Pharmacol. Ther.* **1991**, 51, 377–401.
- [57] M. A. Jordan, L. Wilson, in *Taxane Anticancer Agents*, (Eds.: G. I. Georg, T. T. Chen, I. Ojima, D. M. Vyas), American Chemical Society, Washington, DC, **1995**, pp. 138–153.
- [58] J. B. Olmsted, C. F. Asnes, L. M. Parysek, H. D. Lyon, G. M. Kidder, *Ann. NY Acad. Sci.* **1986**, 466, 292–305.
- [59] a) M. Goedert, R. Jakes, M. G. Spillantini, R. A. Crowther, in *Microtubules* (Eds.: J. Hyams, C. Lloyd), Wiley-Liss, New York, **1994**, pp. 183–200; b) G. Wiche, C. Oberkanins, A. Himmler, *Int. Rev. Cytol.* **1991**, 124, 217–273.
- [60] D. Panda, B. L. Goode, S. C. Feinstein, L. Wilson, *Biochemistry* **1995**, 34, 11117–11127.
- [61] F. I. Raynaud, I. R. Judson, *Drugs Future* **1996**, 21, 65–70.
- [62] C. L. Rieder, R. E. Palazzo, *J. Cell Sci.* **1992**, 102, 387–392.
- [63] R. B. Natale, *Semin. Oncol.* **1997**, 24, 29–37.

- [64] D. L. Sackett, *Pharmacol. Ther.* **1993**, *59*, 163–228.
- [65] a) E. Hamel, *Med. Res. Rev.* **1996**, *16*, 207–231; b) W. B. Derry, L. Wilson, M. A. Jordan, *Biochemistry* **1995**, *34*, 2203–2211; for a review see c) L. Wilson, M. A. Jordan, in *Microtubules* (Eds.: L. Hyams, C. Lloyd), Wiley-Liss, New York, **1994**, pp. 59–84.
- [66] E. Hamel, *Cell. Pharmacol.* **1993**, *1*, S47–S52.
- [67] E. Hamel, *Pharmacol. Ther.* **1992**, *55*, 31–51.
- [68] a) K. Yamada, H. Kigoshi, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1479–1489; b) G. R. Pettit, *Prog. Chem. Org. Nat. Prod.* **1997**, *70*, 1–79; c) M. Namikoshi, K. L. Rinehart, *J. Ind. Microbiol. Biotechnol.* **1996**, *17*, 373–384; d) G. R. Pettit, *Pure Appl. Chem.* **1994**, *66*, 2271–2281.
- [69] a) C. D. Smith, X. Zhang, S. L. Mooberry, G. M. L. Patterson, R. E. Moore, *Cancer Res.* **1994**, *54*, 3779–3784; b) R. E. Moore, T. H. Corbett, G. M. L. Patterson, F. A. Valeriote, *Curr. Pharm. Des.* **1996**, *2*, 317–330; c) R. E. Moore, *J. Ind. Microbiol.* **1996**, *16*, 134–143; d) T. Corbett, F. Valeriote, P. LoRusso, L. Polin, C. Panchapor, S. Pugh, K. White, J. Knight, L. Juiwanna, *Int. J. Pharmacogn.* **1995**, *33* (Suppl.), 102–122.
- [70] M. Fighetti, S. Rubino, P. Cappuccinelli, G. Monaco, *Microbiologica (Bologna)* **1988**, *11*, 269–277.
- [71] a) W. H. Gerwick, P. J. Proteau, D. G. Nagle, E. Hamel, A. Blokin, D. L. Slate, *J. Org. Chem.* **1994**, *59*, 1243–1245; b) B. S. Davidson, *Curr. Opin. Biotechnol.* **1995**, *6*, 284–291; c) M. C. Pirrung, S. K. Nauhaus, *Chemtracts: Org. Chem.* **1994**, *7*, 128–129.
- [72] a) M. A. Jordan, R. J. Torso, D. Thrower, L. Wilson, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 9552–9556; b) J. Liebmman, J. A. Cook, C. Lipschultz, D. Teague, J. Fisher, J. B. Mitchell, *Cancer Chemother. Pharmacol.* **1994**, *33*, 331–339.
- [73] P. B. Schiff, S. B. Horwitz, *Biochemistry* **1981**, *20*, 3247–3252.
- [74] a) P. B. Schiff, J. Fant, S. B. Horwitz, *Nature* **1979**, *277*, 665–667; b) E. Hamel, A. A. del Campo, M. C. Lowe, C. M. Lin, *J. Biol. Chem.* **1981**, *256*, 11 887–11 894.
- [75] A. Wolff, A. Technau, G. Brandner, *Int. J. Oncol.* **1997**, *11*, 123–126.
- [76] a) U. Moll, A. G. Ostermeyer, R. Haladay, B. Winkfield, M. Frazier, G. Zambetti, *Mol. Cell. Biol.* **1995**, *16*, 1126–1137; b) S. C. Goldman, C.-Y. Chen, T. J. Lansing, T. M. Gilmer, M. B. Kastan, *Am. J. Pathol.* **1996**, *148*, 1381–1385.
- [77] J. Parness, S. B. Horwitz, *Biochemistry* **1981**, *91*, 479–487.
- [78] E. K. Rowinsky, E. A. Eisenhauer, V. Chaudhry, S. G. Arbuck, R. C. Donehower, *Semin. Oncol.* **1993**, *20*, 1–15.
- [79] J. B. Hibbs, R. R. Taintor, Z. Vavrin, *Science* **1987**, *235*, 473–476.
- [80] A. Ding, B. Chen, N. Fuortes, E. Blum, *J. Exp. Med.* **1996**, *183*, 1899–1904.
- [81] C. Bogdan, A. Ding, *J. Leukocyte Biol.* **1992**, *52*, 119–121.
- [82] E. F. Ding, F. Porteu, E. Sanchez, C. F. Nathan, *Science* **1990**, *248*, 370–372.
- [83] C. L. Manthey, P.-Y. Perera, C. A. Salkowski, S. N. Vogel, *J. Immunol.* **1994**, *152*, 825–831.
- [84] P. F. Muhlrad, F. Sasse, *Cancer Res.* **1997**, *57*, 3344–3346.
- [85] a) J. H. Schiller, B. Storer, K. Tutsch, R. Arzooanian, D. Alberti, C. Feierabend, D. Spriggs, *J. Clin. Oncol.* **1994**, *12*, 241–248; b) D. H. Johnson, D. M. Paul, K. R. Hande, Y. Shyr, C. Blanke, B. Murphy, M. Lewis, R. F. de Vore, *J. Clin. Oncol.* **1996**, *14*, 2054–2060.
- [86] Total synthesis: a) J. B. Nerenberg, D. T. Hung, P. K. Somers, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 12621–12622; b) A. B. Smith III, Y. Qiu, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **1995**, *117*, 12011–12012; c) S. S. Harried, G. Yang, M. A. Strawn, D. C. Myles, *J. Org. Chem.* **1997**, *62*, 6098–6099; biological activity: d) E. ter Haar, R. J. Kowalski, E. Hamel, M. C. Lin, R. E. Longley, S. P. Gunasekera, H. S. Rosenkranz, B. W. Day, *Biochem.* **1996**, *35*, 243–250; e) D. T. Hung, J. Chen, S. L. Schreiber, *Chem. Biol.* **1996**, *3*, 287–293; f) R. J. Kowalski, P. Giannakakou, S. P. Gunasekera, R. E. Longley, B. W. Day, E. Hamel, *Mol. Pharmacol.* **1997**, *52*, 613–622; isolation: g) S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, *J. Org. Chem.* **1990**, *55*, 4912–4915.
- [87] Total synthesis: a) K. C. Nicolaou, F. van Delft, T. Ohshima, D. Vourloumis, J. Xu, S. Hosokawa, J. Pfefferkorn, S. Kim, T. Li, *Angew. Chem.* **1997**, *109*, 2631–2634; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2520–2524; isolation and biological activity: b) W. Fenical, P. R. Jensen, T. Lindel, US-A 5473057, **1995** [*Chem. Abstr.* **1996**, *124*, 194297z]; c) T. Lindel, P. R. Jensen, W. Fenical, B. H. Long, A. M. Casazza, J. Carboni, C. R. Fairchild, *J. Am. Chem. Soc.* **1997**, *119*, 8744–8745.
- [88] Total synthesis: a) K. C. Nicolaou, J. Y. Xu, S. Kim, T. Ohshima, S. Hosokawa, J. Pfefferkorn, *J. Am. Chem. Soc.* **1997**, *119*, 11353–11354; isolation: b) M. D'Ambrosio, A. Guerriero, F. Pietra, *Helv. Chim. Acta* **1987**, *70*, 2019–2027; c) M. D'Ambrosio, A. Guerriero, F. Pietra, *Helv. Chim. Acta* **1988**, *71*, 964–976; biological activity: d) M. Ciomei, C. Albanese, W. Pastori, M. Grandi, F. Pietra, M. D'Ambrosio, A. Guerriero, C. Battistini, *Proc. Am. Assoc. Canc. Res.* **1997**, *38*, 5.
- [89] L. Wessjohann, *Angew. Chem.* **1997**, *109*, 739–742; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 715–718.
- [90] M. Kalesse, *Eur. Chem. Cron.* **1997**, 7–11.
- [91] M. R. V. Finlay, *Chem. Ind.* **1997**, *24*, 991–996.
- [92] For the development of the olefin metathesis as a ring forming reaction, see a) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446–452; b) W. J. Zuercher, M. Hashimoto, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640; c) P. R. Schwab, H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110; d) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2055; e) J. Tsuji, S. Hashiguchi, *Tetrahedron Lett.* **1980**, *21*, 2955–2959; for some earlier pioneering studies on this reaction, see f) T. J. Katz, S. J. Lee, N. Acton, *Tetrahedron Lett.* **1976**, 4247–4250; g) T. J. Katz, N. Acton, *Tetrahedron Lett.* **1976**, 4241–4254; h) T. J. Katz, J. McGinnis, C. Altus, *J. Am. Chem. Soc.* **1976**, *98*, 606–608; i) T. J. Katz, *Adv. Organomet. Chem.* **1977**, *16*, 283–317; for a number of applications of the olefin metathesis reaction in medium and large ring synthesis, see j) A. Fürstner, K. Langemann, *Synthesis* **1997**, 792–803; (k) B. C. Borer, S. Deerenberg, H. Bieräugel, U. K. Pandit, *Tetrahedron Lett.* **1994**, *35*, 3191–3194; (l) T. D. Clark, M. R. Ghadiri, *J. Am. Chem. Soc.* **1995**, *117*, 12364–12365; (m) A. F. Houri, Z. Xu, D. A. Cogan, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 2943–2944; (n) A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942–3943; (o) S. F. Martin, H.-J. Chen, A. K. Courtney, Y. Liao, M. Pätzelt, M. N. Ramser, A. S. Wagman, *Tetrahedron* **1996**, *52*, 7251–7264; (p) Z. Xu, C. W. Johannes, S. S. Salman, A. H. Hoveyda, *J. Am. Chem. Soc.* **1996**, *118*, 10926–10927.
- [93] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.
- [94] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, *107*, 2179–2181; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039–2041.
- [95] A. F. Houri, Z. Xu, D. A. Cogan, A. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 2943–2944.
- [96] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.* **1996**, *108*, 2554–2556; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2399–2401.
- [97] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Trujillo, *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973.
- [98] Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170–172; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166–168.
- [99] K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991.
- [100] K. C. Nicolaou, H. Vallberg, N. P. King, F. Roschangar, Y. He, D. Vourloumis, C. G. Nicolaou, *Chem. Eur. J.* **1997**, *3*, 1957–1970.
- [101] K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *36*, 757–759.
- [102] K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, N. P. King, M. R. V. Finlay, P. Giannakakou, P. Verdier-Pinard, E. Hamel, *Angew. Chem.* **1997**, *109*, 2181–2187; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097–2103.
- [103] a) K. C. Nicolaou, X.-Y. Xiao, Z. Parandoosh, A. Senyei, M. P. Nova, *Angew. Chem.* **1995**, *107*, 2476–2479; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2289–2291; b) E. J. Moran, S. Sarshar, J. F. Cargill, M. M. Shahbaz, A. Lio, A. M. M. Jalli, R. W. Armstrong, *J. Am. Chem. Soc.* **1995**, *117*, 10787–10788.

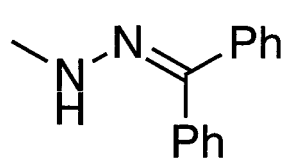
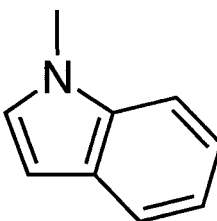
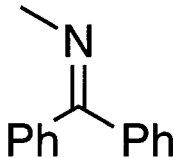
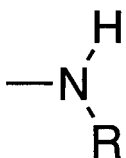
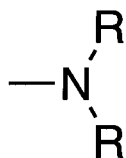
- [104] K. C. Nicolaou, F. Sarabia, S. Ninkovic, Z. Yang, *Angew. Chem.* **1997**, *109*, 539–540; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 525–527.
- [105] G. Höfle, GBF Braunschweig, Personal communication.
- [106] K. C. Nicolaou, Y. He, F. Roschangar, N. P. King, D. Vourloumis, T. Li, *Angew. Chem.* **1998**, *110*, 89–92; *Angew. Chem. Int. Ed.* **1998**, *37*, 84–87.
- [107] A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2976–2978; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801–2803.
- [108] D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, *109*, 775–777; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 757–759.
- [109] D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092.
- [110] D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.
- [111] S. J. Danishefsky, *Aldrichimica Acta* **1986**, *19*, 59–69; b) S. J. Danishefsky, *Chemtracts: Org. Chem.* **1989**, *2*, 273–297.
- [112] D. Meng, E. J. Sorensen, P. Bertinato, S. J. Danishefsky, *J. Org. Chem.* **1996**, *61*, 7998–7999.
- [113] P. Bertinato, E. J. Sorensen, D. Meng, S. J. Danishefsky, *J. Org. Chem.* **1996**, *61*, 8000–8001.
- [114] D. Schinzer, A. Limberg, O. M. Böhm, *Chem. Eur. J.* **1996**, *2*, 1477–1482.
- [115] D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, *Angew. Chem.* **1997**, *109*, 543–544; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523–524.
- [116] J. Mulzer, A. Mantoulidis, *Tetrahedron Lett.* **1996**, *37*, 9179–9182.
- [117] J. Mulzer, A. Mantoulidis, E. Öhler, *Tetrahedron Lett.* **1997**, *38*, 7725–7728.
- [118] E. Claus, A. Pahl, P. G. Jones, H. M. Meyer, M. Kalesse, *Tetrahedron Lett.* **1997**, *38*, 1359–1362.
- [119] T. Gabriel, L. Wessjohann, *Tetrahedron Lett.* **1997**, *38*, 1363–1366.
- [120] R. E. Taylor, J. D. Haley, *Tetrahedron Lett.* **1997**, *38*, 2061–2064.
- [121] J. De Brabander, S. Rosset, G. Bernardinelli, *Synlett* **1997**, 824–826.
- [122] A. Balog, P. Bertinato, D.-S. Su, D. Meng, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Tetrahedron Lett.* **1997**, *38*, 4529–4532.
- [123] K. C. Nicolaou, F. Sarabia, S. Ninkovic, M. R. V. Finlay, C. N. C. Boddy, *Angew. Chem.* **1998**, *110*, 85–89; *Angew. Chem. Int. Ed.* **1998**, *37*, 81–84.
- [124] K. C. Nicolaou, S. Ninkovic, M. R. V. Finlay, F. Sarabia, T. Li, *Chem. Commun.* **1997**, 2343–2344.
- [125] K. C. Nicolaou, F. Sarabia, M. R. V. Finlay, S. Ninkovic, N. P. King, D. Vourloumis, Y. He, *Chem. Eur. J.* **1997**, *3*, 1971–1986.
- [126] J. D. Winkler, P. H. Axelsen, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2963–2966.
- [127] S. Chakravarty, I. Ojima, *Abstr. pap. 214th ACS National Meeting*, Las Vegas, NV (USA), **1997**, MEDI-075.
- [128] K. C. Nicolaou, M. R. V. Finlay, S. Ninkovic, N. P. King, Y. He, T. Li, F. Sarabia, D. Vourloumis, *Chem. Biol.*, in press; K. C. Nicolaou, N. P. King, M. R. V. Finlay, Y. He, F. Roschangar, D. Vourloumis, H. Vallberg, F. Sarabia, S. Ninkovic, D. Hepworth, *Bioorg. Med. Chem.*, in press.
- [129] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney, M. R. Boyd, *J. Natl. Cancer Inst.* **1990**, *82*, 1107–1112.
- [130] C. M. Lin, Y. Q. Jiang, A. G. Chaudhary, J. M. Rimoldi, D. G. I. Kingston, E. Hamel, *Cancer Chemother. Pharmacol.* **1996**, *38*, 136–140.
- [131] B. C. Behrens, T. C. Hamilton, H. Matsuda, K. R. Grotzinger, J. Wang-Peng, K. G. Louie, T. Knutsen, W. M. McKoy, R. C. Young, R. F. Ozols, *Cancer Res.* **1987**, *47*, 414–418.
- [132] P. Giannakakou, D. L. Sackett, Y.-K. Kang, Z. Zhan, J. T. M. Buters, T. Fojo, M. S. Poruchynsky, *J. Biol. Chem.* **1995**, *272*, 17118–17125.
- [133] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Campbell, J. Mayo, M. Boyd, *J. Natl. Cancer Inst.* **1991**, *83*, 757–766.
- [134] Wissenschaftlicher Jahresbericht, Gesellschaft für Biotechnologische Forschung, Braunschweig, 1996, p 112.
- [135] Application of radical-induced opening of trisubstituted epoxides in the synthesis of C1–C12 segment of epothilones; T. K. Chakraborty, S. Dutta, *Tetrahedron Lett.* **1998**, *39*, 101–104.
- [136] Chiral synthesis of the C3–C13 segment of epothilone A; Z. Y. Liu, C. Z. Yu, J. D. Yang, *Synlett*, **1998**, *12*, 1383–1384.
- [137] Enantioselective synthesis of a C7–C15 carboxaldehyde segment of epothilone A; P. Bijoy, M. A. Avery, *Tetrahedron Lett.* **1998**, *39*, 209–212.
- [138] K. C. Nicolaou, *Angew. Chem.* **1996**, *108*, 644–664; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 588–607.

Recent advances in palladium- and nickel-catalyzed chemistry provide new ways to construct C–N and C–O bonds.

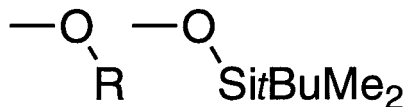
L = P(*o*-tolyl)₃, P(*t*Bu)₃, DPPF, BINAP, PHANEPHOS, CpFe



Y =



R = alkyl, aryl



Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism

John F. Hartwig*

The transition metal catalyzed synthesis of arylamines by the reaction of aryl halides or triflates (triflate = trifluoromethanesulfonyl) with primary or secondary amines has rapidly become a valuable synthetic tool for a variety of applications. This process can form monoalkyl- or dialkylanilines as well as mixed diaryl- or triarylamines. In addition, the chemistry can be extended to the formation of aryl ethers from aryl halides, although this process is currently less general than the synthesis of arylamines. The mechanism of this reaction involves several novel

organometallic reactions. For example, the C–N or C–O bond is formed by reductive elimination of amines or ethers, and the metal–amido complexes that undergo reductive elimination can be formed in the catalytic cycle by N–H activation. Side products are formed by β -hydrogen elimination from amides, examples of which have recently been observed directly. This review covers the development of synthetic methods to form arylamines by this palladium-catalyzed chemistry. In addition to information on syntheses, a description of the pertinent

mechanistic data on the overall catalytic cycle, on each elementary reaction in the catalytic cycle, and on competing side reactions is presented. This review covers manuscripts that appeared in press before July 1, 1997 as well as those submitted by the author and co-workers before this date. A brief discussion of papers that appeared between July 1, 1997 and March 1, 1998 is included as an appendix.

Keywords: aminations • arylations • ethers • nickel • palladium

1. Introduction

1.1. Synthetic Considerations

Arylamines and aryl ethers are commonplace. They are part of molecules with medically important properties, of molecules with structurally interesting properties, and of materials with important electronic and mechanical properties. An arene–nitrogen or arene–oxygen linkage is included in nitrogen or oxygen heterocycles such as indoles^[1, 2] and benzofurans,^[3–6] isodityrosine-based natural products such as vancomycin,^[7–21] conjugated polymers such as polyanilines,^[22–28] readily oxidized triarylamines used in electronic applications such as *N,N'*-diphenyl-*N,N'*-bis(3-methylphenyl)-1,1'-biphenyl-4,4'-diamine (TPD)^[29–32] and thermally stable poly(aryl ether)s such as poly(phenylene oxide) (PPO).^[33–36]

Despite the simplicity of the arylamine and aryl ether moieties, synthesis of these compounds is often difficult.

Procedures involving nitration, reduction, or substitution are incompatible with many functional groups and often involve protection and deprotection steps. Reductive amination, which involves formation of an imine from an arylamine and subsequent reduction of the imine, requires two steps, a preformed C–N bond in an aniline, an excess of the amine, and sluggish reductions.^[37–40] On the other hand, copper-mediated (Ullmann) substitutions occur at high temperatures,^[41–44] often give products from diarylation, and are typically substrate specific. Addition of amines or alcohols to benzyne intermediates gives regioisomers,^[45] and direct nucleophilic substitution of aryl halides typically requires a large excess of reagent, a highly polar solvent, and either high reaction temperatures or highly activated aryl halides.^[46, 47] Alternatively, transition metal–arene complexes have been used to accelerate substitution of the aryl halide, but in this case stoichiometric amounts of the transition metal complex are required.^[48, 49] Therefore, a new, mild, general catalytic method for replacement of aryl halogen atoms or triflate groups (triflate = trifluoromethanesulfonyl) by amine or alcohol moieties would be an invaluable route to aryl ethers and amines.

Palladium-catalyzed coupling chemistry has proven to be a powerful method for formation of a new C–C bond at an aryl halide or triflate by replacement of the aryl halogen or

[*] Prof. J. F. Hartwig
Department of Chemistry
Yale University
PO Box 208107, New Haven, CT 06520-8107 (USA)
Fax: (+1) 203-432-6144
E-mail: john.hartwig@yale.edu

pseudohalogen with a carbon nucleophile.^[50–57] A variety of main group and transition metal reagents are used as the source of the carbon nucleophile. Tin and boron compounds are most commonly used, but aluminum, zinc, magnesium, and silicon reagents are also effective in this cross-coupling chemistry. Nickel and palladium complexes are now the most common catalysts. There are a number of reviews on cross-coupling chemistry, several of which are given in the list of references.

1.2. C–X Bond-Forming Coupling Chemistry Related to the Arylation of Amines and Alcohols

There is a substantial body of literature on the palladium- and nickel-catalyzed formation of aryl sulfides, selenides, and phosphanes from aromatic and heteroaromatic halides. A recent review covers the types of transformations that can be conducted and the types of catalysts that are used.^[58] In general, either a stannyl sulfide, boryl sulfide, or alkali metal thiolate will react under mild conditions with a variety of aromatic and heteroaromatic halides to form mixed sulfides. Reaction of secondary phosphanes or silylphosphanes and aryl or heteroaryl halides and triflates also occurs with palladium and nickel catalysts, and now provides a route to enantiopure 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP) from resolved 1,1'-binaphthol.^[59] The soft thiolate and phosphane makes formation of the palladium thiolate or phosphane favorable; ironically their high nucleophilicity also makes reductive elimination of phosphane and sulfide facile, in accordance with results concerning electronic effects on reductive elimination (Section 8.3.1).^[60] However, C–S bond cleavage can create problems in the synthesis of sulfides. A mixture of sulfides can result from reaction of an aryl halide with an arenethiol containing a different aromatic group.^[61–63]

1.3. Novel Organometallic Chemistry

The reductive elimination to form C–C and C–H bonds^[64] is a crucial step in cross-coupling processes as well as many other transition metal catalyzed reactions. Reductive elimination reactions are the subject of an early chapter in any organometallic textbook. Many examples of these reactions

have been studied, and a great deal is known about the mechanisms of these processes. Similarly, the cleavage of C–H bonds by oxidative addition, including the C–H bond in methane, is now known.^[65] Again, questions remain about how these reactions occur, but a variety of mechanistic studies have revealed key features of these reactions. Even some remarkably mild C–C cleavage reactions have now been observed with soluble transition metal complexes.^[66, 67]

In contrast, few examples of reductive elimination reactions that form the C–N bond in amines and the C–O bond in ethers are known. Only in the past several years have complexes been isolated that undergo these reactions.^[68–73] These reductive eliminations are the crucial C–N and C–O bond-forming step of the aryl halide and triflate amination and etheration chemistry discussed here. Information on how these reactions occur and what types of complexes favor this reaction have been crucial to the development of new amination and etheration catalysts.^[69]

The cleavage of alkylamine N–H bonds by late transition metals is also rare.^[74, 75] Reactions that cause cleavage of N–H bonds—by either oxidative addition or exchange of σ -bonded ligands—produce a transition metal–amido complex. In the case of late transition metals, the resulting amido complexes are highly reactive.^[76, 77] It appears that the amination of aryl halides can involve an unusual N–H activation process by a palladium alkoxide to form a highly reactive palladium amide.^[70] As a result, the discovery of N–H activation processes is crucial to catalysis with amines as substrates, including the amination of aryl halides.

In general, catalytic organometallic chemistry that forms carbon–heteroatom bonds is less developed than that forming C–C bonds and is less well understood. One organometallic oxidation process, the oxidation of ethylene to acetaldehyde (Wacker process),^[78] is conducted on a large industrial scale.^[78, 79] However, the detailed mechanism of the Wacker process and most other oxidation chemistry is not well understood. The oxidation of hydrocarbons remains an area of active research today, despite many years of studies.^[80, 81] Other processes that form carbon–heteroatom bonds by homogeneous catalysis include oxidative carbonylations of amines and alcohols.^[79] These carbonylations avoid the formation of phosgene as an intermediate in the synthesis of urethanes and carbonates. Nonoxidative carbonylation includes the reaction between an aryl halide, CO, and an alcohol



John Hartwig, born in 1964, received his A.B. from Princeton University, and his Ph.D. with Professors Bob Bergman and Dick Andersen at the University of California at Berkeley. He was an American Cancer Society postdoctoral fellow in Professor Steve Lippard's laboratory. In 1992 he accepted an appointment at Yale University, where he is now Associate Professor of Chemistry, and has worked on fundamental and catalytic chemistry of amido, alkoxo, boryl, and borane complexes of metals.

or amine to form esters or amides.^[79] These reactions presumably involve attack of alcohol (or amine) at a metal–phenacyl complex. Additional catalytic processes are the amination and hydration of olefins to form the C–X bonds in amines or alcohols (X=N and O, respectively). An efficient, intermolecular hydration or hydroamination of aryl halides is a highly sought process that is currently unknown, despite some interesting intramolecular^[82, 83] and several slow intermolecular examples.^[84] Other nonoxidative organometallic reactions that form C–N or C–O bonds are rare.

Thus, the selectivities, deactivation mechanisms, and potential transformations of alkoxo and amido intermediates in such reactions are not well understood. It is rare for transition metal–amido and alkoxo complexes to even be clearly identified as intermediates in catalytic chemistry. The hydrogenation of imines and ketones presumably involves such intermediates,^[85] but they have not been clearly detected in these reactions.^[86] The catalytic reduction of CO on surfaces may involve alkoxides, but well-characterized homogeneous analogues are unusual.^[77]

1.4. Organization of the Review

This review will cover the recent developments in palladium- and nickel-catalyzed amination and etheration of aryl halides and triflates. The first sections deal with the useful synthetic methodology that has resulted from recent studies resting upon Kosugi's initial finding^[87, 88] that palladium complexes catalyze the formation of arylamines from tin amides and aryl halides. In the next sections recent developments in the formation of aryl ethers from aryl halides and alkoxides are discussed. The final set of sections present a detailed picture of the mechanism of these processes with different catalysts.

2. Background

2.1. Early Palladium-Catalyzed Amination

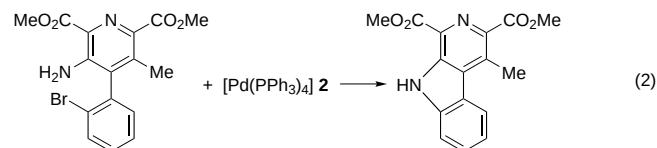
In the 1980s a few results suggested that a general metal-catalyzed method to form arylamines from aryl halides would be possible. In 1983 Kosugi et al. published a short paper on the reaction of tributyltin amides with aryl bromides catalyzed by $[\text{PdCl}_2[\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3]_2]$ (**1**) shown in Equation (1).^[87, 88]



The scope of this reaction appeared to be limited to dialkylamides and electron-neutral aryl halides. For example, the use of aryl halides with nitro, acyl, methoxy, and dimethylamino substituents gave poor yields upon palladium-catalyzed reaction with tributyltin diethylamide. Furthermore, aryl bromides were the only aryl halides that provided any reaction product. Use of vinyl bromides resulted in modest yields of enamines in some cases. Only unhindered

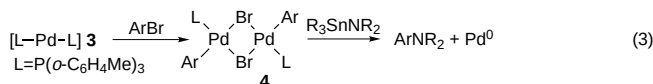
dialkyltin amides gave substantial amounts of amination product. The mechanism did not appear to involve radicals or benzyne intermediates.

Boger et al. reported studies on palladium-mediated cyclization to form the CDE ring system of lavendamycin [Eq. (2)].^[89–91] These reactions were conducted with stoichiometric amounts of $[\text{Pd}(\text{PPh}_3)_4]$ (**2**). When used in a 1 mol %

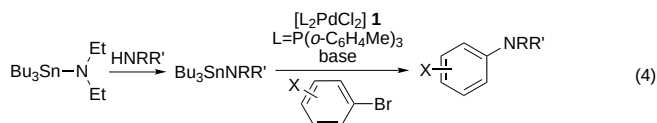


quantity, **2** failed to catalyze these reactions, presumably because of the absence of a base. Until almost ten years later, no palladium-catalyzed amination chemistry was reported, and few citations of the early amination chemistry existed.

Paul, Patt, and Hartwig revealed the reactions involved in the amination chemistry with tin reagents.^[92] Although these studies focused on what is now an outdated synthetic method, the classes of stoichiometric reactions that make up the catalytic cycle are general to many current amination procedures. They showed that the active catalyst was $[\text{Pd}[\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3]_2]$ (**3**), which oxidatively added aryl halides to give dimeric aryl halide complexes **4**. These aryl halide complexes reacted directly with tin amides to form arylamines [Eq. (3)]. Thus, this chemistry could accurately be viewed as a rough parallel to Stille coupling.



Guram and Buchwald showed that the chemistry could be extended beyond electron-neutral aryl halides.^[93] With tin amides derived in situ, this chemistry was extended to aryl halides bearing alkoxycarbonyl, amino, and alkoxo groups [Eq. (4)]. However, reactions that proceeded with 80 % yield or greater were still limited to tin amides derived from secondary amines.



2.2. Initial Synthetic Problems

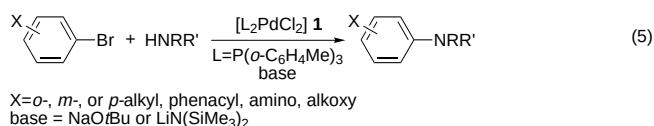
The initial results concerning aryl halide amination and related results in chemistry forming aryl sulfides and phosphanes strongly suggested that a mild, convenient route to arylamines from aryl halides could be developed. However, a source of the amido group must be less toxic, more thermally stable, and less air-sensitive than tin amides. The types of aryl halide that can undergo this reaction must extend beyond electron-neutral aryl halides, for example to aryl chlorides and iodides and aryl triflates. Of course heteroaromatic amines

and halides are also important substrates. Perhaps most important are reactions of primary amines, since the aryl halide amination with primary amines would give secondary alkylarylamines. These substrates are tedious to prepare by classical methods. In addition, it would be highly desirable to extend this type of reaction to the formation of aryl ethers and phenols, since there are no truly mild and convenient methods for this transformation. Finally, the rates and turnover numbers provided by the catalysts must be much higher than those in Kosugi's chemistry and in Boger's stoichiometric cyclization reaction.

3. Initial Tin-Free Aminations of Aryl Halides

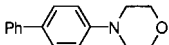
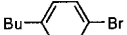
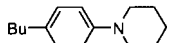
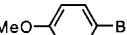
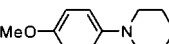
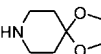
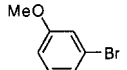
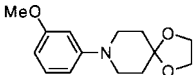
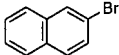
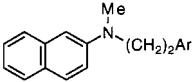
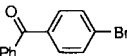
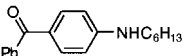
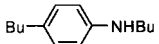
3.1. Intermolecular Amination of Aryl Bromides

In 1995 the research groups of Hartwig and Buchwald published concurrently their results on tin-free amination of aryl halides.^[94, 95] Instead of isolation or generation of a tin amide in situ, the amination reactions were conducted by reaction of an aryl halide with the combination of an amine and either an alkoxide or silylamide base [Eq. (5)]. These



reactions were typically carried out between 80 and 100 °C in toluene. The catalysts used initially were **1**, **3**, or a combination of [Pd₂(dba)₃] (**5a**, dba = *trans*, *trans*-dibenzylideneacetone) and P(*o*-C₆H₄CH₃)₃. Catalysts used subsequently will be described in Section 4. As shown in Table 1, secondary amines were viable substrates, whereas primary amines gave substantial yields with only electron-poor aryl halides. Little product was obtained from reactions of primary amines with

Table 1. Tin-free aminations of aryl halides catalyzed by $[\text{PdCl}_2\{\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3\}_2]$ (**1**).

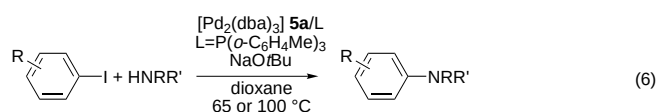
Amine	Aryl halide	Base ^[a]	Product	Yield [%]
		NaOtBu		86
		LiN(TMS) ₂		89
		LiN(TMS) ₂		89
		NaOtBu		81
		NaOtBu		78
H ₂ NC ₆ H ₁₃		NaOtBu		72
H ₂ NBu		LiN(TMS) ₂		< 2 %

[a] TMS = trimethylsilyl.

electron-neutral aryl halides. Arenes were the major product instead. Zhao et al. showed that one could arylate piperazine under conditions of excess piperazine^[96] to form biologically important aryl piperazines by palladium-catalyzed chemistry.

3.2. Intermolecular Amination of Aryl Iodides

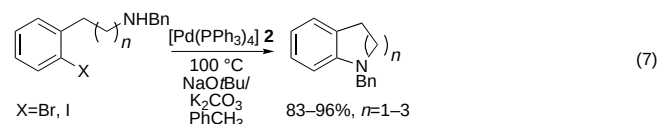
Complexes other than those containing $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ ligands have now been shown to catalyze amination of aryl iodides in high yields.^[69] However, reaction conditions were initially optimized for amination of aryl iodides with the $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ -based catalysts.^[97] It was found that running the reactions in dioxane solvent was important to obtain even modest yields of product. In this solvent, secondary amines are suitable substrates and primary amines couple with *o*-substituted aryl iodides [Eq. (6)]. Primary amines, including



aniline, gave poor yields with unhindered aryl iodides. Even electron-deficient, unhindered aryl iodides were poor substrates for primary amines.

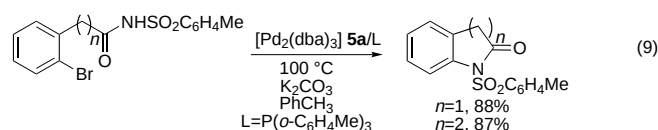
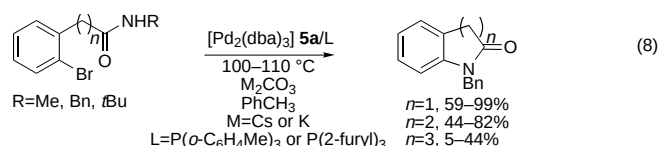
3.3. Intramolecular Amination of Aryl Halides

Intramolecular aryl halide aminations to form nitrogen heterocycles were included in the initial reports on tin-free aryl halide aminations.^[95] For example, the reactions in Equation (7) occurred in greater than 80 % yield. In this case, the halide could be iodide or bromide, and **2** was a more effective catalyst than was **1**.



Subsequent to the initial report, Buchwald and co-workers provided an extensive account of the intramolecular amination reactions.^[98] K_2CO_3 was an efficient base, but a combination of NaOtBu and K_2CO_3 was most effective. Aryl iodides proved to be the preferred substrate under optimized conditions with **2** as catalyst. Iodide substrates also allowed for the use of triethylamine as base. Screening of a variety of combinations of phosphane ligands and palladium precursors showed that chelating ligands such as $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$ ($n = 2-4$) or 1,1'-*bis*-(diphenylphosphanyl)ferrocene (DPPF) gave good yields of cyclized product, as did a combination of **5a** and $\text{P}(\text{2-furyl})_3$, but none were better than **2**.

Amides and sulfonamides also undergo intramolecular chemistry to form arylamides and arylsulfonamides [Eqs. (8) and (9)]. Cs_2CO_3 was the optimal base for cyclization of acetamides, but K_2CO_3 was the best base for cyclization of benzamides. A combination of **5a** and $\text{P}(\text{2-furyl})_3$ was the best



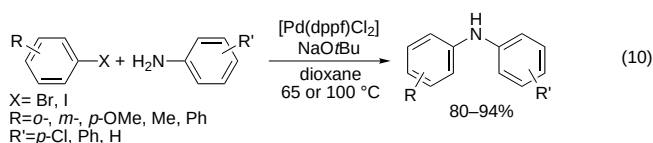
catalyst system for the cyclization of acetamides, and P(*o*-C₆H₄Me)₃ was the optimal ligand for cyclizations of benzamides. For benzamides, reaction times were long; reactions of sulfonamides required either 5 or 14 h depending on ring size, and were conducted with K₂CO₃ and a combination of **5a** and P(*o*-C₆H₄Me)₃ as catalyst. Cyclizations to form five- and six-membered rings gave good yields of heterocyclic product, but they gave poor yields of seven-membered rings.

4. Second-Generation Catalysts with Chelating Phosphanes

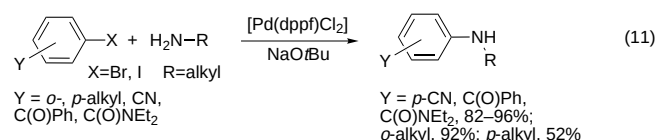
With the exception of intramolecular aminations, all of the reactions described above were catalyzed by palladium complexes containing the sterically hindered P(*o*-C₆H₄Me)₃ ligands. Furthermore, mechanistic studies, which are described in Section 8.6.1, showed that the catalytic cycle involved exclusively mono-phosphane intermediates. However, stoichiometric studies on reductive elimination from PPh₃-ligated palladium amides^[68, 99] and on β -hydrogen elimination from related d⁸ square-planar iridium amides^[100] suggested that palladium complexes with chelating ligands would be particularly effective catalysts for the amination chemistry. In fact, many of the reasons why such complexes should be effective for this amination process parallel the reasons why they are effective for cross-coupling chemistry involving nucleophilic main group alkyl substrates.^[101]

In papers published back-to-back in 1996, the research groups of Hartwig and Buchwald reported amination reactions with palladium complexes of DPPF and BINAP as catalysts.^[69, 102] These palladium complexes provided aminations of aryl bromides and iodides with primary alkyl amines, with cyclic secondary amines, and with anilines. It is ironic that the amination chemistry was first discovered upon use of a particularly labile phosphane, but dramatically improved by the use of chelating ligands.

Palladium complexes with DPPF ligands provided nearly quantitative yields for amination of aryl halides with anilines [Eq. (10)]. Electron-rich, electron-poor, hindered, or unhindered aryl bromides or iodides all participated in the



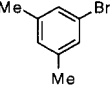
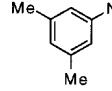
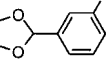
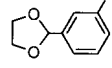
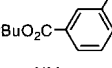
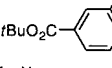
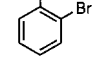
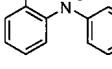
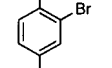
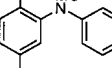
amination chemistry with only a few exceptions. Nitrohaloarenes gave no amination product with aniline substrates. Aryl halides with enolizable carbonyl groups gave poor yields, and esters were converted into the *tert*-butyl ester with *tert*-butoxide as base. These groups have now been shown to be amenable to amination processes that use Cs₂CO₃ as base.^[103] Palladium complexes with DPPF ligands also gave good yields of mixed alkylarylamines with a variety of substrates [Eq. (11)]. With electron-poor aryl halides excellent yields



of *N*-alkylanilines were obtained, and with electron-neutral aryl halides yields of 60–92% were achieved, depending on the location of alkyl substituents.^[69, 104] For the coupling of unhindered and electron-neutral aryl halides with unhindered primary amines, diarylation can occur. In these cases, running the reactions with excess amine prohibits the formation of diarylation products.^[104] For most of these reactions, 5 mol % of catalyst was employed, although 1 mol % can be used in most cases.

Palladium complexes with BINAP ligands provided higher yields than those with DPPF ligands in the case of electron-neutral aryl halides and alkyl amines, as shown in Table 2. The

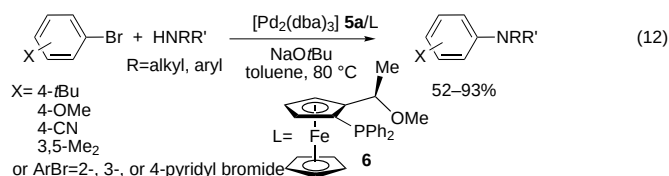
Table 2. Selected aryl bromide aminations catalyzed by BINAP/[Pd₂(dba)₃] (**5a**).

Aryl bromide	Amine	Product	Cat. [mol %]	<i>t</i> [h]	Yield [%]
	RNH ₂		0.5	2	88
			0.5	4	79
			0.05	7	79
	H ₂ NBn		0.5	2	81
	H ₂ NBn		0.5	3.5	71
	MeNHPh		1.0	39	66
	MeNHPh		0.5	36	94

increased yields resulted in large part from the lack of diarylation products. Slightly less reduction product is formed as well, although the yield of arene is low in both cases. Furthermore, in favorable cases, it was shown that 0.05 mol % of catalyst could be used. Racemic and resolved BINAP gave identical results.

Weakly chelating ligands can be beneficial in some of the amination chemistry. Buchwald and co-workers used the

ligand **6** to improve yields in the amination of aryl halides with acyclic secondary amines [Eq. (12)].^[105] It is unclear whether the palladium complexes that are involved in the catalytic

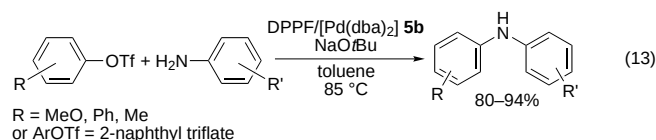


cycle resemble the mono-phosphane complexes with $P(o\text{-C}_6\text{H}_4\text{Me})_3$ ligands or complexes containing chelating ligands such as DPPF or BINAP. The complex isolated from the reaction of the methoxy-substituted phosphane **6**, **5a**, and an aryl halide is a monomer with Pd–O coordination. However, it is difficult to determine if the Pd–O interaction also exists during reactions of the catalytic cycle. Nevertheless, ligand designs based on hemilabile phosphanes^[106] should be profitable.

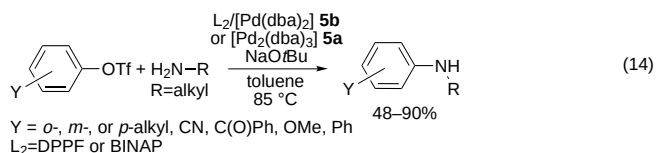
5. New Substrates for the Second-Generation Catalysts

5.1. Aminations of Aryl Triflates

Palladium complexes with chelating ligands are often more effective in C–C bond-forming processes with aryl triflates than are palladium complexes with monodentate ligands such as $P(o\text{-C}_6\text{H}_4\text{Me})_3$.^[107, 108] Similarly, they are not good catalysts for the amination of aryl triflates. However, palladium complexes with the chelating phosphane ligands DPPF and BINAP are effective catalysts for the amination of aryl triflates.^[109, 110] Selected aminations of aryl triflates by aniline are shown in Equation (13), and selected aminations of aryl



triflates by alkylamines are presented in Equation (14). The reaction conditions employed for the amination of aryl triflates are similar to those for the amination of aryl halides



with one exception. Electron-poor aryl triflates were susceptible to cleavage under the basic reaction conditions, presumably because of the stable phenolate that results. This cleavage reaction is likely to be first order with respect to the aryl triflate. In contrast, the catalytic process is likely to be zero order with respect to the aryl triflate, since the catalyst resting

state should be an arylpalladium complex.^[111] Thus, low concentrations of triflate will minimize the relative rate of cleavage versus amination. Slow addition of the triflate in the case of electron-poor triflates therefore allows amination to occur in high yields with these substrates.^[109] Alternatively, the problem of triflate cleavage can be reduced by the use of Cs_2CO_3 as base.^[103]

The amination of aryl triflates does not require added halide and, in fact, added chloride or iodide inhibited the amination process. Reactions in toluene gave higher yields than those in THF, although good yields were obtained in THF in some cases. The use of $[\text{Pd}_n(\text{dba})_m]$ ($n = 2, m = 3$: **5a**; $n = 1, m = 2$: **5b**) or $[\text{Pd}(\text{OAc})_2]$ (**7**) as precursor, rather than $[\text{L}_2\text{PdCl}_2]$, was important for this chemistry; $[(\text{dppf})_2\text{PdCl}_2]$ gave much lower yields than did a combination of **5b** and DPPF.

As was the case for the amination of aryl halides, DPPF was an effective ligand for amination reactions involving anilines or electron poor-aryl triflates. The yields for formation of mixed diarylamines were remarkable. All examples gave yields exceeding 90%.^[109] Reactions of electron-neutral aryl halides with alkylamines provided yields in the range of 42–75% with DPPF as ligand. This combination of substrate gave yields in the range of 54–77% with BINAP or 2,2'-bis(di-*p*-tolylphosphanyl)-1,1'-binaphthyl (Tol-BINAP) as ligand. Several examples, particularly the triflate derived from *p*-methoxyphenol, showed higher yields in reactions employing BINAP as ligand rather than DPPF. The amination of aryl triflates was effective for hindered or unhindered aromatic systems, and for primary or secondary amines.

The amination of aryl triflates allows one to use a phenol OH group as a directing group^[112] to conduct chemistry *ortho* to a substituent, such as methoxy, that can ultimately act as a leaving group. Furthermore, it is possible to conduct amination reactions with aminophenols; the reaction occurs selectively at the amino group.^[113] Thus, the phenol OH group, which can be converted into a triflate or nonaflate group (nonaflate = nonafluorobutanesulfonyl) in the presence of an amino functionality, can act as a convenient source of a leaving group for several applications. In principle, the triflate is recyclable, and one could regenerate triflic anhydride from the sodium triflate by-product. Triflate salts are also less corrosive than alkali halides.

5.2. Amination of Heteroaromatic Halides

Many nitrogen heterocycles are strongly binding ligands for late transition metals. As a result, heteroaromatic halides with basic nitrogen atoms will displace weakly binding ligands such as $P(o\text{-C}_6\text{H}_4\text{Me})_3$, so that the original catalyst system containing $P(o\text{-C}_6\text{H}_4\text{Me})_3$ as ligand was ineffective for aminations with heteroaromatic substrates that could bind to palladium. It has been shown in stoichiometric studies that pyridine displaces $P(o\text{-C}_6\text{H}_4\text{Me})_3$ to form palladium–pyridine complexes.^[114] However, chelating phosphanes are not displaced by pyridines. Thus, the advent of amination reactions with use of chelating ligands now allows for the amination of pyridyl halides.^[115]

Results from aminations with use of two phosphane ligands and two different precursors are presented in Table 3. The most general palladium precursor is $[\text{Pd}(\text{OAc})_2]$ (**7**). Again, BINAP was generally effective for amination with either primary or secondary amines. However, unbranched primary amines gave lower yields than did branched amines such as cyclohexylamine. Propane-1,3-diylbis(diphenylphosphane)

Table 3. Palladium-catalyzed amination of pyridyl halides.

Pyridyl halide	Amine	Product	Catalyst	Yield [%]
	BnNHMe		5a /DPPP	86
			5a /DPPP	87
	BnNHMe		5a /($\pm$)BINAP	77
			5a /($\pm$)BINAP	82
			7 /DPPP	91
	$\text{H}_2\text{NC}_6\text{H}_{13}$		7 /($\pm$)BINAP	67
2 equiv	$\text{H}_2\text{NC}_6\text{H}_{13}$		7 /($\pm$)BINAP	71

(dppp), which is less expensive than BINAP, in combination with **5a** or **7**, acted as an effective catalyst system for amination of pyridyl bromides by secondary amines or amines lacking hydrogen atoms α to the nitrogen atom. As was the case for aminations of aryl halides with use of DPPF and BINAP, acyclic secondary amines gave only low yields of the aminopyridines.

5.3. Aminations of Solid-Supported Aryl Halides

Two groups have reported results on the solid-phase amination of aryl halides with use of both $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ and chelating ligands.^[116, 117] Since the arylamine group is present in many biologically active materials, the application of amination chemistry in combinatorial chemistry may be important for this approach to drug discovery. It has been shown that Stille and Suzuki reactions are reliable, high-yielding process for substrates loaded on solid supports.^[118] Thus, aryl halides are now extremely versatile in solid-phase combinatorial chemistry. They can be used to form new C–C, C–N, and presumably also C–S, C–P, and C–O bonds (see below).

Both Willoughby and Chapman^[116] at Merck and Farina and Ward^[117] at Boehringer Ingelheim have reported success-

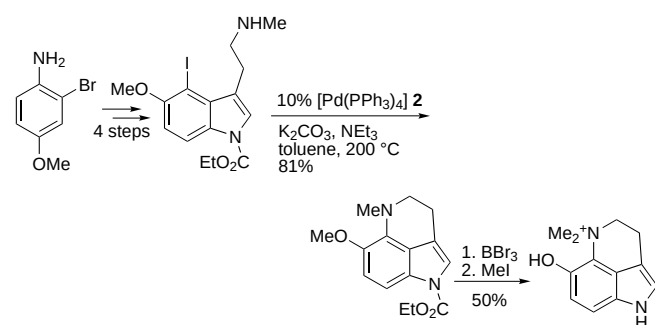
ful amination reactions for aryl halides supported on polystyrene Rink and Rapp TentaGel S RAM resin. The results closely parallel those obtained in the solution phase. Secondary amines are successfully coupled with solid-supported aryl halides in high yields upon use of $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ as the ligand on palladium. Primary amines required either BINAP or DPPF for successful coupling with the aryl halides, and similar results were obtained with either ligand. Compounds with N–H groups for which no arylation chemistry had been reported in the solution phase were not suitable for chemistry on the solid supports. For example, nitroanilines, amino-triazine, 5-aminouracil, 2,6-diaminoanthraquinone, histidine, 2-aminobenzimidazole, imidazole, and pyrazole gave no products of N–C bond formation in the solid phase with use of palladium complexes containing $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$, DPPF, or BINAP ligands.

6. Applications of the Amination Chemistry

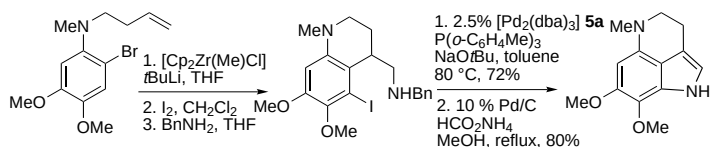
There have not been extensive studies on the applications of the amination chemistry, since the reaction was discovered only a few years ago. However, one application to the total synthesis of biologically active molecules and two applications to the synthesis of materials with potentially interesting electronic properties have been reported.

6.1. Natural-Product Synthesis

Stoichiometric palladium-mediated cyclization was used in natural-product synthesis by Boger et al. a number of years ago, as was noted in the introduction. More recently, Buchwald and co-workers reported the total synthesis or the formal total synthesis of a series of tetrahydropyrroloquinolines by palladium-catalyzed amination.^[119] A brief description of the methods employed are shown in Schemes 1 and 2. One approach involves formation of the six-membered ring through palladium-catalyzed intramolecular amination. The cyclization was carried out at high temperatures employing K_2CO_3 as base. However, the use of NaOtBu , which presumably would have allowed for reaction at lower temperatures, led to cleavage of the carbamate; the cleavage products apparently inhibited catalyst activity.



Scheme 1. Palladium-catalyzed amination in the synthesis of dehydrobufoteanine.

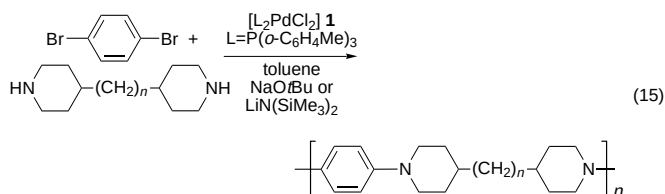


Scheme 2. Palladium-catalyzed amination in the formal total synthesis of makaluvamine C and damirones A and B.

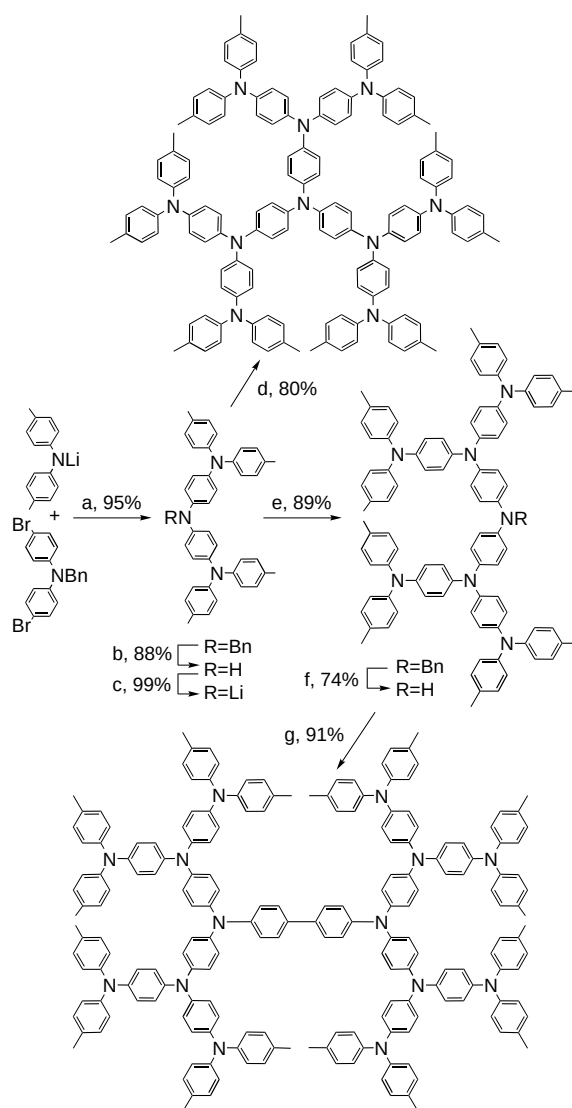
A second approach involved formation of the indole five-membered ring by amination chemistry and the six-membered ring by Zr–benzyne chemistry. This strategy is shown in Scheme 2. In this case, the optimal cyclization conditions could be employed, and the reaction temperature was lower. The product of the cyclization is an intermediate in total syntheses of makaluvamine C and of damirones A and B.

6.2. Applications to Materials Science

Two groups have reported the synthesis of oligomeric or polymeric arylamines by palladium-catalyzed chemistry.^[120, 121] One group used the initial amination of aryl halides with dialkylamines to prepare arylamine polymers.^[120] This chemistry is a step-growth polymerization. A bifunctional diamine and a dihaloarene were used to generate the polymers as shown in Equation (15). The highest molecular weights achieved were in the range of 5000–6000, indicating an average of 20 monomers in each chain.



A second group has prepared highly branched triaryl-amines.^[121] The material contains exclusively *p*-phenylenediamine linkages and triarylamine units. The triarylamines were constructed with a combination of benzyl-protected 4,4'-dibromodiamines and lithium diarylamides. The formation of the triarylamine linkage from aryl bromides and lithium diarylamides occurred in greater than 90% yields under mild conditions with **3** as catalyst. The final products of the reaction sequences in Scheme 3 are discrete oligomers of a *p*-phenylene amine with the highest molecular weight. These materials were characterized by conventional spectroscopic means as well as microanalysis. Each carbon atom could be observed by ¹³C NMR spectrometry, and a molecular ion was observed by mass spectrometry. The electrochemical behavior of the dendrimer at the top of Scheme 3 was complex and showed a large number of reversible redox waves in the cyclovoltammogram. The radical cation was generated in solution, was stable, and was observed by ESR spectroscopy. This material also shows a high glass-transition temperature.



Scheme 3. Palladium-catalyzed synthesis of triarylamine dendrimers. a) **3**, L; b) H₂, Pd/C; c) BuLi; d) N(*p*-C₆H₄Br)₃, **3**, L; e) BnN(*p*-C₆H₄Br)₂, **3**, L; f) H₂, Pd/C; g) **3**, L, NaOtBu, (*p*-C₆H₄Br)₂. L = P(*o*-C₆H₄Me)₃.

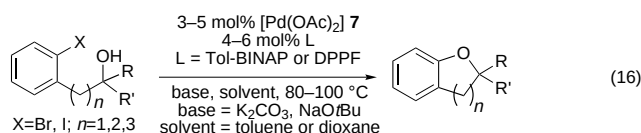
7. Synthesis of Aryl Ethers from Aryl Halides

Our group has shown that reductive elimination reactions that form C–X bonds are faster with more nucleophilic amides and thiolates (Section 8.3). Given this information and the lower nucleophilicity of alkoxides than amides or thiolates, it seems likely that formation of aryl ethers by reductive elimination would be difficult to accomplish. In fact, the first formations of aryl ethers by use of palladium catalysts were observed only with substrates that could undergo intramolecular formation of arene–oxygen bonds.^[122] We have also shown that reductive eliminations are faster when electron-poor aryl groups are bound to palladium. Thus, electron poor-aryl halides might be activated enough toward reductive elimination that they would react to form aryl ethers in the presence of palladium catalysts, alkoxide, and base. Indeed, the first examples of intermolecular formation of aryl ethers involved electron-poor aryl halides as substrates.^[70]

Further work must be conducted to make this process as general as the formation of arylamines from aryl halides.

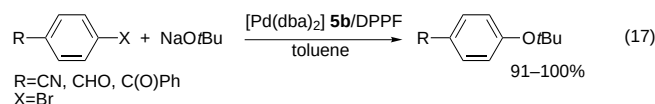
7.1. Intramolecular Palladium-Catalyzed Synthesis of Aryl Ethers

Intramolecular formation of oxygen heterocycles was reported by Buchwald et al.^[122] His group showed that 3–5 mol% of $[\text{Pd}(\text{OAc})_2]$ and either Tol-BINAP or DPPF catalyzed the cyclization of *o*-haloaryl-substituted alcohols [Eq. (16)]. These reactions occur with the highest yields for



tertiary alcohols, but also take place for secondary alcohols. They can produce either five-, six-, or seven-membered rings. It is believed that the reaction occurs by an oxidative addition of the aryl halide, subsequent generation of the palladium oxametallacycle, and C–O bond-forming reductive elimination. Although aryl halide intermediates were generated independently and were shown to be kinetically competent to be intermediates, the oxametallacycles could not be observed or isolated.

The first intermolecular etheration of aryl halides is shown in Equation (17) and was reported by Mann and Hartwig.^[70] In these studies, a combination of DPPF and **5b** was used as



catalyst for the addition of NaOtBu to 4-bromobenzophenone, 4-bromobenzaldehyde, and 4-bromobenzonitrile. The yields for these reactions are now greater than 90%.^[123] Reaction of *n*-butanol gave more reduction product than etheration product. The *tert*-butyl ethers produced by this chemistry are susceptible to deprotection to generate phenol by simple addition of acid directly to the reaction mixture after completion of the etheration.

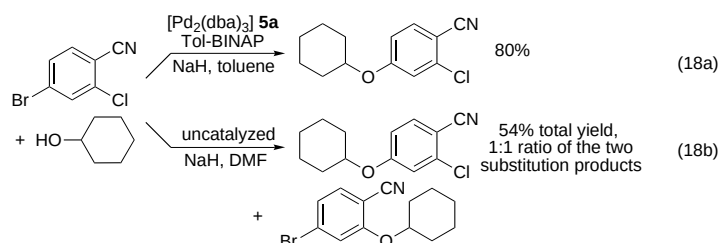
Buchwald et al. reported similar chemistry (Table 4) employing a larger range of alkoxides and showed that BINAP provided improved generality.^[124] Nevertheless, this chemistry remains limited to electron-poor aryl halides. Electron-neutral aryl halides give modest yields for formation of aryl *tert*-butyl ethers. Buchwald also compared the catalyzed and uncatalyzed reactions that can occur in highly polar solvents such as DMF. In some cases, the uncatalyzed reactions in DMF gave yields similar to those for the catalyzed chemistry in nonpolar solvents. However, in several cases the yields were higher for the catalyzed reactions. Furthermore, one could use the higher reactivity of aryl bromides toward palladium and the higher reactivity of aryl chlorides for direct nucleophilic substitutions to conduct selective formation of aryl ethers. The use of palladium catalysts selectively con-

Table 4. Palladium-catalyzed and uncatalyzed formation of aryl ethers from aryl halides and a combination of alcohols and NaH.

Aryl halide	Alcohol	$T[^\circ\text{C}]$	Yield[%]	
			with cat. ^[a]	without cat. ^[b]
		50	80	76
		70	50	48
		70	71	78
	MeOH	70	81	65
	NaOtBu	100	53	< 10
		70	65	< 5

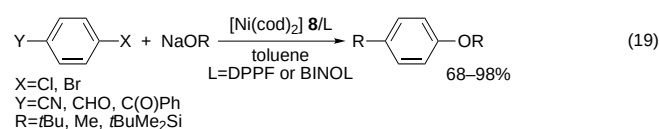
[a] In toluene. [b] In DMF.

verted a bromochloroarene into the chloro aryl ether [Eq. (18a)], while the direct nucleophilic substitution converted the bromochloroarene into a mixture of bromo aryl and chloro aryl ethers [Eq. (18b)].



7.2. Nickel-Catalyzed Etheration

Nickel complexes have been employed successfully in the formation of protected phenols [Eq. (19)].^[123] Selected exam-



ples are presented in Table 5. A combination of $[\text{Ni}(\text{cod})_2]$ (**8**, cod = 1,5-cyclooctadiene) and either DPPF or BINAP successfully formed *tert*-butyl, methyl, and silyl aryl ethers. A combination of **8** and BINAP gave methyl aryl ethers in high yields. A combination of **8** and DPPF provided higher yields than palladium catalysts for the formation of *tert*-butyldimethylsilyl aryl ethers from aryl halides and NaOTBDMS (TBDMS = *tert*-butyldimethylsilyl), and they did so at lower temperatures. However, a combination of BINAP or DPPF and palladium-catalyst precursors gave higher yields than did nickel complexes for the formation of *tert*-butyl aryl ethers. Of course, the methyl ethers are readily deprotected by a variety of reagents including Lewis acids, while the silyl ethers are

Table 5. Nickel- and palladium-catalyzed formation of aryl ethers from aryl halides.

Catalyst	Amount [mol %]	Aryl halide	NaOR	T [°C]	Yield [%]
8 /DPPF	15		NaOtBu	95	84 ^[a]
8 /Tol-BINAP	15		NaOMe	95	84 ^[a]
8 /DPPF	15		NaOMe	95	76 ^[b]
8 /DPPF	15		NaOTBDMS	95	96 ^[a] , 67 ^[b]
8 /DPPF	15		NaOTBDMS	95	98 ^[a]
5b /Tol-BINAP	10		NaOTBDMS	120	75 ^[a]
5b /DPPF	10		NaOTBDMS	120	49 ^[a]

[a] Yields determined by gas chromatography (average of at least two runs). [b] Yields are for pure, isolated product (average of at least two runs).

conveniently deprotected by fluoride. As was the case for the palladium chemistry reported above, the nickel catalysts were effective for reactions of electron-poor aryl halides, but less than 5% yield was achieved for aryl ethers formed from electron-neutral or electron-rich aryl halides. As discussed at the end of Section 7.1, some of the chemistry that forms aryl ethers can occur in an uncatalyzed fashion in highly polar solvents such as DMF. However, the metal-catalyzed chemistry allows for the etheration reactions to occur within shorter reaction times under mild conditions in nonpolar solvents that need not be rigorously dry.

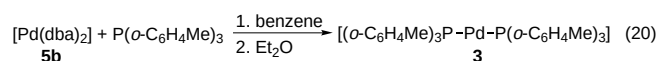
8. Mechanism of Aryl Halide Amination and Etheration

The previous sections described synthetic methods involving palladium- and nickel-catalyzed additions of alcohols and amines to aryl halides and triflates. The development of procedures and catalysts used in these processes has occurred hand in hand with mechanistic analysis of the amination and etheration chemistry. The following sections discuss our current understanding about why these procedures and catalysts are effective and how this understanding led to some of the breakthroughs in synthetic methods presented above.

8.1. Identification and Chemistry of $[\text{Pd}(\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3)_2]$

The original amination chemistry required the use of the bulky monodentate ligand $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$. Although this ligand has been used in a wide range of cross-coupling processes, as well as Heck reactions, few palladium complexes of this ligand had been isolated. $[\text{Pd}(\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3)_2]$ (**3**) was reported in a patent,^[125] but the characterization described was with IR spectroscopy. Paul, Patt, and Hartwig reported a reliable synthesis of this complex as analytically pure yellow

crystals by addition of $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ to **5b** [Eq. (20)].^[92, 114] Although none of the product could be detected in the reac-



tion solution, addition of ether or pentane to the benzene reaction solution led to precipitation of **3**. This synthesis, therefore, relies on rapid equilibria and the low solubility of **3**. The complex is a rare example of a 14-electron two-coordinate transition metal complex.^[126–128] It is air-stable as a solid.

8.1.1. Structural Features of $[\text{Pd}(\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3)_2]$

A crystal structure analysis of **3** (Figure 1) showed a perfectly linear geometry.^[114] The *o*-tolyl hydrogen atoms are located closer to the metal center than those of similar

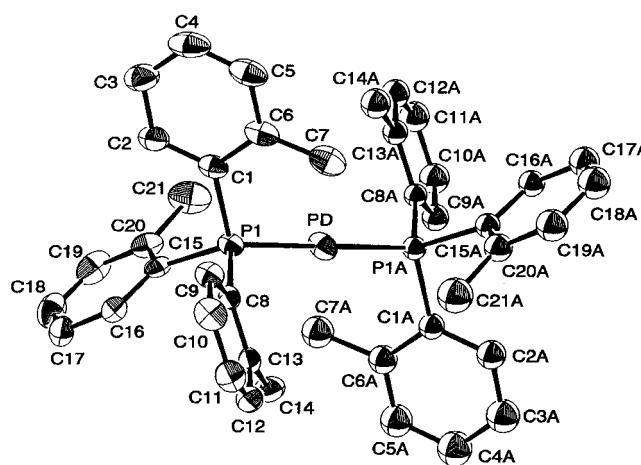
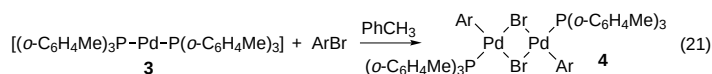


Figure 1. ORTEP drawing of the structure of $[\text{Pd}(\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3)_2]$. Hydrogen atoms have been omitted for clarity.

two-coordinate complexes.^[126–128] However, the absence of unusual IR signals for ν_{CH} or upfield chemical shifts in the ^1H NMR spectrum suggested that an agostic stabilization of **3** was not occurring. Moreover, a derivative of **3** with one deuterium at each methyl group^[129] showed no isotopic perturbation of the NMR chemical shifts,^[130, 131] indicating that any agostic interaction would have to be weaker than those detected previously.^[132, 133]

8.1.2. Oxidative Addition to $[\text{Pd}(\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3)_2]$ and Its Mechanism

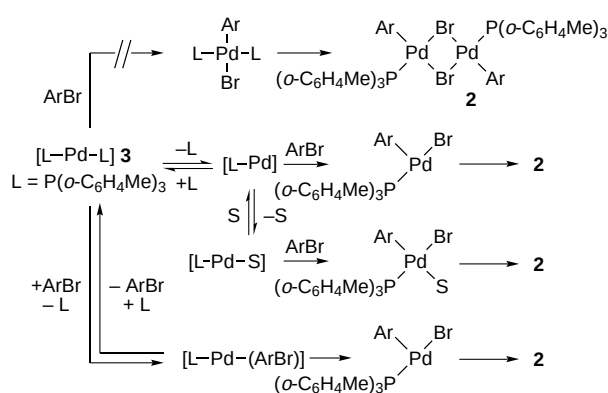
Complex **3** underwent oxidative addition of aryl halides to provide the novel dimeric aryl halide complexes **4** [Eq. (21)].^[92, 114] It is unusual for phosphane-ligated aryl halide complexes formed by oxidative addition to be dimeric. These oxidative addition products were isolated and structur-



ally characterized. They remain dimeric in solution, as determined by molecular-weight measurements in solution, but react as the monomers, as described below.

The mechanism of the oxidative addition was surprising.^[134] It has been well established that aryl halides undergo oxidative addition to L_2Pd fragments.^[135–138] Thus, one would expect oxidative addition of the aryl halide to occur directly to **3** and ligand dissociation and dimerization to take place subsequently. Instead, the addition of aryl halide to **3** occurs after phosphane dissociation, as shown by an inverse first-order dependence of the reaction rate on phosphane concentration and the absence of any tris-phosphane complex in solution.^[134]

Three mechanisms consistent with phosphane dissociation before oxidative addition are shown in Scheme 4. In one case, a one-coordinate 12-electron intermediate adds the aryl



Scheme 4. Potential mechanisms for oxidative addition of aryl halides to **3**. S = solvent.

halide. A second mechanism involves formation of a solvated one-coordinate 12-electron intermediate ligand dissociation and then addition of aryl halide to this solvated species. In a third pathway reversible displacement of a phosphane ligand by aryl halide takes place to generate an aryl halide complex with the carbon–halogen bond intact. Reaction rates in benzene, toluene, and *p*-xylene were all essentially identical, despite their different abilities to coordinate a transition metal. Thus, it is unlikely that a complex with solvent directly bound to the metal is an intermediate. It was not possible to distinguish between the other two intermediates, but a monophosphane complex clearly lies on the reaction pathway for this addition process and on the catalytic cycle for reactions involving **3**.

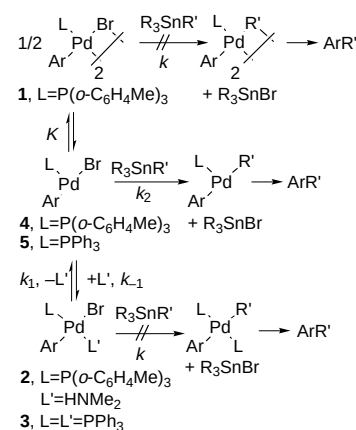
Oxidative addition to a mono-phosphane–palladium complex is unusual, but is a reasonable pathway if one bears in mind that reductive eliminations often occur from mono-phosphane–palladium complexes.^[139, 140] These reductive eliminations from mono-phosphane–Pd^{II} species would form a mono-phosphane–Pd⁰ complex as the initial metal product; these Pd⁰ products are similar to the intermediate in the oxidative addition of aryl halide deduced from kinetic studies.

8.2. Transmetalation Processes

In the case of C–C bond-forming cross-coupling, as well as amination and etheration, transmetalation processes convert the palladium–aryl halide complexes into the intermediate that undergoes reductive elimination of the final organic product.^[50, 51, 139–141] There has been scattered evidence that this reaction involves mono-phosphane intermediates,^[142] but much of this data was based on catalytic processes, rather than direct, stoichiometric observation of the transmetalation process. Further, no information was available on transmetalations involving tin amides or thiolates.

8.2.1. Mechanism of Transmetalation with Tin Amides

The thermodynamics and relative reaction rates for individual steps of the transmetalation and reductive elimination varied depending on the type of tin reagent. However, the mechanisms for the reactions of tin amides, tin thiolates, or trialkylaryltin reagents all involved analogous mono-phosphane–palladium intermediates (Scheme 5).^[143] The dimeric



Scheme 5. Potential mechanism for transmetalation between tin reagents and palladium–aryl halide complexes. R = Me, Bu; R' = Ph, *St*Bu, SAr, NMe₂.

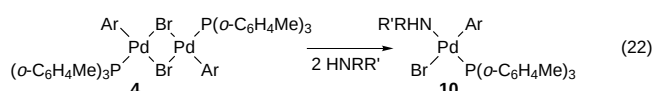
[Pd{P(*o*-C₆H₄Me)₃}(*p*-C₆H₄Me)(Br)}₂ (**4a**) was cleaved reversibly to form a 14-electron mono-phosphane complex before reaction with Bu₃SnPh. The monomeric [Pd(PPh₃)₂(*p*-C₆H₄Me)(Br)] (**9**) underwent reversible dissociation of phosphane before reacting with Bu₃SnPh or Bu₃Sn*S*iBu. The transmetalation process with tin thiolates was endothermic and reversible. Similarly, reaction of Bu₃SnNEt₂ with **4a** reversibly formed the monomeric, mono-phosphane amido intermediate [Pd{P(*o*-C₆H₄Me)₃}(*p*-C₆H₄Me)(NEt₂)] . The reversibility of these reactions was determined by the inverse reaction order in product Bu₃SnBr. As a result of the requirement for monophosphane intermediates, palladium complexes with chelating ligands were not effective in the amination chemistry involving tin amides.^[93]

8.2.2. Mechanism of Palladium–Amide Complex Formation from Amines

The mechanism by which palladium – aryl halide complexes are transformed into palladium – aryl amido complexes by the

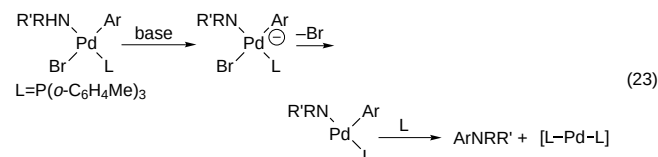
combination of amine and base is clearly very different from that of transmetalation with tin, and is more relevant to the most convenient method for conducting the amination chemistry. One pathway for generation of the amido complex from amine and base would be reaction of the metal complex with the small concentration of amine that is present in the reaction mixtures. This pathway seems unlikely considering the two directly observed alternative pathways discussed below and the absence of benzyne and radical nucleophilic aromatic substitution products that would be generated from a reactive alkali amide.

Paul, Patt, and Hartwig showed that the dimeric aryl halide complexes **4** react with a variety of amines to form monometallic, amine-ligated aryl halide complexes $[\text{Pd}\{\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3\}(\text{amine})(\text{Ar})(\text{Br})]$ (**10**, Eq. (22)).^[114] Buchwald

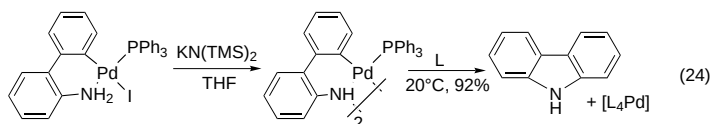


and Widenhoeffer published similar results subsequently and showed that primary amines can even displace the phosphane ligand.^[144–146] These amine complexes are important in the catalytic cycle because the acidity of the N–H bond is enhanced when coordinated to the metal. Amine-ligated aryl halide complexes can be formed in a similar fashion from $[\text{Pd}(\text{PPh}_3)_4]$ in cases where the amine can coordinate intramolecularly.^[68, 99]

The amine-ligated aryl halide complexes react with alkoxide or silylamide bases to form arylamines [Eq. (23)].^[147] The reaction of $[\text{Pd}\{\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3\}(\text{HNEt}_2)(p\text{-C}_6\text{H}_4\text{Bu})(\text{Br})]$ (**10a**) and $\text{LiN}(\text{SiMe}_3)_2$ occurred immediately at room tem-



perature to form the arylamine in greater than 90% yield. Low-temperature reactions conducted in an NMR tube allowed direct observation of the anionic haloamido complex $[\text{Pd}\{\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3\}(\text{NEt}_2)(\text{Ar})(\text{Br})]^-$.^[147] The neutral metalacycle $[\{\text{Pd}(\text{PPh}_3)(\eta^2\text{-NC}_6\text{H}_4\text{C}_6\text{H}_4)\}_2]$ was formed after deprotonation of the azametallacycle $[\text{Pd}(\text{PPh}_3)(\eta^2\text{-NHC}_6\text{H}_4\text{C}_6\text{H}_4)(\text{I})]$ [Eq. (24)].^[68, 99] One experimentally supported mechanism for generation of the amido aryl intermediate is coordination of amine to form a square-planar 16-electron complex that reacts with base.

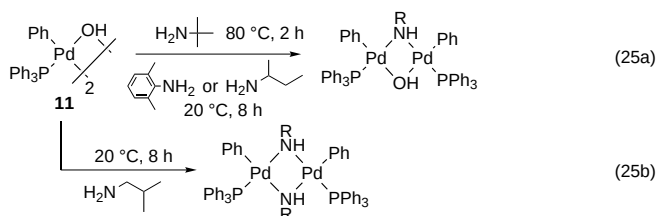


$\text{LiN}(\text{SiMe}_3)_2$ and alkoxides have similar basicities in organic solvents^[148] and are both suitable for the tin-free amination chemistry. $\text{LiO}t\text{Bu}$ is generally unreactive as a base in the amination processes, while $\text{KO}t\text{Bu}$ tends to generate black

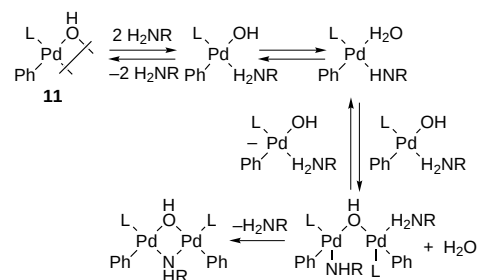
solutions with inactive catalyst.^[94] With the exception of intramolecular chemistry at relatively high reaction temperatures,^[98] bases weaker than alkoxides tend to be ineffective for reactions employing $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ or PPh_3 as ligand because the electron-rich metal center they create is only weakly Lewis acidic.

An alternative pathway would involve reaction of a palladium–amido aryl complex with alkoxide or silylamide base to form an intermediate alkoxide or amide that might react with amine to form the required amido aryl intermediate. This pathway seems to occur for aryl halide aminations catalyzed by complexes with chelating ligands. The inorganic chemistry involved in this transformation is unusual, since the reaction between an alkoxide complex and an alkylamine to form an amido complex had not been observed previous to the work described below.

The reaction of $[\{\text{Pd}(\text{PPh}_3)(\text{Ph})(\mu\text{-OH})\}_2]$ (**11**) with primary alkylamines to generate palladium–amido complexes and water [Eq. (25a,b)]^[75, 149] was an initial indication that the



conversion of an alkoxide into an amide could be occurring during the catalytic cycle. These reactions are reversible, but the equilibrium favors the amido complex. The kinetic behavior of the reaction was counterintuitive. The reaction of **11** with *sec*-butylamine was second order with respect to the amine, even though a single amido group was formed during the reaction [Eq. (25a)]. Extensive kinetic studies supported the mechanism in Scheme 6 involving reversible reaction of

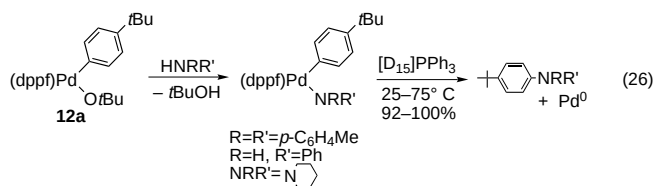


Scheme 6. Mechanism for the reaction of a palladium hydroxide with amine.

two amines to cleave the hydroxo dimer. After cleavage of the dimer, *internal* proton transfer within the square-planar complexes would occur, which is in contrast to the coordination and *external* deprotonation observed for the $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ complexes.

The potential of amines to convert alkoxo complexes into amido complexes in analogous systems with chelating ligands was evaluated recently.^[70] $[\text{Pd}(\text{dppf})(p\text{-C}_6\text{H}_4t\text{Bu})(\text{O}t\text{Bu})]$ (**12a**) reacted with diphenylamine, aniline, or piperidine as

shown in Equation (26) to give the product of amine arylation in high yields.^[70] Since no alkali metal is present in the system, the palladium amide is formed by a mechanism that cannot involve external deprotonation by alkali metal base.



In the actual catalytic process, it is possible that coordination of amine and deprotonation are faster than substitution and N–H bond cleavage. However, stoichiometric reactions of $[\text{Pd}(\text{dppf})(p\text{-C}_6\text{H}_4\text{tBu})(\text{Br})]$ (**13**) with amine and alkoxide base rapidly gave rise to **12a**, indicating that substitution is faster than coordination and deprotonation. This alkoxide forms the arylamine product by reaction with amine.^[150] The exact mechanism for N–H bond cleavages by palladium complexes containing chelating ligands is not clear at this time, but palladium–amido complexes are certainly thermodynamically accessible by reaction of a palladium alkoxide with free amine.

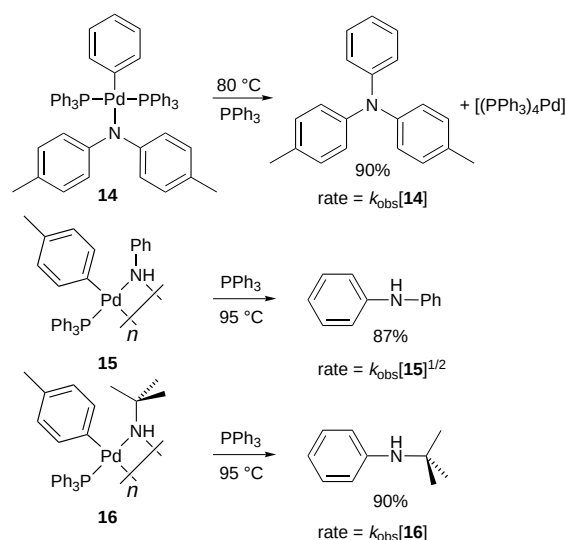
8.3. Reductive Eliminations of Amines and Ethers

Reductive elimination of amines and ethers is the key bond-forming step in the catalytic amination and etheration processes. These reactions were unknown a couple of years ago. There are now several examples, and the factors that control the rates of this process are beginning to be understood. The identity of the intermediates in some of these reductive elimination reactions has recently been uncovered. In some cases the reactions appear concerted. In other cases, particularly related reactions that involve eliminations from nickel complexes to form alkyl–nitrogen bonds, the reductive elimination may involve radical processes.

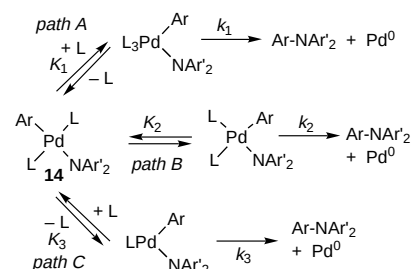
8.3.1. Reductive Elimination of Amines from Palladium Complexes

The best understood examples of reductive eliminations that form the C–N bond in amines involve palladium complexes. Both Boncella et al.^[71] and Hartwig et al.^[68, 69, 99] have observed these reactions from palladium–amido aryl complexes. Our group has studied the mechanism of this process in detail.^[68, 99] Although monomeric and dimeric amido complexes have been isolated, the monomeric species undergoes reductive elimination. For complexes with monodentate ligands, kinetic studies indicated that the actual C–N bond formation occurs simultaneously from both three- and four-coordinate intermediates. With chelating phosphanes, the chemistry is, therefore, likely to occur from the four-coordinate complexes observed in solution. The reductive elimination of arylamines is favored by increasing nucleophilicity of the amido group and increasing electrophilicity of the aryl group.

The mechanisms of the reductive eliminations in Scheme 7 were studied.^[68, 99] Potential pathways for the reaction of **14** are shown in Scheme 8. The reductive eliminations from the monomeric diarylamido aryl complex **14** illustrate two



Scheme 7. Reductive elimination of arylamines from PPh_3 -ligated Pd^{II} -amido complexes.



Scheme 8. Potential mechanisms for reductive elimination of arylamines from PPh_3 -ligated Pd^{II} -amido complexes.

important points of the elimination reactions. First, these reactions were first-order, demonstrating that the actual C–N bond formation occurred from a monomeric complex. Second, the observed rate constant for the elimination reaction contained two terms [Eq. (27)]. One of these terms was

$$-\frac{d[\mathbf{14}]}{dt} = k_{\text{obs}}[\mathbf{14}] \quad (27)$$

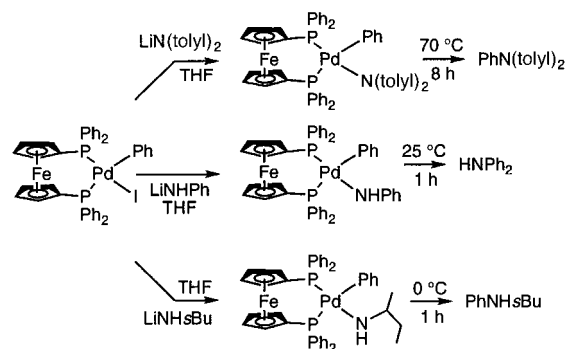
$$\text{where } k_{\text{obs}} = K_2 k_2 + \frac{K_3 k_3}{[\text{PPh}_3]}$$

inverse first order with respect to PPh_3 and the other was zero order with respect to PPh_3 . These results were consistent with two competing mechanisms, path B and path C in Scheme 8, occurring simultaneously. One of these mechanisms involves initial, reversible phosphane dissociation followed by C–N bond formation in the resulting 14-electron, three-coordinate intermediate. The second mechanism involves reductive

elimination from a 16-electron four-coordinate intermediate, presumably after *trans* to *cis* isomerization.

The dimeric amido complexes underwent reductive elimination after cleavage to form two monomeric, three-coordinate, 14-electron amido complexes. In the case of the anilido dimer **15**, a half-order rate dependence in the palladium complexes showed that the reductive elimination occurred after reversible cleavage of the dimer to form two monomers. In the case of the *tert*-butylamido complex **16** rapid reductive elimination occurred after irreversible dimer cleavage. This conclusion was supported by reaction rates that were first order with respect to the palladium dimer and by the lack of crossover during the reductive elimination reactions containing two doubly labeled dimers.

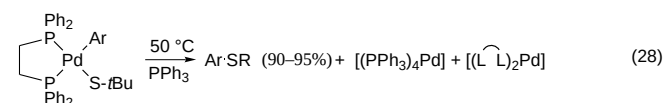
The observation that the reductive elimination process involved a pathway through four-coordinate, presumably *cis*, monomeric amido aryl complexes led to the preparation of palladium–amido complexes with chelating ligands.^[69] Results with these complexes confirmed this conclusion and led to the development in our lab of second-generation catalysts based on palladium complexes with chelating ligands.^[151] The palladium–amido aryl complexes with DPPF ligand in Scheme 9 underwent reductive elimination of arylamines in



Scheme 9. Reductive elimination of arylamines from DPPF-ligated palladium–amido complexes.

high yields.^[69, 99] The rates for these reactions were first order with respect to palladium and zero order with respect to the trapping ligand. Thus, the data on the reductive elimination reactions is consistent with a direct, concerted formation of the C–N bond from the four-coordinate *cis*-DPPF complex.

Because the reductive elimination from DPPF-ligated palladium complexes did not involve geometric rearrangements or changes in coordination number before the rate-determining step, the DPPF complexes allowed for an assessment of the electronic properties of the transition state in this reaction. The relative rates for elimination from amido groups was alkylamido > arylamido > diarylamido. This trend implies that the more nucleophilic the amido group, the faster the elimination process. Variation of the aryl group showed similar results to an extensive study of the electronic aspects of C–S bond-forming eliminations of sulfides [Eq. (28)].^[60]



The data for electronic effects on sulfide and amine eliminations presented in Figure 2 were similar. They point out that electron-withdrawing groups accelerated the reductive elimination process and that substituents with large σ_R values for

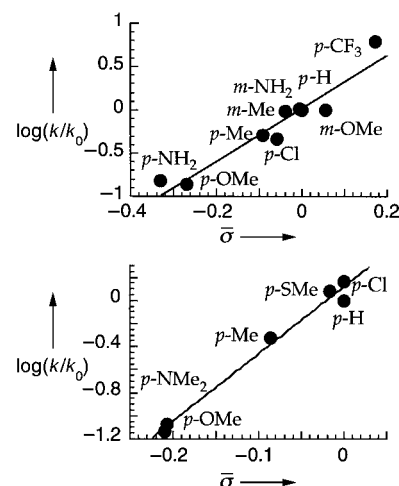
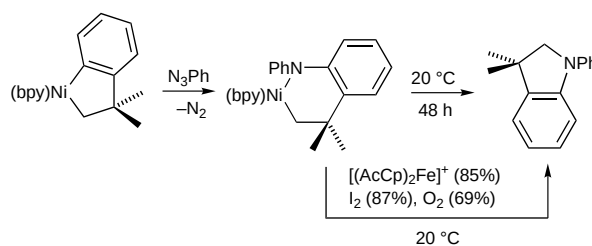


Figure 2. Analysis of electronic effects on the reductive elimination of aryl sulfides (top; $\rho_R/\rho_I=3$, $\rho_R=2.3$, $\rho_I=0.77$) and arylamines (bottom; $\rho_R/\rho_I=2$, $\rho_R=3.9$, $\rho_I=1.9$) by considering a combination of the substitution constants σ_I and σ_R^0 .

the resonance effect affected the reaction rates more than substituents with large σ_I values for the inductive effect. Resonance effects were stronger than inductive effects, perhaps due to arene coordination during the reaction. In a more rough sense, the amido group acts as a nucleophile and the aryl group as the electrophile.

8.3.2. Reductive Elimination of Amines from Nickel Complexes

Koo and Hillhouse have shown that the reductive elimination of amines can also occur from nickel complexes.^[72] This research group has prepared nickel–arylamido alkyl complexes by insertion of the NAr fragment from aryl azides into Ni–C bonds.^[152] A variety of the amido alkyl complexes undergo reductive elimination to form alkylarylamines as shown in Scheme 10. This transformation differs from the

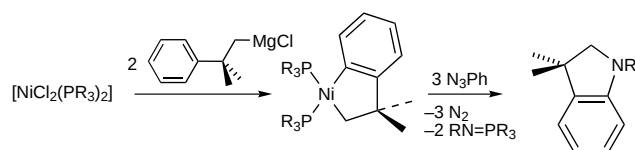


Scheme 10. Oxidatively induced reductive eliminations of amines from Ni^{III}–amido complexes generated in situ. Cp = cyclopentadienyl.

palladium chemistry by forming a C–N bond between an amido group and an alkyl rather than an aryl group. Furthermore, most of these reductive elimination reactions

occurred only after initial oxidation by I_2 , O_2 , or $[Cp_2Fe]^+$, although one example of thermally induced elimination from the bpy–nickel fragment (bpy = 2,2'-bipyridine) was observed. In the case of acyclic amido aryl complexes, the yields were lower for the reductive elimination process. This result, coupled with the information that single-electron oxidation triggers the elimination process, led Hillhouse to propose an alkyl or aminyl radical as an intermediate in these reactions.^[72]

A subsequent report from Hillhouse's lab focused on phosphane-ligated nickel complexes. He showed that consumption of phosphane by the azide led to rapid nonoxidatively induced eliminations to form nitrogen heterocycles (Scheme 11).^[153] Thus, the phosphane-ligated nickel centers may react by different pathways than the bpy-ligated complexes.

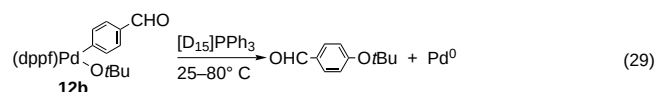


Scheme 11. Reductive elimination of indolines from Ni^{II} amides generated in situ.

8.3.3. Reductive Elimination of Ethers from Palladium Complexes

The reductive elimination of ethers from palladium complexes was recently reported by Mann and Hartwig, and these reactions were the first examples of C–O bond-forming reductive eliminations of aryl ethers.^[70] The ability of transition metal complexes to perform this reaction is crucial to generalization of the catalytic conversion of aryl halides into aryl ethers.

The reductive elimination chemistry reported by Mann and Hartwig is shown in Equation (29). The scope of this reaction

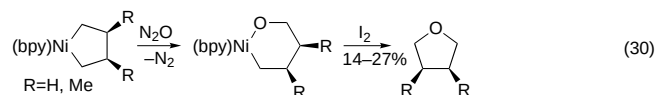


can be understood in terms of the electronic effects on amine and sulfide eliminations. The alkoxo ligand is less nucleophilic than an amide or thiolate. As a result, its participation in high-yielding reductive elimination reactions is so far limited to electrophilic aryl groups. Thus, the DPPF-ligated alkoxo aryl complex with an electron donating substituent, even a weak one, does not undergo reductive elimination of ether in significant yields. However, the alkoxo aryl complex **12b**, in which the aryl group contains a substituent that is an electron acceptor in a resonance fashion, does give high yields of alkoxo aryl complex under thermal reaction conditions.

8.3.4. Reductive Elimination of Ethers from Nickel Complexes

Oxidation induces reductive elimination of ethers from cyclic alkoxo alkyl complexes of nickel in a similar fashion to

the oxidatively induced reductive elimination of amines from bpy–nickel amido alkyl complexes.^[73] Hillhouse's group has prepared oxametallacycles of nickel by insertion of the oxygen atom of N_2O into nickel–alkyl compounds.^[154] Oxidation of these complexes by I_2 , O_2 , and $[Cp_2Fe]^+$ led to the reductive elimination of oxygen heterocycles, albeit in fairly low yields [Eq. (30)].^[73] The yields are only mildly



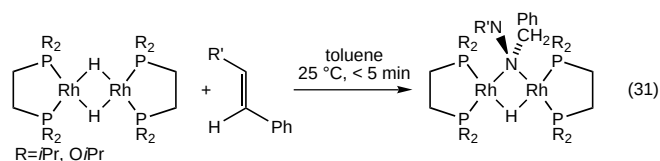
dependent on substitution of the metallacycle. Acyclic alkoxo alkyl complexes did not undergo oxidatively induced reductive elimination to form acyclic ethers. The reduced nucleophilicity of the alkoxo group relative to the amido group may also be important in the mechanistically distinct chemistry of the bpy–nickel complexes, or the greater M–O bond dissociation energy relative to that of M–N^[149, 155] may disfavor the proposed radical intermediates.

8.4. Competing β -Hydrogen Elimination

The amination chemistry depends on the absence of irreversible β -hydrogen elimination from the amido complexes before reductive elimination of amine. The conversion of aryl halides into aryl ethers similarly depends on reductive elimination being faster than β -hydrogen elimination from an alkoxide. At the early stages of the development of the amination chemistry, it was remarkable that the unknown reductive elimination of arylamines could be faster than the presumed rapid^[76, 77] β -hydrogen elimination from late transition metal amides. In fact, directly observed β -hydrogen elimination from late transition metal–amido complexes was rare, and no examples occurred irreversibly from a simple monomeric amido species.^[86] At this point, it is clear that C–N bond-forming reductive elimination of amines and ethers can be rapid, and that β -hydrogen elimination can be slow.

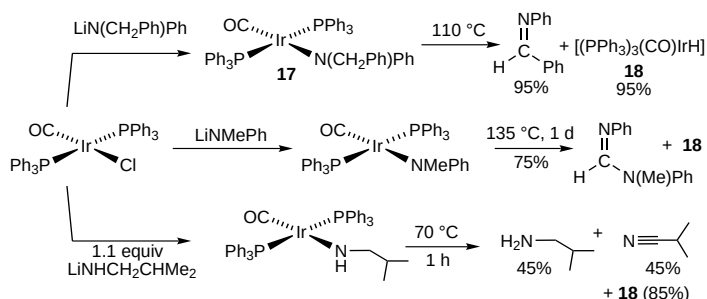
8.4.1. β -Hydrogen Elimination from Amides

β -Hydrogen elimination from amido complexes is a process that was assumed to be rapid, but that had not been observed directly with monomeric amido complexes until recently. Fryzuk et al. have studied the related insertion of imines into a dimeric, bridging hydride of Rh^I [Eq. (31)].^[86] Their results showed that imine insertion was reversible upon use of isoquinoline, suggesting that insertion and elimination processes are nearly thermoneutral.



Recently, Hartwig prepared 16-electron, square-planar amido complexes that undergo irreversible β -hydrogen elim-

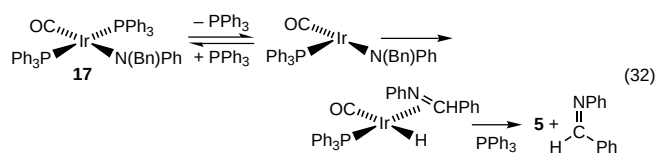
ination.^[100] This observation allowed the beginning of a mechanistic understanding of this process, but also highlighted the unfounded assumption that this β -hydrogen elimination process is typically rapid. Three different monomeric amido complexes with β -hydrogen atoms were prepared from Vaska's complex (Scheme 12). All three com-



Scheme 12. β -Hydrogen elimination from Ir^{I} -amido complexes.

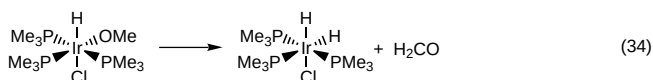
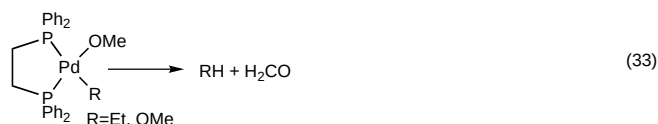
plexes underwent high-yielding β -hydrogen elimination processes, two of which gave unexpected products from imine disproportionation. In the case of elimination from the *N*-benzyl anilide **17** the reaction produced iridium hydride **18** and imine in nearly quantitative yields. β -Hydrogen elimination from the anilides required temperatures of 100 °C or above, and elimination from the alkylamide proceeded at 70 °C. In contrast, Schwartz et al. showed that the analogous alkyl complexes underwent β -hydrogen elimination below room temperature.^[156, 157]

The mechanism for β -hydrogen elimination from **17**, which forms a stable imine product, involved monomeric amido complexes. The intermediate that underwent C–H bond cleavage was a 14-electron, three-coordinate complex that formed by reversible phosphane dissociation [Eq. (32)].



Importantly, there was no detectable competing β -hydrogen elimination from a 16-electron, four-coordinate complex. The mechanism for β -hydrogen elimination from a 14-electron intermediate parallels that for β -hydrogen elimination from square-planar alkyl complexes.^[158, 159] β -Hydrogen elimination from the alkylamido complex and from the *N*-methyl anilide were less well defined, and firm conclusions on the coordination number of the complex that loses the β -hydrogen atom requires further study.

β -Hydrogen elimination from alkoxo complexes has been observed previously on two different types of systems, but these studies led to ambiguous mechanistic conclusions. The presence of a chelating phosphane on the complexes in Equation (33) prevented determination of the coordination number of the species undergoing β -elimination, and the value of 1.33 obtained for the order with respect to MeOH for the reaction in Equation (34) was difficult to explain.

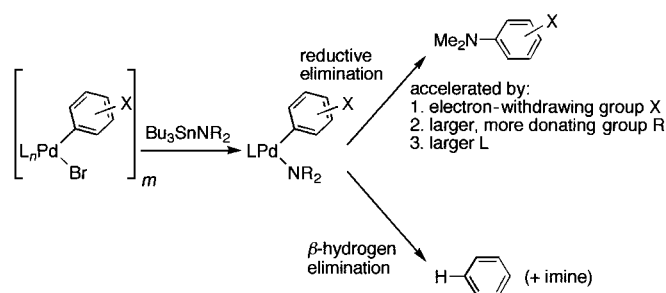


Unpublished studies on β -hydrogen elimination from Vaska-type alkoxo complexes that are analogous to the amides in Scheme 12 suggest a mechanism for β -hydrogen elimination from alkoxo complexes that is distinct from that for β -hydrogen elimination from amides.^[160] The rates for β -hydrogen eliminations from the alkoxides are also faster than in the case of the amides.

8.5. Selectivity: Reductive Elimination versus β -Hydrogen Elimination

Two studies have been conducted on the effect of steric and electronic properties of ligands on the relative rates for reductive elimination of amine and β -hydrogen elimination from amides. One investigation focused on the amination chemistry catalyzed by palladium complexes with $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ ligands,^[161] while the second dealt with the chemistry catalyzed by complexes containing chelating ligands.^[104]

Studies of aryl halide amination with secondary aminostannanes and palladium catalysts bearing $\text{P}(o\text{-C}_6\text{H}_4\text{Me})_3$ ligands is summarized in Scheme 13. They revealed four



Scheme 13. Factors controlling the selectivity for amination versus hydrodehalogenation of aryl halides.

factors that control the relative degrees to which aryl halide hydrodehalogenation and amination occur. First, a certain amount of arene was formed by the reduction of Pd^{II} dihalides to the active Pd^0 catalyst; the mechanism for this reduction was not explored. Second, electron-withdrawing groups on the aryl ring gave more amination and less hydrodehalogenation than those with electron-donating groups. This result is consistent with the faster reductive elimination of amines with electron-poor aromatic groups discussed above. *N*-Alkyl arylamides provided more hydrodehalogenation, consistent with arylamides undergoing reductive elimination of amines more slowly than the dialkylamides. Further, deuterium-labeling experiments showed that the majority of the dehalogenation product formed after catalyst initiation resulted from β -hydrogen elimination from the amido group.

The final point concerned the steric effects of the phosphane aryl groups on the relative amounts of arene and

arylamine produced. Careful monitoring of the products from both stoichiometric and catalytic reactions employing palladium complexes containing $P(o\text{-C}_6\text{H}_4\text{Me})_3$, $P(o\text{-C}_6\text{H}_4\text{Me})_2\text{Ph}$, $P(o\text{-C}_6\text{H}_4\text{Me})\text{Ph}_2$, and PPh_3 ligands showed monotonically decreasing ratios of amine to arene as the size of the ligand decreased. Since arene formation by hydrodehalogenation occurred predominantly by β -hydrogen elimination, it is clear that larger phosphane ligands enhance the reductive elimination of amines at the expense of β -hydrogen elimination processes. Reductive elimination of amine decreases the metal's coordination number, while β -hydrogen elimination from an amide either increases the metal's coordination number because of formation of a coordinated imine along with the hydride or maintains the same coordination number if imine is extruded without coordination. Large groups on the phosphane ligand will enhance the rate of the reaction that decreases the coordination number, and will, therefore, increase the rate for reductive elimination^[162] of amines relative to that for β -hydrogen elimination.

Results obtained with chelating ligands that display varied steric properties contrasted those with monodentate ligands.^[104] Large, chelating phosphane ligands such as bis-1,1'-(di-*o*-tolylphosphanyl)ferrocene gave more hydrodehalogenation product than did DPPF. Reactions employing electron-poor DPPF derivatives, which should generate a more electron-poor metal that favors reductive elimination of amine, produced more arene than did those employing electron-rich DPPF derivatives. Furthermore, ligands with large bite angles gave more arene than those with small bite angles, which is in contrast to what would be expected from previous studies that showed an increase in rate of C–C bond-forming reductive elimination with increasing bite angle.^[163] Although the origin of the unusual results with chelating phosphanes in the amination chemistry are not fully understood at this time, it is clear that chemistry other than reductive elimination of amine and β -hydrogen elimination from an amide is occurring. The arene produced from reactions of amines that are deuterated at the position α to the nitrogen atom or at the N–H group was primarily protiated when the catalysts contained any of several chelating phosphane ligands. The source of hydrogen is currently unclear, but much of the arene generated in reactions employing DPPF or BINAP does not form by a simple β -hydrogen elimination and C–H bond-forming reductive elimination sequence.

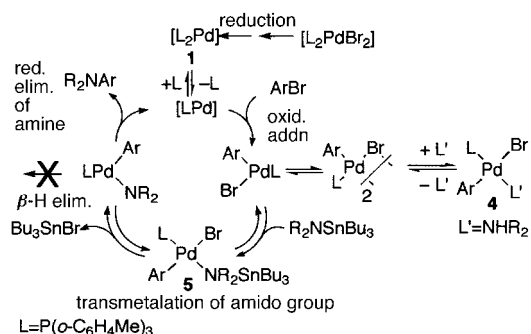
8.6. Overall Catalytic Cycle with Specific Intermediates

At this time, one can put together the results on reductive elimination and oxidative additions to make a justified prediction about the mechanism for the amination chemistry catalyzed by palladium complexes containing both monodentate and chelating ligands. The catalytic cycles differ in the coordination number of the palladium complexes involved and the factors that control amination or etheration versus aryl halide reduction. We have shown that the catalytic cycle for the amination of aryl halides catalyzed by palladium complexes with $P(o\text{-C}_6\text{H}_4\text{Me})_3$ ligands exclusively contains

mono-phosphane intermediates. In contrast, the chemistry catalyzed by palladium complexes with DPPF or BINAP ligands involves bis-phosphane complexes as a result of ligand chelation and the fact that reductive elimination can occur without ligand dissociation.

8.6.1. Mechanism for Amination Catalyzed by Palladium Complexes with $P(o\text{-C}_6\text{H}_4\text{Me})_3$ Ligands

Scheme 14 shows an experimentally supported mechanism for amination catalyzed by $P(o\text{-C}_6\text{H}_4\text{Me})_3$ complexes. The Pd^0 complex is a 14-electron two-coordinate species that loses one

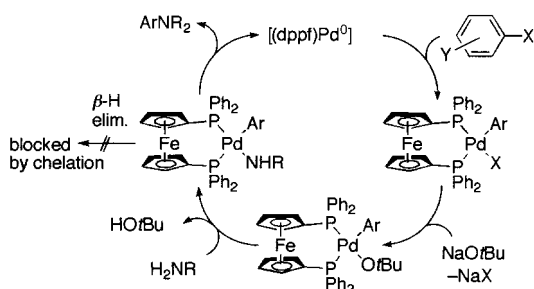


Scheme 14. Overall mechanism for aryl halide amination catalyzed by palladium complexes with $P(o\text{-C}_6\text{H}_4\text{Me})_3$ ligands.

of the phosphane ligands before oxidative addition of the aryl halide. This conclusion was supported by kinetic studies on the stoichiometric oxidative addition of aryl halides to **3**. This process generates an aryl halide complex that is isolated as a dimer, but which reacts in the catalytic cycle as a monomer. During reactions involving amines in the presence of base, amine cleaves the dimeric aryl halide complexes to form a mono-phosphane, amine-ligated aryl halide complex. Stoichiometric reactions of these amine complexes with base show that the coordinated amine is deprotonated by base to generate a three-coordinate amido species that undergoes rapid reductive elimination. In addition to these stoichiometric studies, studies on the rates of kinetically well-behaved catalytic reactions involving tin amides showed that monomeric, mono-phosphane complexes of palladium were the intermediates of the actual catalytic cycle. Furthermore, the kinetic studies revealed an inhibition by tin bromide by-product, and this product inhibition allowed for kinetic detection of the monomeric, mono-phosphane amido aryl intermediate. In the case of monodentate ligands, the use of large phosphanes accelerates the overall rate by favoring the formation of mono-phosphane complexes, and leads to high yields by accelerating reductive elimination relative to β -hydrogen elimination.

8.6.2. Mechanism for Amination Catalyzed by Palladium Complexes with Chelating Ligands

Scheme 15 shows a mechanism for the amination of aryl halides catalyzed by DPPF–palladium complexes which is presumably similar to that for reactions catalyzed by



Scheme 15. Overall mechanism for aryl halide amination catalyzed by palladium complexes with DPPF ligands.

BINAP–palladium complexes. In this case, the resting state of the catalyst, the relative rates and reversibility of the various steps, and the reaction orders with respect to the different components for the overall reaction are not known. Furthermore, a variety of ligand transformations can occur over the course of the reaction. However, existing data do provide a reasonable mechanism for the catalytic process, assuming that ligand transformations do not disrupt the chelating properties of the ligand.^[164] In the case of palladium complexes with chelating ligands, the Pd⁰ complex that undergoes oxidative addition of aryl halide most likely contains one chelating ligand. This reaction would lead to a [PdL₂(Ar)(X)] complex.^[163] The amido aryl complex that would result from reaction of the aryl halide complex with amine and base is also a bis-phosphane complex.^[70] Mechanistic studies on the reductive elimination of amine from amido aryl complexes show that these complexes would undergo reductive elimination directly from the 16-electron, four-coordinate complex, in contrast to reductive elimination from the mono-phosphane, 14-electron, three-coordinate amido complex containing P(*o*-C₆H₄Me)₃ ligands. For reactions involving chelating phosphanes, the selectivity for reductive elimination rather than β -hydrogen elimination results from chelation blocking phosphane dissociation and accompanying pathways for β -hydrogen elimination from 14-electron, three-coordinate species. Although many mechanistic questions have not been answered at this point, these results provided a general, experimentally supported pathway for reactions catalyzed by complexes with monodentate and chelating phosphane ligands.

9. Summary

The amination of aryl halides and triflates catalyzed by palladium complexes is suitable for use in complex synthetic problems. Many substrates will produce high yields of mixed arylamines with one of the existing catalyst systems. Nevertheless, there are also many combinations of substrates for which the amination chemistry must be substantially improved. For the most part, these reactions involve nitrogen centers, such as those in pyrroles, indoles, amides, histidines, and other heterocyclic groups that are less basic than standard alkylamines, or they involve arenes that are electron-rich. Furthermore, it is important to develop increasingly mild reaction conditions and to increase the number of turnovers.

The palladium-catalyzed synthesis of aryl ethers from aryl halides is more limited at this time, but could become a synthetic method that may ultimately provide a general route to aryl ethers. Currently, alkoxides will react with electron-deficient aryl halides in good yields in nonpolar solvents to generate ether products upon use of either palladium or nickel catalysts. Diaryl ethers have recently been formed from palladium-catalyzed substitutions of aryl halides with phenols, but again this process is limited to electron-deficient aryl halides. This combination of substrates is clearly important since these ethers are not produced conveniently under mild conditions by classical methods, and, as discussed in the introduction, since they are important structural types in thermally stable polymers and biologically active natural products.

10. Appendix

Synthetic improvements, new mechanistic information, further applications, and new classes of amination reactions are constantly appearing. Several papers that describe important synthetic results have been published since the submission of this manuscript. Thus, they are included in this appendix for readers interested in the most recent developments.

Nishiyama et al. reported the use of tri-*tert*-butylphosphane for the amination of piperazine at low catalyst loadings.^[165] Rossen, Pye, and co-workers described the amination of a dibromocyclophane for kinetic resolution.^[166] They also showed that 4,12-bis(diphenylphosphanyl)[2.2]paracyclophane (PHANPHOS) is a more effective ligand than BINAP for amination of some aryl halides.

Buchwald's group has reported the amination of aryl chlorides with nickel complexes,^[167] Tanaka's group the palladium-catalyzed amination of aryl chlorides with use of tricyclohexylphosphane,^[168] and Beller and Herrmann the amination of electron-poor aryl chlorides with a palladacycle.^[169] Senanayake et al. described the amination of a 2-chloro-1,3-diazole derivative for the synthesis of H₁-antihistaminic norastemizole.^[170]

Buchwald and co-workers have published the use of Cs₂CO₃ in combination with Kumada's ligand to give improved functional group compatibility for the amination of aryl halides,^[171] and the use of Cs₂CO₃ for the amination of aryl triflates^[172] to alleviate competing triflate cleavage. His group has also reported the use of benzophenone imine as a surrogate for ammonia.^[173] Darses et al. described the room-temperature amination of arene diazonium salts,^[174] and Buchwald et al. reported the room temperature amination of aryl halides with use of crown ether additives.^[175]

In 1996 Ma and Yao had reported a synthesis of chiral *N*-aryl- α -amino acids by Pd/Cu-catalyzed couplings of chiral α -amino acids with aryl halides,^[176] and Buchwald and co-workers recently evaluated the enantiomeric integrity of products obtained from the palladium-catalyzed arylation of optically active amines in the absence of copper.^[177] Beletskaya et al. reported the amination of polyamines,^[178] and

Buchwald's group prepared end-functionalized oligomers of poly(*p*-aniline).^[179]

Buchwald's group published mechanistic studies on the reductive elimination of aryl ethers from aryl alkoxo complexes generated *in situ*, but not isolated,^[180] and Hillhouse and co-workers reported data on the selectivity for reductive elimination versus β -hydrogen elimination from nickel-alkoxo complexes.^[181]

Hartwig's group reported the polymerization of *N*-aryl-bromoanilines, as well as the copolymerization of dihaloarenes and diamines for formation of donor-acceptor polymers.^[182] They extended aryl ether formation to the preparation of diaryl ethers from aryl halides and phenols; increased yields were obtained upon use of electron-poor phosphane ligands.^[183] They also reported the arylation of pyrroles, indoles, carbazoles, and benzophenone imine with DPPF-ligated palladium complexes, along with information that allows for a comparison of the relative rates for reductive eliminations of arylamines, *N*-aryl azoles, and *N*-aryl imines.^[184] Finally, they have demonstrated the arylation of hydrazones and have isolated hydrazone complexes that allow for direct observation of the reductive elimination of *N*-aryl hydrazones in high yields.^[185]

Portions of my group's contributions to this work have been supported by the National Institutes of Health and the Department of Energy. We also gratefully acknowledge a DuPont Young Professor Award, a Union Carbide Innovative Recognition Award, a National Science Foundation Young Investigator Award, a Dreyfus Foundation New Faculty Award, and a Camille Dreyfus Teacher-Scholar Award for support for this work. The author is a fellow of the Alfred P. Sloan Foundation. We also thank Johnson-Matthey Alpha/Aesar for donations of palladium chloride. I am deeply indebted to Fred Paul, Michael Driver, Janis Louie, Grace Mann, Blake Hamann, David Barañano, Anna Davis, Steve Richards, and Joe Patt, the graduate students, postdoctoral associates, and undergraduate students in my laboratory who have contributed to this project experimentally and intellectually.

Received: July 8, 1997 [A 241 IE]

German version: *Angew. Chem.* **1998**, *110*, 2154–2177

- [1] R. A. Glennon, *J. Med. Chem.* **1987**, *30*, 1–12.
- [2] H. Hugel, D. J. Kennaway, *Org. Prep. Proced. Int.* **1995**, *27*, 1–31.
- [3] D. H. R. Barton, D. M. X. Donnelly, J. Finet, P. J. Guiry, J. M. Kiely, *Tetrahedron Lett.* **1990**, *46*, 6637–6640.
- [4] G. J. S. Doad, J. A. Barltrop, C. M. Petty, T. C. Owen, *Tetrahedron Lett.* **1989**, *30*, 1597–1598.
- [5] K. Hiroya, K. Hashimura, K. Ogasawara, *Heterocycles* **1994**, *38*, 2463–2472.
- [6] J. Setsune, T. Ueda, K. Shikata, K. Matsukawa, T. Iida, T. Kitao, *Tetrahedron Lett.* **1986**, *42*, 2647–2656.
- [7] D. L. Boger, D. Yohannes, *Tetrahedron Lett.* **1989**, *30*, 2053–2056.
- [8] D. L. Boger, D. Yohannes, *Tetrahedron Lett.* **1989**, *30*, 5061–5064.
- [9] D. L. Boger, D. Yohannes, *J. Org. Chem.* **1990**, *55*, 6000–6011.
- [10] D. L. Boger, D. Yohannes, *J. Am. Chem. Soc.* **1991**, *113*, 1427–1429.
- [11] D. L. Boger, D. Yohannes, J. Zhou, M. A. Patane, *J. Am. Chem. Soc.* **1993**, *115*, 3420–3430.
- [12] D. L. Boger, J. Zhou, *J. Am. Chem. Soc.* **1993**, *115*, 11426–11433.
- [13] D. A. Evans, J. A. Ellman, *J. Am. Chem. Soc.* **1989**, *111*, 1063–1072.
- [14] H. Itokawa, K. Takeya, *Heterocycles* **1993**, *35*, 1467–1501.
- [15] A. J. Pearson, J. G. Park, *J. Org. Chem.* **1992**, *57*, 1744–1752.
- [16] S. Nishiyama, K. Nakamura, Y. Suzuki, S. Yamamura, *Tetrahedron Lett.* **1986**, *27*, 4481–4484.
- [17] T. Kato, Y. Suzumura, S. Takamoto, K. Ota, *Anticancer Res.* **1987**, *7*, 329–334.
- [18] K. Matsuzaki, H. Ikeda, T. Ogino, A. Matsumoto, H. B. Woodruff, H. Tanaka, S. Omura, *J. Antibiotics* **1994**, *47*, 1173–1174.
- [19] M. Nagai, M. Kubo, M. Fujita, T. Inoue, M. Matsuo, *J. Chem. Soc. Chem. Commun.* **1976**, 338–339.
- [20] N. Naruse, M. Oka, M. Konishi, T. Oki, *J. Antibiotics* **1993**, *46*, 1812–1817.
- [21] A. J. Pearson, K. S. Lee, *J. Org. Chem.* **1994**, *59*, 2304–2313.
- [22] A. Kitani, M. Kaya, J. Yano, K. Yoshikawa, K. Sasaki, *Synth. Met.* **1987**, *18*, 341.
- [23] F.-L. Lu, F. Wudl, M. Nowak, A. J. Heeger, *J. Am. Chem. Soc.* **1986**, *108*, 8311.
- [24] A. G. MacDiarmid, J. C. Chiang, A. F. Richter, A. J. Epstein, *Synth. Met.* **1987**, *18*, 285–290.
- [25] A. G. MacDiarmid, A. J. Epstein, *Faraday Discuss. Chem. Soc.* **1989**, *88*, 317–332.
- [26] A. G. MacDiarmid, A. J. Epstein in *Science and Applications of Conducting Polymers* (Eds.: W. R. Salaneck, D. T. Clark, E. J. Samuelsen), Hilger, New York, **1991**, p. 117.
- [27] A. Ray, A. F. Richter, D. L. Kershner, A. J. Epstein, *Synth. Met.* **1989**, *29*, E141–E150.
- [28] D. Vachon, R. O. Angus, F. L. Lu, M. Nowak, Z. X. Liu, H. Schaffer, F. Wudl, A. J. Heeger, *Synth. Met.* **1987**, *18*, 297.
- [29] M. Stolk, J. F. Yanus, D. M. Pai, *J. Phys. Chem.* **1984**, *88*, 4707.
- [30] E. Ueta, H. Nakano, Y. Shirota, *Chem. Lett.* **1994**, 2397.
- [31] Y. Kuwabara, H. Ogawa, H. Inada, N. Noma, Y. Shirota, *Adv. Mater.* **1994**, *6*, 677.
- [32] M. Strukelj, R. H. Jordan, A. Dodabalapur, *J. Am. Chem. Soc.* **1996**, *118*, 1213.
- [33] P. E. Cassidy *Thermally Stable Polymers: Synthesis and Properties*, Marcel Dekker, New York, **1980**.
- [34] T. M. Miller, T. X. Neenan, E. W. Kwock, S. M. Stein, *J. Am. Chem. Soc.* **1993**, *115*, 356–357.
- [35] A. P. Melissaris, M. H. Litt, *Macromolecules* **1994**, *27*, 888–892.
- [36] J. A. Irvin, C. J. Neef, K. M. Kane, P. E. Cassidy, G. Tullos, A. K. St. Clair, *J. Polym. Sci. Part A: Polym. Chem.* **1992**, *30*, 1675–1679.
- [37] J. March, *Advanced Organic Chemistry*, 3rd ed., Wiley, New York, **1985**.
- [38] G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, J. L. Johnson, *J. Am. Chem. Soc.* **1974**, *96*, 7812–7814.
- [39] P. Marchini, G. Liso, A. Reho, *J. Org. Chem.* **1975**, *40*, 3453–3456.
- [40] C. F. Lane, *Synthesis* **1975**, 135–146.
- [41] J. Lindley, *Tetrahedron* **1984**, *40*, 1433–1456.
- [42] H. L. Aalten, G. van Koten, D. M. Grove, *Tetrahedron* **1989**, *45*, 5565–5578.
- [43] A. J. Paine, *J. Am. Chem. Soc.* **1987**, *109*, 1496–1502.
- [44] H. Weingarten, *J. Org. Chem.* **1964**, *29*, 977–978.
- [45] H. Heaney, *Chem. Rev.* **1962**, *62*, 81–97.
- [46] R. Rossi, R. H. de Rossi, *Aromatic Substitution by the S_{RN}1 Mechanism*, Vol. 178, American Chemical Society, Washington, DC, **1983**.
- [47] J. E. Shaw, D. C. Kunerth, S. B. Swanson, *J. Org. Chem.* **1976**, *41*, 732–733.
- [48] A. J. Pearson, J. G. Park, S. H. Yang, Y.-H. Chuang, *J. Chem. Soc. Chem. Commun.* **1989**, 1363–1364.
- [49] J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, **1987**.
- [50] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524.
- [51] J. K. Stille, *Pure Appl. Chem.* **1985**, *57*, 1771–1780.
- [52] A. Suzuki, *Pure Appl. Chem.* **1994**, *66*, 213.
- [53] A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749.
- [54] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.
- [55] E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348.
- [56] T. Hayashi, Y. Hagihara, Y. Katsuro, M. Kumada, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 363–364.

- [57] T. N. Mitchell, *Synthesis* **1992**, 803–815.
- [58] D. Barañano, G. Mann, J. F. Hartwig, *Curr. Org. Chem.* **1997**, *1*, 287–305.
- [59] D. Cai, J. F. Payack, D. R. Bender, D. L. Hughes, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1994**, *59*, 7180.
- [60] D. Barañano, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, *117*, 2937–2938.
- [61] K. Takagi, *Chem. Lett.* **1987**, 2221–2224.
- [62] M. Kosugi, T. Ogata, M. Terada, H. Sano, T. Migita, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657–3658.
- [63] H. J. Cristau, B. Chabaud, A. Chéne, H. Christol, *Synthesis* **1981**, 892.
- [64] J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, Principles and Applications of Transition Metal Chemistry, 2nd ed., University Science Books, Mill Valley, **1987**, pp. 279–354.
- [65] R. H. Crabtree, *Chem. Rev.* **1995**, *95*, 987–1007.
- [66] S.-Y. Liou, M. Gozin, D. Milstein, *J. Am. Chem. Soc.* **1995**, *117*, 9774–9775, and references therein.
- [67] S. Y. Liou, M. Gozin, D. Milstein, *J. Chem. Soc. Chem. Commun.* **1995**, 1965–1966.
- [68] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, *117*, 4708–4709.
- [69] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.
- [70] G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110.
- [71] L. A. Villanueva, K. A. Abboud, J. M. Boncella, *Organometallics* **1994**, *13*, 3921–3931.
- [72] K. Koo, G. L. Hillhouse, *Organometallics* **1995**, *14*, 4421–4423.
- [73] P. T. Matsunaga, J. C. Mavropoulos, G. L. Hillhouse, *Polyhedron* **1995**, *14*, 175–185.
- [74] E. G. Bryan, B. F. G. Johnson, J. Lewis, *J. Chem. Soc. Dalton Trans.* **1977**, 1328–1330.
- [75] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *108*, 4206–4207.
- [76] M. D. Fryzuk, C. D. Montgomery, *Coord. Chem. Rev.* **1989**, *95*, 1–40.
- [77] H. Bryndza, W. Tam, *Chem. Rev.* **1988**, *88*, 1163–1188.
- [78] P. M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*, Vol. 2, Reidel, Boston, **1980**.
- [79] *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Two Volumes* (Eds.: B. Cornils, W. A. Herrmann), VCH, New York, **1996**.
- [80] R. A. Sheldon, J. K. Kochi, *Metal Catalyzed Oxidations of Organic Compounds: Mechanistic Principles and Synthetic Methodology Including Biochemical Processes*, Academic Press, New York, **1981**.
- [81] G. Cainelli *Chromium Oxidations in Organic Chemistry*, Springer, New York, **1984**.
- [82] M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1989**, *111*, 4108–4109.
- [83] M. R. Gagné, S. P. Nolan, T. J. Marks, *Organometallics* **1990**, *9*, 1716–1718.
- [84] A. L. Casalnuovo, J. C. Calabrese, D. Milstein, *J. Am. Chem. Soc.* **1988**, *110*, 6738–6744, and references therein.
- [85] Recent review: B. R. James, *Chem. Ind.* **1995**, 62, 167–180.
- [86] M. D. Fryzuk, W. E. Piers, *Organometallics* **1990**, *9*, 986–98.
- [87] M. Kosugi, M. Kameyama, T. Migita, *Chem. Lett.* **1983**, 927–928.
- [88] M. Kosugi, M. Kameyama, H. Sano, T. Migita, *Nippon Kagaku Kaishi* **1985**, 3, 547–551.
- [89] D. L. Boger, J. S. Panek, *Tetrahedron Lett.* **1984**, 25, 3175–3178.
- [90] D. L. Boger, S. R. Duff, J. S. Panek, M. Yasuda, *J. Am. Chem. Soc.* **1985**, *50*, 5790–5795.
- [91] D. L. Boger, S. R. Duff, J. S. Panek, M. Yasuda, *J. Org. Chem.* **1985**, *50*, 5782–5789.
- [92] F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970.
- [93] A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902.
- [94] J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, 36, 3609–3612.
- [95] A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem.* **1995**, *107*, 1456–1459; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348–1350.
- [96] S. Zhao, A. K. Miller, J. Berger, L. A. Flippin, *Tetrahedron Lett.* **1996**, 37, 4463–4466.
- [97] J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 1133–1135.
- [98] J. P. Wolfe, R. A. Rennels, S. L. Buchwald, *Tetrahedron* **1996**, *52*, 7525–7546.
- [99] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245.
- [100] J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7010–7011.
- [101] T. Hayashi, M. Konoshi, Y. Kabori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158–163.
- [102] J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
- [103] J. F. Marcoux, R. Widenhoefer, A. Zhong, S. L. Buchwald, results presented at the 213th American Chemical Society National Meeting, San Francisco, CA, **1997**.
- [104] B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, submitted.
- [105] J.-F. Marcoux, S. Wagaw, S. L. Buchwald, *J. Org. Chem.* **1997**, *62*, 1568–1569.
- [106] J. C. Jeffrey, T. B. Rauchfuss, *Inorg. Chem.* **1979**, *18*, 2658–2666.
- [107] K. Takagi, Y. Sakakibara, *Chem. Lett.* **1989**, 1957–1958.
- [108] S. Cacchi, P. G. Ciattini, E. Morera, G. Ortar, *Tetrahedron Lett.* **1986**, 27, 3931–3934.
- [109] J. Louie, M. S. Driver, B. C. Hamann, J. F. Hartwig, *J. Org. Chem.* **1997**, *62*, 1268–1273.
- [110] J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **1997**, *62*, 1264–1267.
- [111] V. Farina, B. Krishnan, D. R. Marshall, G. P. Roth, *J. Org. Chem.* **1993**, *58*, 5434–5444, and references therein.
- [112] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.
- [113] J. Louie, J. F. Hartwig, **1997**, unpublished results.
- [114] F. Paul, J. Patt, J. F. Hartwig, *Organometallics* **1995**, *14*, 3030–3039.
- [115] S. Wagaw, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 7240–7241.
- [116] C. A. Willoughby, K. T. Chapman, *Tetrahedron Lett.* **1996**, *37*, 7181–7184.
- [117] Y. D. Ward, V. Farina, *Tetrahedron Lett.* **1996**, *37*, 6993–6996.
- [118] P. H. H. Hermkens, H. C. J. Ottenheim, D. Rees, *Tetrahedron* **1997**, *52*, 4527–4554.
- [119] A. J. Peat, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 1028–1030.
- [120] T. Kanbara, A. Honma, K. Hasegawa, *Chem. Lett.* **1996**, 1135–1136.
- [121] J. Louie, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 11695–11696.
- [122] M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.
- [123] G. Mann, J. F. Hartwig, *J. Org. Chem.* **1997**, *62*, 5413–5418.
- [124] M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 3395.
- [125] The preparation provides mixtures of L_2Pd and $[L_2PdCl_2]$ in low yields (only citation in the *Chemical Abstracts* database): S. Enomoto, H. Wada Nishida, S. Y. Mukaida, M. Yanaka, H. Takita, *Jpn. Kokai Tokkyo Koho*, **1978**, 7pp, (JP-A 53144552, [*Chem. Abstr.* **1979**, *90*, P205124y]).
- [126] S. Otsuka, T. Yoshida, M. Matsumoto, K. Nakatsu, *J. Am. Chem. Soc.* **1976**, *98*, 5850–5858.
- [127] T. Yoshida, S. Otsuka, *J. Am. Chem. Soc.* **1977**, *99*, 2134–2140.
- [128] T. Yoshida, S. Otsuka, *Inorganic Syntheses*, Vol. 28, **1985**, pp. 113–119.
- [129] A. Davis, J. F. Hartwig, **1996**, unpublished results.
- [130] M. Saunders, L. Telkowski, M. R. Kates, *J. Am. Chem. Soc.* **1977**, *99*, 8070–8071.
- [131] R. B. Calvert, J. R. Shapley, *J. Am. Chem. Soc.* **1978**, *100*, 7726.
- [132] M. Brookhart, M. L. H. Green, L.-L. Wong, *Prog. Inorg. Chem.* **1988**, *36*, 1–124.
- [133] M. Brookhart, M. L. H. Green, *J. Organomet. Chem.* **1983**, *250*, 395.
- [134] J. F. Hartwig, F. Paul, *J. Am. Chem. Soc.* **1995**, *117*, 5373–5374.
- [135] E. Negishi, T. Takahashi, K. Akiyoshi, *J. Chem. Soc. Chem. Commun.* **1986**, 1338.
- [136] A recent synopsis of these mechanisms and their accompanying data is included in C. Amatore, F. Pfluger, *Organometallics* **1990**, *9*, 2276–2282.
- [137] C. Amatore, A. Jutand, A. Suarez, *J. Am. Chem. Soc.* **1993**, *115*, 9531.
- [138] J. K. Stille, K. S. Y. Lau, *Acc. Chem. Res.* **1977**, *10*, 434.
- [139] A. Gillie, J. K. Stille, *J. Am. Chem. Soc.* **1980**, *102*, 4933–4941.
- [140] A. Moravskiy, J. K. Stille, *J. Am. Chem. Soc.* **1981**, *103*, 4182–4186.
- [141] C. Mateo, D. J. Cárdenas, C. Fernández-Rivas, A. M. Echavarren, *Chem. Eur. J.* **1996**, *2*, 1596–1606.
- [142] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
- [143] J. Louie, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, *117*, 11598–11599.
- [144] R. A. Widenhoefer, S. L. Buchwald, *Organometallics* **1996**, *15*, 3534–3542.
- [145] R. A. Widenhoefer, S. L. Buchwald, *Organometallics* **1996**, *15*, 2755–2763.
- [146] R. A. Widenhoefer, H. A. Zhong, S. L. Buchwald, *Organometallics* **1996**, *15*, 2745–2754.
- [147] J. Louie, F. Paul, J. F. Hartwig, *Organometallics* **1996**, *15*, 2794–3005.

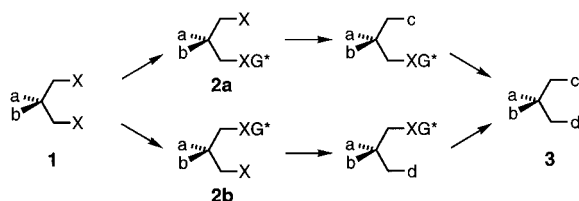
- [148] A. Streitwieser, Jr., **1997**, personal communication.
- [149] M. S. Driver, J. F. Hartwig, *Organometallics* **1997**, *16*, 5706.
- [150] J. F. Hartwig, G. Mann, unpublished results.
- [151] The use of BINAP in Buchwald's lab was initiated by studies on kinetic resolution of chiral amines.
- [152] P. T. Matsunaga, C. R. Hess, G. L. Hillhouse, *J. Am. Chem. Soc.* **1994**, *116*, 3665–3666.
- [153] K. Koo, G. L. Hillhouse, *Organometallics* **1996**, *15*, 2669–2671.
- [154] P. T. Matsunaga, G. L. Hillhouse, A. L. Rheingold, *J. Am. Chem. Soc.* **1993**, *115*, 2075–2077.
- [155] H. E. Bryndza, L. K. Fong, R. A. Paciello, W. Tam, J. E. Bercaw, *J. Am. Chem. Soc.* **1987**, *109*, 1444–1456.
- [156] J. B. Cannon, J. Schwartz, *J. Am. Chem. Soc.* **1974**, *96*, 2276–2278.
- [157] J. Evans, J. Schwartz, P. W. Urquhart, *J. Organomet. Chem.* **1974**, *81*, C37–C39.
- [158] R. J. Cross in *The Chemistry of the Metal-Carbon Bond*, Vol. 2 (Eds.: F. R. Hartley, S. Patai), Wiley, New York, **1985**, p. 559.
- [159] G. M. Whitesides, J. F. Gaasch, E. R. Stedronsky, *J. Am. Chem. Soc.* **1972**, *94*, 5258–5270.
- [160] H. S. Hesslink, J. F. Hartwig, unpublished results.
- [161] J. F. Hartwig, S. Richards, D. Barañano, F. Paul, *J. Am. Chem. Soc.* **1996**, *118*, 3626–3633.
- [162] W. D. Jones, V. L. Kuykendall, *Inorg. Chem.* **1991**, *30*, 2615–2622.
- [163] J. M. Brown, P. J. Guiry, *Inorg. Chim. Acta* **1994**, *220*, 249–259.
- [164] We recently observed backbone-cleavage processes with both DPPF and BINAP: L. Alcazar-Roman, J. F. Hartwig, **1997**, unpublished results.
- [165] M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett.* **1998**, *39*, 617–620.
- [166] K. Rossen, P. J. Pye, A. Maliakal, R. P. Volante, *J. Org. Chem.* **1997**, *62*, 6462–6463.
- [167] J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058.
- [168] N. P. Reddy, M. Tanaka, *Tetrahedron Lett.* **1997**, *38*, 4807–4810.
- [169] M. Beller, T. H. Reirmeier, C. Reisinger, W. A. Herrmann, *Tetrahedron Lett.* **1997**, *38*, 2073–2074.
- [168] J. P. Wolfe, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6359–6362.
- [170] Y. P. Hong, G. J. Tanoury, H. S. Wildinson, R. P. Bakale, S. A. Wald, C. H. Senanyake, *Tetrahedron Lett.* **1997**, *38*, 5663–5666.
- [171] J. P. Wolfe, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6359–6362.
- [172] J. Åhman, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6363–6366.
- [173] J. P. Wolfe, J. Åhman, J. P. Sadighi, R. A. Singer, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6367–6370.
- [174] S. Darses, J.-P. Genêt, J.-L. Brayer, J.-P. Demoute, *Tetrahedron Lett.* **1997**, *38*, 4393–4396.
- [175] J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **1997**, *62*, 6066–6068.
- [176] D. Ma, J. Yao, *Tetrahedron: Asymmetry* **1996**, *7*, 3075–3078.
- [177] S. Wagaw, R. A. Rennels, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 8451–8458.
- [178] I. P. Beletskaya, A. G. Bessmertnykh, R. Guillard, *Tetrahedron Lett.* **1997**, *38*, 2287–2290.
- [179] R. A. Singer, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 213–214.
- [180] R. A. Widenhoefer, H. A. Zhong, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6787–6795.
- [181] R. Han, G. L. Hillhouse, *J. Am. Chem. Soc.* **1997**, *119*, 8135.
- [182] F. E. Goodson, J. F. Hartwig, *Macromolecules* **1998**, *31*, 1700–1703.
- [183] G. Mann, J. F. Hartwig, *Tetrahedron Lett.* **1997**, *38*, 8005–8008.
- [184] G. Mann, M. S. Driver, C. Fernández-Rivas, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 827–828.
- [185] J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2249–2252; *Angew. Chem. Int. Ed.* **1998**, *37*, 2090–2093.

Stereoselection at the Steady State: The Design of New Asymmetric Reactions**

Thomas Wirth*

A reaction leading to an optically pure product in quantitative yield is the dream of every chemist working in the field of asymmetric synthesis. If only catalytic amounts of a chiral compound are needed to achieve this goal, then it is like paradise. But only very few asymmetric reactions have been developed thus far. Compounds with asymmetric centers can be obtained from prochiral starting molecules by either face-selective reactions (stereoheterotopic facial addition) or group-selective reactions (stereoheterotopic ligand substitution). The transition states of these selective stereodivergent reactions must be diastereomeric, and the kinetics are the same as those of parallel reactions with different products (enantiomers or diastereomers). The selectivity in the stereo-selective event leading to the different transition states can never be exceeded by the final yield of the major stereoisomer.

In two recent publications Curran et al. described the theoretical as well as the mathematical background of stereoconvergent reactions.^[1] They give further evidence for their analysis by providing some examples from the field of radical chemistry to demonstrate this strategy called "complex stereoselection". The process of stereoconvergent synthesis was already proposed by Fischli et al. in 1975.^[2] The first step in this process is the nonselective monoprotection of a reactive group (X in **1**) by a chiral agent (G*, Scheme 1).

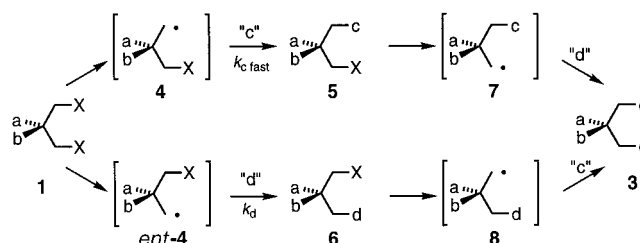


Scheme 1. General progress of a stereoconvergent synthesis.

After separation of the diastereomers **2a** and **2b**, the still reactive groups are converted into "c" and "d". These derivatives generate **3** with a theoretical enantiomeric excess

of 100 % and without destroying any material. The ratio **2a:2b** has no influence on the outcome of the reaction.

Although the subsequent discussion describes the stereoselection at the steady state through the example of radical reactions, the analysis and principles are general for any reaction profile that fits into the scheme of complex stereoselective reactions. In the process proposed and analyzed by Curran et al., the activation of compounds of type **1** is done, for example, by radical formation. The group selectivity in this first step has again no effect on the stereomeric nature of the product. To obtain a stereoconvergent process it is crucial, however, that the reaction is operating at the steady state. This means that the concentrations of the radical intermediates (compounds in brackets in Scheme 2) are low and stationary, while their absolute concentrations are determined by the different rates of reaction.



Scheme 2. Stereoselection at the steady state with the example of a radical reaction.

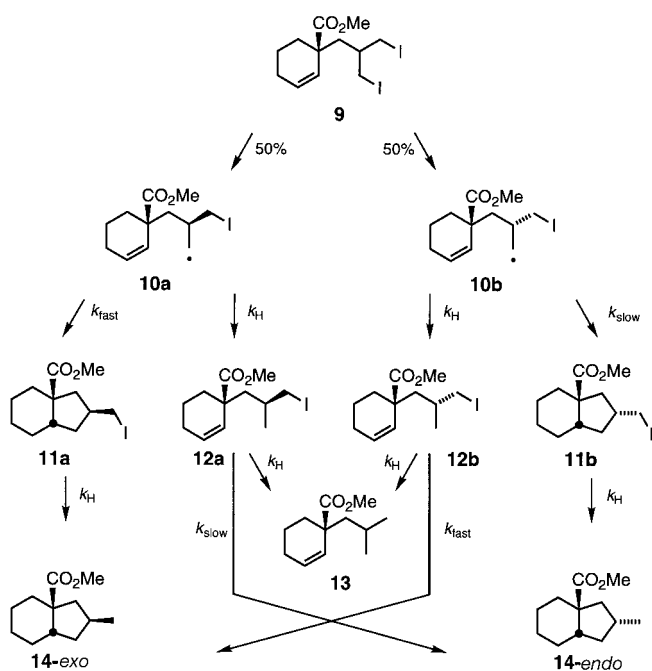
The radicals **4** and *ent*-**4** formed in the first reaction must have competing reaction rates for c and d: The second process must have a reaction rate in competition with the two rates of the first process ($k_{c \text{ fast}} > k_d > k_{c \text{ slow}}$). This means that radical **4** reacts much faster with c than with d yielding product **5**. Radical *ent*-**4**, however, will react faster with d than with c, and **6** will be produced. Compounds **5** and **6** are then activated again by conversion into **7** and **8**. Radical **7** is mismatched for the reaction with c ($k_{c \text{ slow}} < k_d$), and reaction with d provides product **3**. Radical **8** is converted also into **3** as shown in Scheme 2. The achiral products (disubstitution of X with either c or d) result from a leakage out of one convergence and are only minor products because of the reaction rates. Furthermore, it is necessary for the stereoconvergence at the steady state that at least one of these processes (reaction with either c or d) is stereoselective.

[*] Dr. T. Wirth

Institut für Organische Chemie der Universität
St. Johannis-Ring 19, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-1105
E-mail: wirth@ubaclu.unibas.ch

[**] I would like to thank Prof. D. P. Curran for valuable suggestions.

The mathematical description of this and related reaction schemes are complex and will not be discussed here. To verify the analysis of the stereoselection at the steady state experimentally, diastereoselective radical cyclization reactions were selected. Although face-selective radical cyclizations are much more common than the group-selective counterparts,^[3] several model compounds were suggested by Curran et al.^[1] Molecules which have two radical precursors and one radical acceptor group such as **9** were selected to provide experimental verification (Scheme 3). This choice



Scheme 3. Diastereoselective synthesis of **14-exo** and **14-endo** from **9**.

also seems wise from a different point of view: Because the intermediates are radicals, the two competing reactions are an intramolecular cyclization and an intermolecular hydrogen-transfer reaction. The latter is dependent upon the tin hydride concentration. In other words, by varying the tin hydride concentration it is possible to influence the stereochemical outcome of the reaction.

At low tin hydride concentrations the product ratio of **14-exo**:**14-endo** is approximately 1:1; this ratio confirms that there is no selectivity in the first abstraction of iodine by the tin radical. The radicals **10a** and **10b** are formed in equal amounts. Product **13** is not detected. The rate for the subsequent cyclization reaction is, however, different for **10a** and **10b**. Cyclization of radical **10a** to the *exo*-derivative **11a** is faster than the generation of the *endo*-derivative **11b** from **10b**. With increasing tin hydride concentration the competing hydrogen-transfer reaction is opening new paths on the reaction topography. If the faster cyclizing radical **10a** is reduced to **12a** before cyclization occurs, most of the product **12a** will end up as the doubly reduced compound **13**. When the slower cyclizing radical **10b** is reduced, however, most of the resulting product **12b** follows the pathway to the major product **14-exo**. The yield of **14-exo** is, therefore, both

eroded (**12a**→**13**) and supplemented (**12b**→**14-exo**). However, because the concentration of the slower cyclizing radical **10b** always exceeds the concentration of the faster cyclizing radical **10a**, the yield of **14-exo** is supplemented faster than it is eroded (Scheme 3).^[4] This situation is visualized in Figure 1.

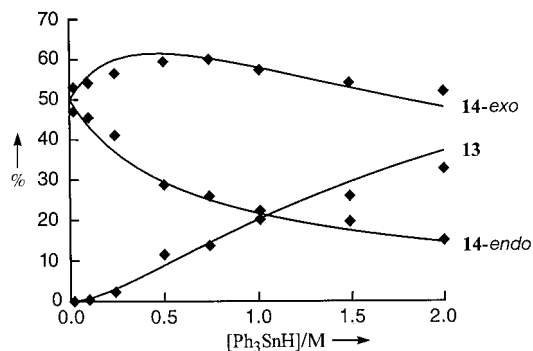


Figure 1. The effect of the tin hydride concentration on the formation of **13**, **14-exo**, and **14-endo** (selectivity approximately five). The experimental results (♦) are compared with the calculated ones (lines).^[5]

The data fits nicely to a $k_{\text{fast}}:k_{\text{slow}}$ ratio of about five. With this selectivity between the major and the minor stereoconvergence, the maximum yield of **14-exo** is about 60 %. The importance of this concept, however, becomes apparent when a selectivity of 500 is assumed. Figure 2 shows the

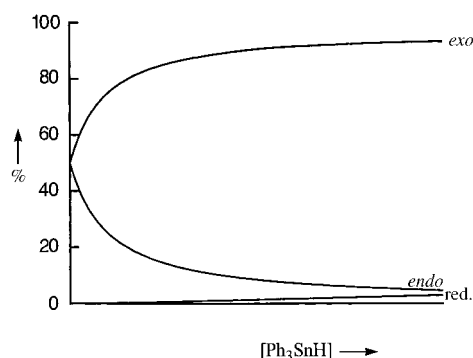


Figure 2. Calculated curves showing the effect of the tin hydride concentration on the formation of **13**, **14-exo**, and **14-endo** when a selectivity of 500 is assumed.

calculated curves for this scenario, whereby an increase in the tin hydride concentration leads to a large *exo*:*endo* ratio.

The reaction of **9** to products **14** is one simple example of a complex stereoselective reaction. Other reactions based on radical chemistry have been suggested by Curran et al., but these reactions with a stereoselection at the steady state are by no means restricted to radical chemistry. Organometallic reactions can also involve transient intermediates which may fulfil the crucial need for competing reactions with different rates, with the rate of the nonselective reaction lying between the rates of the two selective ones. In this context catalytic enantioselective reactions are especially challenging and

could have a high preparative value. The stage is now set for the discovery of new stereoconvergent reactions orchestrated by stereoselection at the steady state.

German version: *Angew. Chem.* **1998**, *110*, 2179–2181

Keywords: asymmetric synthesis • chirality • radical reactions • steady state

- [1] a) N. C. DeMello, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 329–341.
b) D. P. Curran, C.-H. Lin, N. DeMello, J. Junggebauer, *J. Am. Chem. Soc.* **1998**, *120*, 342–351.
- [2] A. Fischli, M. Klaus, H. Meyer, P. Schönholzer, R. Rüegg, *Helv. Chim. Acta* **1975**, *58*, 564–584.
- [3] a) D. P. Curran, S. J. Geib, C. H. Lin, *Tetrahedron: Asymmetry* **1994**, *5*, 199–202. b) D. P. Curran, W. Shen, J. Zhang, S. J. Geib, C.-H. Lin, *Heterocycles* **1994**, *37*, 1773–1788.
- [4] The pairs of fast and slow rate constants are assumed to be equal to simplify the theoretical analysis.
- [5] The following rate constants were used for the calculation: $k_{\text{fast}} = 4.6 \times 10^7 \text{ s}^{-1}$; $k_{\text{slow}} = 1.0 \times 10^7 \text{ s}^{-1}$; $k_{\text{H}} = 2.0 \times 10^7 \text{ s}^{-1}$.

Phosphanides of the Heavier Alkali Metals

J. David Smith*

Much of the fascination of inorganic chemistry lies in the study of trends in the periodic table, up and down groups, across periods, and diagonally. Compounds of the same stoichiometry are compared, similarities noted, and attempts made to understand subtle differences. It has been commonplace in teaching inorganic chemistry to cover the marked changes from carbon to lead or from nitrogen to bismuth in considerable detail, and to pass rather quickly over some of the other groups—for example, the alkali metals, alkaline earths, or halogens—because the variation from the top to the bottom of the periodic table is much smaller. In these groups near the sides of the table the chemistry is dominated by one oxidation state, but it is rash to assume that the chemistry of those elements which have been less fully studied will simply mirror that of the compounds that are well known. Factors other than oxidation state, for example size and polarizability, have to be considered, and these may give much greater variety in the chemistry of, for example, elements from Groups 1, 2, 3, or 17 than is sometimes acknowledged.

This point is illustrated for the chemistry of the Group 1 elements in the recent paper by Rabe et al.^[1] on the structure of the rubidium and cesium phosphanides M₂PHR (M = Rb, Cs, R = 2,6-dimesitylphenyl (**1**)). General interest in the reactions of alkali metals with phosphanes comes from their widespread use in the synthesis of phosphorus-containing ligands. The lithium phosphanides of general formula LiPHR or LiPR₂ show a wide variety of structures that were summarized recently by Becker et al.^[2] A few compounds—especially

those in which the lithium atom is complexed by large ligands, for example, [12]crown-4—are ionic,^[2, 3] that is, [LiL_n][PR₂]. Monomeric molecular structures are rare. More commonly, the molecules associate to give ladder or helical structures which may be oligomeric or polymeric^[2, 4] (Figure 1) like the

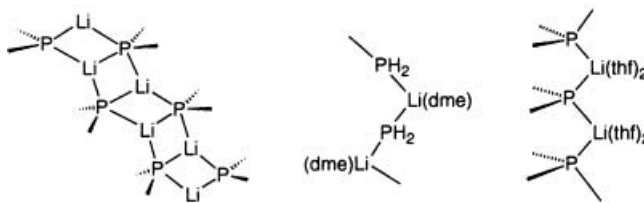


Figure 1. Some structures of lithium phosphanides (taken from reference [4]). dme = 1,2-dimethoxyethane.

corresponding amido compounds.^[5] Information on the structures of sodium and potassium phosphanides is sparse, but the few examples that have been reported show that they fit into the same overall pattern. Polymeric ladder structures, based on alkali metal–phosphorus bonds, predominate.^[6]

The general principles underlying this pattern of structures were defined in a seminal paper^[7] many years ago, and they apply to most groups of oligomeric compounds containing an element from Groups 1–3 (M) and one from Groups 15–17 (E). Firstly, for the formation of higher from lower oligomers, the enthalpy change associated with the formation of additional M–E bonds must be sufficient to overcome the unfavorable entropic contribution to the free energy. Secondly, the oligomerization or polymerization is curtailed by the attachment of large groups to either element. In the last few years very bulky aryl groups such as **1** have been used for this purpose, and a range of main group compounds showing highly unusual structural features have been obtained.^[3, 8]

Rabe et al.^[1] studied the reactions of the heavier alkali metals rubidium and cesium with the very bulky 2,6-dimesi-

[*] Dr J. D. Smith
School of Chemistry, Physics and Environmental Science
University of Sussex, BN1 9QJ (UK)
Fax: (+44) 1273-677-196
E-mail: j.d.smith@sussex.ac.uk

tylphenylphosphane. Yellow crystals of the rubidium compound RbPHR were obtained from toluene, and crystals of the cesium compound from toluene containing the bases tetrahydrofuran (THF) or *N*-methylimidazole (*N*-MeIm). X-ray studies showed that the solid-state structures differed from those of previously described alkali metal salts of primary phosphanes.

The rubidium compound adopts a cubane structure [RbPHR]₄ (Figure 2a) of the kind that is common among the alkoxo, thiolato, and imido derivatives of main group

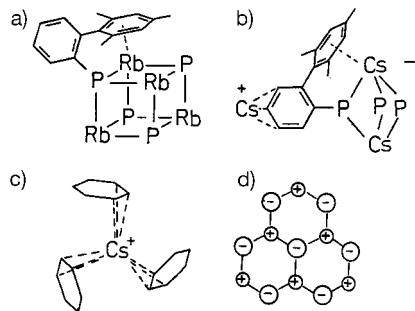


Figure 2. Partial structures of the rubidium and cesium phosphanides **2** and **3**. a) Partial structure of **2**; b) partial structure of **3**; c) coordination of the cation in **3**; d) the two-dimensional net in **3** showing the cavities occupied by solvent.

elements. For compounds in which $M = \text{alkali metal}$ examples of $(MCl)_4$ and $(MOR)_4$ are known: [RbPHR]₄ (**2**) extends the isoelectronic series. However, whereas many halides and alkoxo derivatives require lone pairs from bases such as THF to complete the coordination sphere of the alkali metal, for example $[\text{Li}\{\text{OP}(\text{NMe}_2)_3\}\text{Cl}]_4$ or $[\text{Li}(\text{thf})\text{OC}t\text{Bu}=\text{CH}_2]_4$,^[9] these are excluded in **2**, and electrons are donated instead from the mesityl rings from phosphanido ligands encapsulating the rubidium atoms (Figure 2a). The metal–aryl interactions must therefore compete successfully with the metal–lone pair interactions.

The cesium compound forms a two-dimensional ionic structure described by the formula $\text{Cs}^+[\text{Cs}_2(\text{PHR})_3]^-$ (**3**). Within the anion the two cesium atoms are linked by three PHR bridges and protected by mesityl groups on the periphery of the ligands R, rather like the rubidium atoms in **2** (Figure 2b). The cesium cations are coordinated by the central phenyl groups of the phosphane ligands at the 3-, 4-, and 5-positions. The two-dimensional structure as a whole has threefold symmetry about axes through the two cesium atoms of the anion. Since each cesium cation is bound to ligands from three separate anions, its coordination resembles that of a paddle wheel (Figure 2c). The net of cations and anions has a series of holes which accommodate toluene solvate molecules as in a host–guest compound (Figure 2d). The toluene molecules are readily removed under reduced pressure to leave a solid which will not redissolve in toluene without the addition of a base such as THF, pyridine, or *N*-MeIm; however, upon crystallization the metal–aryl interactions are, as in **2**, sufficiently strong to exclude the base from the cesium coordination sphere.

What other general points can be made about these two unexpected new structures? Firstly, they provide examples of

a general pattern which is now recognized to be widely applicable. In a series of compounds with the same overall stoichiometry, for example $M^+[\text{EAr}_n]^-$, the lighter alkali metals lithium and sodium tend to make bonds with the electronegative elements E, whereas the heavier, softer, more polarizable alkali metals rubidium and cesium frequently interact most strongly with aryl groups on the ligand periphery. There are exceptions to this rule, but the general tendency is clear as shown by data on organometallic compounds^[10] as well as aryloxo and arylthiolato derivatives.^[11] This is illustrated here by just one example chosen from many others in the literature. The structure of the mixed alkoxide $\text{Cs}_2\text{La}(\text{OAr})_5$ ($\text{Ar} = 2,6\text{-diisopropylphenyl}$)^[12] consists of layers of two-dimensional sheets containing cesium cations and $\text{La}(\text{OAr})_5$ anions linked by cesium–aryl interactions, and the sheets are linked by additional cesium–aryl contacts into a three-dimensional framework leaving channels which can accommodate toluene solvate molecules (c.f. **2**). The coordination sphere of each of the three independent cesium atoms in the complex structure is made up entirely of 19 Cs–C contacts, and there is no Cs–O distance that is smaller than 450 pm.

Secondly, the structures suggest that the balance between metal–aryl and metal–phosphorus interactions is subtle. A small change from rubidium to cesium can produce a drastic change in structure. Since the ligand remains the same the difference must arise from the relative strengths of metal–phosphorus and metal–aryl interactions. It would be interesting to know whether systematic changes in structure can be induced by changes in substituents on the aryl rings, and what part is played by the steric requirements of the ligand in determining the structures of compounds in which there are lithium–aryl interactions, for example $[\text{LiR}'\text{LiPHR}']_2$ (**4**, $\text{R}' = 2,4,6\text{-}t\text{Bu}_3\text{C}_6\text{H}_2$)^[12] (Figure 3). The increased importance of metal–aryl interactions for the heavier alkali metals has been demonstrated in a number of computational studies.^[13]

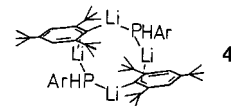


Figure 3. Aryl–lithium interactions in **4**.

Thirdly, structures studied by X-ray diffraction are those of compounds which crystallize; they do not necessarily indicate the species in solution, though they may provide strong pointers. The development of modern gloveboxes and improvements in equipment for vacuum lines allow rigorous control of blanket-gas composition so that very air- and moisture-sensitive organo, alkoxo, amido, and phosphanido compounds may be safely manipulated. It is likely that many more compounds of the heavier alkali and alkaline earth metals will be studied in the next few years. The incentive will come both from interest in the new structures themselves and from those engaged in the preparation of phosphanes for incorporation into catalysts for asymmetric syntheses or polymerization.^[14] If the compounds of rubidium and cesium prove to be more reactive than the analogous compounds of lithium and sodium, they could be used as ligand transfer reagents at lower temperatures and therefore with fewer side reactions and less racemization. The extent to which the metal–aryl interactions can be broken down in solution is not

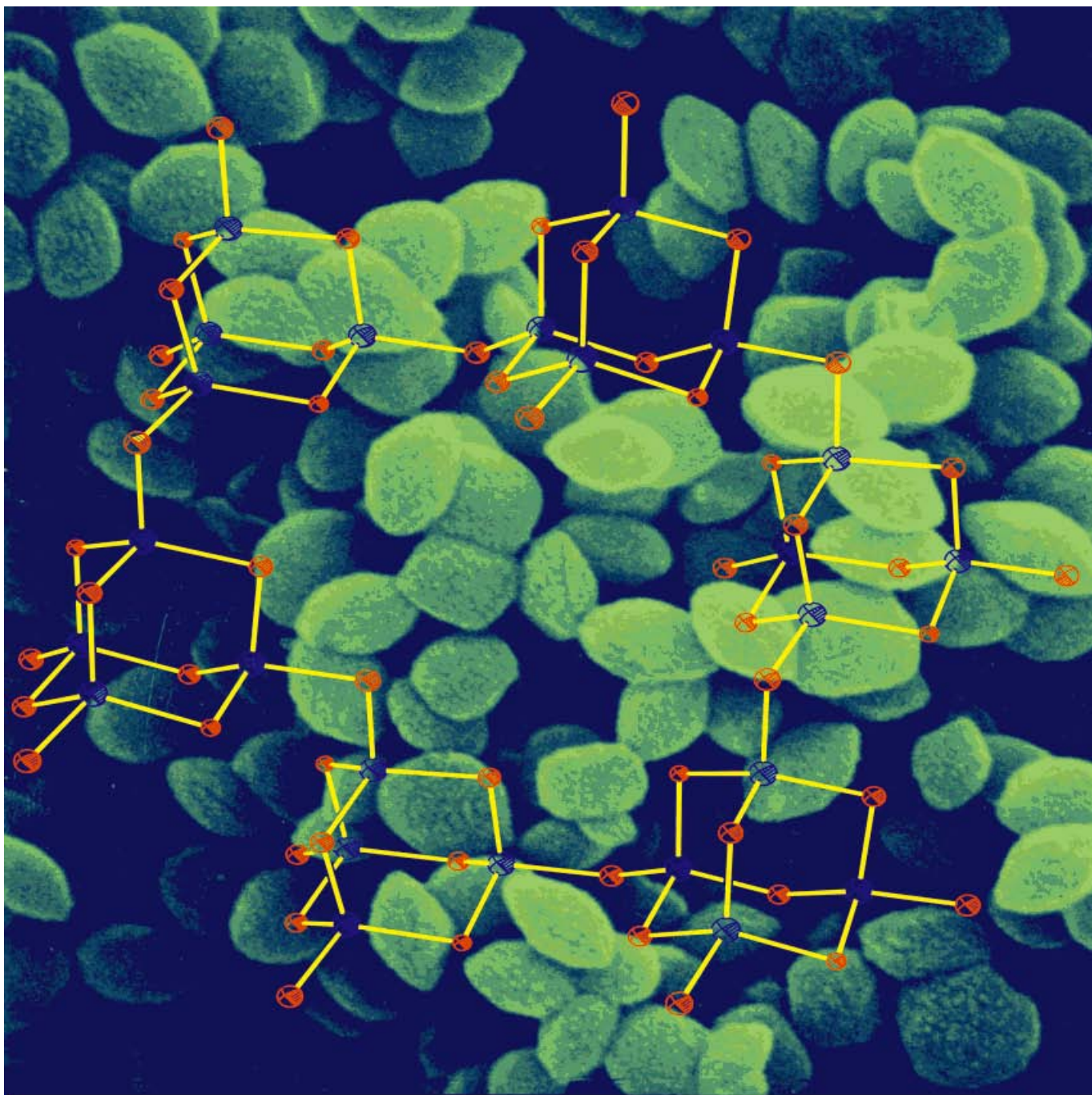
yet clear. Compounds **2** and **3** proved to be insoluble in organic solvents in the absence of base. Is this a general characteristic for such compounds?

Good research answers some questions but raises others. There is considerable scope for further investigation before the chemistry of the heavier alkali metal phosphanides is understood.

German version: *Angew. Chem.* **1998**, *110*, 2181–2183

Keywords: alkali metals • cesium • P ligands • rubidium • solid-state structures

-
- [1] G. W. Rabe, S. Kheradmandan, L. M. Liable-Sands, I. A. Guzei, A. L. Rheingold, *Angew. Chem.* **1998**, *110*, 1495; *Angew. Chem. Int. Ed.* **1998**, *37*, 1404.
- [2] G. Becker, B. Eschbach, D. Käshammer, O. Mundt, *Z. Anorg. Allg. Chem.* **1994**, *620*, 29.
- [3] H. Hope, M. M. Olmstead, P. P. Power, X. Xu, *J. Am. Chem. Soc.* **1984**, *106*, 819; R. A. Bartlett, H. V. Rasika Dias, H. Hope, B. D. Murray, M. M. Olmstead, P. P. Power, *J. Am. Chem. Soc.* **1986**, *108*, 6921.
- [4] M. Driess, G. Huttner, N. Knopf, H. Pritzkow, L. Zsolnai, *Angew. Chem.* **1995**, *107*, 354; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 316.
- [5] R. E. Mulvey, *Chem. Soc. Rev.* **1991**, *20*, 167.
- [6] G. W. Rabe, G. P. A. Yap, A. L. Rheingold, *Inorg. Chem.* **1997**, *36*, 1990.
- [7] O. T. Beachley, G. E. Coates, *J. Chem. Soc.* **1965**, 3241.
- [8] R. J. Wehmschulte, J. J. Ellison, K. Ruhlandt-Senge, P. P. Power, *Inorg. Chem.* **1994**, *33*, 6300; R. J. Wehmschulte, P. P. Power, *Inorg. Chem.* **1996**, *35*, 3262; J. Su, X.-W. Li, R. C. Crittendon, G. H. Robinson, *J. Am. Chem. Soc.* **1997**, *119*, 5471.
- [9] D. Barr, W. Clegg, R. E. Mulvey, R. Snaith, *J. Chem. Soc. Chem. Commun.* **1984**, 79; R. Amstutz, W. B. Schweizer, D. Seebach, J. D. Dunitz, *Helv. Chim. Acta*, **1981**, *64*, 2617.
- [10] J. D. Smith, *Adv. Organomet. Chem.* **1998**, im Druck.
- [11] M. Niemeyer, P. P. Power, *Inorg. Chem.* **1996**, *35*, 7264; S. Chadwick, U. Englich, K. Ruhlandt-Senge, *Organometallics* **1997**, *16*, 5792.
- [12] D. L. Clark, G. B. Deacon, T. Feng, R. V. Hollis, B. L. Scott, B. W. Skelton, J. G. Watkin, A. H. White, *Chem. Commun.* **1996**, 1729.
- [13] J. W. Caldwell, P. A. Kollman, *J. Am. Chem. Soc.* **1995**, *117*, 4177; D. Hoffmann, W. Bauer, F. Hampel, N. J. R. van Eikema Hommes, P. von R. Schleyer, P. Otto, U. Pieper, D. Stalke, D. S. Wright, R. Snaith, *J. Am. Chem. Soc.* **1994**, *116*, 528; H. Bock, K. Ruppert, C. Näther, Z. Havlas, H.-F. Herrmann, C. Arad, I. Göbel, A. John, J. Meuret, S. Nick, A. Rauschenbach, W. Seitz, T. Vaupel, B. Solouki, *Angew. Chem.* **1992**, *104*, 564; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 550.
- [14] S. Kurz, E. Hey-Hawkins, *Organometallics* **1992**, *11*, 2729.
- [15] *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**.
-



The high-temperature high-pressure phase of GeS_2 (δ) has been formed under very mild conditions by a rational assembly of adamantanoid $[\text{Ge}_4\text{S}_{10}]^{4-}$ clusters. An X-ray structure determination revealed two interpenetrating expanded cristobalite networks. Find out more on the following pages.

Synthesis and Crystal Structure of δ -GeS₂, the First Germanium Sulfide with an Expanded Framework Structure**

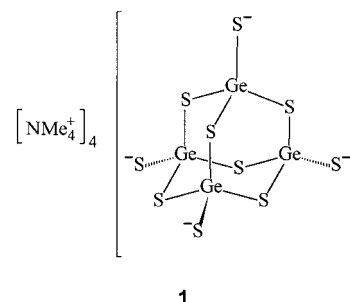
Mark J. MacLachlan, Srebri Petrov, Robert L. Bedard, Ian Manners,* and Geoffrey A. Ozin*

Germanium sulfides are attractive materials because of their interesting electronic and optical properties.^[1] They have potential applications in hologram recording media, optical coatings, fiber optics, solid-electrolyte lithium batteries, and semiconductors.^[1–4] Although one might expect germanium sulfides to adopt the myriad of topologies found in silicates and aluminosilicates (for example, zeolites), only dense phases of GeS₂ are known to date, and they are generally prepared under extreme conditions. Here we report the low-temperature self-assembly of adamantanoid [Ge₄S₁₀]^{4–} clusters to form a crystalline modification of GeS₂ with an expanded framework.

The two common dense phases of GeS₂ are the α modification, a layered semiconductor that crystallizes in the monoclinic space group *Pc*, and the β modification, which crystallizes in the monoclinic space group *P2₁/c*.^[5] Prewitt and Young reported a dense high-temperature and high-pressure γ -GeS₂ structure in which GeS₄ units are connected in a three-dimensional tetragonal cristobalite-related network (space group *I*4̄2*d*).^[6] Moreover, Viaene and Moh reported a high-pressure/high-temperature (γ) form of GeS₂ that is stable above 3000 bar at 600 °C and can be quenched to give a metastable phase at room temperature.^[7] This phase was subsequently obtained by Wang and Horn from α -GeS₂ by hydrothermal synthesis at 1000 bar and 840 °C for 2 d, then 5000 bar at 575 °C for 7 d.^[8] From powder diffraction data (ICCD PDF-2 Database, file no. 27-0239), they identified the crystalline phase as a tetragonal compound in the space group *I*4₁/*acd* with *Z* = 32, but were unable to deduce its structure. Since 1973 this phase of GeS₂ has been absent from the literature. Although structures of other modifications were reported, no further studies of γ -GeS₂ were undertaken. In discussions of GeS₂, this form was frequently omitted or assumed to be identical to the phase described by Young et al.

To avoid confusion with the γ -GeS₂ of Young et al., we renamed the phase described by Wang et al. as δ -GeS₂.

We have now discovered a low-temperature route to δ -GeS₂ which involves the polycondensation of [(CH₃)₄N]⁺₄-Ge₄S₁₀ (**1**) under acidic conditions. A representative scanning



electron micrograph of crystals synthesized at 50 °C is shown in Figure 1. The material consists of fairly monodisperse rounded prisms. Energy dispersive X-ray analysis of the

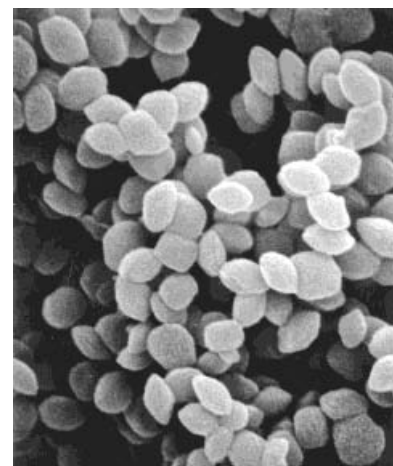


Figure 1. A scanning electron micrograph of crystalline δ -GeS₂ shows its fairly monodisperse rounded prism morphology. Average particle size approximately 200 nm.

material established the composition to be GeS₂. Comparison of the Raman spectrum with that of the precursor **1** confirmed the presence of the adamantanoid cluster in the product (Figure 2). Notably, the spectra are similar in the skeletal

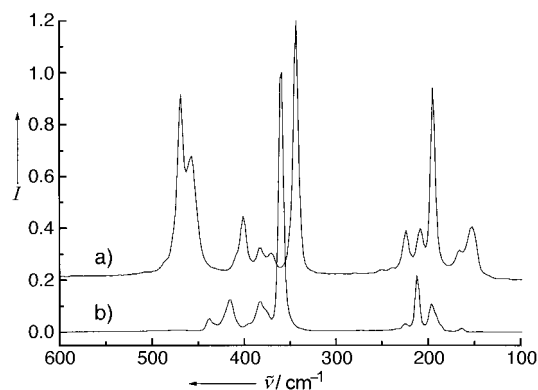


Figure 2. The Raman spectra of **1** (a) and crystalline δ -GeS₂ (b) are remarkably similar in the Ge–S stretching region. This confirms the presence of [Ge₄S₁₀] clusters in the structure.

[*] Prof. Dr. I. Manners, Prof. Dr. G. A. Ozin, M. J. MacLachlan, Dr. S. Petrov
Lash Miller Chemical Laboratories
University of Toronto
80 St. George Street, Toronto, M5S 3H6 (Canada)
Fax: (+1) 416-971-2011
E-mail: imanners@alchemy.chem.utoronto.ca
gozin@alchemy.chem.utoronto.ca

Dr. R. L. Bedard
UOP Research Center, Des Plaines, IL 60017–5017 (USA)

[**] Generous financial support of this work by the Natural Sciences and Engineering Research Council of Canada (NSERC) is deeply appreciated. Continuing support of the microporous metal chalcogenide work by UOP is gratefully acknowledged. G.A.O. acknowledges the Killam Foundation for the award of an Isaac Walton Killam Research Fellowship (1995–1999). I.M. and M.J.M. are indebted to NSERC for a Steacie Fellowship (1997–1999) and a post-graduate scholarship (1995–1999), respectively. We thank Dr. Neil Coombs for assistance with the recording of the SEM image.

region (470–140 cm⁻¹), and the most intense fully symmetrical Ge–S_t and Ge–S_b stretching frequencies (S_t and S_b = terminal and bridging S atoms) of the product are blue-shifted with respect to the precursor by about 20 cm⁻¹. This implies that the clusters are intact and interlinked in the product. Extremely weak Raman bands in the regions of C–H and S–H stretches indicate the presence of traces of surface-bound organic groups and thiol groups.

A detailed analysis of 47 unique reflections of the powder X-ray diffraction (PXRD) data confirmed the tetragonal space group *I*₄/acd (no. 142). Moreover, besides the necessary extinction conditions for this space group, additional special conditions were revealed: *hkl*: *l*, *h* + *k* = 2*n* + 1 and *hkl*: *l* = 2*n*, 2*k* + *l* = 4*n*. These suggest the presence of atoms in special positions with the Wyckoff notations *e* (*x*, 0, 1/4) and *d* (0, 1/4, *z*). On the assumption that tetrahedral GeS₄ units would be the primary building blocks, as in all other GeS₂ structures, we concluded that the Ge atom and one S atom occupy general positions, and two S atoms special positions.

A suitable starting model for Rietveld refinement of δ-GeS₂ was an extremely hygroscopic polymorph of ZnI₂, which has a similar space group to δ-GeS₂.^[9, 10] The result of the high-quality Rietveld refinement (*R*_p = 8.4 %) of δ-GeS₂ is shown in Figure 3. Atomic coordinates and isotropic displacement

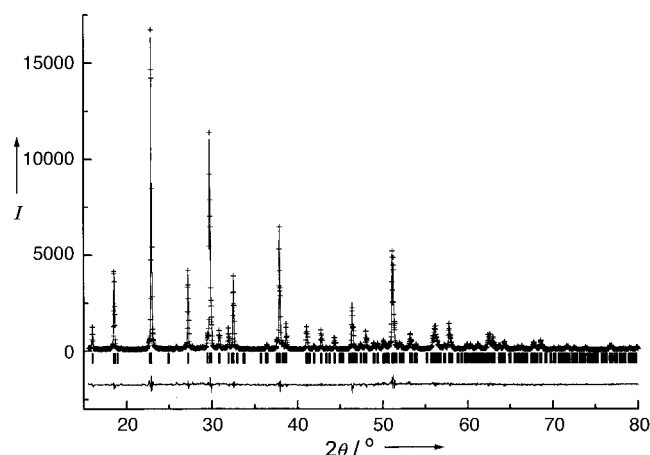


Figure 3. Observed (+), calculated (solid line), and difference (lower solid line) profiles from Rietveld refinement of the PXRD data of δ-GeS₂. *I* = intensity in arbitrary units.

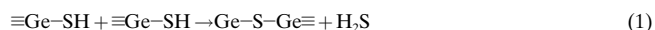
factors are presented in Table 1. Views of the adamantanoid [Ge₄S₁₀] cluster in the structure and the 24-atom ring composed of six Ge(μ-S)Ge-linked Ge₄S₆S_{4/2} clusters in the network are shown in Figures 4a and 4b, respectively. The Ge–S bond lengths in the structure (2.194(4)–2.225(4) Å) are nearly identical and, like the bond angles, are consistent with those observed in the other Ge₄S₁₀-based structures.^[11–15]

Table 1. Atomic coordinates and isotropic displacement factors *U*_{iso} [Å²] for δ-GeS₂

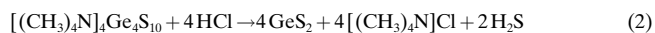
Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>U</i> _{iso} × 10 ²
Ge	0.3745(1)	0.3439(2)	0.0604(1)	2.77
S(1)	0.0	0.25	0.0124(2)	1.23
S(2)	0.2876(5)	0.0	0.25	2.18
S(3)	0.0345(3)	1.0166(3)	0.3760(2)	1.84

There is an intriguing topological relationship between the γ-GeS₂ structure of Young et al. and that of the new phase δ-GeS₂. Both are based on tetrahedral building blocks: GeS₄ in the former and Ge₄S₁₀ in the latter. This can best be visualized by focusing on the Ge atoms and omitting the S atoms for the sake of clarity. Replacing the Ge atom in γ-GeS₂ by an adamantanoid Ge₄ cluster and applying the acentric space group of γ-GeS₂ (*I*₄2*d*) produces one of the interpenetrating frameworks of δ-GeS₂ (Figure 4c, d). The second interpenetrating framework of the δ form is the enantiomer of the first, to which it is related by a center of symmetry (Figure 4e, f), as indicated by the centric space group of the δ-form (*I*₄/acd). In essence, the new structure is an expanded version of the earlier cristobalite-like structure of γ-GeS₂. An interesting analogy exists between the pairs γ-GeS₂/δ-GeS₂ and cristobalite/silica faujasite, in which tetrahedral SiO₄ units are replaced by Si₂₄O₄₈ sodalite cages to give the zeolite structure.^[16] The expansion from Ge to Ge₄ structural units generates sufficient empty space for the co-crystallization of a second framework, which is the mirror image of the first.

We propose that the formation of δ-GeS₂ in the aqueous acidic medium occurs by a bimolecular nucleophilic substitution (“S_N2”) reaction in which protonated [Ge₄S₁₀]⁴⁺ clusters undergo condensation polymerization [Eq. (1)].



This leads to formation of the unexpected crystalline product δ-GeS₂ from the organized assembly of [Ge₄S₁₀]⁴⁺ clusters [Eq. (2)], rather than the amorphous cross-linked network that would be expected from random polymerization of the clusters.



In situ high-temperature powder X-ray diffraction indicates that the δ-GeS₂ phase is still stable above 620 °C. The volume of the unit cell increases steadily up to this temperature, while the *c* axis of the unit cell contracts slightly. Differential expansion/contraction effects of this type are well documented in uniaxial crystal systems whose lattices are composed of four-connected three-dimensional networks.^[17] The phenomenon originates from thermally induced changes in bond angles between tetrahedral building blocks, which result in an untwisting of the entire network.

We have demonstrated, for the first time, the preparation of the high-pressure/high-temperature phase δ-GeS₂ in aqueous solution. This mild sol–gel process provides a novel route to a new type of 1v/1 binary metal dichalcogenide whose structure is based upon two interpenetrating expanded cristobalite frameworks. The structure may serve as a model for other expanded XY₂ phases. With a suitable template or solvent, we believe the interpenetration of the networks can be eliminated to generate a new family of crystalline open-framework germanium sulfides with wide range of potential applications in the materials sciences.

Experimental Section

[(CH₃)₄N]₄Ge₄S₁₀ (**1**) was prepared by a literature procedure.^[12] δ-GeS₂ was prepared by two methods: a) Hydrochloric acid (9.6 mL, 0.22 M,

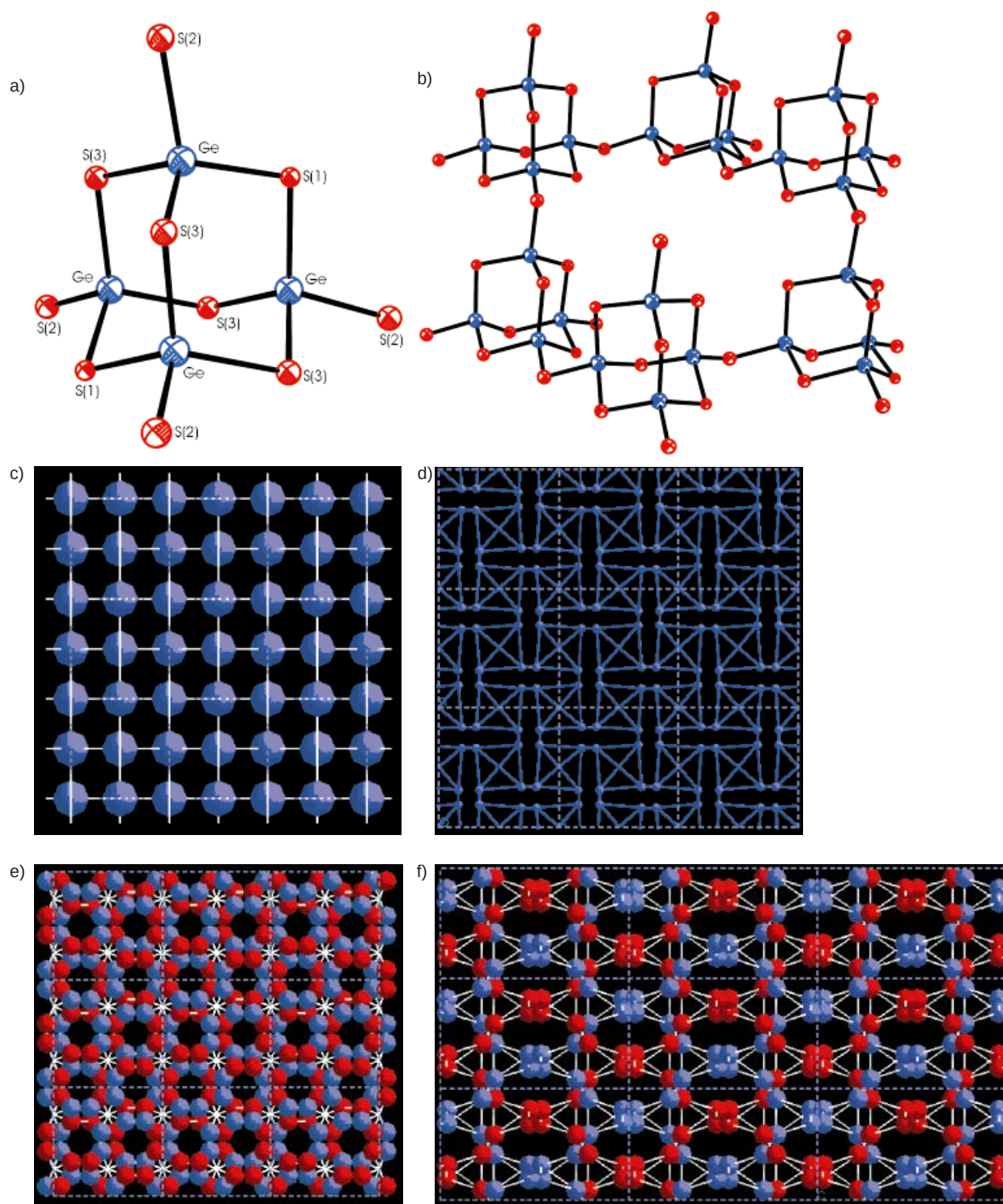


Figure 4. a) The adamantoid [Ge₄S₁₀] cluster secondary building block of δ -GeS₂. b) The largest ring in each interpenetrating network of the δ -GeS₂ structure is a 24-atom [Ge₁₂S₁₂] ring that consists of six Ge(μ -S)Ge-linked [Ge₄S₆S_{4/2}] clusters. c) Projection of the structure of γ -GeS₂ reported by Young and Prewitt on the *ab* plane. d) Projection of the structure of one of the interpenetrating cristobalite-like networks in δ -GeS₂ on the *ab* plane. e) Projection of the two interpenetrating cristobalite-like networks in δ -GeS₂ on the *ab* plane. They are related by a center of symmetry to give interpenetrating enantiomeric frameworks. f) As in e), but with projection on the *ac* plane. (The S atoms are omitted from c)–f) for clarity.)

2.1 mmol) was added dropwise to a stirred solution of **1** (343 mg, 0.38 mmol) in 8.0 mL of water. The solution became viscous and cloudy, and H₂S was evolved. After 24 h at 50 °C, the off-white precipitate was isolated by centrifugation and washed with water, THF, and acetone to obtain 44 mg (22%) of product. b) In a Teflon-lined vessel, **1** (579 mg, 0.638 mmol) in H₂O (1 mL) and hydrochloric acid (10 mL, 0.25 M,

2.5 mmol) were combined. A cloudy white mixture resulted. The vessel was sealed in a stainless-steel hydrothermal autoclave and heated to 150 °C for 24 h. Once cooled to room temperature, the off-white precipitate was isolated on a Buchner funnel and washed with water, THF, and acetone to give 157 mg (44%) of δ -GeS₂. PXRD confirmed the crystallinity of both δ -GeS₂ products.

The PXRD analysis of δ -GeS₂ was carried out on a Siemens D5000 diffractometer with Bragg–Brentano $\theta/2\theta$ geometry. The source radiation (Cu_{K α} , $\lambda = 1.54059 \text{ \AA}$) was obtained from a high-power line-focus Cu target, and the secondary beam was monochromatized by a Kevex solid-state detector. The diffraction pattern was initially indexed with the program ITO,^[18] which provided a tetragonal, I-type unit cell. Further lattice refinement was performed with the Appleman and Evans program^[19] by using the first 51 measured reflections (34 unique) within the range $14 \leq 2\theta \leq 70^\circ$. The refinement [$M_{20} = 23.3$, $F_{30} = 27.5$ (0.012, 89)] gave the space group $I4_1/acd$ (no. 142) based on both general and special conditions for systematic absences/extinctions, as discussed in the text. Several other related space groups were also tested as possible sub- or superlattices, but were not fitted successfully. The final structure was obtained by refinement of atomic parameters with the program GSAS 6.0 (PC version).^[20] Crystallographic data for δ -GeS₂: $I4_1/acd$, $a = 11.0650(1)$, $c = 18.7178(2) \text{ \AA}$, $V = 2291.71 \text{ \AA}^3$, $\rho_{\text{calc}} = 3.17 \text{ g cm}^{-3}$, $Z = 32$, $R_{\text{wp}} = 0.1159$, $R_p = 0.0842$, $R_{\text{Bragg}} = 0.0927$, $\chi^2 = 4.351$, measurement range $12 \leq 2\theta \leq 80^\circ$, 3400 data points, 372 observed reflections, 34 parameters refined. The peak profiles were fitted by a pseudo-Voigt function,^[21] and a Finger–Cox–Jephcoat asymmetry correction was applied.^[22]

Raman spectra were recorded on a Bomems MB-157 FT spectrometer with an InGaAs NIR laser (100 mW). The instrument was configured in the 180° backscattering mode, and samples were sealed in glass capillary tubes. Spectra were recorded with a resolution of 4 cm^{-1} , and about 100 scans were made to achieve an excellent signal-to-noise ratio.

Received: January 22, 1998 [Z11391 IE]
German version: *Angew. Chem.* **1998**, *110*, 2185–2189

Keywords: clusters • germanium • solid-state structures • sulfur • sol–gel processes

- [1] a) M. Saji, H. Kubo, *Nagoya Kogyo Daigaku Gakuho* **1981**, *32*, 213; b) Z. G. Ivanova, *Thin Solid Films* **1995**, *256*, 257; c) A. A. Lavrentyev, A. N. Gusatinskii, I. Y. Nikiforov, N. Y. Safontseva, *Physica B* **1995**, *209*, 344; d) D. R. Simons, A. J. Faber, H. Dewaal, *J. Non-Cryst. Solids* **1995**, *185*, 283; e) D. Marchese, G. Kakarantzas, A. Jha, B. N. Samson, J. Wang, *J. Mod. Optics* **1996**, *43*, 963.
- [2] P. P. Pogoretskii, E. N. Sal'kova, M. S. Soskin, D. I. Bletskan, I. F. Kopinets (Institute of Physics, Academy of Sciences, Ukrainian S.S.R.), SU-B 453976, **1976** [*Chem. Abstr.* **1976**, *85*, 134491z].
- [3] M. Haase, H. Bechtel, W. Czarnojan, D. Waedow (Philips Electronics N.V.), EP-B 714966, **1996** [*Chem. Abstr.* **1996**, *125*, 99556v].
- [4] S. Kondo, K. Takada (Matsushita Electric Ind. Co. Ltd.), JP-B 05205741, **1993** [*Chem. Abstr.* **1994**, *120*, 34524k].
- [5] a) G. Dittmar, H. Schäfer, *Acta Crystallogr. B* **1976**, *32*, 1188; b) G. Dittmar, H. Schäfer, *Acta Crystallogr. B* **1975**, *31*, 2060; c) D. I. Bletskan, I. M. Mitrovtsev, V. A. Stefanovich, M. V. Potorii, Yu. V. Voroshilov, V. Yu. Slivka, *Sov. Phys. Crystallogr. (Engl. Transl.)* **1987**, *32*, 224.
- [6] C. T. Prewitt, H. S. Young, *Science* **1965**, *149*, 535.
- [7] W. Viaene, G. H. Moh, *Neues Jahrb. Mineral. Abh.* **1973**, *119*, 113.
- [8] N. Wang, E. Horn, *Neues Jahrb. Mineral. Monatsh.* **1973**, 413.
- [9] P. P. H. Fourcroy, D. Carré, J. Rivet, *Acta Crystallogr. B* **1978**, *34*, 3160.
- [10] Other structures with similar frameworks are known. For example, an Na₂SnAs₂ Zintl phase which is isostructural and isoelectronic to δ -GeS₂ has been prepared from the elements: M. A. Asbrand, B. Eisenmann, *Z. Naturforsch. B* **1993**, *48*, 452.
- [11] O. M. Yaghi, Z. Sun, D. A. Richardson, T. L. Groy, *J. Am. Chem. Soc.* **1994**, *116*, 807.
- [12] C. L. Bowes, A. J. Lough, A. Malek, G. A. Ozin, S. Petrov, D. Young, *Chem. Ber.* **1995**, *129*, 283.
- [13] C. L. Cahill, J. B. Parise, *Chem. Mater.* **1997**, *9*, 807.
- [14] T. Kemin, A. Darovsky, J. B. Parise, *J. Am. Chem. Soc.* **1995**, *117*, 7039.
- [15] K. Tan, Y. Ko, J. B. Parise, A. Darovsky, *Chem. Mater.* **1996**, *8*, 448.
- [16] W. M. Meier, D. H. Olson, *Atlas of Zeolite Structure Types*, 3rd ed., Butterworth-Heinemann, Toronto, **1992**.
- [17] D. Taylor, *Br. Ceram. Trans. J.* **1992**, *9*, 217.
- [18] J. W. Visser, *J. Appl. Crystallogr.* **1969**, *2*, 89.

- [19] D. E. Appleman, H. T. Evans, Jr., Job 9214, *U.S. Geol. Survey* **1973** NTIS, Doc. PB2–16188; revised PC version by P. H. Benoit, **1987**.
- [20] R. B. von Dreele, A. C. Larson, *General Structure Analysis System*, Los Alamos National Laboratory Report LAUR 86–748, **1990**.
- [21] P. Thompson, D. E. Cox, J. B. Hastings, *J. Appl. Crystallogr.* **1987**, *20*, 79.
- [22] L. W. Finger, D. E. Cox, A. P. Jephcoat, *J. Appl. Crystallogr.* **1994**, *27*, 892.

Metal–Metal “Communication” of Rh or Pd with Nd in Novel Heterobinuclear Complexes**

Anke Spannenberg, Markus Oberthür, Henrik Noss, Annegret Tillack, Perdita Arndt, and Rhett Kempe*

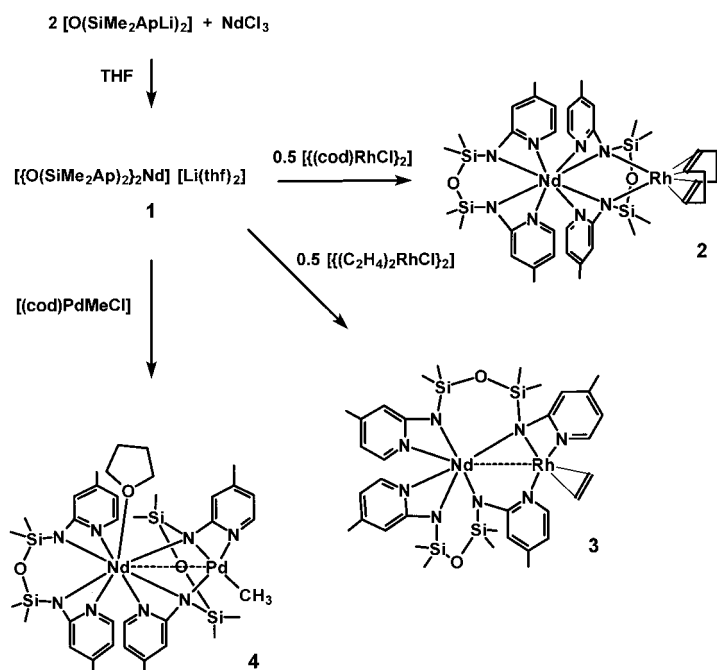
*Dedicated to Professor Carl Krüger
on the occasion of his 65th birthday*

For heterobinuclear complexes which contain an early and a late transition metal and in which the metal centers can “communicate” with one another, interesting properties have been predicted, such as multifunctionality and cooperative effects.^[1] However, the problems encountered in the realization of the differing coordination chemical requirements of both metals in close proximity to one another are just as great as the expectations.^[2] We report here on the synthesis and structure of heterobinuclear complexes in which interactions of Group 9 (Rh) or Group 10 (Pd) metals with a lanthanide (Nd) are possible.^[3] A decisive factor for this enlargement of the class of “early–late heterobimetals” (ELHB) is a novel ligand system incorporating bisaminopyridinato ligands.^[4]

If two equivalents of dilithiated $\text{O}(\text{SiMe}_2\text{ApH})_2$ are treated in situ with NdCl_3 in THF, the neodymium “ate” complex **1** is obtained in good yields as a violet, crystalline compound (Scheme 1; $\text{O}(\text{SiMe}_2\text{ApH})_2 = \text{O}[\text{Si}(\text{CH}_3)_2\text{NH}-(4-\text{CH}_3\text{C}_5\text{H}_3\text{N})]_2$). The IR spectrum of **1** displays the signals typical for $\text{O}(\text{SiMe}_2\text{Ap})_2$, and the elemental analysis is in agreement with the formula given in Scheme 1. The reaction of **1** with $[(\text{cod})\text{RhCl}]_2$ ($\text{cod} = 1,5\text{-cyclooctadiene}$) in *n*-hexane gives yellow crystals of the heterobinuclear compound **2** (Scheme 1). The X-ray crystal structure analysis^[5] of this compound (Figure 1) shows there is an almost square-planar coordination geometry at the rhodium center,^[6] and that two amido N atoms coordinate the $\{\text{Rh}(\text{cod})\}$ fragment ($\text{N}(1)\text{-Rh}(1)\text{-N}(3) \ 84.1(5)^\circ$). For the aminopyridinato fragments,

[*] Dr. R. Kempe, Dr. A. Spannenberg, Dr. M. Oberthür, Dipl.-Chem. H. Noss, Dr. A. Tillack, Dr. P. Arndt
Abt. Komplekxkatalyse
Institut für Organische Katalyseforschung an der Universität
Buchbinderstrasse 5–6, D-18055 Rostock (Germany)
Fax: (+49) 381-466-9374
E-mail: rkempe@chemie1.uni-rostock.de

[**] This work was supported by the Max-Planck-Gesellschaft and by the Fonds der Chemischen Industrie. We are grateful to Prof. Rosenthal for his support of our work.



Scheme 1. Synthesis of **1**–**4**.

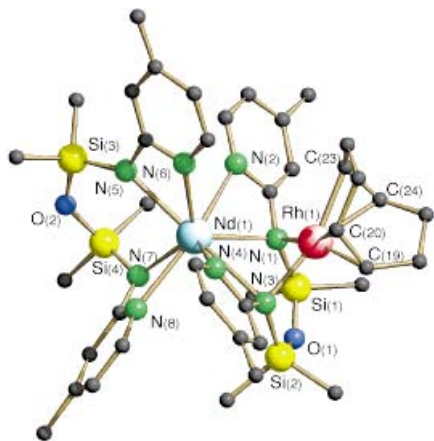


Figure 1. Crystal structure of **2**. Selected bond lengths[Å] and angles[°]: N(1)–Rh(1) 2.142(12), N(1)–Nd(1) 2.646(12), N(2)–Nd(1) 2.585(12), N(3)–Rh(1) 2.138(11), N(3)–Nd(1) 2.699(10), N(4)–Nd(1) 2.603(12), N(5)–Nd(1) 2.514(11), N(6)–Nd(1) 2.478(13), N(7)–Nd(1) 2.463(10), N(8)–Nd(1) 2.527(13), Rh(1)–Nd(1) 3.228(2); N(1)–Rh(1)–N(3) 84.1(5), N(1)–Rh(1)–D[C(23)/C(24)] 96.2(6), D[C(23)/C(24)]–Rh(1)–D[C(19)/C(20)] 86.1(6), N(3)–Rh(1)–D[C(19)/C(20)] 93.5(6), N(7)–Nd(1)–N(6) 133.1(5), N(6)–Nd(1)–N(5) 53.0(4), N(7)–Nd(1)–N(8) 54.3(4), N(2)–Nd(1)–N(1) 51.4(4), N(4)–Nd(1)–N(3) 50.9(4).

which act as bridges between the two metal centers, the elongation of the Nd–N distances is about 0.1 Å. The differences in the lengths of the Nd–N_{amido} and the Nd–N_{pyridine} bonds are slight, which indicates a delocalized bonding mode.^[7]

The magnetic moment^[8] of **2** $\mu_{\text{eff}} = 4.38 \mu_{\text{B}}$ corresponds to the value expected for a 4 f³ electron configuration. A metal–metal bond (the Nd–Rh distance is 3.2283(15) Å) can be excluded, since the only orbitals on the rhodium atom which are eligible for an interaction (orthogonal to the coordination plane)^[9] are not directed towards the neodymium atom.^[10] On the other hand, such an orientation of the orbitals is present in

the Nd–Rh–ethylene complex **3**,^[10] which is formed by the treatment of **1** with $[(\text{C}_2\text{H}_4)_2\text{RhCl}]_2$ in *n*-hexane (Scheme 1). Its molecular structure, determined by X-ray crystallography,^[5] is depicted in Figure 2. The Nd–Rh distance in **3** is

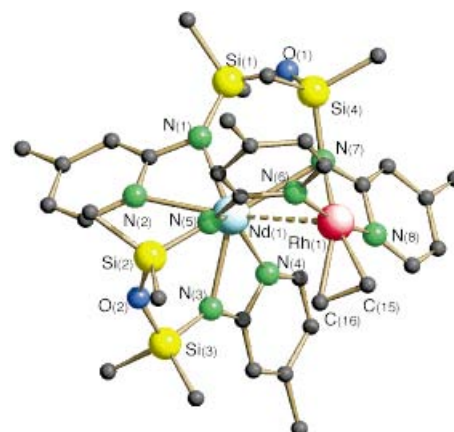


Figure 2. Crystal structure of **3**. Selected bond lengths[Å] and angles[°]: N(1)–Nd(1) 2.465(4), N(2)–Nd(1) 2.509(4), N(3)–Nd(1) 2.382(5), N(4)–Nd(1) 2.566(5), N(5)–Nd(1) 2.449(5), N(6)–Rh(1) 2.050(5), N(7)–Rh(1) 2.128(4), N(7)–Nd(1) 2.626(4), N(8)–Rh(1) 2.035(5), Rh(1)–Nd(1) 2.974(2); N(8)–Rh(1)–N(7) 64.9(2), N(6)–Rh(1)–N(7) 103.2(2), N(6)–Rh(1)–D[C(15)/C(16)] 90.9(3), N(8)–Rh(1)–D[C(15)/C(16)] 101.6(3), N(3)–Nd(1)–N(5) 92.2(2), N(1)–Nd(1)–N(2) 54.0(2), N(3)–Nd(1)–N(4) 54.1(2).

2.9744(15) Å,^[11] which is in good agreement with the value for a M–M single bond.^[12] There is an almost planar coordination geometry^[6] at the rhodium atom. Three of the coordination sites are used by the two bis(Ap) ligands (bis(Ap) = bis(amino)pyridinato); one ligand contributes a pyridine and the other an aminopyridinato functionality. It is remarkable how strained amido ligands can still coordinate to late transition metal centers (N(8)–Rh(1)–N(7) 64.9(2)°) as the combination of a soft metal center with the hard amido ligand is unfavorable.^[13]

The general applicability of this stabilization concept for heterobimetallic compounds by the use of bis(amino)pyridinato ligands is evident from the reaction of **1** with $[(\text{cod})\text{PdMeCl}]$,^[14] which produces the Nd–Pd–alkyl complex **4** (Scheme 1) as a light yellow powder. Crystals suitable for a X-ray structural analysis^[5] were obtained from a mixture of *n*-hexane and THF. The molecular structure of **4** (Figure 3) shows a planar coordination geometry, characteristic of Pd^{II} compounds,^[6] and a Nd–Pd distance of 3.0345(12) Å. In contrast to the situation in **3**, the two metal centers in **4** are bridged by only one bis(Ap) ligand.

Decisive for the preparation as well as the stabilization of the heterobimetallic compounds **2**–**4** is that lanthanide “ate” complexes react with chlorides of electron-rich transition metals by salt elimination and that bis(amino)pyridinato ligands can prevent the ligand transfer from early to late transition metals and thus the decomposition of the bimetallic complex.^[15] The flexible coordination mode of the bis(Ap) ligands allows a coordinative saturation of the lanthanide metal center, leaving two or three nitrogen donor groups for a square-planar coordination geometry at the late transition metal as well as an interaction between the two metals. Currently, we are investigating the consequences of this

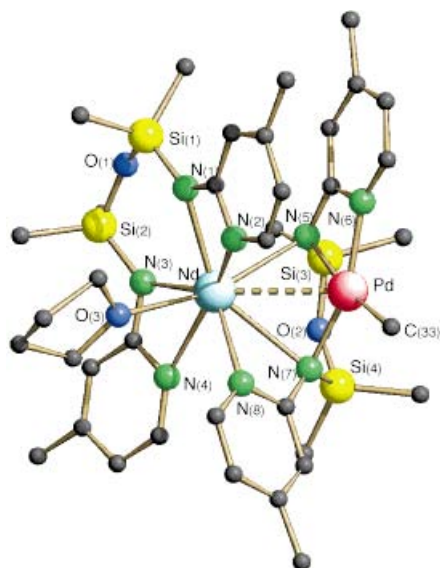


Figure 3. Crystal structure of **4**. Selected bond lengths [Å] and angles [°]: Nd–N(3) 2.475(8), Nd–N(1) 2.480(8), Nd–N(2) 2.542(9), Nd–N(4) 2.547(9), Nd–N(8) 2.612(9), Nd–N(5) 2.659(8), Nd–N(7) 2.761(8), Nd–Pd 3.0345(12), Pd–N(6) 2.048(9), Pd–N(7) 2.062(8), Pd–N(5) 2.187(8); N(3)–Nd–N(1) 84.8(3), N(1)–Nd–N(2) 54.4(3), N(3)–Nd–N(4) 54.0(3), C(33)–Pd–N(6) 104.7(4), C(33)–Pd–N(7) 95.3(4), N(6)–Pd–N(5) 64.9(3), N(7)–Pd–N(5) 95.1(3).

“communication” in stoichiometric and catalytic reactions, and whether such reactions are also transferable to other “ate” complexes, for example to the complexes containing bisalkoxy ligands reported by Shibasaki et al.^[16]

Experimental Section

All work was performed with the exclusion of oxygen and moisture under an atmosphere of argon. NMR spectra were recorded in [D₈]THF at 25 °C.

1: O(SiMe₂ApH)₂ (5.45 g, 15.7 mmol) in THF (20 mL) was treated at –78 °C with *n*BuLi in *n*-hexane (2.5 M, 12.6 mL, 31.5 mmol), stirred for a further 2 h at room temperature, and subsequently added to a hot suspension of NdCl₃ (1.97 g, 7.86 mmol) in THF (50 mL). The mixture was stirred for 16 h at room temperature, filtered, concentrated to about 30 mL, and then treated with diethyl ether. After removal of LiCl by filtration, violet crystals of **1** (5.22 g, 67%) were obtained at –30 °C. M.p. 212 °C; elemental analysis calcd for C₄₀H₆₈LiN₈NdO₄Si₄ (984.52): C 48.80, H 6.55, N 11.38; found: C 48.88, H 6.57, N 10.31; ¹H NMR (400 MHz): δ = –0.02 (s, 3H), 0.13 (s, 2H), 1.78 (m, 4H), 3.63 (m, 4H), 4.75 (s, 6H), 4.83 (s, 1H), 5.61 (s, 1H), 10.90 (s, 1H); ¹³C NMR (100.6 MHz): δ = 12.8, 20.7, 26.3, 68.1, 115.6, 122.7, 125.4, 147.1, 148.6; ²⁹Si NMR (79.5 MHz): δ = –10.6, –18.1; IR (Nujol): $\tilde{\nu}$ (cm^{–1}) = 1595 vs and 1530 s (arom. C=C), 1332 s, 1294 vs, 1243 vs (MeSi), 1178 vs, 1026 vs, 990 vs (SiOSi), 883 vs, 838 s, 792 vs (SiMe₂), 728 s, 674 m, 575 s, 428 m.

2–4: Compound **1** (985 mg, 1 mmol) and either [(cod)RhCl]₂ (247 mg, 0.5 mmol), [(C₂H₅)₂RhCl]₂ (194 mg, 0.5 mmol), or [(cod)PdMeCl]₂^[14] (265 mg, 1 mmol) were suspended in *n*-hexane (60 mL) and stirred at room temperature for 16 h. The mixture was filtered, the residue was washed several times with *n*-hexane/diethyl ether, and the combined filtrates were concentrated to about 15 mL. Crystals were obtained at –30 °C: **2** (595 mg, 57%, yellow crystals), **3** (424 mg, 44%, yellow crystals), and **4** (431 mg, 42%, light yellow powder), respectively.

2: M.p. 150 °C; elemental analysis calcd for C₄₀H₆₀N₈NdO₂RhSi₄ (1044.46) · 0.5 C₂H₅OC₂H₅: C 46.64, H 6.06, N 10.36; found: C 46.87, H 5.97, N 10.32; IR (Nujol): $\tilde{\nu}$ (cm^{–1}) = 1604 vs, 1545 m and 1533 m (arom. C=C), 1410 s, 1395 s, 1331 m, 1315 m, 1295 s, 1286 s, 1249 s (MeSi), 1171 s, 1054 s, 1016 m, 995 s, br (SiOSi), 966 m, 887 s, 877 s, 847 m, 839 m, 807 s (SiMe₂), 784 s, 774 s, 726 m, 675 w, 630 w, 624 w, 588 m, 581 m, 565 w, 529 w; μ_{eff} = 4.38 μ_{B} .

3: M.p. 171 °C; elemental analysis calcd for C₃₄H₅₂N₈NdO₂RhSi₄ (964.33) · 0.5 C₆H₁₄: C 44.11, H 5.90, N 11.12; found: C 43.95, H 5.82, N 11.00; IR (Nujol): $\tilde{\nu}$ (cm^{–1}) = 1607 vs and 1530 m (arom. C=C), 1418 s, 1324 s, 1289 s, 1251 s (MeSi), 1216 m, 1180 s, 1160 m, 1123 w, 1023 vs, 1006 vs (SiOSi), 965 s, 879 s, 858 m, 845 m, 794 vs (SiMe₂), 726 s, 678 w, 651 w, 617 w, 599 m, 587 s, 555 w, 528 w, 434 m; μ_{eff} = 4.33 μ_{B} .

4: M.p. > 280 °C; elemental analysis calcd for C₃₇H₅₉N₈NdO₃PdSi₄ (1026.93): C 43.28, H 5.79, N 10.91; found: C 43.05, H 5.88, N 10.72; IR (Nujol): $\tilde{\nu}$ (cm^{–1}) = 1604 vs, 1546 w and 1531 w (arom. C=C), 1328 m, 1291 m, 1250 s (MeSi), 1177 m, 1026 s, br (SiOSi), 970 m, 880 s, 847 m, 786 s (SiMe₂), 725 m, 581 w, 443 w; μ_{eff} = 4.46 μ_{B} .

Received: December 12, 1997 [Z11258IE]
German version: *Angew. Chem.* **1998**, *110*, 2190–2192

Keywords: lanthanides • metal–metal interactions • N ligands • palladium • rhodium

- [1] D. W. Stephan, *Coord. Chem. Rev.* **1989**, *95*, 41–107.
- [2] W. A. Herrmann, B. Cornils, *Angew. Chem.* **1997**, *109*, 1074–1095; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1049–1067.
- [3] The combination of a lanthanide with metals of Groups 9 and 10 are rare. For examples of nondistal heterobinuclear complexes, see a) L. F. Lindoy, H. C. Lip, H. W. Louie, M. G. B. Drew, M. J. Hudson, *J. Chem. Soc. Chem. Commun.* **1977**, 778–780; b) C. J. Burns, R. A. Andersen, *J. Am. Chem. Soc.* **1987**, *109*, 915–917; c) D. J. Schwartz, G. E. Ball, R. A. Andersen, *J. Am. Chem. Soc.* **1995**, *117*, 6027–6040.
- [4] a) M. Oberthür, P. Arndt, R. Kempe, *Chem. Ber.* **1996**, *129*, 1087–1091; b) M. Oberthür, G. Hillebrand, P. Arndt, R. Kempe, *Chem. Ber.* **1997**, *130*, 789–794.
- [5] Crystal structure analyses of **2–4**: General: STOE-IPDS-diffractometer, MoK α radiation (graphite monochromator, λ = 0.71069 Å), the structure was solved by direct methods (SHELXS-86: G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467), and refined by full-matrix least squares against F^2 (SHELXL-93); graphical representation: Schakal-92. The crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100884. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+ 44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Compound **2**: crystal dimensions: 0.4 × 0.2 × 0.2 mm, yellow prisms, space group $P2_1/c$, monoclinic, a = 13.146(3), b = 11.787(2), c = 32.939(7) Å, β = 90.80(3)°, V = 5103.5(18) Å³, Z = 4, ρ_{calcd} = 1.378 g cm^{–3}; of 6056 reflections measured, 3601 were independent of symmetry and 2726 were observed ($I \geq 2\sigma(I)$); R = 0.052, wR^2 (all data) = 0.149, 511 parameters. Compound **3**: crystal dimensions: 0.5 × 0.4 × 0.4 mm, yellow prisms, space group $P\bar{1}$, triclinic, a = 11.664(2), b = 11.712(2), c = 23.150(5) Å, α = 97.44(3), β = 95.09(3), γ = 115.65(3)°, V = 2789.5(9) Å³, Z = 2, ρ_{calcd} = 1.353 g cm^{–3}; of 8185 reflections measured, 8185 were independent of symmetry and 6799 were observed ($I \geq 2\sigma(I)$); R = 0.048, wR^2 (all data) = 0.141, 539 parameters. Compound **4**: crystal dimensions: 0.3 × 0.3 × 0.1 mm, light yellow platelets, space group $P2_1/c$, monoclinic, a = 13.744(3), b = 12.948(3), c = 30.208(6) Å, β = 91.96(3)°, V = 5373(2) Å³, Z = 4, ρ_{calcd} = 1.323 g cm^{–3}; of 10379 reflections measured, 5528 were independent of symmetry and 4229 were observed ($I \geq 2\sigma(I)$); R = 0.049, wR^2 (all data) = 0.154, 509 parameters.
- [6] The maximum deviations were 0.07 (2), 0.15 (3), and 0.06 Å (4).
- [7] The negative charge on the aminopyridinato ligand is not localized on the amido nitrogen atom.
- [8] The magnetic moments were determined by the method according to Evans: a) D. F. Evans, *J. Chem. Soc.* **1959**, 2003–2005; b) J. L. Deutsch, S. M. Poling, *J. Chem. Educ.* **1969**, *46*, 167–168; c) J. Löliger, R. Scheffold, *J. Chem. Educ.* **1972**, *49*, 646–647.
- [9] T. A. Albright, J. K. Burdett, M.-H. Whangbo, *Orbital Interactions in Chemistry*, Wiley, New York, **1985**.
- [10] The angle between the vectors parallel to the shortest metal–metal distance and orthogonal to the coordination plane of the rhodium center were 50.6° (2) and 26.9° (3).

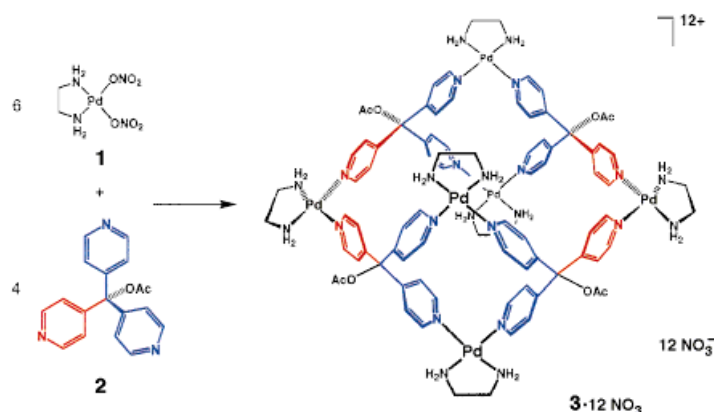
- [11] A Nd–Rh single bond, in the sense of a σ bond, cannot be assumed here. It is conceivable that there is an interaction of the d_z orbital, which are directed orthogonal to the coordination plane, with the neodymium atom.
- [12] Metal–metal distances for unbridged single bonds have not, as far as we know, been reported for the combinations Ln–M (M = Co, Rh, Ir, Ni, Pd, Pt). The Lu–Ru distance in $[\text{Cp}_2(\text{thf})\text{LuRuCp}(\text{CO})_2]$ is 2.955(2) Å: I. P. Beletskaya, A. Z. Voskoboynikov, E. B. Chuklanova, N. I. Kirillova, A. K. Shestakova, I. N. Parshina, A. I. Gusev, G. K.-I. Magomedov, *J. Am. Chem. Soc.* **1993**, *115*, 3156–3166. The shortest metal–metal distance in bridged systems was found for $[\text{Cp}_2^*\text{Yb}(\mu\text{-H})(\mu\text{-CH}_3)\text{Pt}(\text{dippe})]^{3+}$ and is 3.388(9) Å. $\text{Cp}^* = \text{C}_5\text{Me}_5$, $\text{dippe} = i\text{Pr}_2\text{P}(\text{CH}_2)_2\text{P}i\text{Pr}_2$.
- [13] a) R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539; b) R. G. Pearson, *J. Chem. Educ.* **1968**, *45*, 581–587; c) R. G. Pearson, *J. Chem. Educ.* **1968**, *45*, 643–654.
- [14] R. E. Rülke, J. M. Ernsting, A. L. Spek, C. J. Elsevier, P. W. N. M. van Leeuwen, K. Vrieze, *Inorg. Chem.* **1993**, *32*, 5769–5778.
- [15] A. Spannenberg, P. Arndt, R. Kempe, *Angew. Chem.* **1998**, *110*, 824–827; *Angew. Chem. Int. Ed.* **1998**, *37*, 832–835.
- [16] a) H. Sasai, T. Arai, Y. Satow, K. N. Houk, M. Shibasaki, *J. Am. Chem. Soc.* **1995**, *117*, 6194–6198; b) T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1369–1372.

Self-Assembly of Nanometer-Sized Macrotricyclic Complexes from Ten Small Component Molecules**

Makoto Fujita,* Shu-Yan Yu, Takahiro Kusukawa, Hidenori Funaki, Katsuyuki Ogura, and Kentaro Yamaguchi

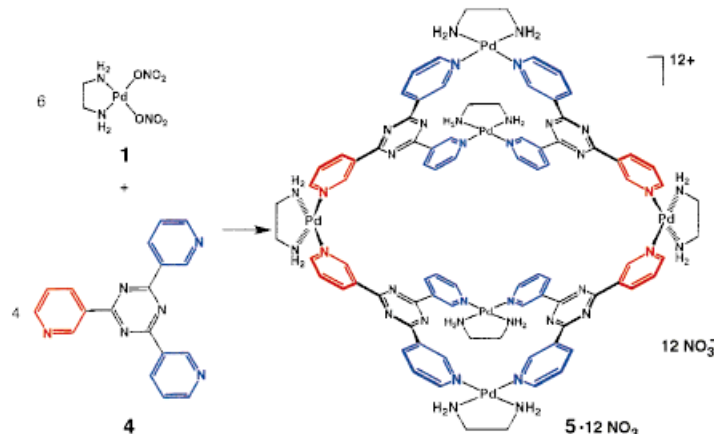
Transition metals with specific coordination geometries have been employed for the rational design and construction of highly ordered supramolecular structures.^[1] We have shown that the simple combination of the square-planar coordination geometry of palladium (90° bond angle) with pyridine-based bridging ligands leads to the quantitative self-assembly of nanometer-sized, discrete organic frameworks^[2] such as “molecular squares”^[3, 4] and an adamantanoid cages.^[5] Here we report the efficient self-assembly of nanometer-sized

macrotricycles from ten small components. Treatment of $[\text{Pd}(\text{NO}_3)_2(\text{en})]$ (**1**) with the tripyridylmethane **2**^[6] results in self-assembly to the nanometer-sized macrotricyclic framework **3**, in which four ligand molecules are held together by six metal ions (Scheme 1). A similar ten-component self-assem-



Scheme 1. Synthesis of **3**.

bly process leads to formation of the nanoscale macrotricycle **5** from **1** and the triazine-based ligand **4** (Scheme 2). Recently, there were a few reports of the metal-directed self-assembly of nanometer-sized macrocycles.^[7, 8] However, their structures



Scheme 2. Synthesis of **5**.

have often been deduced from spectroscopic data.^[8] In contrast, the structures of nanometer-sized macrotricycles **3** and **5** were unambiguously determined by X-ray crystallographic analyses.

Ligand **2** was suspended in an aqueous solution of **1** (1.5 equiv), and the mixture was heated at 70 °C.^[9] After 40 min a colorless clear solution was obtained. Analysis by NMR spectroscopy of the solution obtained by carrying out the reaction in D₂O showed the quantitative self-assembly of **1** and **2** to form a single product. The addition of aqueous NaClO₄ (1M) resulted in precipitation of **3**·12 ClO₄[−] in 85 % yield. When ethanol/water was employed as the solvent, the product was obtained from the solution directly as a NO₃[−] salt by cooling to about 5 °C for several days. The elemental analyses agreed with the empirical formulas of **3**·12 ClO₄·8H₂O and **3**·12 NO₃·12H₂O. The NMR spectra of **3** contain only one acetoxyl signal (¹H NMR: δ = 2.24 (Figure 1); ¹³C

[*] Prof. Dr. M. Fujita,^[+] Dr. S.-Y. Yu, Dr. T. Kusukawa
Coordination Chemistry Laboratories
Institute for Molecular Science
Myodaiji, Okazaki 444-8595 (Japan)
Fax: (+81) 564-55-5245
E-mail: mfujita@ims.ac.jp

H. Funaki, Prof. Dr. K. Ogura
Department of Applied Chemistry
Faculty of Engineering, Chiba University
Yayoicho, Inageku, Chiba 263 (Japan)

Prof. Dr. K. Yamaguchi^[++]
Chemical Analysis Center, Chiba University
Yayoicho, Inageku, Chiba 263 (Japan)

[+] Prof. Fujita is responsible for the CREST project of the Japan Science and Technology Corporation (JST) at the Institute for Molecular Science.

[++] Crystal structure analysis.

[**] This work was supported by the CREST (Core Research for Evolutional Science and Technology) project of Japan Science and Technology Corporation. S.-Y.Y. thanks the Japan Society for the Promotion of Science for a JSPS postdoctoral fellowship.

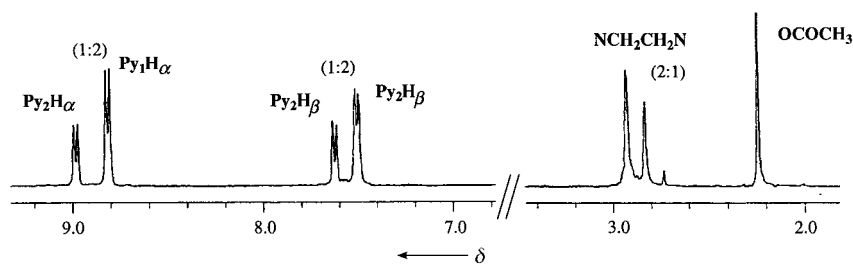


Figure 1. ^1H NMR spectrum of **3** (300 MHz, D_2O).

NMR: $\delta = 20.80$), although two inequivalent pyridyl groups are present in a 2:1 ratio in the self-assembled product (e.g., for PyH_α : ^1H NMR: $\delta = 8.98$ and 8.81 (Figure 1); ^{13}C NMR: $\delta = 151.8$ and 151.6). Furthermore, two different $\text{Pd}(\text{en})$ units are present in a ratio of 2:1 (^{13}C NMR: $\delta = 46.86$ and 46.82). Therefore, the NMR data are fully consistent with the structure of **3**, that is, the pyridyl groups drawn in blue and red in Scheme 1 are inequivalent, but all acetyl groups are equivalent.

This somewhat unusual M_6L_4 structure was confirmed by an X-ray crystallographic analysis. A single crystal suitable for X-ray analysis was obtained by allowing a solution of **3** in ethanol/water to stand at ambient temperature for ten days. The ball-and-stick representation of the crystal structure (Figure 2) corresponds to our proposed structure. The most

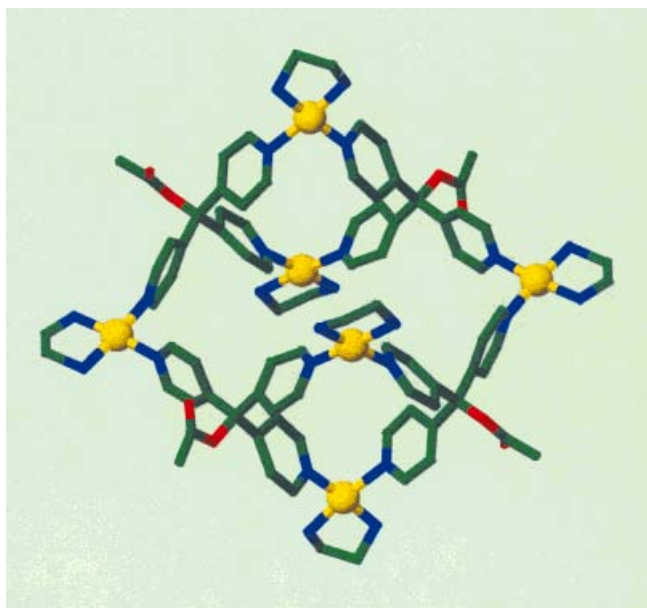


Figure 2. The X-ray crystal structure of **3**.

significant aspect is that the compound has nanometer dimensions in spite of the small size of the component molecules. The molecular dimensions of **3** are approximately $30 \times 23 \times 22 \text{ \AA}$, and the longest Pd–Pd distance is $19.2 \text{ \AA}$. From the top view of **3**, a roughly elliptical cavity ($14 \times 5 \text{ \AA}$) can be seen (Figure 3, top). Viewed from the side, a macrocyclic dinuclear structure with a Pd–Pd distance of $9.2 \text{ \AA}$ is evident (Figure 3, bottom).

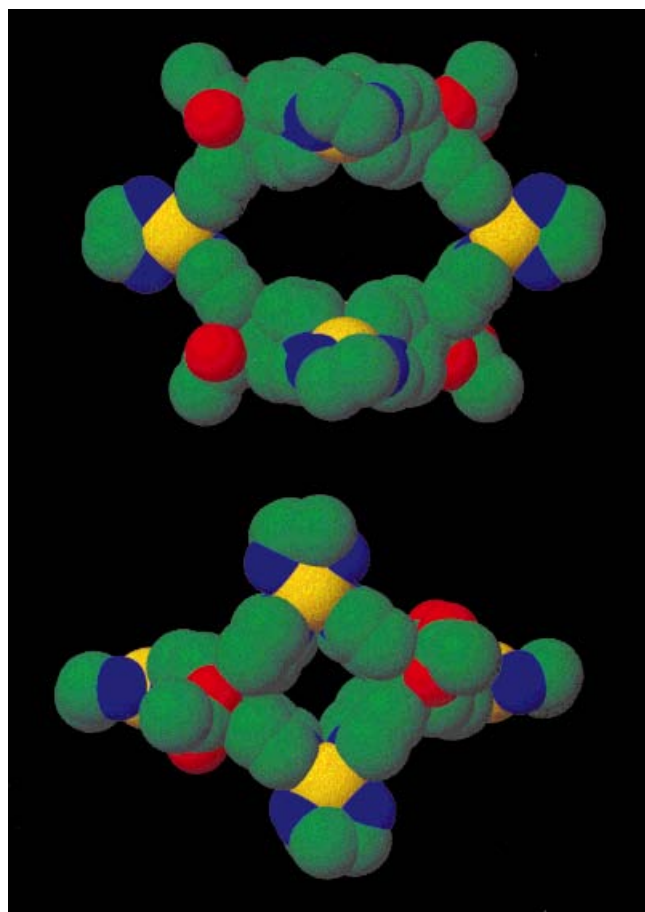
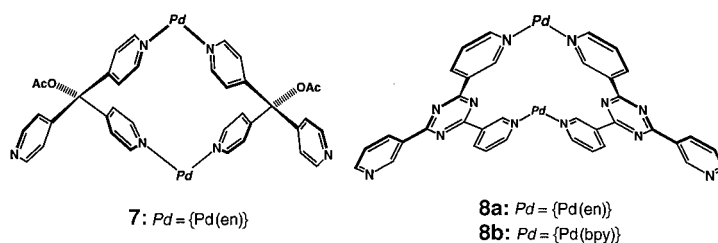


Figure 3. Space-filling (CPK) representation of the crystal structure of **3**. Top: top view, bottom: side view.

analysis (Figure 4). The macrotricyclic **5** has the same topology as **3**, but a different molecular shape; that is, **5** has a bowl-shaped structure with the approximate dimensions $27 \times 24 \times 14 \text{ \AA}$ and a longest Pd–Pd distance of $19.1 \text{ \AA}$.

A proposed pathway leading to **3** or **5** involves a two-step self-assembly. First, two pyridyl groups of the ligand **2** or **4** are involved in the formation of the dinuclear macrocycle **7** or **8a**,



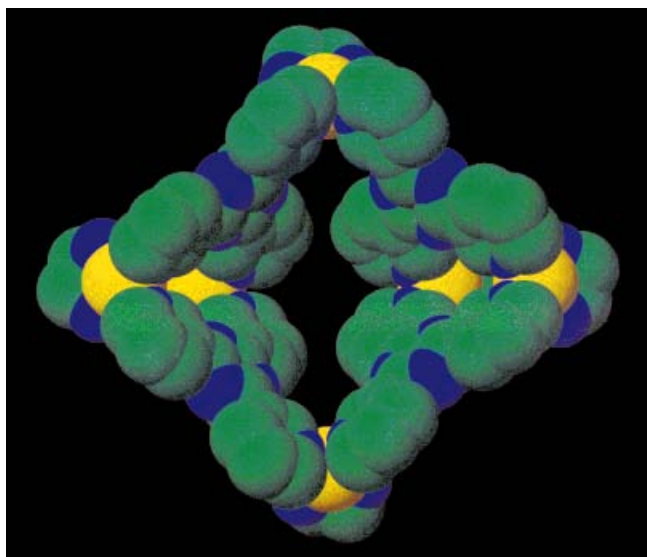


Figure 4. Space-filling (CPK) representation of the X-ray crystal structure of **5**.

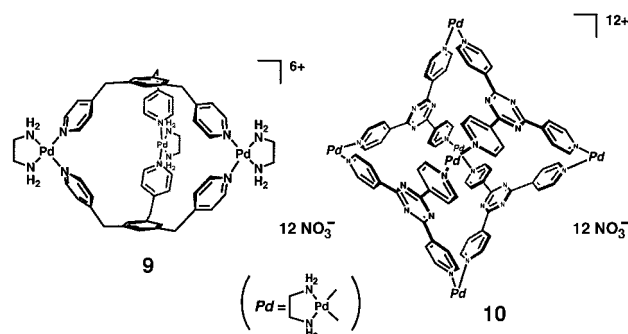
respectively, in which two pyridyl groups are uncoordinated. In the second step, these pyridyl groups are intermolecularly linked together by Pd(en) units to give a large M_6L_4 macrotricyclic structure. This pathway appears reasonable because bis(4-pyridyl)methane, which has the partial framework of **3**, gives a dinuclear macrocycle corresponding to **7**.^[10] Furthermore, when the en ligands were replaced by 2,2'-bipyridine (bpy), the dinuclear intermediate **8b** was obtained. This complex was isolated as single crystals from the crude reaction solution upon treatment of [Pd(bpy)(NO₃)₂] (**6**) with **4** and characterized by X-ray analysis (Figure 5).^[11]



Figure 5. The X-ray crystal structure of **8b**.

It is noteworthy that complexes **3** and **5** can bind dicarboxylate dianions. A significant upfield shift was observed for the aromatic protons of the dianion of 1,4-phenylenediacetic acid in D₂O upon complexation with an equimolar amount of **3** or **5** ($\Delta\delta = -0.29$ and -1.60 , respectively). Another dicarboxylate, sodium terephthalate, was also bound in the cavity ($\Delta\delta = -0.13$ and -0.44 in **3** and **5**, respectively). For host **3**, the complexation is probably due to two-point electrostatic attraction between negative (COO⁻) and positive charges (Pd²⁺), since a simple monocarboxylate such as *p*-methoxyphenylacetate was hardly complexed by **3**. In contrast, host **5** also bound *p*-methoxyphenylacetate ($\Delta\delta = -1.20$ and -1.35 for the aromatic protons). Thus, the large, bowl-shaped framework of **5**, which

is formed by sixteen aromatic rings, is a very effective cavity for molecular recognition. The self-assembly of **3** and **5** depends on a delicate thermodynamic balance, since their structures are quite different from the previously reported three-dimensional cage structures of **9**^[12] and **10**,^[5a] although their ligands are very similar to those used here.



Experimental Section

Self-assembly of 3: Compound **2** (0.1 mmol) was suspended in an aqueous solution (1.5 mL) of **1** (0.15 mmol), and the mixture was heated to 70 °C for 40 min. A very small amount of insoluble product was removed by filtration, and an aqueous solution of NaClO₄ (1M, 1.5 mL) was added to the filtrate. A colorless powder precipitated immediately and was collected by filtration and dried under reduced pressure to give pure **3**·12ClO₄ in 85% yield. Colorless powder; m.p. > 300 °C; ¹H NMR (300 MHz, D₂O, 25 °C, TMS): δ = 8.94 (d, J = 6.8 Hz, 8H, PyH_a), 8.80 (d, J = 6.8 Hz, 16H, PyH_a), 7.60 (d, J = 6.8 Hz, 8H, PyH_b), 7.49 (d, J = 6.8 Hz, 16H, PyH_b), 2.95 (s, 16H, NCH₂CH₂N), 2.83 (s, 16H, NCH₂CH₂N), 2.24 (s, 12H, OCOCH₃); ¹³C NMR (125 MHz, D₂O, 25 °C, TMS): δ = 171.1 (Cq), 152.4 (Cq), 151.8 (CH), 151.6 (CH), 149.0 (CH), 128.7 (CH), 124.7 (CH), 83.80 (Cq), 46.86 (CH₂), 46.82 (CH₂), 20.80 (CH₃); IR (KBr): $\tilde{\nu}$ = 3450, 2940, 1652, 1123, 668, 622 cm⁻¹; elemental analysis calcd for C₈₄H₁₀₈N₂₄O₅₆Cl₁₂Pd₆·8H₂O: C 28.36, H 3.51, N 9.45; found: C 28.35, H 3.32, N 9.24.

Crystallographic analysis of 3·12NO₃: A solution of **2** (0.02 mmol) in ethanol (0.25 mL) was combined with an aqueous solution (0.25 mL) of **1** (0.030 mmol), and the clear solution was allowed to stand at ambient temperature for 10 d to give single crystals of **3**·12NO₃. M.p. > 300 °C; IR (KBr): $\tilde{\nu}$ = 3451, 1617, 1383, 668, 599, 490, 456 cm⁻¹; elemental analysis calcd for C₈₄H₁₀₈N₃₆O₄₄Pd₆·12H₂O: C 31.72, H 4.18, N 15.85; found: C 31.58, H 3.99, N 15.93. A single crystal with dimensions of 0.25 × 0.15 × 0.05 mm was coated with a sealing material and mounted on a glass fiber. All measurements were made on a Rigaku RAXIS II imaging plate area detector with graphite-monochromated MoK α radiation. The data were collected at 173 K. The crystallographic molecule contains half a molecule of **3**·12NO₃. Crystal data: C₈₄H₁₀₈N₃₆O₄₄Pd₆·12H₂O, M_r = 3180.57, monoclinic, space group $P2_1/c$ (no. 14), a = 19.450(7), b = 14.586(2), c = 26.40(1) Å, β = 94.13(4)°, V = 7470(3) Å³, ρ_{calcd} = 1.414 g cm⁻³, Z = 2, $F(000)$ = 3224, $\mu(\text{MoK}\alpha)$ = 7.97 cm⁻¹, $\lambda(\text{MoK}\alpha)$ = 0.71070 Å; 6703 reflections measured, 4121 observed reflections ($I > 3.50\sigma(I)$); number of parameters 723; $R1$ = 0.131; $wR2$ = 0.161. Owing to the high degree of disorder of the counteranions and water molecules, further refinement was unsuccessful.^[13]

Self-assembly of 5: Addition of ligand **4** (0.1 mmol) to an aqueous solution (1.5 mL) of **1** (0.15 mmol) followed by heating at 70 °C for 30 min gave a clear colorless solution, from which a yellowish microcrystalline powder was obtained by evaporation. Recrystallization from water/methanol gave colorless microcrystals of **5**·12NO₃ in 81% yield. M.p. > 300 °C; ¹H NMR (500 MHz, D₂O, 25 °C, TMS): δ = 10.56 (d, J = 1.5 Hz, 8H), 9.93 (brs, 4H), 9.27 (d, J = 4.9 Hz, 8H), 9.22–9.15 (m, 12H), 9.12 (d, J = 5.6 Hz, 4H), 7.9–7.8 (m, 12H), 3.2–2.8 (m, 24H, NCH₂CH₂N); ¹³C NMR (125.65 MHz, D₂O, 25 °C, TMS): δ = 170.2 (Cq), 170.0 (Cq), 155.5 (CH), 155.2 (CH), 153.3 (CH), 153.1 (CH), 141.4 (CH), 141.3 (CH), 134.7 (Cq), 134.6 (Cq), 128.1 (CH), 127.9 (CH), 47.8 (CH₂); IR (KBr): $\tilde{\nu}$ = 3402, 3067, 1653, 1584, 1529, 1382, 1058, 803, 698 cm⁻¹; elemental analysis calcd for C₈₄H₉₆N₄₈O₃₆Pd₆·12H₂O: C 31.44, H 3.77, N 20.95; found: C 31.38, H 3.65, N 20.81.

Crystallographic analysis of $5 \cdot 12\text{NO}_3$: colorless prisms of $5 \cdot 12\text{NO}_3$ were grown by diffusion of diethyl ether into a solution of the complex in water/methanol for two weeks at room temperature. A single crystal of dimensions $0.40 \times 0.20 \times 0.10$ mm was coated with a sealing material and mounted on a glass fiber. All measurements were made on a Rigaku RAXIS II imaging plate area detector with graphite-monochromated $\text{MoK}\alpha$ radiation. The data were collected at 173 K. Crystal data for $5 \cdot 12\text{NO}_3$: $\text{C}_{84}\text{H}_{96}\text{N}_{48}\text{O}_{36}\text{Pd}_6 \cdot 4\text{H}_2\text{O}$, $M_r = 3064.44$, triclinic, space group $P1$, $a = 20.17(1)$, $b = 22.73(1)$, $c = 19.17(1)$ Å, $\alpha = 95.68(5)$, $\beta = 98.70(2)$, $\gamma = 113.47(2)^\circ$, $V = 7845(8)$ Å³, $\rho_{\text{calcd}} = 1.297$ g cm⁻³, $Z = 2$, $F(000) = 3080$, $\mu(\text{MoK}\alpha) = 7.51$ cm⁻¹, $\lambda(\text{MoK}\alpha) = 0.71070$ Å; 18566 reflections measured, 15736 observed ($I > 3.50\sigma(I)$); number of variables 1460; $R1 = 0.133$; $wR2 = 0.179$.^[13]

Received: March 24, 1998 [Z11631 IE]
German version: *Angew. Chem.* **1998**, *110*, 2192–2196

Keywords: metallacycles • molecular recognition • N ligands • palladium • supramolecular chemistry

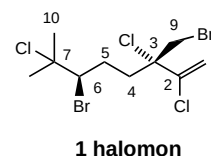
- [1] Reviews: a) P. N. W. Baxter in *Comprehensive Supramolecular Chemistry*, Vol. 9 (Ed.: J.-M. Lehn), Pergamon, Oxford, **1996**, chap. 5; b) J. R. Fredericks, A. D. Hamilton in *Supramolecular Control of Structure and Reactivity* (Ed.: A. D. Hamilton), Wiley, New York, **1996**, chap. 1.
- [2] a) M. Fujita in *Comprehensive Supramolecular Chemistry*, Vol. 9 (Ed.: J.-M. Lehn), Pergamon, Oxford, **1996**, chap. 7; b) M. Fujita, K. Ogura, *Coord. Chem. Rev.* **1996**, *148*, 249–264; c) M. Fujita, K. Ogura, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1471–1482.
- [3] a) M. Fujita, J. Yazaki, K. Ogura, *J. Am. Chem. Soc.* **1990**, *112*, 5645–5647; b) M. Fujita, J. Yazaki, K. Ogura, *Tetrahedron Lett.* **1991**, *32*, 5589–5592; c) M. Fujita, J. Yazaki, K. Ogura, *Chem. Lett.* **1991**, 1031–1032; d) M. Fujita, O. Sasaki, T. Mitsuhashi, T. Fujita, J. Yazaki, K. Yamaguchi, K. Ogura, *Chem. Commun.* **1996**, 1535–1536.
- [4] Phosphine-protected analogues: a) P. J. Stang, D. H. Cao, *J. Am. Chem. Soc.* **1994**, *116*, 4981–4982; b) P. J. Stang, B. Olenyuk, *Acc. Chem. Res.* **1997**, *30*, 502–518.
- [5] a) An adamantanoid M_6L_4 complex: M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi, K. Ogura, *Nature* **1995**, *378*, 469–471; b) an adamantanoid M_4L_6 complex: R. W. Saalfrank, A. Stark, K. Peters, H. G. von Schnering, *Angew. Chem.* **1988**, *100*, 878–880; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 851–853; R. W. Saalfrank, R. Burak, A. Breit, D. Stalke, R. Herbst-Irmer, J. Daub, M. Porsch, E. Bill, M. Muther, A. X. Trautwein, *Angew. Chem.* **1994**, *106*, 1697–1699; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1621–1623.
- [6] Easily prepared by the addition of 4-pyridyllithium (2.5 equiv) to ethyl 4-pyridinecarboxylate (Et_2O , room temperature, 2.5 h) followed by acetylation with acetic anhydride (50 equiv) and 4-dimethylamino-pyridine (0.5 equiv) at room temperature for 3 d (22% overall yield). M.p. 174–176 °C; ¹H NMR (CDCl_3) $\delta = 8.41$ (d, $J = 6.0$ Hz, 6H), 7.09 (d, $J = 6.0$ Hz, 6H), 2.17 (s, 3H).
- [7] B. Hasenknopf, J.-M. Lehn, N. Boumediene, A. Dupont-Gervais, A. Van Dorsselaer, B. Kneisel, D. Fenske, *J. Am. Chem. Soc.* **1997**, *119*, 10956–10962.
- [8] J. Manna, J. A. Whiteford, P. J. Stang, *J. Am. Chem. Soc.* **1996**, *118*, 8731–8732.
- [9] Heating was necessary to give a homogeneous mixture. We confirmed by NMR spectroscopy ($\text{D}_2\text{O}/\text{CD}_3\text{OD}$) that the self-assembly event occurs immediately at room temperature under homogeneous conditions.
- [10] M. Fujita, M. Aoyagi, K. Ogura, *Inorg. Chim. Acta* **1996**, *246*, 53–57.
- [11] Crystal data for **8b**: yellowish prism, crystal dimensions $0.08 \times 0.20 \times 0.25$ mm, $\text{C}_{56}\text{H}_{40}\text{N}_{16}\text{F}_{24}\text{P}_4\text{Pd}_2 \cdot \text{CH}_3\text{CN}$, $M_r = 1770.75$, orthorhombic, space group $C22_1$ (no. 20), $a = 13.280(5)$, $b = 24.43(1)$, $c = 20.869(3)$ Å, $V = 6771(3)$ Å³, $\rho_{\text{calcd}} = 1.737$ g cm⁻³, $Z = 4$, $F(000) = 3512$, $\mu(\text{MoK}\alpha) = 7.46$ cm⁻¹, $\lambda(\text{MoK}\alpha) = 0.71070$ Å; 2802 reflections measured, 2219 observed ($I > 3.50\sigma(I)$); number of variables 502; $R1 = 0.083$; $wR2 = 0.098$.^[13]
- [12] M. Fujita, S. Nagao, K. Ogura, *J. Am. Chem. Soc.* **1995**, *117*, 1649–1650.

- [13] Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-408575, CSD-408576, and CSD-408577.

Total Synthesis of (±)-Halomon by a Johnson–Claisen Rearrangement**

Thierry Schlama, Rachid Baati, Véronique Gouverneur, Alain Valleix, John R. Falck, and Charles Mioskowski*

The antitumor agent halomon (**1**) has generated enormous interest owing to its unique mode of action that allows it to display differential cytotoxicity against various tumor cell lines.^[1] Details of its discovery and structural characterization have been reported;^[2] however, further elucidation of its atypical biological activity has been hampered by the limited amount of naturally occurring halomon that can be extracted from the red alga *Portieria hornemannii* and by the synthetic challenge posed in creating such a polyhalogenated molecule. A total synthesis is, consequently, needed to establish the basis for generating a wide range of analogues to expedite the structure and activity assessment of this novel class of anticancer agents.



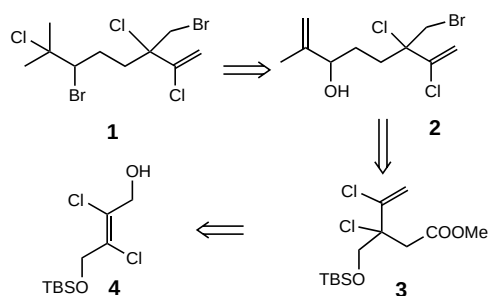
The clearest chemical challenge posed by a total synthesis of **1** is the fashioning of the chlorinated tertiary carbon atom C_3 bearing the α -chlorovinyl group. A further complication is the regiospecificity in the introduction of the bromine and chlorine atoms on C_6 and C_7 , respectively. Herein, we disclose the first total synthesis of halomon featuring as key steps two novel chemical transformations to address these synthetic problems.

Current methodologies for the construction of tertiary chlorinated carbons such as C_3 involve either β -elimination of

[*] Dr. C. Mioskowski, T. Schlama, R. Baati, Dr. V. Gouverneur
Université Louis Pasteur, Faculté de Pharmacie
Laboratoire de Synthèse Bioorganique associé au CNRS
74, route du Rhin, BP-24, 67401 Illkirch (France)
Fax: (+33) 3-88-67-88-91
E-mail: mioskow@aspirine.u-strasbg.fr
A. Valleix
CEA Saclay, Service des Molécules Marquées, Bat. 547
Département de Biologie Cellulaire et Moléculaire
F-91191 Gif-sur-Yvette (France)
J. R. Falck
Department of Biochemistry, Southwestern Medical Center
University of Texas
5323 Harry Hines Blvd., Dallas, TX 75235–9038 (USA)

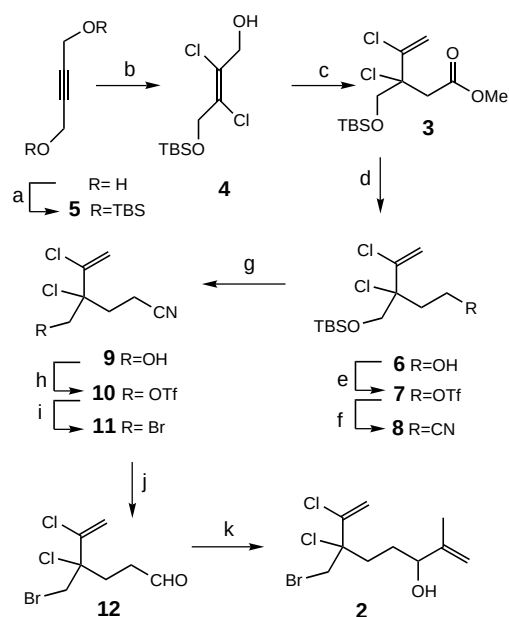
[**] This work was financially supported by Rhône–Poulenc (fellowship to T.S.), National Institutes of Health (NIHGM31278 to J.R.F.), and NATO (CRG.971096 to C.M.). We are grateful to Dr. M. Boyd of the National Cancer Institute for a generous gift of natural halomon.

a polyhalogenated compound^[3] or chlorination of the corresponding allene.^[4] Unfortunately, both these methods involve precursors that are not readily accessible, and they also suffer from very low selectivities and yields. In our retrosynthetic plan (Scheme 1), we reasoned that such a tertiary chlorinated carbon atom can be formed by a [2,3]- or [3,3]-sigmatropic rearrangement of a dichlorinated alkene. This approach also provides a general method for generating different halogenated analogues by varying the substitution of the starting alkene. We chose a route with compounds **2** and **3** as intermediates in the total synthesis of halomon.



Scheme 1. Retrosynthesis of halomon (**1**). TBS = *t*BuMe₂.

To commence the synthesis, the readily available but-2-yne-1,4-diol was bisilylated quantitatively giving **5**. This product was then chlorinated with concomitant monodesilylation with one equivalent of Et₄N⁺Cl₃[−], a new reagent developed in this laboratory,^[5] to give the *trans*-dichlorinated alkene **4** (Scheme 2). An extensive investigation was then undertaken

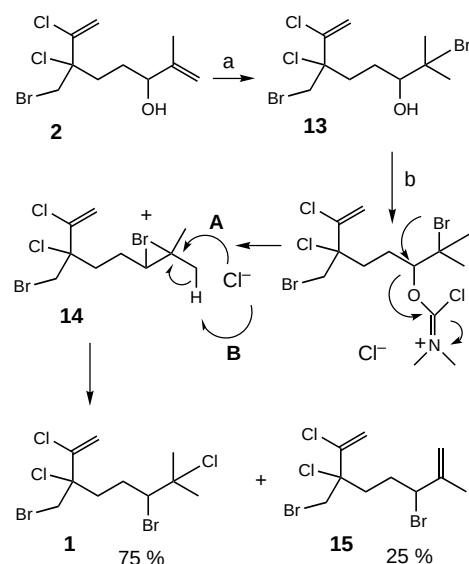


Scheme 2. a) TBSCl (2 equiv), imidazole, CH₂Cl₂, 0 °C, 100%; b) Et₄N⁺Cl₃[−] (1 equiv), CH₂Cl₂, 0 °C, 59%; c) CH₃C(OCH₃)₃, TsOH, 170 °C, 55%; d) LiAlH₄ (4 equiv), THF, 0 °C, 93%; e) Tf₂O, 2,6-di-*tert*-butylpyridine, CH₂Cl₂, 0 °C, crude product; f) Et₄N⁺CN[−] (10 equiv), 95%; g) TsOH, MeOH, reflux, 7 h, 95%; h) Tf₂O, 2,6-di-*tert*-butylpyridine, CH₂Cl₂, 0 °C, 89%; i) Et₄N⁺CN[−] (10 equiv), 0 °C, 98%; j) DIBAL-H, THF, −78 °C, 90%; k) isopropenylmagnesium bromide (3 equiv), hexaethylguanidinium chloride (3 equiv), THF, 0 °C, 87%. TsOH = *p*-toluenesulfonic acid, Tf₂O = trifluoromethanesulfonic acid anhydride, DIBAL-H = diisobutylaluminum hydride.

to validate the rearrangement step of compound **4**. All attempts to promote Cope, Stevens, Claisen, or Ireland–Claisen rearrangements were unsuccessful.^[6] However, the rearrangement was accomplished using Johnson–Claisen acidic conditions.^[7] When the reaction was carried out for five days with methyl orthoacetate and propionic acid in refluxing toluene, the desired rearranged compound **3** was isolated in 30 % yield. The absence of solvent and the use of *p*-toluenesulfonic acid instead of propionic acid resulted in an improved yield (55 %) and a shorter reaction time (less than 24 hours).^[8]

Compound **3** was then transformed into the intermediate compound **2** by an eight-step procedure. Ester **3** was reduced with LiAlH₄,^[9] and the resultant primary alcohol **6** was converted into **8** in 88 % overall yield, via the triflate **7**^[10] with tetraethylammonium cyanide.^[11] The silyloxy group of nitrile (**8**) was transformed first to an alcohol (**9**), then to a triflate (**10**), and finally into the corresponding bromide (**11**).^[12] The aldehyde **12** was obtained by a controlled reduction of the cyanide group with Dibal-H at −78 °C. After an extensive investigation of a variety of protocols, we finally established that the reaction of the sensitive aldehyde **12** with three equivalents of isopropenylmagnesium bromide and three equivalents of hexaethylguanidinium chloride proceeded smoothly to give the allyl alcohol **2** in 87 % yield after chromatography on silica gel. Grignard addition in the absence of the guanidinium salt never exceeded 20 % yield.^[13]

The completion of the synthesis is outlined in Scheme 3. Addition of Et₄N⁺HBr₂[−] to the allylic alcohol **2** resulted in regiospecific hydrobromination of the nonchlorinated double



Scheme 3. a) Et₄N⁺HBr₂[−], CH₂Cl₂, 0 °C, 97 %; b) Cl₂C=NMe₂⁺Cl[−], CH₂Cl₂, 0 °C.

bond to afford the desired bromohydrin **13** in almost quantitative yield (97 %).^[14] Surprisingly, treatment of the bromohydrin **13** with one equivalent of dichlorophosgeniminium chloride (Viehe's salt)^[15] gave halomon (**1**) directly^[16] in 75 % yield with simultaneous formation of the allyl bromide **15** (25 %). This unusual transformation probably involves

neighboring-group participation of the bromine positioned on C₇ through the three-membered bromonium intermediate **14**. The chloride counterion could act either as a nucleophile to furnish halomon (path A) or as a weak base to yield the allyl bromide **15** (path B). To our knowledge, this complete 1,2-shift of the bromine atom of a bromohydrin in the presence of a chlorinating reagent has no precedent in the literature.^[17] This transformation appears to be a general method for rearranging bromohydrins.

The four stereoisomers of **1** were separated by HPLC (see Experimental Section). The 6*R*,3*S* and 6*S*,3*R* diastereoisomers eluted prior to the 6*R*,3*R* and 6*S*,3*S* diastereoisomers. The 6*R*,3*R* and 6*S*,3*S* enantiomers were separated by HPLC on a chiral column. Comparisons with natural halomon allowed us to assign unambiguously the stereochemistry of both signals. All four stereoisomers will be tested for biological activity.

In summary, the first total synthesis of halomon (**1**) has been accomplished in 13 steps from but-2-yne-1,4-diol with an overall yield of 13%. The following significant new findings were made: 1. The Johnson–Claisen [3,3]-sigmatropic rearrangement of a dichlorinated alkene for the construction of a tertiary chlorinated carbon;^[18] 2. the hexaethylguanidinium chloride mediated addition of Grignard reagents to sensitive aldehydes; and 3. a new rearrangement of bromohydrins for the regiospecific introduction of the bromine and chlorine atoms on C₆ and C₇, respectively. The versatility of the methods developed herein can be adapted to produce enantiomerically pure halomon^[19] as well as a variety of analogues to investigate fully the potential of this novel anticancer agent.

Experimental Section

3: A solution of alcohol **4** (147 mg), trimethyl orthoacetate (1 mL), and a catalytic amount of *p*-toluenesulfonic acid (7 mg) was heated in a sealed tube until the starting material had disappeared. After dilution of the reaction mixture with dichloromethane, the crude mixture was washed successively with water, 5% NaHCO₃, and then brine, and dried over MgSO₄. The solvent was removed in vacuo. The crude oil was purified by column chromatography (SiO₂, hexane/ethyl acetate (95/5)) to yield **3** (93 mg, 55%).

1: Dichlorophosgeniminium chloride (0.11 mmol) was added in one portion to a solution of alcohol **13** (0.1 mmol) in dry CH₂Cl₂ (3 mL) at 0 °C. After the mixture was stirred for 6 hours at 0 °C and 10 h at room temperature, the solvent was removed in vacuo and the crude oil purified by column chromatography (SiO₂, hexane) to yield halomon (**1**, 75%) contaminated with **15** (25%). HPLC (Zorbax SBC18 column, methanol/water (75/25)): Diastereoisomers 6*R*,3*S* and 6*S*,3*R* eluted prior to diastereoisomers 6*R*,3*R* and 6*S*,3*S*. Separation of the 6*R*,3*S* and 6*S*,3*R* enantiomers: OJ-R column, acetonitrile/water (55/45).

Received: January 28, 1998 [Z114151E]
German version: *Angew. Chem.* **1998**, *110*, 2226–2228

Keywords: antitumour agents • halomon • natural products
• rearrangements • total synthesis

- G. N. Gray, J. R. Steiner, J. Clardy, E. Menez, R. H. Shoemaker, D. J. Newman, K. M. Snader, M. R. Boyd, *J. Med. Chem.* **1994**, *37*, 4407.
- [3] E. G. E. Hawkins, M. D. Philpot, *J. Chem. Soc.* **1962**, 3204.
- [4] J. E. Bäckvall, C. Jonasson, *Tetrahedron Lett.* **1997**, *38*, 291; M. Poustma, *J. Org. Chem.* **1968**, *33*, 4080; W. Smadja, *Chem. Rev.* **1983**, *83*, 263; M.-C. Lasne, A. Thuillier, *Bull. Soc. Chim. Fr.* **1974**, 249.
- [5] T. Schlama, K. Gabriel, V. Gouverneur, C. Mioskowski, *Angew. Chem.* **1997**, *109*, 2440; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2342; the monosilyloxyalkene **4** was contaminated with 20% of the diprotected alkene, which was cleanly separated by column chromatography.
- [6] Oxy-Cope rearrangements were tested on 5,6-*trans*-dichloronona-1,5-dien-3-ol as a model compound. Rearrangements of 2,3-*trans*-dichlorodec-2-enyl acetate under basic conditions (Ireland–Claisen) are not compatible with the formation of the rearranged compound; spontaneous decarboxylation with concomitant dehydrochlorination of the initial rearranged product afforded the corresponding 2-chloro-1,3-diene. For the decomposition of β -chlorocarboxylic acid derivatives under basic conditions, see J. L. Belletire, D. R. Walley, *Tetrahedron Lett.* **1983**, *24*, 1475; W. R. Vaughan, W. F. Cartwright, B. Henzi, *J. Am. Chem. Soc.* **1972**, *94*, 4978.
- [7] W. S. Johnson, L. Werthermann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741; G. W. Daub, J. P. Edwards, C. R. Okada, J. W. Allen, C. T. Maxey, M. S. Wells, A. S. Goldstein, M. J. Dibley, C. J. Wang, D. P. Oстерcamp, S. Chung, P. S. Cunningham, M. A. Berliner, *J. Org. Chem.* **1997**, *62*, 1976.
- [8] The yield could not go beyond 55% since the product slowly underwent elimination under the rearrangement conditions.
- [9] The use of three equivalents allowed selective reduction of the ester group with no side reactions resulting from the reduction of the halogen atoms.
- [10] A. P. Kosikowski, J. Lee, *J. Org. Chem.* **1990**, *55*, 863.
- [11] The use of two equivalents of Et₄N⁺CN⁻ instead of ten equivalents gave the cyclized 3-chloro-3-chlorovinyl tetrahydrofuran as the only product in 98% yield.
- [12] Attempts to convert the silyloxy group directly into a bromide were unsuccessful.
- [13] The use of guanidinium salts as additives was inspired by the work of Chastrette et al., who described that ammonium salts could be used as efficient additives for the addition of an organomagnesium halide to a carbonyl group: M. Chastrette, R. Amouroux, *Bull. Soc. Chim. Fr.* **1970**, 4348. In our case, the use of an ammonium salt was less efficient than hexaethylguanidinium chloride.
- [14] J. Cousseau, *Synthesis* **1980**, 805.
- [15] H. G. Viehe, Z. Janousek, *Angew. Chem.* **1973**, *85*, 837; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 806; H. G. Viehe, Z. Janousek in *Encyclopedia of Reagents for Organic Synthesis*, Vol. 3 (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 17019–17210.
- [16] The synthetic substance was identical to natural halomon by spectroscopic (¹H NMR, ¹³C NMR, IR, and MS) and chromatographic analysis (TLC and HPLC).
- [17] T. Schlama, R. Baati, V. Gouverneur, C. Mioskowski, unpublished results.
- [18] During the course of this study, the use of a [2,3]-sigmatropic rearrangement of a carbene as the key step for the synthesis of a polyhalogenated diene of the halomon class was published by M. E. Jung, M. H. Parker, *J. Org. Chem.* **1997**, *62*, 7094.
- [19] New asymmetric [3,3]-sigmatropic rearrangements are under current investigation in our laboratory.

- [1] B. J. Burreson, F. X. Woolard, R. E. Moore, *Chem. Lett.* **1975**, 1111; N. Ichikawa, Y. Naya, S. Enomoto, *Chem. Lett.* **1974**, 133.
- [2] R. W. Fuller, J. H. Cardellina II, Y. Kato, L. S. Brinen, J. Clardy, K. M. Snader, M. R. Boyd, *J. Med. Chem.* **1992**, *35*, 3007; R. W. Fuller, J. H. Cardellina, J. Jurek, P. J. Scheuer, B. Alvarado-Lindner, M. McGuire,

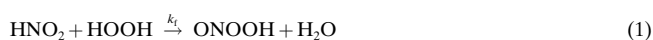
Fast Oxidation of Organic Sulfides by Hydrogen Peroxide by In Situ Generated Peroxynitrous Acid**

Stéphane Vayssié and Horst Elias*

Dedicated to Professor Bernt Krebs
on the occasion of his 60th birthday

The oxidation of organic sulfides RSR' by hydrogen peroxide to form sulfoxides and, in a consecutive slower step, sulfones is a well established procedure.^[1] The rate of such oxidations can be enhanced by the use of organic peroxides or peroxy acids instead of H₂O₂ and, catalytically, by the activation of H₂O₂ through coordination to metal centers.^[1] The reaction of H₂O₂ with nitrous acid at low pH leads to peroxynitrous acid ONOOH,^[2] an isomer of nitric acid which is a much more powerful oxidant than H₂O₂.^[3] The use of ONOOH for the oxidation of organic substrates is limited by the fact, however, that this peroxy acid is an unstable species that isomerizes at ambient temperature with a half-life of about 1 s to form nitric acid. Since ONOOH is also generated by the reaction of superoxide with NO, its role in biological systems is currently of great interest.^[4]

The peroxynitrite anion ONOO⁻ is considerably more stable than the acid ONOOH. As a result, most of the studies with the oxidant peroxynitrous acid have been carried out in such a way that, after the fast generation of ONOOH from H₂O₂ and HNO₂ at low pH,^[2] the decay of ONOOH was blocked by the addition of alkali. The cooled, stable alkaline peroxynitrite solutions thus prepared were taken as stock material.^[5] The approach presented here is basically different in that the short-lived oxidant ONOOH is generated in situ as a very reactive intermediate according to Equation (1). This



reaction is a fast process. After its generation, ONOOH is used for the fast second-order oxidation of suitable organic substrates A [Eq. (3)]. The oxidation competes with the decay of ONOOH [Eq. (2)]. As a consequence, this approach is applicable only when the rate of reaction (3) is higher than that of (2), that is when $k_A[\text{A}]$ is much greater than k_d . One should note that reactions (1) and (3) form a catalytic cycle, in which the catalyst HNO₂ converts H₂O₂ into the more powerful oxidant ONOOH. The number of cycles is controlled by the competition between reactions (2) (decay

of ONOOH) and (3) (oxidation of the substrate by ONOOH).

For solubility reasons, organic substrates require organic media. To our knowledge, the generation of ONOOH according to Equation (1) in organic media has not yet been investigated. The time dependence of the absorbance at 260 nm for the reaction of H₂O₂ with HNO₂ in acetonitrile^[6] at 293 K is shown in Figure 1.^[7] The fast formation of

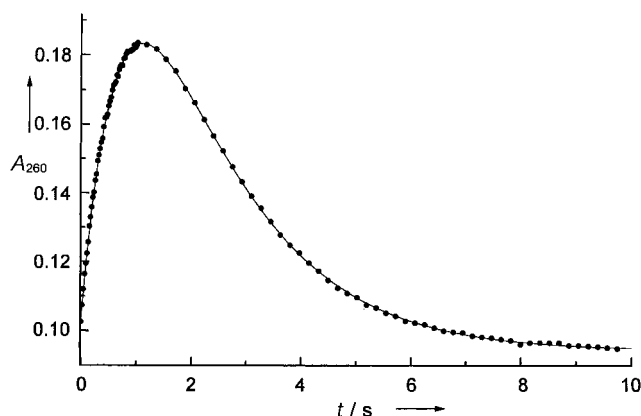


Figure 1. Time dependence of the absorbance at 260 nm for the reaction of H₂O₂ with nitrous acid in acetonitrile at 293 K ([H₂O₂] = 5 mM, [NaNO₂] = 0.5 mM, [HClO₄] = 0.1 M, I = 0.6 M (NaClO₄), [H₂O] = 5 M). The rate constants $k_f = 1.2 \text{ s}^{-1}$ and $k_d = 0.61 \text{ s}^{-1}$ for the formation and decay of peroxynitrous acid were obtained from the sum of two exponentials^[7] (solid line).

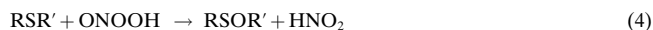
ONOOH with an experimental pseudo-first-order rate constant $k_f = 1.2 \pm 0.2 \text{ s}^{-1}$ is followed by its first-order decay to HNO₃ with $k_d = 0.61 \pm 0.05 \text{ s}^{-1}$. Under comparable conditions, the rate constant k_d for the reaction in water is $1.07 \pm 0.05 \text{ s}^{-1}$.^[9] This means that acetonitrile (with an admixture of 5 M H₂O) is suitable for the generation of ONOOH according to Equation (1), and that the rate of decay of ONOOH in acetonitrile is close to that in water.

We have tested the practical applicability of in situ generated peroxynitrous acid as an oxygen-transfer agent in acetonitrile for several classes of organic substrates under standardized conditions.^[10] These conditions were such that there was a 2.5-fold excess of organic substrate relative to H₂O₂, and the reaction was monitored cerimetrically by the loss of H₂O₂. Houk et al.^[11] reported recently the results of calculations suggesting that oxygen transfer from ONOOH to ethylene is energetically feasible. This led us to study the epoxidation of several olefins according to reaction sequence (1)–(3) at [HNO₂]:[H₂O₂] = 1:4.4. The result was negative in the sense that the consumption of H₂O₂ for substrate oxidation was zero for cyclohexene and allyl alcohol, and very minor for 2-methoxypropene, ethylvinyl ether, and 2,3-dimethyl-2-butene. Under the given conditions, the reaction of these olefins with ONOOH is apparently too slow to compete with the isomerization of ONOOH to HNO₃ [Eq. (2)]. It was not surprising to find that N-oxidation of amines such as pyridine and substituted pyridines was not to be observed. In the given acidic medium, protonation reduces the concentration of free amine to a minimum.

[*] Prof. Dr. H. Elias, Dipl.-Ing. S. Vayssié
Institut für Anorganische Chemie der Technischen Universität
Petersenstrasse 18, D-64287 Darmstadt (Germany)
Fax: (+49) 6151-166-040
E-mail: elias@hrz1.hrztu-darmstadt.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Verband der Chemischen Industrie, and the Otto-Röhm-Stiftung. This contribution presents the main results of the Dr.-Ing. Dissertation to be submitted to the Technische Universität Darmstadt, D17, by S.V.

Organic sulfides RSR' turned out to be very suitable substrates for the fast sulfoxidation with in situ generated ONOOH [Eq. (4)]. As shown in Figure 2 for the system



$\text{PhSMe}/\text{H}_2\text{O}_2/\text{NaNO}_2$, the sulfoxidation of PhSMe in the absence of nitrite is a rather slow process.^[12] The addition of 15 mM of nitrite triggers an instantaneous, partial oxidation of

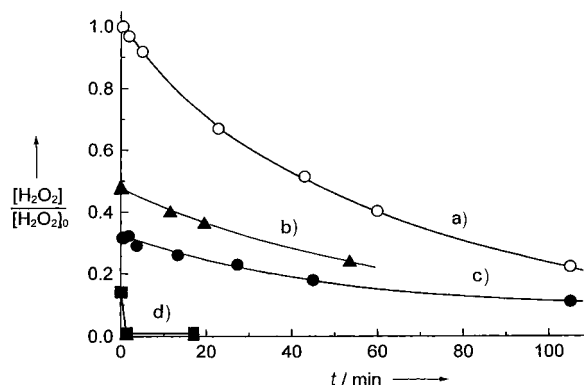


Figure 2. Time dependence of the concentration of H_2O_2 for the reaction of PhSMe with H_2O_2 in acidified acetonitrile at variable concentrations of HNO_2 under standard conditions^[10] ($[\text{H}_2\text{O}_2] = \text{constant} = 0.2 \text{ M}$; $[\text{NaNO}_2] = 0 \text{ M}$ (a), 0.015 M (b), 0.020 M (c), 0.030 M (d)).

PhSMe , as monitored by a sharp drop in the H_2O_2 concentration. The size of this instantaneous drop increases with the concentration of nitrite. For $[\text{NaNO}_2] = 30 \text{ mM}$ (which corresponds to $[\text{H}_2\text{O}_2]:[\text{NaNO}_2] = 6.7:1$), all of the H_2O_2 oxidant is consumed within one minute. This means that, in terms of catalysis, one molecule of HNO_2 passes almost seven cycles according to reactions (1) and (3), thus “activating” seven molecules of H_2O_2 by the formation of ONOOH . Owing to the greater reactivity of ONOOH relative to that of H_2O_2 , the sulfoxidation of PhSMe is drastically accelerated.

The sulfoxidation of dimethyl sulfide according to Equations (1)–(3) is accelerated by nitrite in an analogous manner. The noncatalyzed oxidation in the absence of nitrite is faster by a factor of 19 than that of PhSMe . Correspondingly, a nitrite concentration of only 10 mM ($[\text{H}_2\text{O}_2]:[\text{NaNO}_2] = 20:1$) is sufficient to make the oxidation of Me_2S complete within one minute. These data mean that the catalyst HNO_2 cycles twenty times. As outlined above, the condition for a maximum number of cycles in the system $\text{Me}_2\text{S}/\text{H}_2\text{O}_2$ is given by $k_{\text{Me}_2\text{S}}[\text{Me}_2\text{S}] \gg k_d$.^[14] The validity of this condition was tested by a series of experiments with variable concentrations of Me_2S and constant concentrations of H_2O_2 and NaNO_2 . As shown in Figure 3, in the absence of Me_2S there is an initial loss of 10 % of H_2O_2 . This loss corresponds to the conversion of HNO_2 into ONOOH , which decays to HNO_3 with the rate constant k_d .^[16] At $[\text{Me}_2\text{S}] = 5 \text{ mM}$ the oxidation of Me_2S by ONOOH begins to compete with the decay of ONOOH , an indication that the size of $k_{\text{Me}_2\text{S}}[\text{Me}_2\text{S}]$ is getting closer to that of k_d . This effect is more pronounced at $[\text{Me}_2\text{S}] = 10 \text{ mM}$. Finally, at $[\text{Me}_2\text{S}] = 50 \text{ mM}$ the peroxynitrous acid formed reacts preferentially with Me_2S ; the condition

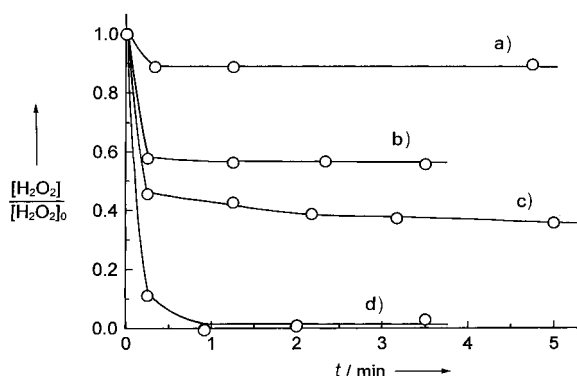


Figure 3. Time dependence of the concentration of H_2O_2 for the reaction of Me_2S with H_2O_2 in acidified acetonitrile at various concentrations of Me_2S at 20°C ($[\text{H}_2\text{O}_2] = 0.005 \text{ M}$, $[\text{NaNO}_2] = 0.0005 \text{ M}$, $[\text{H}_2\text{SO}_4] = 0.08 \text{ M}$, $[\text{H}_2\text{O}] = 5 \text{ M}$; $[\text{Me}_2\text{S}] = 0 \text{ M}$ (a), 0.005 M (b), 0.010 M (c), 0.050 M (d)).

$k_{\text{Me}_2\text{S}}[\text{Me}_2\text{S}] \gg k_d$ is fulfilled and all of the H_2O_2 is consumed by substrate oxidation within one minute. These results allow the estimate^[17] that $k_{\text{Me}_2\text{S}}$ is greater than $10^2 \text{ M}^{-1} \text{ s}^{-1}$. This means that, compared to the second-order rate constant k for the noncatalyzed Me_2S oxidation by H_2O_2 (Table 1), the reactivity

Table 1. Kinetic data for the sulfoxidation of organic sulfides by H_2O_2 in acidified acetonitrile in the absence and presence of nitrous acid.

Sulfide	$10^4 k^{[a]}$ [$\text{M}^{-1} \text{ s}^{-1}$]	$([\text{HNO}_2]:[\text{H}_2\text{O}_2])_{\text{lim}}^{[b]}$ [mm]:[mm]	Catalytic cycles
PhSMe	31 ± 3	30:200	6.7
$(\text{PhCH}_2)_2\text{S}$	70 ± 6	20:200	10
Me_2S	580 ± 50	10:200	20

[a] Second-order rate constant k for the sulfoxidation at 293 K in the absence of the catalyst under standard conditions.^[10] [b] Limiting concentration ratio at which (and above which) catalyzed sulfoxidation is complete within one minute under standard conditions.^[10]

of ONOOH is more than three orders of magnitude greater than that of H_2O_2 .

Product formation in the systems $\text{PhSMe}/\text{H}_2\text{O}_2/\text{NaNO}_2$ and $\text{Me}_2\text{S}/\text{H}_2\text{O}_2/\text{NaNO}_2$ was additionally controlled by GC analysis.^[18] Under standard conditions ($[\text{substrate}] > [\text{H}_2\text{O}_2]$),^[10] the sulfoxides PhSOCH_3 and CH_3SOCH_3 were the only products. Further oxidation to the corresponding sulfones is slower by several orders of magnitude than the sulfoxidation [Eq. (4)],^[3] and is only observed when the substrate concentration is less than that of H_2O_2 and with long reaction times.

The sulfoxidation of dibenzyl sulfide was also studied in detail. It follows from the data summarized in Table 1 that, at $[\text{H}_2\text{O}_2]:[\text{NaNO}_2] = 10:1$, formation of dibenzyl sulfoxide is complete within one minute. $(\text{PhCH}_2)_2\text{S}$ was chosen as a model compound to test the synthetic potential of the method for the fast preparation of sulfoxides at the gram level. An aqueous solution of NaNO_2 was quickly added to an acidified, well-stirred acetonitrile solution of $(\text{PhCH}_2)_2\text{S}$ containing an excess of H_2O_2 .^[19] After a reaction time of only five minutes at ambient temperature, pure dibenzyl sulfoxide was isolated in a yield of 91 %.

In conclusion, the present approach provides an experimentally simple and time-saving method for the fast and convenient preparation of sulfoxides. The method is based on

nonexpensive, commercial chemicals (H_2O_2 , NaNO_2 , H_2SO_4 , and CH_3CN) and can be classified as a sulfoxidation reaction with “activated” H_2O_2 . The activation consists of the fast reaction of H_2O_2 with HNO_2 in acidified CH_3CN to form the unstable, yet highly reactive, oxidant peroxynitrous acid ONOOH as an intermediate species in situ. The experimental conditions can be easily set in such a way that the reaction of the electrophile ONOOH with the nucleophile RSR' is fast enough to compete successfully with the decay of ONOOH to nitric acid. Under these optimized conditions, HNO_2 acts as a catalyst, quickly carrying oxygen atoms from H_2O_2 to the sulfide in the form of ONOOH .

Received: February 23, 1998 [Z11508IE]

German version: *Angew. Chem.* **1998**, *110*, 2246–2249

Keywords: homogeneous catalysis • O–O activation • oxidations • peroxides • synthetic methods

- [1] S. Uemura in *Comprehensive Organic Synthesis*, Vol. 7 (Eds: B. M. Trost, I. Fleming, S. V. Ley), Pergamon, Oxford, **1991**, pp. 762–769.
- [2] W. G. Keith, R. E. Powell, *J. Chem. Soc. A* **1969**, 90.
- [3] P. Amels, H. Elias, K.-J. Wannowius, *J. Chem. Soc. Faraday Trans.* **1997**, *93*, 2537–2544.
- [4] In vivo, the reaction of O_2^- with NO leads to the anion ONOO^- , which is in equilibrium with the acid ONOOH . The reaction of superoxide with NO is faster than that with superoxide dismutase (SOD). For the biological relevance of ONOOH see, for example, W. A. Pryor, G. L. Squadrito, *Am. J. Physiol.* **1995**, *268*, L699–L722.
- [5] See, for example, a) R. Radi, J. S. Beckman, K. S. Bush, B. A. Freeman, *J. Biol. Chem.* **1991**, *266*, 4244–4250; b) W. A. Pryor, X. Jin, G. L. Squadrito, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 11173–11177; c) A. Al-Ajlouni, E. S. Gould, *Inorg. Chem.* **1996**, *35*, 7892–7896; d) S. Goldstein, G. Czapski, *Inorg. Chem.* **1995**, *34*, 4041–4048.
- [6] The use of commercial H_2O_2 as a reagent necessarily introduces some water into the system. The solvent acetonitrile with a constant admixture of water (5 M) was therefore taken as the standard reaction medium.
- [7] The absorbance/time data shown in Figure 1 were obtained with a multi-wavelength stopped-flow spectrophotometer described earlier.^[8] The absorptivity of ONOOH in the range 250–350 nm is greater than that of nitrous and nitric acid. The initial increase in absorbance A at 260 nm corresponds therefore to the formation of ONOOH , the consecutive decrease to its decay. The rate constants k_t and k_d were obtained from Equation (5) using the A/t data (a_1 , a_2 = amplitudes).

$$A = a_1 \exp(-k_t t) + a_2 \exp(-k_d t) + A_\infty \quad (5)$$
- [8] C. Drexler, H. Elias, B. Fecher, K. J. Wannowius, *Fresenius J. Anal. Chem.* **1991**, *340*, 605–615.
- [9] D. J. Benton, P. J. Moore, *J. Chem. Soc. A* **1970**, 3179–3182.
- [10] Standard procedure and conditions: A solution of H_2O_2 , H_2SO_4 , and H_2O in CH_3CN (1 mL) was quickly mixed with a solution of the organic substrate A and NaNO_2 in CH_3CN (1 mL) to obtain the reaction mixture with $[\text{H}_2\text{O}_2] = 0.2 \text{ M}$, $[\text{HNO}_2] = 0–45 \text{ mM}$, $[\text{A}] = 0.5 \text{ M}$, $[\text{H}_2\text{SO}_4] = 0.08 \text{ M}$, and $[\text{H}_2\text{O}] = 5 \text{ M}$ (the $\text{p}K_a$ of HNO_2 is 3.3; to liberate HNO_2 from NaNO_2 , the condition $-\lg[\text{H}^+] < 3$ has to be fulfilled). The mixture was stirred at ambient temperature. At adequate time intervals, samples (0.2 mL) were taken and diluted with water for the cerimetric determination of H_2O_2 .
- [11] K. N. Houk, K. R. Condroski, W. A. Pryor, *J. Am. Chem. Soc.* **1996**, *118*, 13002–13006.
- [12] The value of $k = (31 \pm 3) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ (see Table 1) was obtained by fitting of the $[\text{H}_2\text{O}_2]/t$ data shown in Figure 2a to Equation 6. This

$$[\text{H}_2\text{O}_2] = [\text{H}_2\text{O}_2]_0 \exp(-k[\text{PhSMe}]t) \quad (6)$$
value is very close to $k = 37.3 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ as reported for the sulfoxidation of PhSMe with H_2O_2 in EtOH (6 % H_2O).^[13]
- [13] G. Modena, L. Maiola, *Gazz. Chim. Ital.* **1957**, *87*, 1306–1316.

- [14] The reaction between Me_2S and ONOOH in water was recently shown to be second-order, first-order in both reactants.^[3] The oxidation of organic sulfides by hydroperoxides is generally found to be a second-order process.^[15]
- [15] J. O. Edwards in *Peroxide Reaction Mechanisms* (Ed.: J. O. Edwards), Wiley-Interscience, New York, **1962**, pp. 67–106.
- [16] It was confirmed by experiment that ONOOH , when generated according to Equation (1), does not decompose H_2O_2 according to the reaction $\text{ONOOH} + \text{H}_2\text{O}_2 \rightarrow \text{HNO}_2 + \text{H}_2\text{O}$.
- [17] At the lowest Me_2S concentration, $[\text{Me}_2\text{S}] = 5 \text{ mM}$, almost half of the H_2O_2 is consumed for the fast Me_2S oxidation by ONOOH (see Figure 3). This means that the Me_2S concentration at which $k_{\text{Me}_2\text{S}}[\text{Me}_2\text{S}] = k_d$ is smaller than 5 mM and, hence, $k_{\text{Me}_2\text{S}} > 0.61/0.005 = 122 \text{ M}^{-1} \text{ s}^{-1}$.
- [18] GC analysis was carried out with an Auto System Gas Chromatograph with FI detector (Perkin-Elmer) and a 15-m capillary column (Alltech; Heliflex AT-1000) at 150 °C (Me_2S) and 170 °C (PhSMe). The samples were neutralized with NaOH before injection.
- [19] Concentrated H_2SO_4 (1 mL, 98 %) and technical grade, stabilized 35 % H_2O_2 (4 mL, 47 mmol) were added to a well-stirred solution of $(\text{PhCH}_2)_2\text{S}$ (5.3 g, 25 mmol) in CH_3CN (250 mL) at ambient temperature. To start the fast catalyzed reaction, a solution of NaNO_2 (320 mg, 4.7 mmol) in water (2 mL) was added in one portion (**caution:** the reaction is exothermic! In the case of larger batches the reaction mixture should be efficiently thermostated). After a reaction time of five minutes the solution was set to pH 7 with a solution of NaOH (1 M) diluted with water (70 mL) and extracted with chloroform ($3 \times 130 \text{ mL}$). The chloroform phase was dried with MgSO_4 and taken to dryness in vacuo. The residue was recrystallized from EtOH. Yield: 5.1 g (91 %). M.p. 133 °C (134–135 °C^[20]). ^1H NMR and IR spectroscopy as well as $\text{C}_2\text{H}_5\text{N}$ analysis proved the identity of the product as dibenzyl sulfoxide.
- [20] *Handbook of Chemistry and Physics*, 51st ed., The Chemical Rubber Co. **1970–1971**.

Synthesis, Structure, and Reactivity of a Palladium Hydrazonato Complex: A New Type of Reductive Elimination Reaction To Form C–N Bonds and Catalytic Arylation of Benzophenone Hydrazone**

John F. Hartwig*

Reductive elimination reactions which form C–N bonds in amines^[1–4] are important primary reactions in practical catalytic cycles for the synthesis of arylamines from aryl halides.^[1, 5–8] Reductive elimination reactions that result in *N*-arylhydrazones would be an important new method for C–N bond formation by means of reductive elimination. The hydrazone products could be used in Fischer indole syntheses or, after conversion into the *N*-arylhydrazine, in condensation reactions to produce *N*-arylpyrazoles and *N*-arylpyrazolones.

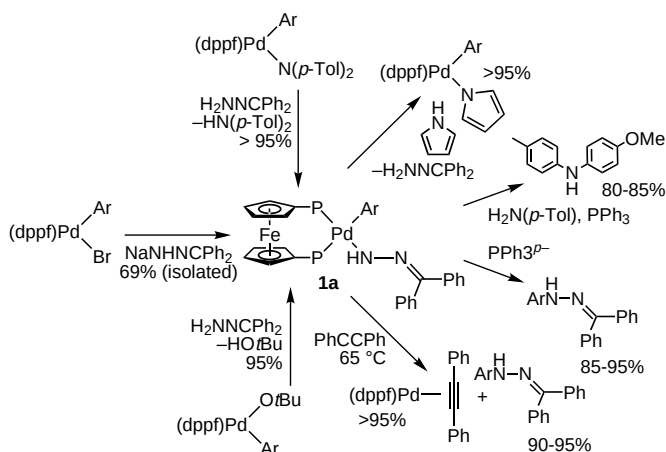
[*] Prof. J. F. Hartwig

Department of Chemistry, Yale University
P.O. Box 208107, New Haven, CT 06520-8107 (USA)
Fax: (+1) 203-432-6144
E-mail: john.hartwig@yale.edu

[**] I thank the Department of Energy and the NIH for supporting portions of this work. I also appreciate support through a National Science Foundation Young Investigator Award, a Camille Dreyfus Teacher-Scholar award, and the Eli Lilly Grantee Program. J.F.H. is a fellow of the Alfred P. Sloan Foundation.

A large number of hydrazone complexes have been prepared, but many display either μ^2 ^[9] or η^2 coordination modes^[10, 11] which lead to stable complexes. Here the first monomeric, η^1 -hydrazone complex characterized by X-ray diffraction is reported, together with reactions to evaluate its stability in comparison with related amido and pyrrolyl complexes. In addition, the reductive elimination of *N*-arylhydrazone, and the palladium-catalyzed arylation of a representative hydrazone are discussed.

The synthesis and reactivity of [Pd(dppf)(*p*-MeOC₆H₄)-(NH=N=CPh₂)] (**1a**) are shown in Scheme 1. Reaction of NaNH=N=CPh₂ with [Pd(Br)(dppf)(*p*-MeOC₆H₄)] cleanly



Scheme 1. Synthesis and reactions of [Pd(dppf)(Ar)(NH=N=CPh₂)] (**1a**). Ar = *p*-MeOC₆H₄, DPPF = 1,1'-bis(diphenylphosphanyl)ferrocene, Tol = tolyl.

gave **1a**, which was isolated in 69% yield.^[2] The ³¹P NMR spectrum of **1a** shows two sharp doublets, demonstrating that DPPF remains chelated to the metal center, and that the complex is square planar in solution. The IR spectrum of **1a** showed a C=N band at 1575 cm⁻¹, which is consistent with an η^1 coordination mode since free diphenylhydrazone vibrates at 1571 cm⁻¹.

An ORTEP drawing of a more crystalline analogue [Pd(dppf)(*o*-MeC₆H₄)(NH=N=CPh₂)] (**1b**)^[12] is provided in Figure 1.^[13] Complex **1b** is monomeric, square planar, and contains a terminal hydrazone ligand. The sum of the four angles about the Pd center is 360.4°. The nitrogen atom in the position β to the Pd center lies nearly within the square plane, which precludes any formulation of the complex as a square-based pyramid; the distance between the Pd center and the second nitrogen atom is greater than 3 Å. No previous examples of simple η^1 , μ^1 hydrazone complexes were found in the Cambridge Crystallographic Database. The Pd1–N1 bond length of 2.035(9) Å is 0.06 Å shorter than that in the related DPPF-ligated palladium diarylamido complex.^[2] The N1–N2 bond length of 1.35(1) Å in **1b** is shorter than the typical N–N bond lengths in hydrazones (1.38–1.41 Å),^[14] but the C1=N2 bond of 1.32(1) Å is no longer than usual for hydrazones,^[14] and the $\tilde{\nu}_{\text{CN}}$ value is not reduced from that for free diphenylhydrazone. The P1–Pd1–P2 angle of 99.8(1)° is roughly 1.5° smaller than the corresponding angle in the more

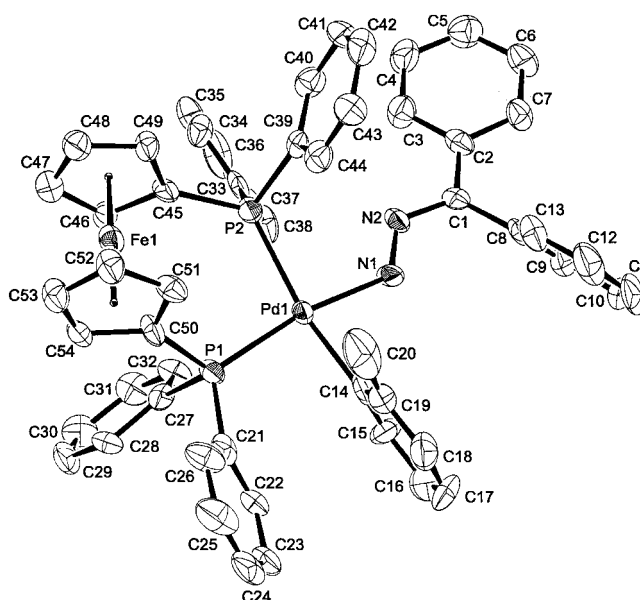


Figure 1. ORTEP drawing of **1b**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd1–P1 2.293(3), Pd1–P2 2.374(4), Pd1–N1 2.035(9), Pd1–C14 2.03(1), N1–N2 1.35(1), N2–C1 1.32(1); P1–Pd1–P2 99.8(1), P1–Pd1–C14 88.9(3), P2–Pd1–N1 89.8(3), N1–Pd1–C14 81.9(4).

sterically crowded diarylamido complex. The palladium-bound aryl group is twisted by 99° out of the palladium square plane, and this geometry, coupled with hindered rotation, gives rise to eight cyclopentadienyl resonances in the ¹H NMR spectrum.

Scheme 1 includes reactions that result in **1a** upon exchange of the σ -bonded ligands. These simple exchange reactions were complete within 30 minutes at room temperature. Complex **1a** was generated in essentially quantitative yield by the reaction of benzophenone hydrazone with the diarylamido complex [Pd(dppf)(*p*-MeOC₆H₄)[N(*p*-Tol)₂].^[2] The palladium alkoxide [Pd(dppf)(*p*-MeOC₆H₄)(*o*-Bu)]^[18] reacted with benzophenone hydrazone to form **1a** and *t*BuOH in a process that is similar to reactions with amine substrates.^[15–17]

Reaction of **1a** with pyrrole generated the palladium pyrrolyl complex [Pd(dppf)(*p*-MeOC₆H₄)(NC₄H₄)].^[19] Although treatment with toluidine did not afford the arylamido complex [Pd(dppf)(*p*-MeOC₆H₄)(NH-*p*-Tol)] in observable quantities, the mixture of **1a** and toluidine produced *p*-MeOC₆H₄NH-*p*-Tol in 80–85% yield after 12 h at room temperature. Thus, reaction of **1a** most likely forms small amounts of [Pd(dppf)(*p*-MeOC₆H₄)(NH-*p*-Tol)]; this complex is analogous to related complexes that eliminate diarylamines at room temperature.^[1, 2] Overall, the stability of **1a** lies in the middle of the stability range for complexes known to undergo C–N bond formation by reductive elimination.

This data on relative stability suggests that **1a** should undergo reductive elimination to form C–N bonds. Indeed, when a solution of **1a** was warmed to 70 °C for 2 h with either PPh₃ or diphenylacetylene to trap the Pd⁰ product, *N*-arylhydrazone was formed in greater than 85% yield, as determined by ¹H NMR spectroscopy with an internal standard. For reactions carried out in the presence of PPh₃,

the Pd⁰ products were a combination of [Pd(dppf)₂] and PPh₃ complexes of Pd⁰.^[20] For reactions with diphenylacetylene as the trapping reagent, [Pd(dppf)(PhCCPh)] was formed as the Pd⁰ product. This compound was not isolated, but its identity was confirmed by independent synthesis from [Pd(P(*o*-Tol)₃)₂], DPPF (1 equiv), and PhCCPh (1 equiv). Quantitative rate studies showed that the reaction was first order in the palladium complex and zero order in trapping reagents. The *k*_{obs} values for reactions with 0.022–0.11 M [D₁₅]PPh₃ averaged 3.8 × 10^{−4} with an estimated standard deviation of only 0.4 × 10^{−4}, while the *k*_{obs} value for reactions with PhCCPh as the trapping reagent averaged (3.7 ± 0.1) × 10^{−4}. The lack of an influence of the concentration of the trapping reagent on the reaction rate has also been observed for other C–N bond-forming reductive elimination reactions from DPPF-ligated palladium complexes,^[2] and suggests that the reductive elimination of **1a** follows a similar intramolecular elimination pathway.

These findings imply that one could produce *N*-arylhydrazones catalytically from aryl halides, inexpensive diphenylhydrazone, an alkoxide base, and a DPPF-ligated palladium complex. The results from such studies are summarized in Table 1. Electron-rich, electron-poor, sterically hindered, or

of DPPF as a ligand enabled cesium carbonate to be used as a base for aryl halide substrates that are not electron-poor. No competing diarylation^[8, 22] of the hydrazone was observed in the reactions in Table 1, and only trace amounts of diphenylmethane (<2%), possibly generated from Wolf–Kischner reduction,^[23] were detected.

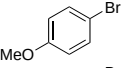
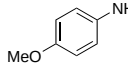
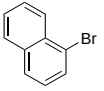
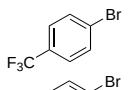
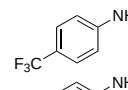
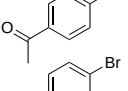
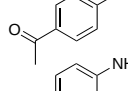
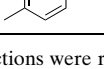
In conclusion, this work demonstrates that an η¹-hydrazone is a viable intermediate in reductive elimination reactions to form C–N bonds in palladium-catalyzed arylation chemistry. This complex is more stable than the related amido derivatives, both thermally and toward proton transfer. Nevertheless, the reductive elimination process occurs in high yields at mild temperatures. The stronger acidity of the hydrazone relative to amines and arylamines allows the catalytic reaction to be carried out with simple ligands and a carbonate base.^[25]

Experimental Section

1: Solid NaNHNCPh₂ (33 mg, 0.15 mmol) was added with stirring to a slurry of [Pd(I)(dppf)(*p*-MeOC₆H₄)] (90 mg, 0.10 mmol) in THF (2 mL). This mixture was stirred for 5 min, during which time the solution became orange and the solid starting complex was consumed. The solvent was removed under reduced pressure, and the resulting solid was extracted with toluene (5 mL). The toluene extract was filtered through celite, the volume was reduced by half, and pentane was layered onto the solution. After the mixture was cooled at −35 °C for 12 h, 66 mg (69% yield) of orange **1** were isolated by removal of the supernatant with a pipette and washing of the solid with pentane. ¹H NMR (300 MHz, [D₆]benzene, 25 °C, TMS): δ = 8.51 (pseudo t, *J* = 8.3 Hz, 4H), 7.54 (dd, *J* = 8.7, 11.0 Hz, 4H), 6.8–7.3 (m, 25H), 6.44 (d, ³*J*_{H,H} = 7.1 Hz, 2H), 4.60 (d, ³*J*_{H,H} = 1.7 Hz, 2H), 4.00 (s, 2H), 3.79 (s, 2H), 3.76 (s, 2H), 3.37 (s, 3H); ³¹P{¹H} NMR (122 MHz, [D₆]benzene, 25 °C, 85% H₃PO₄): δ = 27.52 (d, ²*J*_{PP} = 30.5 Hz), 13.83 (d, ²*J*_{PP} = 30.5 Hz); IR (Nujol): ν_{N–H} = 3228, ν_{C–N} = 1575 cm^{−1}; elemental analysis calcd for C₅₅H₄₆FeN₂O₂Pd · C₇H₈: C 69.43, H 5.16, N 2.65; found: C 69.65, H 5.19, N 2.45.

Hydrazone arylation: [Pd(OAc)₂] (2.2 mg, 0.01 mmol), DPPF or BINAP (0.015 mmol), NaOtBu or Cs₂CO₃ (1.5 mmol), and benzophenone hydrazone (235 mg, 1.2 mmol) were placed into a screw-capped vial with a stir bar. An aryl halide (1.0 mmol) was placed into a separate vial and dissolved in toluene (0.5–2.0 mL). The solution was then transferred to the screw-capped vial. The vial was sealed with a cap containing a teflon-lined septum and then placed in an oil bath (90 or 100 °C). GC/MS analysis of the reaction mixture showed complete consumption of the aryl halide after 12 h. The reaction mixture was filtered, the solid was washed with ethyl acetate, and the solvent was removed under reduced pressure. The resulting oil was purified by chromatography (silica gel, elution with hexane/ethyl acetate).

Table 1. Palladium-catalyzed arylation of diphenylhydrazone.^[a]

Entry	Substrate	Ligand	Base	Product ^[b]	Yield [%] ^[c]
1		BINAP	NaOtBu		80
2		DPPF	NaOtBu		99
3		DPPF	NaOtBu		91
4		DPPF	NaOtBu		86
5		DPPF	Cs ₂ CO ₃		91
6		DPPF	Cs ₂ CO ₃		96
7		DPPF	Cs ₂ CO ₃		86

[a] All reactions were run with 1 mol % [Pd(OAc)₂], 1.5 mol % ligand, 1.5 equiv of base, 1.2 equiv of diphenylhydrazone, and 1.0 mmol of substrate. The reactions in entries 1–6 were run for 8 h at 90 °C with 2 mL of toluene as solvent. The reaction in entry 7 was run for 12 h at 100 °C with 0.5 mL of toluene as solvent. [b] All isolated products were judged pure by ¹H and ¹³C NMR spectroscopy and GC analysis. New compounds in entries 4–6 were also characterized by elemental analysis. The product in entry 1 discolored upon standing at room temperature and was analyzed by HR-MS. Products in entries 2, 3, and 7 have been prepared previously.^[24] [c] Yield of the isolated product.

unhindered aryl bromides or iodides all reacted with benzophenone hydrazone in the presence of a base and 1 mol % of a palladium complex formed in situ from [Pd(OAc)₂] and DPPF or 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP). Cesium carbonate was an effective base for these reactions, so that even base-sensitive functionalities on the aryl halide could be tolerated.^[21] For example, entry 7 shows that the use

Received: February 27, 1998 [Z11534IE]
German version: *Angew. Chem.* **1998**, *110*, 2249–2252

Keywords: aminations • arylations • cross-coupling • hydrazones • palladium

- [1] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.
- [2] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245.
- [3] K. Koo, G. L. Hillhouse, *Organometallics* **1995**, *14*, 4421–4423.
- [4] L. A. Villanueva, K. A. Abboud, J. M. Boncella, *Organometallics* **1994**, *13*, 3921–3931.
- [5] Review: J. F. Hartwig, *Synlett* **1996**, 329–340; J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067.
- [6] J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609–3612.
- [7] A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem.* **1995**, *107*, 1456–1459; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348–1350.

- [8] J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
- [9] For a structurally characterized example, see K. Burgess, B. F. G. Johnson, J. Lewis, P. R. Raithby, *J. Chem. Soc. Dalton Trans.* **1982**, 263–269.
- [10] S. Gambarotta, M. Basso-Bert, C. Floriani, C. Gaustini, *J. Chem. Soc. Chem. Commun.* **1982**, 374–375.
- [11] S. Gambarotta, C. Floriani, A. Chiesi-Villa, C. Guastini, *Inorg. Chem.* **1983**, *22*, 2029–2034.
- [12] This complex was prepared in a similar fashion to **1a**. ^1H NMR (300 MHz, $[\text{D}_6]\text{benzene}$, 25°C , TMS): δ = 8.52 (pseudo q, J = 9 Hz, 4H), 7.88 (m, 4H), 6.65–7.45 (m, 25H), 6.44 (d, $^3J_{\text{HH}}$ = 7.2 Hz, 2H), 4.98 (br s, 1H), 4.23 (s, 1H), 4.09 (s, 1H), 3.96 (s, 1H), 3.93 (s, 1H), 3.78 (s, 1H), 3.73 (s, 1H), 3.68 (s, 1H), 2.66 (s, 3H); in addition, a ratio of 0.5 toluene molecules per **1b** molecule was determined; $^{31}\text{P}\{^1\text{H}\}$ NMR (122 MHz, $[\text{D}_6]\text{benzene}$, 25°C , 85% H_3PO_4): δ = 27.22 (d, $^2J_{\text{PP}}$ = 30.6 Hz), 13.97 (d, $^2J_{\text{PP}}$ = 30.6 Hz); IR (Nujol) $\tilde{\nu}_{\text{N-H}}$ = 3224, $\tilde{\nu}_{\text{C-N}}$ = 1571, 1594 cm^{-1} .
- [13] Crystal structure analysis of **1b**: space group $P\bar{1}$ (no. 2), a = 13.36(1), b = 18.30(2), c = 10.04(1) Å, α = 103.26(9), β = 91.85(9), γ = 78.32(8)°, V = 2339(4) Å³, Z = 2, ρ_{calc} = 1.39 g cm^{−3}, $2\theta_{\text{max}}$ = 50.0°, $\text{MoK}\alpha$ (λ = 0.71069 Å), ω – 2θ , 8.0°min^{-1} (in ω), $(1.26 + 0.3 \tan\theta)^\circ$, -105°C , 8616 reflections with 8231 unique. The data were corrected for Lorentz and polarization factors. No absorption correction was applied. The structure was solved by direct methods and refined with Fourier techniques and teXan software. Number of observations ($I > 3.00\sigma(I)$) 3147 and number of variables 577. H atoms were included but not refined. R = 0.056, wR = 0.64, refined against $|F|$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101249. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [14] P. A. S. Smith, *Derivatives of Hydrazone and other Hydronitrogens Having N-N Bonds*, Benjamin, Reading, MA, **1983**, p. 46.
- [15] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 4206–4207.
- [16] G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110.
- [17] M. S. Driver, J. F. Hartwig, *Organometallics* **1997**, *16*, 5706–5715.
- [18] This complex was prepared in similar fashion to the *p*-*t*Bu analogue.
- [19] G. Mann, M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 827–828.
- [20] A recent synopsis of these mechanisms and their accompanying data is included in C. Amatore, F. Pflüger, *Organometallics* **1990**, *9*, 2276–2282.
- [21] J. P. Wolfe, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6359–6362.
- [22] B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, in press.
- [23] J. March, *Advanced Organic Chemistry*, 3rd ed., Wiley, New York, **1985**.
- [24] M. Busch, S. Schäffner, *Chem. Ber.* **1923**, *56*, 1612–1616.
- [25] Note added in proof (July 22, 1998). Buchwald et al. have recently reported a variety of indoles prepared by the hydrazone arylation strategy. S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6621–6622.

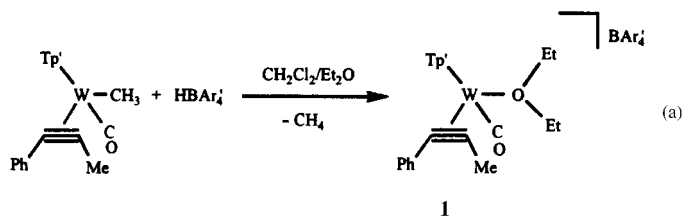
Spectra, Structure, Ligand Exchange, and Decomposition of a Tungsten(II) Ether Complex**

Thomas Brent Gunnoe, Jennifer L. Caldarelli, Peter S. White, and Joseph L. Templeton*

Ether ligands can reversibly bind to Lewis acidic metal moieties and thus stabilize reactive metal fragments and provide useful precursors for catalysts.^[1–6] Ether complexes of the Group 6 elements^[6–11] have been prepared from alkylidene complexes^[7, 8] and by protonation of $[\text{WCp}^*(\text{CO})_3(\text{Me})]$ ($\text{Cp}^* = \text{C}_5\text{Me}_5$) with HBAr'_4 in Et_2O .^[9, 10] Addition of acid to $[\text{WCp}(\text{H})(\text{CO})_3]$ ($\text{Cp} = \text{C}_5\text{H}_5$) and benzaldehyde dimethyl acetal gives the ether complex $[\text{WCp}(\text{CO})_3(\text{PhCH}_2\text{OME})][\text{X}]$ ($\text{X} = \text{CF}_3\text{SO}_3^-, \text{BAr}'_4$; $\text{Ar}' = 3,5\text{-bis(trifluoromethyl)phenyl}$).^[11] The synthesis of diethyl ether and dimethyl ether complexes of rhenium is also pertinent.^[12]

We have now synthesized $[\text{WTp}'(\text{CO})(\text{OEt}_2)(\text{PhC}\equiv\text{CMe})][\text{BAr}'_4]$ (**1**; $\text{Tp}' = \text{hydridotris(3,5-dimethylpyrazol-1-yl)borate}$). To determine whether **1** is a convenient precursor for the reactive fragment $[\text{WTp}'(\text{CO})(\text{PhC}\equiv\text{CMe})]^+$,^[13] we studied the substitution of the labile ether ligand by acetonitrile and the decomposition of **1** in dichloromethane.

Reaction of $[\text{WMeTp}'(\text{CO})(\text{PhC}\equiv\text{CMe})]$ ^[14] with HBAr'_4 in $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (ca. 2/1) yields **1** in 70% yield [Eq. (a)].



Formation of **1** is accompanied by a color change from dark blue to light blue, and the CO stretching frequency increases from 1875 to 1923 cm^{-1} . Complex **1** is stable for days at room temperature in dichloromethane in the presence of an excess of diethyl ether. However, if no excess of diethyl ether is present, **1** decomposes rapidly (ca. 2 h, see below). In the solid state, **1** is stable for weeks in air and indefinitely under an inert atmosphere.

The ^1H NMR spectrum of **1** in CD_2Cl_2 at -80°C reflects restricted rotation about the tungsten–ether bond. Thus, four multiplets are observed for the four methylene protons of the ether ligand in the range δ = 3–5. Each multiplet consists of five lines, and this is consistent with nearly equal geminal and vicinal coupling constants ($^2J_{\text{HH}} \approx ^3J_{\text{HH}} \approx 7$ Hz). Two triplets are observed for the methyl groups of the coordinated ether. The ^{13}C NMR spectrum (-80°C) displays typical resonances for the ligands (alkyne as four-electron donor) and the

[*] Dr. J. L. Templeton, T. B. Gunnoe, J. L. Caldarelli, P. S. White
Department of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-3290 (USA)
Fax: (+1) 919-962-2388
E-mail: joetemp@unc.edu

[**] This work was supported by the National Science Foundation (grant CHE-9727500). T.B.G. wishes to thank the Department of Education for support through a GAANN Fellowship.

[BAR₄]⁺ counterion.^[14] The signals of the methylene carbon atoms of the coordinated ether are at $\delta = 80.6$ and 71.9 (each a triplet, $J_{\text{CH}} = 145$ Hz).

Recrystallization of **1** (Et₂O/hexanes) provided a crystal suitable for an X-ray diffraction study (Figure 1).^[27] The geometric features of the [WTP'(CO)(PhC≡CMe)]⁺ ion are

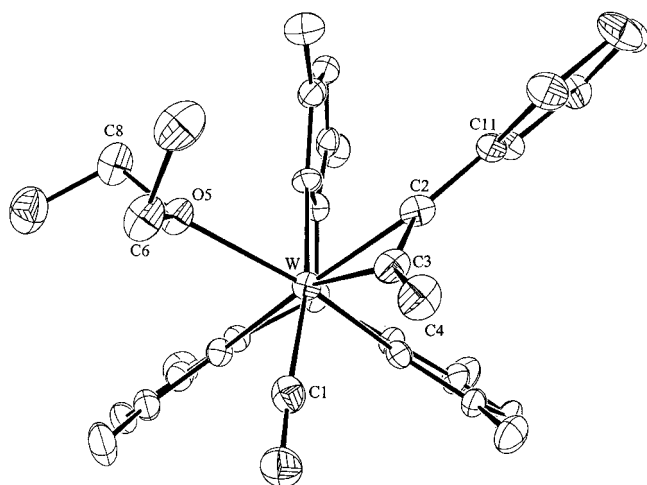


Figure 1. ORTEP diagram of the cation of **1**. Selected bond lengths [Å] and angles [°]: W–O5 2.210(4), W–C2 2.027(6), W–C3 2.073(5), W–C1 1.930(7), O5–C8 1.461(8), O5–C6 1.457(7), C2–C3 1.308(9); W–O5–C8 127.4(3), W–O5–C6 119.9(4), C6–O5–C8 112.8(5), W–C1–O1 176.8(5), W–C2–C11 145.4(4), W–C3–C4 147.3(5).

typical of such compounds.^[15] The W–O bond length (2.210(4) Å) is similar to those of [WCp(CO)₃(PhCH₂O–Me)][OTf] (2.206(11) Å) and [WCp*(CO)₃(OEt₂)] [BAR₄]⁺ (2.197(7) Å).^[9, 11] The W–O5–C6 and W–O5–C8 bond angles are 119.9(4) and 127.4(3)°, respectively. The larger angle perhaps results from the proximity of the ethyl group to the bulky Tp' ligand.

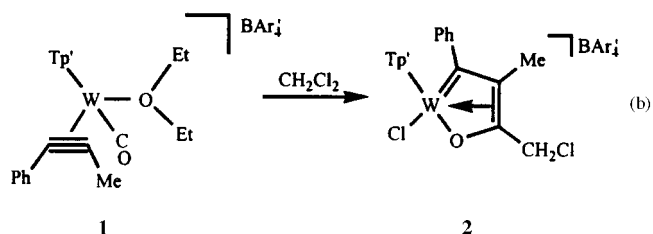
Dissolution of **1** in CD₂Cl₂ at –78 °C followed by addition of an excess of acetonitrile and warming of the solution to room temperature results in quantitative conversion into [WTP'(CO)(N≡CMe)(PhC≡CMe)] [BAR₄]⁺.^[16] The kinetics of this substitution reaction were studied by treating **1** with various amounts of acetonitrile (10–45 equiv) and monitoring the ligand exchange under pseudo-first-order conditions by ¹H NMR spectroscopy at 0 °C. Rate constants for the exchange process are invariant with respect to the range of standard deviations; the reaction is zero order in acetonitrile.

In a second series of experiments with 15 equivalents of acetonitrile, the temperature was varied from –5 °C to room temperature. An Eyring plot allowed the determination of activation parameters for this exchange: $\Delta H^\ddagger = 74.0(4.6)$ kJ mol^{–1}, $\Delta S^\ddagger = -15.5(16.3)$ eu. The large enthalpy and small entropy of activation suggest a dissociative mechanism, perhaps an interchange mechanism. Activation parameters for the dissociative exchange of dimethyl sulfide when the complex [Re(O)(Ph)Tp(OSMe₂)] [OTf] (Tp = hydridotris(pyrazol-1-yl)borate) is treated with free Me₂S ($\Delta H^\ddagger = 67.3$ kJ mol^{–1}, $\Delta S^\ddagger = -10.9$ eu)^[17] resemble the values for nitrile/ether exchange of complex **1**.

An important development in the application of positively charged metal fragments is the use of noncoordinating

counterions.^[18] Although these counterions can hinder the decomposition of electrophilic metal species, other factors can limit the synthetic application of this class of compounds. An example is the ability of highly electrophilic metal complexes to activate and react with a variety of solvents.

At room temperature in dichloromethane, **1** decomposes to the metallacycle **2** [Eq. (b)]. Monitoring the decomposition of **1** by ¹H NMR spectroscopy in CD₂Cl₂ showed nearly quantitative conversion into deuterated **2**.



An ORTEP diagram of metallacycle **2** is shown in Figure 2.^[27] The W–C6 bond length of 1.93(1) Å is consistent with a carbene complex.^[19] To achieve an 18-electron count,

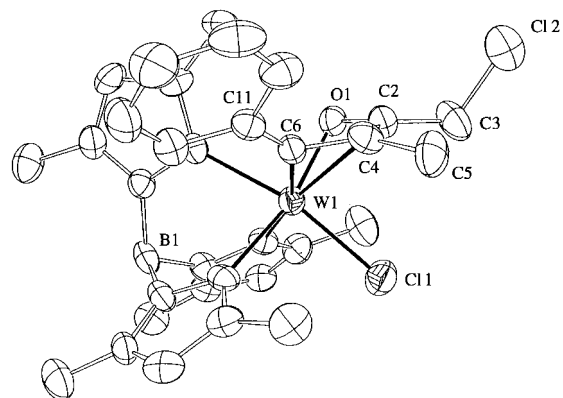
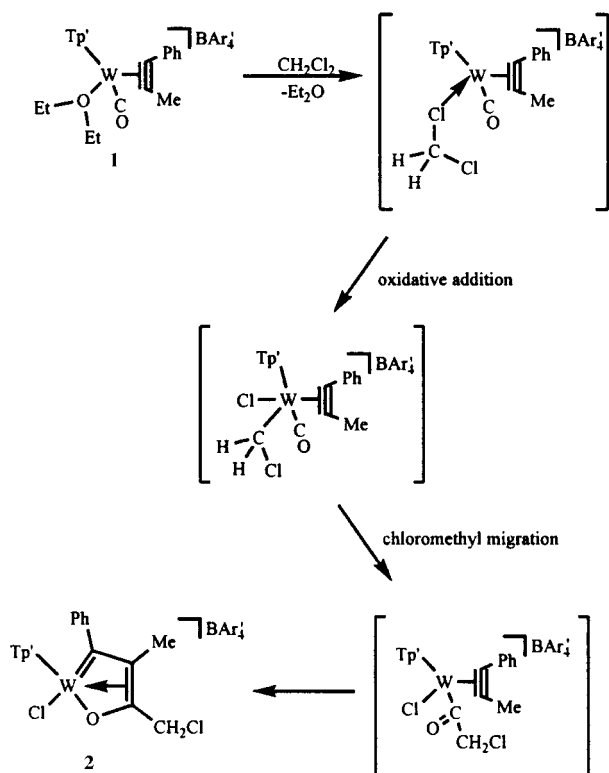


Figure 2. ORTEP diagram of the cation of **2**. Selected bond lengths [Å] and angles [°]: W–O1 2.016(8), W–C11 2.311(4), W–C6 1.931(13), W–C4 2.286(12), W–C2 2.321(13), C4–C6 1.392(18), C2–C4 1.437(20), O1–C2 1.379(16); W–C6–C11 147.3(9), W–O1–C2 84.0(7), W–C6–C4 85.3(8).

the unsaturated C2–C4 bond must interact with the tungsten center; indeed, the ring binds to the tungsten through all four atoms. The W–C2 and W–C4 bond lengths of 2.32(1) and 2.29(1) Å, respectively, are within the range of W–C single bonds.^[20] The W–O bond length of 2.01(8) Å is consistent with those of other alkoxotungsten complexes.^[14] Examples of η^4 metallacycles of this type are sparse^[21] relative to the more common η^2 mode of coordination.^[22]

A plausible mechanism for the formation of **2** is shown in Scheme 1. Dissociation of Et₂O from **1** would open a coordination site for binding CH₂Cl₂. Formation of an acyl complex by C–Cl bond cleavage and migration of the chloromethyl group to carbon monoxide would form an acyl intermediate. The mechanistic details of this sequence are unknown, although the process could occur by oxidative addition of a C–Cl bond (shown in Scheme 1) or a radical pathway. Since the formation of a seven-coordinate intermediate by oxidative addition is presumably sterically inhibited, such a route is unlikely.^[23] However, as has been observed for other metal complexes, labilization of one arm of the Tp'



Scheme 1. Proposed mechanism for formation of metallacycle **2**.

ligand could precede oxidative addition.^[24] Coupling of the alkyne and the acyl fragment, known to yield metallacycles in other systems,^[21a, b, 25, 26] would form the metallacycle **2**.

In conclusion, we have structurally characterized the unusually stable ether complex $[\text{W}(\text{Tp}')(\text{CO})(\text{OEt}_2)(\text{PhC}\equiv\text{CMe})][\text{BAr}_4']$ (**1**), the ether ligand of which can be displaced by acetonitrile. In CH_2Cl_2 , **1** decomposes and reacts with one equivalent of solvent to form a tungsten metallacycle.

Experimental Section

1: In a representative reaction, a dark blue solution of $[\text{WMeTp}'(\text{CO})(\text{PhC}\equiv\text{CMe})]$ (0.3365 g) in dichloromethane was cooled to -78°C and added by cannula to HBAr_4' (0.532 g, 1 equiv) at -78°C . At the same temperature, an excess of diethyl ether (ca. 15 mL) was added. The solution was then warmed to room temperature, and the solvent removed under reduced pressure. The remaining blue powder was washed with hexanes (2×20 mL) and dried under vacuum. Layering a solution of **1** in diethyl ether with hexanes yielded blue crystals in 70% yield. IR (CH_2Cl_2): $\tilde{\nu}_{\text{CO}} = 1923\text{ cm}^{-1}$; ^1H NMR (CD_2Cl_2 , 400 MHz): $\delta = 7.70$ (brs, 8H, *o*-H of Ar'), 7.55 (brs, 4H, *p*-H of Ar'), 7.29, 6.59 (m, 5H, Ph), 6.13, 5.88, 5.74 (3s, 3H, CH of Tp'), 4.69, 4.39, 3.42, 3.14 (each quint., 4H, $^2J_{\text{HH}} = 7$, $^3J_{\text{HH}} = 7$ Hz, $[\text{W}] - \text{O}(\text{CH}_2\text{CH}_3)_2$), 3.80 (3H, PhC_2CH_3), 2.70, 2.56, 2.52, 2.46, 1.30, 1.23 (18H, CH_3 of Tp'), 0.98, 0.82 (each t, 6H, $^3J_{\text{HH}} = 7$ Hz, $[\text{W}] - \text{O}(\text{CH}_2\text{CH}_3)_2$); ^{13}C NMR (CD_2Cl_2 , 400 MHz): $\delta = 226.5$ (CO); 209.2, 205.0 (PhC_2Me), 162.1 (q, $^1J_{\text{BC}} = 49$ Hz, *ipso*-C of Ar'), 153.9, 151.8, 150.6, 147.7, 147.6, 145.6 (CCH_3 of Tp'), 135.0 (*ipso*-C of Ph), 134.3 (*o*-C of Ar'), 130.0, 128.7, 128.4 (*o*-, *m*-, and *p*-C of Ph), 128.2 (q, $^2J_{\text{CF}} = 40$ Hz, *m*-C of Ar'), 124.3 (q, $^1J_{\text{CF}} = 270$ Hz, CF_3), 117.2 (*p*-C of Ar'), 108.2, 108.0, 107.3 (CH of Tp'), 80.6, 71.9 (t, $^1J_{\text{CH}} = 145$ Hz, $[\text{W}] - \text{O}(\text{CH}_2\text{CH}_3)_2$), 22.2, 15.6, 14.9, 14.1, 12.8, 12.7, 12.5, 11.7, 11.5 (CCH_3 of Tp' , alkyne CH_3 , and ether CH_3); elemental analysis: calcd: C 46.89, H 3.35, N 5.38; found: C 47.10, H 3.46, N 5.42.

2: ^1H NMR (CD_2Cl_2 , 400 MHz): $\delta = 7.73$, 7.56 (2s, 8:4, Ar'), 7.55–6.82 (m, 5H, Ph), 6.31, 6.12, 5.55 (3s, 3H, CH of Tp'), 5.75 (d, 1H, $^2J_{\text{HH}} = 14$ Hz, CHHCl), 5.53 (d, 1H, $^2J_{\text{HH}} = 14$ Hz), 2.91, 2.71, 2.52, 2.45, 2.35, 1.93, 0.84

(6s, 21H, CCH_3 of Tp' , $\text{W}=\text{C}(\text{Ph})-\text{C}(\text{CH}_3)_2$); ^{13}C NMR (CD_2Cl_2 , 400 MHz): $\delta = 254.1$ (α -C of metallacycle), 162.2 (q, $^1J_{\text{BC}} = 49$ Hz, *ipso*-C of Ar'), 157.3, 154.6, 152.9, 151.9, 148.5, 147.6 (CCH_3 of Tp'), 134.6, 130.8, 128.4, 128.2 (Ph of metallacycle), 135.2 (br, *o*-C of Ar'), 129.3 (q, $^2J_{\text{CF}} = 31$ Hz, *m*-C of Ar'), 125.0 (q, $^1J_{\text{CF}} = 271$ Hz, CF_3), 117.9 (br, *p*-C of Ar'), 111.3, 109.8, 109.3 (CH of Tp'), 97.8 (β -C of metallacycle), 35.9 (CH_2Cl), 17.9, 15.1, 15.0, 14.8, 13.3, 13.2, 12.5 (CCH_3 of Tp' and Me of metallacycle); the signal for the γ -C atom of the metallacycle could not be located due to likely overlap with signals in the phenyl region of the spectrum; elemental analysis: calcd: C 49.06, H 2.82, N 5.34; found: C 49.09, H 2.86, N 5.55%.

Received: October 27, 1997

Revised version: April 22, 1998 [Z11084IE]

German version: *Angew. Chem.* **1998**, *110*, 2207–2210

Keywords: Lewis acids • metallacycles • O ligands • oxidative additions • tungsten

- a) S. H. Bergens, B. Bosnich, *J. Am. Chem. Soc.* **1991**, *113*, 959–967; b) P. A. White, J. Calabrese, K. H. Theopold, *Organometallics* **1996**, *15*, 5473–5475.
- F. C. Rix, M. Brookhart, *J. Am. Chem. Soc.* **1995**, *117*, 1137–1138
- F. C. Rix, M. Brookhart, P. S. White, *J. Am. Chem. Soc.* **1996**, *118*, 2436–2448.
- L. K. Johnson, S. Mecking, M. Brookhart, *J. Am. Chem. Soc.* **1996**, *118*, 267–268.
- L. K. Johnson, C. M. Killian, M. Brookhart, *J. Am. Chem. Soc.* **1995**, *117*, 6414–6415.
- E. L. Muetterties, E. Band, *J. Am. Chem. Soc.* **1980**, *102*, 6572–6574.
- A. S. Gamble, J. M. Boncella, *Organometallics* **1993**, *12*, 2814–2819.
- W. M. Vaughan, K. A. Abboud, J. M. Boncella, *Organometallics* **1995**, *14*, 1567–1577.
- C. S. Yi, D. Wódka, A. L. Rheingold, G. P. A. Yap, *Organometallics* **1996**, *15*, 2–4.
- A similar Cp compound has been reported: K. Sünkel, G. Urban, W. Beck, *J. Organomet. Chem.* **1985**, *290*, 231–240.
- J. Song, D. J. Szalda, R. M. Bullock, *J. Am. Chem. Soc.* **1996**, *118*, 11134–11141.
- S. K. Agbossou, J. M. Fernández, J. A. Gladysz, *Inorg. Chem.* **1990**, *29*, 476–480.
- Review on the chemistry of $[\text{W}(\text{Tp}')(\text{CO})(\text{RC}\equiv\text{CR})]^+$ cations: a) J. L. Caldarelli, P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **1992**, *114*, 10097; b) D. M. Schuster, P. S. White, J. L. Templeton, *Organometallics* **1996**, *15*, 5467; c) M. B. Wells, P. S. White, J. L. Templeton, *Organometallics* **1997**, *16*, 1857; d) T. B. Gunnoe, P. S. White, J. L. Templeton, *Organometallics* **1997**, *16*, 3794; e) T. B. Gunnoe, P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **1996**, *118*, 6916; f) S. G. Feng, C. C. Philipp, A. S. Gamble, P. S. White, J. L. Templeton, *Organometallics* **1991**, *10*, 3504; g) T. B. Gunnoe, P. S. White, J. L. Templeton, L. Casarrubios, *J. Am. Chem. Soc.* **1997**, *119*, 3171.
- J. L. Caldarelli, L. E. Wagner, P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **1994**, *116*, 2878–2888.
- See, for example, a) T. B. Gunnoe, P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **1996**, *118*, 6916–6923; b) L. W. Francisco, P. S. White, J. L. Templeton, *Organometallics* **1996**, *15*, 5127–5136.
- Synthesis of $[\text{W}(\text{Tp}')(\text{CO})(\text{N}\equiv\text{CMe})(\text{PhC}\equiv\text{CMe})][\text{BF}_4']$: a) S. G. Feng, J. L. Templeton, *J. Am. Chem. Soc.* **1989**, *111*, 6477–6478; b) S. G. Feng, J. L. Templeton, *Organometallics* **1992**, *11*, 1295–1303.
- S. N. Brown, J. M. Mayer, *J. Am. Chem. Soc.* **1996**, *118*, 12119–12133.
- S. H. Strauss, *Chem. Rev.* **1993**, *93*, 927–942.
- See, for example, a) S. G. Feng, P. S. White, J. L. Templeton, *Organometallics* **1993**, *12*, 2131–2139; b) S. G. Feng, P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **1992**, *114*, 2951–2960.
- See, for example, a) R. R. Schrock, R. M. Kolodziej, A. H. Liu, W. M. Davis, M. G. Vale, *J. Am. Chem. Soc.* **1990**, *112*, 4338–4345; b) M. B. O'Regan, A. H. Liu, W. C. Finch, R. R. Schrock, W. M. Davis, *J. Am. Chem. Soc.* **1990**, *112*, 4331–4338; c) R. R. Schrock, T. E. Glassman, M. G. Vale, M. Kol, *J. Am. Chem. Soc.* **1993**, *115*, 1760–1772; d) A. H. Liu, R. C. Murray, J. C. Dewan, B. D. Santarsiero, R. R. Schrock, *J. Am. Chem. Soc.* **1987**, *109*, 4282–4291.
- a) M. Etienne, P. S. White, J. L. Templeton, *Organometallics* **1993**, *12*, 4010–4015; b) M. D. Curtis, J. Real, W. Hirpo, W. M. Butler,

- Organometallics* **1990**, *9*, 66–74; c) M. Etienne, F. Biasotto, R. Mathieu, J. L. Templeton, *Organometallics* **1996**, *15*, 1106–1112; d) W. Hirpo, M. D. Curtis, *Organometallics* **1994**, *13*, 2706–2712.
- [22] J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science, Mill Valley, CA, **1987**, chap. 9, pp. 459–520, and references therein.
- [23] See, for example, a) M. D. Curtis, K. Shiu, W. M. Butler, *J. Am. Chem. Soc.* **1986**, *108*, 1550; b) M. D. Curtis, K. Shiu, *Inorg. Chem.* **1985**, *24*, 1213; c) M. D. Curtis, K. Shiu, W. M. Butler, *J. Am. Chem. Soc.* **1986**, *108*, 3335.
- [24] a) S. E. Bromberg, H. Yang, M. C. Asplund, T. Lian, B. K. McNamara, K. T. Kotz, J. S. Yeston, M. Wilkens, H. Frei, R. G. Bergman, C. B. Harris, *Science* **1997**, *278*, 260; b) for related chemistry, see D. D. Wick, K. I. Goldberg *J. Am. Chem. Soc.* **1997**, *119*, 10235.
- [25] a) C. A. Rusik, M. A. Collins, A. S. Gamble, T. L. Tonker, J. L. Templeton, *J. Am. Chem. Soc.* **1989**, *111*, 2550–2560; b) L. W. Francisco, P. S. White, J. L. Templeton, *Organometallics* **1997**, *16*, 2547.
- [26] a) H. G. Alt, H. E. Engelhardt, *J. Organomet. Chem.* **1985**, *288*, 165–177; b) P. L. Watson, R. G. Bergman, *J. Am. Chem. Soc.* **1979**, *101*, 2055–2062.
- [27] Crystal structure analyses: a) **1**: $C_{61}H_{52}B_2F_{24}O_2N_6W$, $M_r = 1562.54$, triclinic, space group $P\bar{1}$, $a = 12.735(3)$, $b = 13.356(4)$, $c = 20.296(7)$ Å, $\alpha = 73.19(3)$, $\beta = 76.68(3)$, $\gamma = 82.63(2)^\circ$, $Z = 2$, $V = 3208.7(17)$ Å³, $\rho_{\text{calcd}} = 1.617$ g cm⁻³, blue plates, crystal dimensions: $0.45 \times 0.40 \times 0.06$ mm³, Rigaku diffractometer, monochromated (graphite) $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = 173$ K, $5.00 < 2\theta < 46.00^\circ$. Of 8884 independent reflections measured, 7060 with $I > 2.5\sigma(I)$ were used in the refinement, $R_1 = 0.045$, $R_2 = 0.041$. b) **2**: $C_{58}H_{44}B_2Cl_2F_{24}ON_6W$, $M_r = 1573.35$, monoclinic, space group $C2/c$, $a = 38.016(7)$, $b = 13.562(2)$, $c = 26.329(4)$, $Z = 8$, $V = 12856(4)$ Å³, $\rho_{\text{calcd}} = 1.626$ g cm⁻³, blue plates, crystal dimensions: $0.25 \times 0.20 \times 0.20$ mm³, Rigaku diffractometer, monochromated (graphite) $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = 295$ K, $5.00 < 2\theta < 45.00^\circ$. Of 8396 independent reflections measured, 4661 with $I > 2.5\sigma(I)$ were used in the refinement, $R_1 = 0.048$, $R_2 = 0.052$. c) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101794 (**1**) and CCDC-101793 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

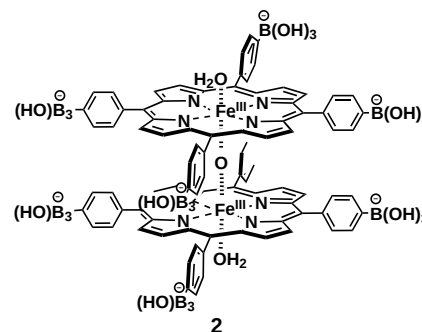
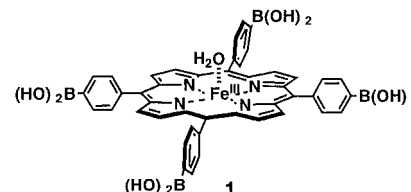
A Strong Positive Allosteric Effect in the Molecular Recognition of Dicarboxylic Acids by a Cerium(IV) Bis[tetrakis(4-pyridyl)-porphyrinate] Double Decker**

Masayuki Takeuchi, Tomoyuki Imada, and Seiji Shinkai*

Positive and negative allosteric effects are ubiquitous in nature where biological events must be efficiently regulated in response to chemical or physical signals from the outside world. Typical examples^[1–4] are the cooperative binding of dioxygen to hemoglobin,^[1] the hexamerization of the arginine

repressor,^[2] and a cooperative effect that depends on the concentration of arachidonate-containing phospholipids in cytosolic phospholipase A₂.^[3] The biomimetic design of such allosteric systems is of great significance for regulating the complexation properties or catalytic activity of artificial receptors by means of allosteric effects.^[5] Furthermore, the methodology is very useful for amplifying weak chemical or physical signals and converting them into forms that can be more conveniently measured. Several allosteric systems have been reproduced.^[5–7] To the best of our knowledge, however, there is only one precedent for a positive allosteric effect with a large Hill coefficient n which involves cooperative binding of saccharides to a cyclic tetrameric resorcinol derivative ($n = 4$).^[6]

We previously synthesized a porphyrinatoiron(III) complex bearing four boronic acid groups (**1**).^[7] The μ -oxo dimer **2** is formed from **1** at alkaline pH values and shows extraordinarily high affinity and selectivity for glucose and galactose. However, only one pair of boronic acid groups is used to form 1:1 complexes with saccharides, and the remaining three pairs of boronic acids do not bind saccharides.^[7] The strong negative allosterism was attributed

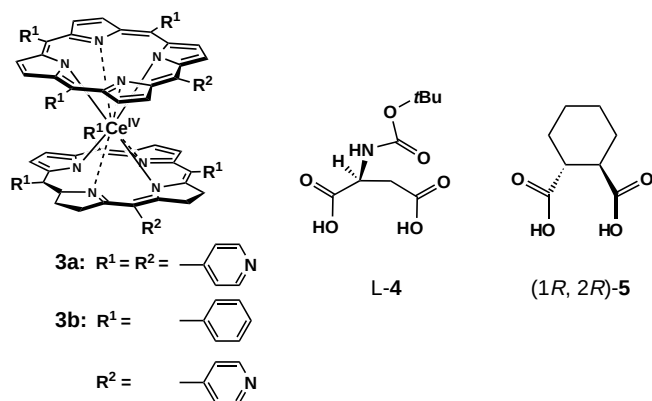


to an inclination of the two porphyrin planes, which was induced by the binding of the first saccharide guest. Hence, if the first guest could suppress the rotation of the two porphyrin planes and maintain their parallel arrangement, the second guest should be bound more efficiently, and the system should exhibit positive allosterism.

To construct such a porphyrin-based positively allosteric system, we chose a cerium(IV) bis(porphyrinate) double decker,^[8,9] namely, the tetrakis(4-pyridyl)porphyrin derivative **3a**.^[8a, f–h] This molecule satisfies our requirements: First, slow rotation of the two porphyrin planes with respect to one another should be possible at room temperature, in analogy to similar cerium(IV) bis(diarylporphyrin) and bis(tetraarylporphyrin) complexes studied by Aida et al.;^[9,10] second, tilting of the two porphyrin planes is more difficult than in **2**; and third, the four pairs of 4-pyridyl groups are available as hydrogen-bond acceptor sites for diols, hydroxycarboxylic acids, and dicarboxylic acids. Compound **3b**, which has only one pair of pyridyl groups, was used as a reference. Compound

[*] Prof. S. Shinkai, Dr. M. Takeuchi, Dr. T. Imada
Department of Chemical Science and Technology
Faculty of Engineering, Kyushu University
Fukuoka 812 (Japan)
Fax: (+81)92-642-3611
E-mail: seijitcm@mbox.nc.kyushu-u.ac.jp

[**] This work was supported by a Grant-in-Aid for COE Research “Design and Control of Advanced Molecular Assembly Systems” from the Ministry of Education, Science and Culture, Japan (#08CE2005).



3a has a sharp positive allosteric effect with $n = 4$ and shows high selectivity for the enantiomers of BOC-aspartic acid (**4**; BOC = *tert*-butoxycarbonyl) and of 1,2-cyclohexanedicarboxylic acid (**5**).

Compounds **3a** and **3b** were synthesized from 5,10,15,20-tetrapyrrolylporphyrin^[11] and 5,10,15-triphenyl-20-pyridylporphyrin,^[11] respectively, according to the method reported by Buchler and Nawra.^[8a] The products were identified by ¹H NMR spectroscopy, mass spectrometry, and elemental analyses (see Experimental Section). The ¹H NMR spectra were recorded in dichloromethane/ethyl acetate (30/1) at 25 °C. As chiral guest molecules, we chose five α -amino acid derivatives,^[12] L-tartaric acid, dimethyl L-tartrate, and **5**.

First, circular dichroism (CD) spectra of **3a** and **3b** were recorded in the presence of each of the eight guest molecules. As shown in Figure 1, exciton-coupling CD bands were clearly

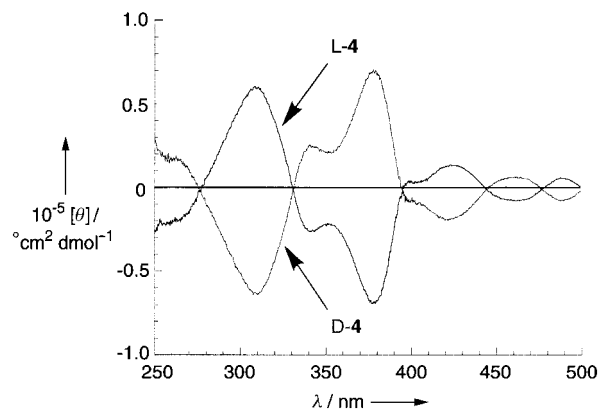


Figure 1. CD spectra of **3a** (0.1 mM) in the presence of **4** (10 mM) at 25 °C in dichloromethane/ethyl acetate (30/1). Similar CD spectra were obtained in the presence of the enantiomers of **5**. The circular dichroism of (1R,2R)-**5** has the same sign as that of that of L-**4**. $[\theta]$ = molar ellipticity.

observed for **3a** in the presence of **4** or **5**. Compound **3a** was CD-inactive in the presence of the other six guest molecules. Compound **3b** was CD-inactive in the presence of all guest molecules. Therefore, the strong CD bands in Figure 1 can be observed for a only a portion of the host–guest combinations. In Figure 2, $[\theta]_{\max}$ at 310 nm is plotted against the guest concentration. The sigmoidal curvature indicates that the binding of the guest to **3a** is “self-accelerating”. This

cooperative guest binding can be analyzed with the Hill equation^[13] [Eq. (1)] where $[G]$ is the concentration of the

$$\lg(y/(1-y)) = n \lg[G] + \lg K \quad (1)$$

guest, K the association constant, and n the Hill coefficient, and $y = K/([G]^{-n} + K)$. From the slope and the intercept of the

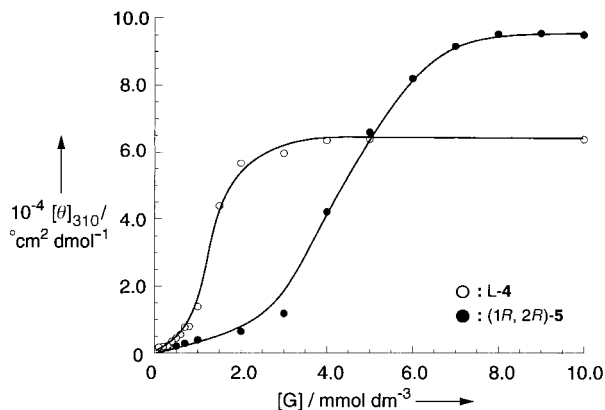


Figure 2. Plots of $[\theta]_{\max}$ at 310 nm for **3a** versus the concentration of the guest compound $[G]$ (measurement conditions as in Figure 1).

linear plots we obtained $K = 2.63 \times 10^{11} (\text{mol dm}^{-3})^{-4}$ and $n = 3.9$ for L-**4** (correlation coefficient 0.988), and $K = 2.75 \times 10^9 (\text{mol dm}^{-3})^{-4}$ and $n = 4.0$ for (1R,2R)-**5** (correlation coefficient 0.995). The 1:4 composition of the CD-active complexes was further corroborated by a Job diagram.^[14] As shown in Figure 3, a plot of $[\theta]_{\max}$ at 310 nm against

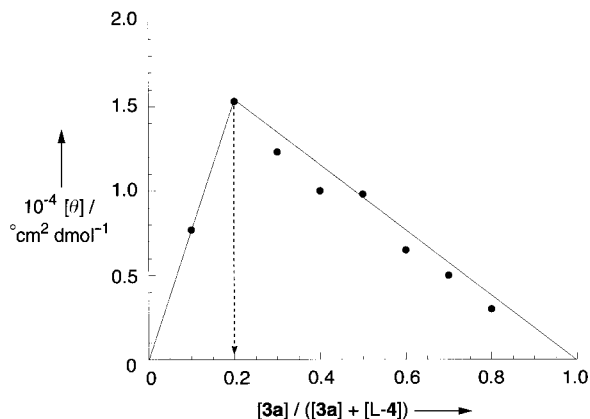


Figure 3. Job diagram. The sum $[\mathbf{3a}] + [\mathbf{L-4}]$ was kept constant (1 mM).

$[\mathbf{3a}]/([\mathbf{3a}] + [\mathbf{L-4}])$ has a maximum at 0.2. This supports the view that the complex consists of one **3a** host and four L-**4** guests. These findings consistently indicate that four pairs of pyridyl groups in **3a** cooperatively bind these chiral guest molecules and that the two porphyrin planes are immobilized in a chiral conformation to give the CD-active complexes. Hence, this is a rare example of an artificial system with a strong positive allosteric effect and $n = 4$.

At this point, two important questions come to mind: First, why can **3a** bind dicarboxylic acids, whereas **3b** cannot? Second, why do only **4** and **5** form CD-active complexes with

3a? To clarify the first question, we recorded the ^1H NMR spectra [25°C , $\text{CD}_2\text{Cl}_2/\text{CD}_3\text{CO}_2\text{C}_2\text{D}_5$ (30/1)] of **L-4** in the presence of **3a** (1.00 mM). The resonances of the NH, α -CH, and β -CH₂ protons of **L-4** were shifted to lower field (from $\delta = 5.59$ to 5.70 for NH, from $\delta = 4.56$ to 4.62 for α -CH, and from $\delta = 2.95$ to 3.06 for β -CH₂; [**L-4**] = 1.00 mM) owing to the anisotropic effect of the porphyrin rings of **3a**, and the plots of $\Delta\delta$ versus [**L-4**] showed sigmoidal curvature. In contrast, **3b** does not induce such a downfield shift for these protons of **L-4**. The difference reveals the mechanism that is responsible for the positive allosteric effect in this system. Although host **3b** has a pair of pyridyl groups and could therefore potentially bind **4** or **5** by hydrogen bonding, the unchanged chemical shifts in the ^1H NMR spectrum suggest that this site exhibits at most a very weak interaction with dicarboxylic acids. In other words, the first association constant K_1 for binding the first guest is very small for **3b**. Conceivably, the gain in Gibbs free energy from the pyridine/carboxylic acid interaction is overcompensated by the loss of Gibbs free energy associated with suppression of the rotation of the porphyrin rings. This is also the case in **3a** for the binding of the first guest. In **3a**, however, once the rotation of the porphyrin rings has been suppressed by the first guest, successive binding of the second, third, and fourth guests can occur without such a loss of Gibbs free energy. Thus, as the number of the bound guests increases, rotation of the porphyrin rings becomes more strongly suppressed, and guest binding becomes increasingly favorable (Figure 4). This type of guest binding is possible only in the 1:4 complex.

According to the X-ray crystallographic studies of the cerium(IV) bis(porphyrinate) double decker, the distance between the two porphyrin planes is about $3.4 \text{ \AA}$.^[8c] This

distance is comparable with that between two the carboxylic acid groups in **4** and **5**, which are separated by a C₂ spacer, and they can therefore quadruply bridge two porphyrin rings with eight hydrogen bonds. In these complexes, the two porphyrin rings are twisted in the right-or left-handed direction, depending on the configuration of the guest, but the distance between two porphyrin planes should not be changed by cooperative guest binding. The enantiomers of BOC-glutamic acid, which have a C₃ spacer, cannot satisfy these requirements and therefore do not result in CD-active species. It is surprising that a difference of one methylene unit can be recognized in an all-or-nothing manner. This is due to multiplication of the small difference by the allosteric binding process. On the other hand, L-tartaric acid, which has a C₂ spacer, satisfies the basic structural requirement as a guest molecule. When a solution of **3a** in dichloromethane and an solution of L-tartaric acid in ethyl acetate were mixed, a colored precipitate formed immediately. The elemental analysis of this precipitate established that it consists of one **3a** host and four L-tartaric acid guests.^[15] These results answer our second question regarding host–guest selectivity.

In conclusion, we have demonstrated that the cerium(IV) bis[tetrakis(4-pyridyl)porphyrinate] double decker shows a high positive allosteric effect with a Hill coefficient of 4. Such strong allosteric effects are very rare in artificial systems.^[6] The origin of the cooperative guest binding is attributable to the successive suppression of the rotation of the porphyrin rings without deformation of the basic structure of the cerium double decker.^[10] Thus, the present system should be readily applicable to the regulation of association processes and catalytic activity: For example, **3a** is useful for the efficient release or capture of **4** and **5** in solution, and the catalytic activity of porphyrins can be regulated by means of **4** or **5**.

Experimental Section

3a: This compound was synthesized from 5,10,15,20-tetrapyrrolylporphyrin according to the method of Buchler and Nawra.^[8a] ^1H NMR (250 MHz, CD_2Cl_2 , 27°C , TMS): $\delta = 6.35$ (brs, 8H, ArH), 8.34 (brs, 16H, pyrrole β -H), 8.60 (brs, 8H, ArH), 9.45 (m, 16H, ArH); MS (positive SI-MS): m/z calcd for $\text{C}_{80}\text{H}_{48}\text{N}_{16}\text{Ce}$: 1372 [M^+]; found: 1372; elemental analysis calcd for $\text{C}_{80}\text{H}_{48}\text{N}_{16}\text{Ce}$: C 69.96, H 3.51, N 16.32; found: C 69.92, H 3.23, N 16.06.

3b: To a solution of 5,10,15-triphenyl-20-(4-pyridyl)porphyrin (128 mg, 0.2 mmol) in 1,2,4-trichlorobenzene (TCB, 60 mL, distilled) was added *t*BuLi (1.6 M in *n*-hexane, 1.5 mL, excess). The color of the solution changed from purple to green. The solution was stirred under N₂ for 30 min at room temperature, [Ce(acac)₃]·H₂O (270 mg, 0.6 mmol) added, and the mixture heated to reflux under N₂ for 5 h. After removal of TCB under reduced pressure, the crude product was dissolved in CH_2Cl_2 and purified by chromatography on a silica gel column

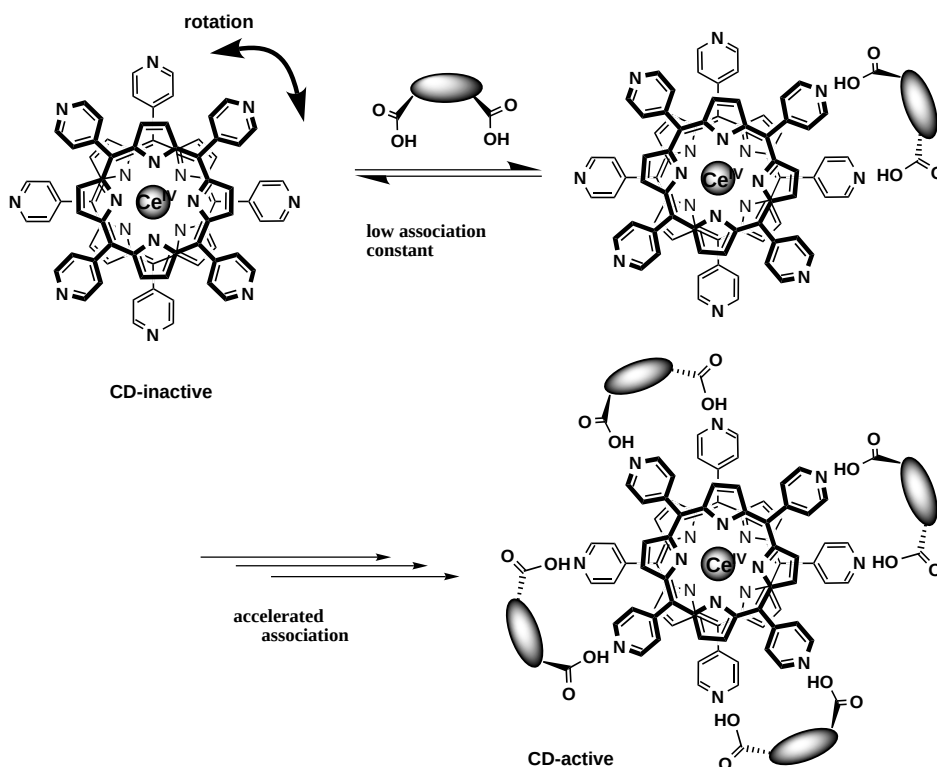


Figure 4. Schematic representation of the cooperative binding of **4** or **5** to **3a**.

In the course of a further study of the 1,4-addition reaction, we have found that **1** reacts with lower order butylcyanocuprate [BuCu(CN)Li]^[3] to yield with high selectivity *cis*-**2** (R = *n*Bu). This is the first *cis*-selective 1,4-addition of organocopper reagents to 5-substituted 2-cyclohexenones,^[4] and enables the preparation of both enantiomers of **3** (R = *n*Bu) starting from a single enantiomer of **1** (Scheme 1).

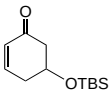
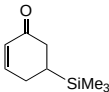
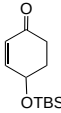
The significance of this result from the viewpoint of synthetic chemistry, as well as organocopper chemistry, prompted us to carry out further study. The objective of our work was centered on the examination of the generality of the reaction by changing the R group in [RCu(CN)Li], and also to reveal whether this phenomenon was characteristic of the particular substrate **1** or not.

Table 1 summarizes the results of the reaction of **1** with a variety of lower order cyanocuprates ([RCu(CN)Li]) and, for comparison, those obtained when the higher order dilithium cyanocuprate [R₂Cu(CN)Li₂] was used.^[1, 6] The reaction in Et₂O with a variety of lower order cyanocuprates, except for the vinyl derivative, proceeds with high *cis* selectivity, al-

though the phenylcyanocuprate gives the 1,4-addition product only in a moderate yield. Especially noteworthy is the very high selectivity observed with the methyl derivative (entry 1), primary alkyl derivatives (entries 2 and 4), and secondary alkyl derivatives (entry 6); in these cases the corresponding *cis*-**2** product can be obtained in an almost pure form after usual workup of the reaction mixture. The reaction of tertiary-alkyl and phenyl derivatives, however, proceeded with lower diastereomeric ratio (*dr*), 75:25–80:20 (entries 8 and 9). Even if the selectivity was somewhat diminished, the lower order cyanocuprate [RCu(CN)MgX] derived from Grignard reagents also yielded mainly the *cis*-addition product (entries 3, 5, and 7). The only exception to the *cis*-selective addition of lower order cyanocuprates to **1** is the case of the vinyl derivative which gave the *trans*-addition product selectively (entry 10); the explanation for this result must await further study.

To see whether this highly *cis*-selective 1,4-addition of [RCu(CN)Li] was characteristic of **1**, we carried out the reaction of [*n*BuCu(CN)Li] with 5-methyl- and 5-trimethyl-

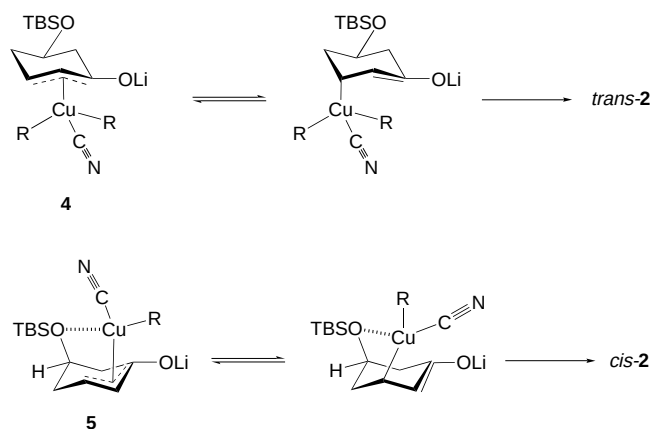
Table 1. 1,4-Addition of lower order cyanocuprates [RCu(CN)M] onto 2-cyclohexenones.

Entry	Enone	R	M	Conditions ^[a]	Yield [%] ^[b]	<i>cis:trans</i> ^[c]	Reaction with [R ₂ Cu(CN)Li ₂] Yield [%] ^[b]	<i>cis:trans</i> ^[c]
1		Me	Li	A	77 ^[d]	> 99:1 ^[e]	83 ^[d]	3:97 ^[e]
2		<i>n</i> Bu	Li	B ^[f]	91 ^[d]	> 99.5:0.5 ^[e]	92 ^[d]	2:98 ^[e]
3		<i>n</i> Bu	MgBr	C ^[g]	73	90:10	—	—
4			Li	B	87 ^[d]	98:2	—	—
5			MgBr	B	— ^[h]	70:30	—	—
6		<i>s</i> Bu	Li	A	84 ^[d]	> 98:2	^[h]	< 2:98
7		cyclohexyl	MgCl	D	75	65:35	—	—
8		<i>t</i> Bu	Li	A	78	75:25	92	< 2:98
9		Ph	Li	D	25	80:20	80 ^[d]	3:97 ^[e]
10		H ₂ C=CH	Li	D	45	25:75	75	5:95
11		<i>n</i> Bu	Li	B	95	< 1:99 ^[e]	—	—
12		<i>n</i> Bu	Li	B	— ^[h]	< 1:99 ^[e]	—	—
13		<i>n</i> Bu	Li	B	80	> 98:2	87	10:90 ^[e]
14		<i>n</i> Bu	Li	D	91 ^[d]	3:97 ^[e]	—	—

[a] All reactions were performed with 2.40 equiv of lower order cyanocuprate, unless otherwise stated. A: Et₂O, –78 °C → 0 °C, 1 h; B: Et₂O, –78 °C, 1 h; C: THF, –78 °C, 1 h; D: Et₂O, –78 °C → 0 °C, 2 h. [b] *cis/trans* mixture, determined by NMR spectroscopy. [c] Determined by NMR spectroscopy. [d] Yield of isolated product. [e] Determined by gas chromatography. [f] 1.2 Equiv of [*n*BuCu(CN)MgBr] yielded 82 % of the product with a *cis:trans* ratio of > 98:2. [g] 1.2 Equiv of [*n*BuCu(CN)Li] were used. [h] Not determined.

silyl-2-cyclohexenone: the reactions yielded almost exclusively the corresponding *trans*-3,5-disubstituted cyclohexanones (entries 11 and 12). This result strongly indicates that the alkoxy functionality in the substrate **1** plays a crucial role in the control of the stereochemistry of the 1,4-addition. We confirmed this assumption by carrying out the reaction of 5-benzyloxy-2-cyclohexenone^[8] with $[n\text{BuCu}(\text{CN})\text{Li}]$, which yielded almost exclusively the corresponding *cis* adduct (entry 13). With the evidence that an alkoxy group is essential to attain excellent *cis* selectivity, we then turned our attention to the reaction of $[n\text{BuCu}(\text{CN})\text{Li}]$ with the 4-(*tert*-butyldimethylsiloxy)-2-cyclohexenone^[9] to examine the effect of the position of the alkoxy group on the diastereoselectivity of the addition.^[10] The reaction furnished the *trans*-addition product almost exclusively (entry 14), indicating that the selectivity is also highly dependent on the position of the alkoxy group on the cyclohexenone ring.

The foregoing results may be explained by assuming that the reaction proceeds via a d, π^* -complex intermediate as suggested by Corey et al.^[11] Based on this model, the reaction with the higher order cuprates $[\text{R}_2\text{Cu}(\text{CN})\text{Li}]_2$ proceeds via the d, π^* -complex **4**, which has the TBSO functionality in a pseudo-equatorial position, while the reaction with the lower order cuprate $[\text{BuCu}(\text{CN})\text{Li}]$ proceeds via **5** in which the copper atom is coordinated by the oxygen atom of the alkoxy group (Scheme 2).^[12]



Scheme 2. Proposed intermediates for the reaction of **1** with higher (top) and lower order (bottom) cyanocuprates. TBS = *tert*-butyldimethylsilyl.

In conclusion, the reaction of **1** with lower order cyanocuprates (except for the vinyl derivative) gives the *cis*-1,4-addition products with high selectivity. This is the first *cis*-selective 1,4-addition of organocopper compounds to a 5-substituted-2-cyclohexenone and opens up an easy and practical access to both enantiomers of 5-alkyl-2-cyclohexenones **3** from the readily available **1**.^[13]

Experimental Section

Entry 2 in Table 1: $\text{CuCN}^{[14]}$ (1.2 mmol, 107 mg) and dry Et_2O (10 mL) were introduced into a flame-dried Schlenk tube flushed with argon. The mixture was cooled to -78°C under magnetic agitation and $n\text{BuLi}$ (1.59 M in *n*-hexane, 1.2 mmol; 0.75 mL) was slowly added. The resulting mixture was stirred for 30 min at -78°C (until complete dissolution of the copper salt; the mixture can be warmed up to 0°C if needed), and enone **1** (0.5 mmol,

113 mg) in ether (1 mL) was added dropwise at -78°C (addition time: about 5 min). Stirring was continued for a further hour before the mixture was quenched with saturated NH_4OH . After extraction with Et_2O , the combined organic layers were dried over MgSO_4 . Evaporation of the solvent gave a colorless oil, *cis:trans* = >99.5:0.5 by GC measurement, purification by flash chromatography (SiO_2 ; hexanes: Et_2O (9:1)) yielded the corresponding product as a colorless oil (130 mg, 91%). ^1H NMR (300 MHz, CDCl_3): δ = 3.80 (dddd, J = 10.6, 10.6, 4.8, 4.8 Hz, 1H), 2.60–2.50 (m, 1H); 2.35–2.23 (m, 2H), 2.08–1.98 (m, 1H), 1.88 (dd, J = 13.2, 13.2 Hz, 1H), 1.62–1.44 (m, 1H), 1.40–1.15 (m, 7H), 0.95–0.70 (m, 12H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 209.6(4), 69.6(3), 51.5(2), 46.9(2), 41.5(2), 36.1(2), 32.7(3), 28.6(2), 25.6(1), 22.5(2), 17.8(4), 13.8(1), –4.96(1), –4.98(1).

Received: January 9, 1998

Revised version: March 30, 1998 [Z11349 IE]

German version: *Angew. Chem.* **1998**, *110*, 2221–2223

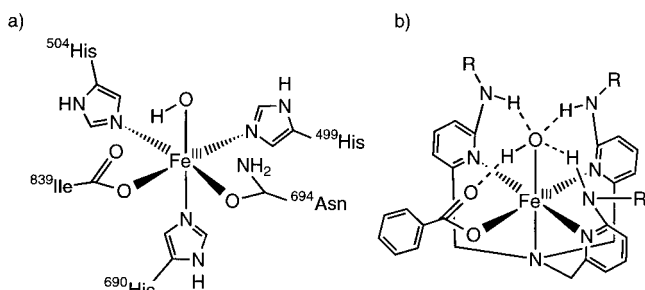
Keywords: cuprates • enones • nucleophilic additions • reaction mechanisms • synthetic methods

- [1] S. Hikichi, G. P.-J. Hareau, F. Sato, *Tetrahedron Lett.* **1997**, *38*, 8299–8302.
- [2] For other chiral 2,5-cyclohexadienone synthons, see a) M. Asaoka, K. Shima, H. Takei, *Tetrahedron Lett.* **1987**, *28*, 5669–5672; M. Asaoka, H. Takei, *J. Synth. Org. Chem. Jpn* **1990**, *48*, 216–228; b) S. Takano, Y. Higashi, T. Kamikubo, M. Moriya, K. Ogasawara, *Synthesis* **1993**, 948–950; K. Ogasawara, *Pure Appl. Chem.* **1994**, *66*, 2119–2122.
- [3] Lower order lithium cyanocuprates ($[\text{RCuCNLi}]$): a) J. P. Gorlier, L. Hamon, J. Levisalles, *J. Chem. Soc. Chem. Commun.* **1973**, 88; b) R.-D. Acker, *Tetrahedron Lett.* **1977**, 3407–3410; c) L. Hamon, J. Levisalles, *J. Organomet. Chem.* **1983**, *251*, 133–138.
- [4] The conjugate addition of organocuprates to 5-substituted-2-cyclohexenones yields generally a very high proportion of *trans*-adduct; see the following reviews and references therein: Y. Yamamoto, *Methods Org. Chem. (Houben-Weyl)* 4th ed., Vol. E21b, **1995**, pp. 2041–2067; B. H. Lipshutz, *Comprehensive Organic Synthesis*, Vol. 1 (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon, Oxford, **1991**, pp. 107–138; J. A. Kozlowski, *Comprehensive Organic Synthesis*, Vol. 4 (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhock), Pergamon, Oxford, **1991**, pp. 169–198.
- [5] M. Asaoka, K. Takenouchi, H. Takei, *Chem. Lett.* **1988**, 921–922.
- [6] $[\text{RCuCNLi}]$ and $[\text{R}_2\text{Cu}(\text{CN})\text{Li}]_2$ indicate that the reagents have been prepared stoichiometrically by mixing CuCN and RLi in a ratio of 1:1 and 1:2, respectively.
- [7] The chemical shift of $\text{CH}-\text{OTBS}$ appears at around δ = 3.8 for *cis*-2 and δ = 4.4 for *trans*-2.
- [8] L. Dumortier, J. Carda, J. Van der Eyken, G. Snatzke, *Tetrahedron: Asymmetry* **1991**, *2*, 789–792; M. Suemune, M. Takahashi, S. Maeda, Z.-F. Xie, K. Sakai, *Tetrahedron: Asymmetry* **1990**, *1*, 425–428.
- [9] S. J. Danishefsky, B. Simoneau, *J. Am. Chem. Soc.* **1989**, *111*, 2599–2604.
- [10] A selectivity of 92:8 in favor of the *cis* isomer has been reported on a 4-oxy-substituted spirocyclohexenone: E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6015–6018. *cis*-Michael-type addition has been observed on 4-oxy-substituted-2-cyclohexenone: L. O. Jeroncio, M. P. Cabal, S. J. Danishefsky, *J. Org. Chem.* **1991**, *56*, 387–395.
- [11] E. J. Corey, F. J. Hannon, N. W. Boaz, *Tetrahedron* **1989**, *45*, 545–555; E. J. Corey, F. J. Hannon, *Tetrahedron Lett.* **1990**, *31*, 1393–1396.
- [12] For some recent progress on the mechanism of the 1,4-addition of cuprates to enones, see N. Krauze, *J. Org. Chem.* **1992**, *57*, 3509–3512; A. S. Vellekoop, R. A. J. Smith, *J. Am. Chem. Soc.* **1994**, *116*, 2902–2913; J. P. Snyder, *J. Am. Chem. Soc.* **1995**, *117*, 11025–11026; K. Nilsson, C. Ullenius, N. Krause, *J. Am. Chem. Soc.* **1996**, *118*, 4194–4195, and references therein.
- [13] For the synthesis of optically active 5-substituted cyclohexenones, see J. B. Schwarz, P. N. Devine, A. I. Meyers, *Tetrahedron* **1997**, *53*, 8795–8806, and references therein.
- [14] CuCN was purchased from Koso Chemical Co., Ltd. Tokyo, Japan, and was used without further purification.

Synthesis, Structure, and Spectroscopic Properties of $[\text{Fe}^{\text{III}}(\text{tnpa})(\text{OH})(\text{PhCOO})]\text{ClO}_4$: A Model Complex for an Active Form of Soybean Lipoxigenase-1**

Seiji Ogo, Senji Wada, Yoshihito Watanabe,* Masakazu Iwase, Akira Wada, Manabu Harata, Koichiro Jitsukawa, Hideki Masuda,* and Hisahiko Einaga

Lipoxygenases (LOs) are mononuclear non-heme iron enzymes that catalyze the peroxidation of polyunsaturated fatty acids and fatty acid esters containing the *cis,cis*-1,4-diene moiety to the corresponding 1-hydroperoxy-*trans,cis*-2,4-diene. The proposed active oxidizing species in the catalytic cycle of soybean lipoxygenase-1 (SLO-1) probably has a six-coordinate iron(III) core structure with three histidine imidazole units, one carboxylato ligand from the C-terminal isoleucine, one asparagine carboxamidato carbonyl oxygen atom, and one hydroxo ligand (Scheme 1 a).^[1–5]



Scheme 1. a) A proposed (hydroxo)iron(III) core structure of the active species in the catalytic cycle of soybean lipoxygenase-1. Adapted from ref. [1 a] p. 285. b) The six-coordinate (hydroxo)iron(III) complex **1**. Dashed lines represent intramolecular hydrogen bonds. R = $\text{CH}_2\text{C}(\text{CH}_3)_3$.

Although structures of mononuclear six-coordinate iron(III) complexes with oxygen-donor ligands such as methoxo, CH_3OH , carboxylato, or carboxamidato, and dinuclear iron(III) complexes with terminal or bridging hydroxo ligands have been reported as models for the iron(III) form of SLO-1 (ferric SLO-1),^[6] mononuclear six-coordinate (hydroxo)-iron(III) complexes have, until now, not been reported. Herein, we report the synthesis, structure, and spectroscopic properties of such a complex: $[\text{Fe}(\text{tnpa})(\text{OH})(\text{PhCOO})]\text{ClO}_4$ (**1**,

tnpa = tris(6-neopentylamino-2-pyridylmethyl)amine); this is the first structural model for the active center of ferric SLO-1 with a hydroxo ligand. Complex **1** has been characterized by X-ray structure analysis, UV/Vis, IR, and EPR spectroscopy, and electrospray ionization mass spectrometry (ESI-MS).

A new tetradentate tripodal ligand tnpa was designed and synthesized that would complex to an Fe^{III} center (Scheme 1 b) and mimic specific attributes of ferric SLO-1. The ligand would bind to the Fe^{III} center in a four-coordinate mode (by one tertiary amine and three pyridine units) leaving two vacant coordination sites on the metal center free to accommodate fifth and sixth exogenous (e.g. carboxylato and hydroxo) ligands. Complex **1** was synthesized by a reaction of $\text{Fe}(\text{ClO}_4)_3 \cdot x\text{H}_2\text{O}$ with an equimolar amount of tnpa and PhCOONa in acetonitrile containing a small amount of H_2O . To establish the origin of the hydroxo ligand in **1**, the same synthesis of **1** has also been carried out in acetonitrile containing a small amount of H_2^{18}O . ESI-MS results confirm that the labeled oxygen atom is incorporated into the hydroxo ligand. The IR spectrum of **1** shows the O–H vibration at 3277 cm^{-1} shifts to 3273 cm^{-1} when H_2^{18}O is added.^[7] Complex **1** is stable for months under air at ambient temperature.

Purple crystals of **1** used in the X-ray structure analysis (Figure 1) were obtained by diffusion of diethyl ether into a solution of **1** in acetonitrile.^[8] All hydrogen atoms, which were located at the positions generated by Fourier-difference syntheses, were included in the least-squares calculation of **1**. The iron atom adopts a distorted octahedral coordination, it

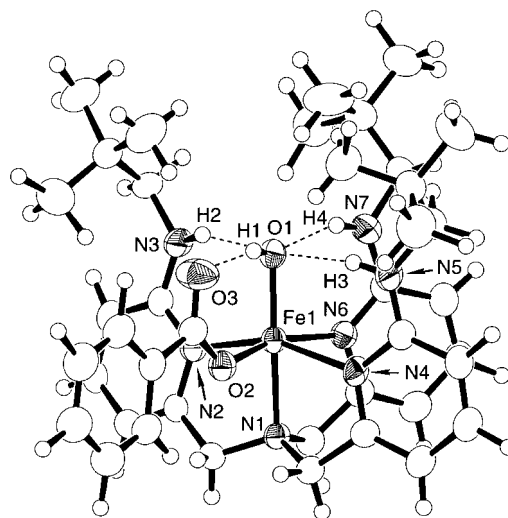


Figure 1. ORTEP drawing of **1**. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$] as well as interatomic distances [$\text{\AA}$]: Fe1–O1 1.876(2), Fe1–O2 1.988(2), Fe1–N1 2.158(3), Fe1–N2 2.183(2), Fe1–N4 2.182(2), Fe1–N6 2.228(3), O1–H1 0.83(3); O1–Fe1–N1 174.0(1), O2–Fe1–N6 164.9(1), N2–Fe1–N4 156.8(1), O1–Fe1–O2 97.2(1), O1–Fe1–N2 100.13(9), O1–Fe1–N4 103.04(9), O1–Fe1–N6 95.4(1), O2–Fe1–N1 88.2(1), O2–Fe1–N2 90.06(9), O2–Fe1–N4 88.83(9), N1–Fe1–N2 77.37(9), N1–Fe1–N4 79.39(9), N1–Fe1–N6 79.5(1), N2–Fe1–N6 95.86(9), N4–Fe1–N6 80.23(9), O1–H1–O3 157(4); O1–O3 2.680(3), O1–N3 2.857(3), O1–N5 2.894(3), O1–N7 2.835(3).

is surrounded by the tetradentate, tripodal tnpa and the monodentate PhCOO^- and OH^- ligands. The Fe–OH bond length of $1.876(2)\text{ \AA}$ agrees well with that of ferric SLO-1 ($1.88\text{ \AA}$) as established by EXAFS (extended X-ray absorp-

[*] Prof. Y. Watanabe, Dr. S. Ogo, Dr. S. Wada
Institute for Molecular Science
Myodaiji, Okazaki 444-8585 (Japan)
Fax: (+81) 564-54-2254
E-mail: yoshi@ims.ac.jp

Prof. H. Masuda, M. Iwase, A. Wada, M. Harata, Dr. K. Jitsukawa,
Prof. H. Einaga
Department of Applied Chemistry, Nagoya Institute of Technology
Gokiso-cho, Showa-ku, Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5254
E-mail: masuda@ach.nitech.ac.jp

[**] Financial support for this research by the Ministry of Education, Science, and Culture Grant-in-Aid for Scientific Research to Y.W. (Molecular Biometallics), S.O. (09740503), and H.M., and Ichihara International Science Foundation to H.M. is gratefully acknowledged. S.O. thanks Prof. L. Que, Jr. for valuable discussions.

tion fine structure) analysis.^[3a] Complex **1** has a *cis* configuration between the OH[−] ligand and the PhCOO[−] ligand as well as with the three NH ligands of tnpa, which enables the formation of four intramolecular hydrogen bonds (Figure 1; H1–O3 = 1.89(4), H2–O1 = 2.04(4), H3–O1 = 2.08(4), and H4–O1 = 2.03(3) Å). These hydrogen bonds may contribute to the stabilization of the (hydroxo)iron(III) core structure of **1**. Such stabilization by hydrogen bonds was also demonstrated in [Cu(tppa)(OH)]ClO₄ and [Cu(bppa)(OOH)]ClO₄^[9] (tppa = tris(6-pivalamido-2-pyridylmethyl)amine; bppa = bis(2-pyridylmethyl)(6-pivalamido-2-pyridylmethyl)amine). Moreover, the steric bulk of the neopentylamino groups of tnpa prevents the complex from polymerizing and thus these groups are required to form a stable (hydroxo)-iron(III) complex **1**.

The EPR spectrum of **1** in acetonitrile at 77 K is dominated by signals at *g* = 5.16 and 1.97, which are ascribed to a rhombic high-spin Fe^{III} center. Magnetic susceptibility measurements of **1** show $\mu_{\text{eff}} = 5.9 \mu\text{B}$. (with an estimated maximal error of $\pm 10\%$) at 297 K, corresponding to a high-spin Fe^{III} atom (*S* = 5/2).^[10] Complex **1** exhibits a quasi-reversible cyclic voltammetric wave in acetonitrile at ambient temperature with *E*_{1/2} = −0.125 V (vs. Ag⁺/AgCl, ΔE = 100 mV), which is assigned to the Fe³⁺/Fe²⁺ couple. It was confirmed by ESI-MS that the structure of **1** is preserved in acetonitrile (Figure 2 a).^[11] The positive-ion mass spectrum of **1** in the range of *m/z* 100 to 2000 shows prominent signals at *m/z* 739.6 (relative intensity (*I*) = 100 %) and *m/z* 617.4 (*I* = 70 %). The signal at *m/z* 739.6 has a characteristic distribution of isotopomers that matches well with the calculated isotopic distribution for [Fe(tnppa)(OH)(PhCOO)]⁺ ([**1** – ClO₄]⁺, Figure 2 c, d). MS/MS measurements show that the signal at *m/z* 617.4 is a product ion ([**1** – ClO₄ – PhCOOH]⁺) of [**1** – ClO₄]⁺.

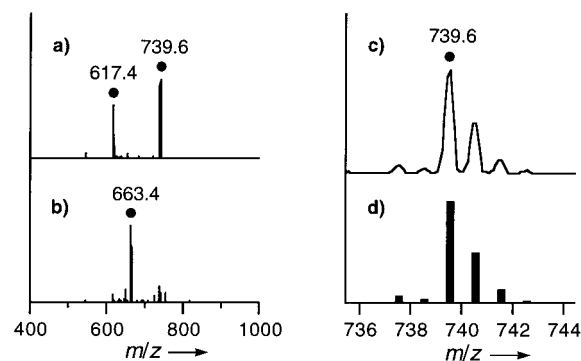


Figure 2. a) The positive-ion ESI mass spectrum of **1** in acetonitrile. The signal at *m/z* 739.6 corresponds to [**1** – ClO₄]⁺, that at *m/z* 617.4 is a product ion of [**1** – ClO₄]⁺. b) The positive ion ESI mass spectrum of **1** in methanol. Magnified representation of the signal at *m/z* 663.4 corresponds to [**2** – ClO₄]⁺. c) The signal at *m/z* 739.6. d) The calculated isotopic distribution for [**1** – ClO₄]⁺.

Complex **1** exhibits a UV/Vis spectrum with a distinct band at 536 nm ($\epsilon = 1000 \text{ M}^{-1} \text{ cm}^{-1}$) in acetonitrile (Figure 3). This observation is in contrast to reports of yellow ferric SLO-1 having its broad absorption band at 330 nm ($\epsilon = 1600 \text{ M}^{-1} \text{ cm}^{-1}$ in H₂O).^[12] Interestingly, complex **1** gives a yellow-orange (dimethoxo)iron(III) complex [Fe(tnppa)(OMe)₂]ClO₄ (**2**) in

methanol as evident from the UV/Vis (Figure 3) and ESI mass (Figure 2 b) spectra. A prominent signal at *m/z* 663.4 (*I* = 100 %) in the ESI mass spectrum corresponds to [Fe(tnppa)(OMe)₂]⁺

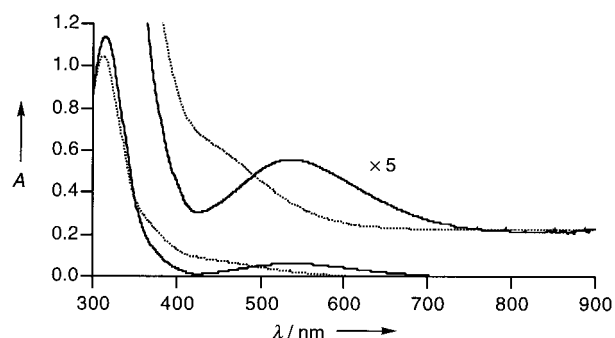


Figure 3. UV/Vis spectra of **1** in acetonitrile (solid line) and in methanol (dotted line).

([**2** – ClO₄]⁺). Complex **2** was isolated as a yellow-orange powder from the solution of **1** in methanol.^[13] Complex **2** exhibits an EPR signal at *g* = 4.25, indicating a rhombic high-spin Fe^{III} center. Scarrow et al. have indicated that the coordination in ferric SLO-1 is less affected by the presence of alcohols than the site in the iron(II) form of SLO-1 (ferrous SLO-1).^[3a] However, the OH group in the non-heme iron complex **1** is readily substituted by methanol.

In summary, a new six-coordinate (hydroxo)iron(III) complex **1** with four N-donor (one tertiary amino and three pyridyl) ligands and two O-donor (hydroxo and carboxylato) ligands has been prepared. These ligands are similar to those of the proposed active center of ferric SLO-1 with three N-donor (imidazolyl) ligands and three O-donor (hydroxo, carboxylato, and carboxamidato) ligands. Furthermore, complex **1** has a *cis* configuration between the OH[−] ligand and the PhCOO[−] and the three NH ligands of tnppa. The proposed core structure of ferric SLO-1 also has a *cis* configuration between the hydroxo ligand and the carboxylato ligand of a C-terminal isoleucine or carboxamidato ligand of asparagine. The *cis* configurations appear to be important for the formation of intramolecular hydrogen bonds which stabilize the (hydroxo)iron core structure of ferric SLO-1.

Experimental Section

Fe(ClO₄)₃·xH₂O and PhCOONa were purchased from Wako Pure Chemical Industries, Ltd. and used without further purification. **Caution!** The perchlorate salts in this study are all potentially explosive and should be handled with care.

tnppa: A solution of tris(6-pivalamide-2-pyridylmethyl)amine^[14] (588 mg, 1 mmol) in tetrahydrofuran (20 mL) was added to a mixture of pyridine (20 mL) and LiAlH₄ (380 mg, 10 mmol) in tetrahydrofuran (70 mL). The reaction mixture was stirred for 10 h at 70 °C. After cooling, the reaction was stopped by the addition of H₂O. The aqueous mixture was extracted with ethyl acetate. The resulting solution was washed with an aqueous solution of sodium hydrogen carbonate and dried over MgSO₄. After removal of the solvent, the product was purified by column chromatography on silica gel with chloroform/methanol as eluent. Needle-like shaped crystals of tnppa were obtained by recrystallization from acetonitrile/diethyl ether (yield: 20 %). ¹H NMR (270 MHz, CDCl₃, 23 °C, TMS): δ = 0.97 (s, 27H; CH₃), 3.01 (d, ³*J*(H,H) = 6.2 Hz, 6H; CH₂(CH₃)₃), 3.68 (s, 6H; NCH₂), 4.52 (t, ³*J*(H,H) = 6.2 Hz, 3H; NH), 6.23 (d, ³*J*(H₅,H₄) = 7.8 Hz,

3H; H5), 6.96 (d, $^3J(\text{H4}, \text{H3}) = 7.8 \text{ Hz}$, 3H; H3), 7.39 (dd, $^3J(\text{H3}, \text{H4}) = 7.8 \text{ Hz}$, $^3J(\text{H4}, \text{H5}) = 7.8 \text{ Hz}$, 3H; H4). Elemental analysis (%) calcd for $\text{C}_{33}\text{H}_{51}\text{N}_7$: C 72.62, H 9.42, N 17.96; found: C 72.59, H 9.20, N 17.80.

1: A solution of PhCOONa (72 mg, 0.05 mmol) in H_2O (2.5 mL) was added to a solution of $\text{Fe}(\text{ClO}_4)_3 \cdot x\text{H}_2\text{O}$ (177.1 mg, 0.5 mmol) and tnpa (273.0 mg, 0.5 mmol) in acetonitrile (10 mL). After stirring for 1 h, the solution was concentrated to give a purple powder of **1**, which was collected by filtration, washed with a small amount of diethyl ether, and dried in vacuo (yield: 89%). Elemental analysis (%) calcd for $\text{C}_{40}\text{H}_{59}\text{N}_7\text{O}_8\text{Cl}_2\text{Fe}$: C 55.70, H 7.15, N 11.37; found: C 56.04, H 6.94, N 11.44.

2: $\text{Fe}(\text{ClO}_4)_3 \cdot x\text{H}_2\text{O}$ (177.1 mg, 0.5 mmol) was dissolved in methanol containing molecular sieves (3 Å). After 24 h, tnpa (273.0 mg, 0.5 mmol) was added to this solution. After stirring for 30 min, the mixture was concentrated to give a yellow-orange powder of **2**, which was collected by filtration and dried in vacuo (yield: 65%). Elemental analysis (%) calcd for $\text{C}_{38}\text{H}_{57}\text{N}_7\text{O}_6\text{Cl}_2\text{Fe}$: C 55.08, H 7.53, N 12.85; found: C, 54.90, H, 7.72, N, 12.72.

Received: January 16, 1998 [Z113851E]
German version: *Angew. Chem.* **1998**, *110*, 2198–2200

Keywords: bioinorganic chemistry • enzyme mimetics • iron

- [1] Reviews: a) M. J. Nelson, S. P. Seitz in *Active Oxygen in Biochemistry* (Eds.: J. S. Valentine, C. S. Foote, A. Greenberg, J. F. Liebman), Chapman & Hall, London, **1995**, pp. 276–312; b) L. Que, Jr., R. Y. N. Ho, *Chem. Rev.* **1996**, *96*, 2607–2624; c) T. Funabiki in *Oxygenases and Model Systems* (Ed.: T. Funabiki), Kluwer Academic, Dordrecht, **1997**, pp. 69–77, 140–145.
- [2] EPR studies: a) S. Slappendel, G. A. Veldink, J. F. G. Vliegthart, R. Aasa, B. G. Malmström, *Biochim. Biophys. Acta* **1981**, *667*, 77–86; b) E. K. Pistorius, B. Axelrod, G. Palmer, *J. Biol. Chem.* **1976**, *251*, 7144–7148; c) M. J. Nelson, *J. Am. Chem. Soc.* **1988**, *110*, 2985–2986.
- [3] X-ray absorption spectroscopy studies: a) R. C. Scarrow, M. G. Trimitsis, C. P. Buck, G. N. Grove, R. A. Cowling, M. J. Nelson, *Biochemistry* **1994**, *33*, 15023–15035; b) L. M. Van der Heijdt, M. C. Feiters, S. Navaratnam, H.-F. Nolting, C. Hermes, G. A. Veldink, J. F. G. Vliegthart, *Eur. J. Biochem.* **1992**, *207*, 793–802.
- [4] Magnetic circular dichroism studies: a) M. A. Pavlosky, Y. Zhang, T. E. Westre, Q.-F. Gan, E. G. Pavel, C. Campochiaro, B. Hedman, K. O. Hodgson, E. I. Solomon, *J. Am. Chem. Soc.* **1995**, *117*, 4316–4327; b) Y. Zhang, M. S. Gebhard, E. I. Solomon, *J. Am. Chem. Soc.* **1991**, *113*, 5162–5175.
- [5] Crystallographic studies of the catalytically inactive iron(II) form of SLO-1: a) J. C. Boyington, B. J. Gaffney, L. M. Amzel, *Science* **1993**, *260*, 1482–1486; b) W. Minor, J. Steczko, J. T. Bolin, Z. Otwinowski, B. Axelrod, *Biochemistry* **1993**, *32*, 6320–6323.
- [6] a) S. K. Mandal, L. Que, Jr., *Inorg. Chem.* **1997**, *36*, 5424–5425; b) R. T. Jonas, T. D. P. Stack, *J. Am. Chem. Soc.* **1997**, *119*, 8566–8567; c) Y. Zang, T. E. Elgren, Y. Dong, L. Que, Jr., *J. Am. Chem. Soc.* **1993**, *115*, 811–813; d) Y. Zang, J. Kim, Y. Dong, E. C. Wilkinson, E. H. Appelman, L. Que, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 4197–4205; e) D. D. Cox, S. J. Benkovic, L. M. Bloom, F. C. Bradley, M. J. Nelson, L. Que, Jr., D. E. Wallick, *J. Am. Chem. Soc.* **1988**, *110*, 2026–2032; f) S. Hikichi, T. Ogihara, K. Fujisawa, N. Kitajima, M. Akita, Y. Morooka, *Inorg. Chem.* **1997**, *36*, 4539–4547; g) J. W. Buchler, K. L. Lay, Y. J. Lee, W. R. Scheidt, *Angew. Chem.* **1982**, *94*, 456; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 432; h) Y. Dong, H. Fujii, M. P. Hendrich, R. A. Leising, G. Pan, C. R. Randall, E. C. Wilkinson, Y. Zang, L. Que, Jr., B. G. Fox, K. Kauffman, E. Münck, *J. Am. Chem. Soc.* **1995**, *117*, 2778–2792; i) A. Hazell, K. B. Jensen, C. J. McKenzie, H. Toftlund, *Inorg. Chem.* **1994**, *33*, 3127–3134.
- [7] IR spectra of the compounds in acetonitrile at ambient temperature were measured on a ReactIR 1000 spectrometer (ASI Applied Systems) over the range 4000–650 cm^{-1} .
- [8] Purple crystals suitable for X-ray structure analysis were obtained from an acetonitrile/diethyl ether solution. Crystal data for **1**: $\text{C}_{40}\text{H}_{59}\text{FeClO}_8\text{N}_7$, $M_w = 857.25$, monoclinic, space group $P2_1/c$ (No. 14), $a = 10.720(1)$, $b = 16.390(2)$, $c = 26.23(1)$ Å, $\beta = 100.40(2)^\circ$, $V = 4532(1)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.256 \text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 4.46 \text{ cm}^{-1}$, $R =$

0.079, and $R_w = 0.113$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101084. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [9] a) M. Harata, K. Jitsukawa, H. Masuda, and H. Einaga, *Chem. Lett.* **1996**, 813–814; b) A. Wada, M. Harata, K. Hasegawa, M. Mukai, T. Kitagawa, H. Masuda, H. Einaga, *Angew. Chem.* **1998**, *110*, 874–875; *Angew. Chem. Int. Ed.* **1998**, *37*, 798–799.
- [10] S. Slappendel, B. G. Malmström, L. Petersson, A. Ehrenberg, G. A. Veldink, J. F. G. Vliegthart, *Biochem. Biophys. Res. Commun.* **1982**, *108*, 673–677.
- [11] An API 300 triple quadrupole mass spectrometer (PE-Sciex) in positive-ion detection mode, equipped with an ion spray interface, was used for these ESI-MS experiments. The sprayer was held at a potential of 4.5 kV and compressed N_2 was employed to assist liquid nebulization. The orifice potential was maintained at 25 V.
- [12] M. R. Egmond, P. M. Fasella, G. A. Veldink, J. F. G. Vliegthart, J. Boldingh, *Eur. J. Biochem.* **1977**, *76*, 469–479.
- [13] Another example of a (methoxo)iron(III) complex with such a color (red-orange) is $[\text{Fe}\{2,6-[(2\text{-C}_5\text{H}_4\text{N})\text{CH}_2\text{OCH}_2]_2\text{C}_5\text{H}_3\text{N}\}(\text{OMe})]-(\text{OSO}_2\text{CF}_3)_2$ (2-C₅H₄N = 2-Pyridyl, C₅H₃N = 2,6-Pyridindyl),^[6b].
- [14] M. Harata, K. Jitsukawa, H. Masuda, H. Einaga, *Chem. Lett.* **1995**, 61–62.

A Photochemical Switch for Controlling Protein–Protein Interactions**

Sonia K. Pollitt and Peter G. Schultz*

Photocaged small molecules and proteins, molecules that can rapidly be converted from inactive into active form with light, have proven to be very useful tools in biology.^[1] The ability to control protein–protein binding interactions would further extend this approach to a large number of cellular processes including signal transduction pathways, gene regulation, and protein trafficking. Chemical modification has been used to introduce photocleavable groups into proteins, but this method depends on a uniquely reactive residue being present on the protein surface in order to achieve high selectivity.^[2] Here we use unnatural amino acid mutagenesis to photocage the interaction of the p21^{ras} (ras) protein with its downstream effector p120–GAP (GAP = GTPase-activating protein). The caged ras protein, in which Asp 38 is substituted with the β -o-nitrobenzyl ester of aspartic acid (Nb-Asp), retains its intrinsic GTPase activity but is unable to interact

[*] P. G. Schultz, S. K. Pollitt
Howard Hughes Medical Institute and
Department of Chemistry
University of California, Berkeley and
Lawrence Berkeley National Laboratory
Berkeley, CA 94720 (USA)
Fax: (+1) 510-643-6890
E-mail: pgschultz@lbl.gov

[**] We thank N. Damrauer and J. McCusker for helpful advice and the use of their laser, and H. Chung for the GAP protein. We are grateful for financial support for this work from the National Institutes of Health (grant no. R02 GM49220). P.G.S. is a Howard Hughes Medical Institute Investigator.

with p120–GAP until uncaged by irradiation with light at a wavelength of 355 nm. This approach should be applicable to the side chains of other amino acids that can be blocked with photocleavable protecting groups including serine, threonine, glutamate, and lysine. It may provide a general method for the study of signal transduction pathways and other biological processes, both in vitro and in vivo, in which specific protein interactions can be identified.

Mammalian proteins encoded by the *ras* genes function as key regulators in various signal transduction processes involved in cell growth and differentiation.^[3] Activity is controlled by conformational changes that depend on bound guanine nucleotides: the *ras*–GTP complex (*ras*·GTP) adopts a conformation that is able to bind to, and interact with, downstream effectors, whereas the GDP-bound conformation of the *ras* protein is inactive.^[4] The ratio of *ras*·GTP to *ras*·GDP is controlled by the protein's intrinsic GTPase activity, as well as by proteins that increase the dissociation of GDP from the complex (guanine nucleotide release factors, GNRFs)^[5] or accelerate the rate of GTP hydrolysis (GAPs).^[6] In this capacity, p120–GAP is a negative regulator of *ras* function;^[7] p120–GAP can also act as a downstream effector of *ras*, and hence as a positive regulator of *ras* function in some systems.^[5, 8]

The interaction of *ras* and p120–GAP was caged by replacing Asp38 in the *ras* protein with the photocleavable Nb-Asp by unnatural amino acid mutagenesis.^[9] Mutagenesis^[10] and structural studies^[11] have shown that amino acids 30–38 (loop 2 or switch I)^[12] and amino acids 60–76 (loop 4 or switch II)^[13] are critical for the ability of *ras* to interact with its effector proteins. In particular, the mutation of Asp38 to Ala prevents GTPase stimulation by p120–GAP and results in the loss of transforming capacity in NIH3T3 cells;^[14] moreover, this mutation abrogates binding of *ras* to raf^[15] and phosphatidylinositol-3 kinase^[16] (other downstream effectors of *ras*) in vitro. In addition, the recent crystal structure of the *ras*–p120–GAP complex^[11] shows the Asp38 side chain oriented towards the Lys949 residue of p120–GAP, thus forming a hydrogen-bonding interaction with this residue through a bound water molecule.^[17]

The Nb-Asp was introduced into the *ras* protein by in vitro suppression of an Asp38→TAG amber mutant (amber codon = terminations codon UAG) using a chemically aminoacylated suppressor tRNA as previously described.^[9, 18] Both wild-type (WT) and mutant proteins carry a shortened version of the *ras* gene in which the 18 carboxy-terminal amino acids are removed and replaced with a six-residue histidine tail to aid purification.^[19] The aspartate residue was N-protected with allyl chloroformate and then converted into the bis-nitrobenzyl ester using dicyclohexylcarbodiimide, 4-dimethylaminopyridine (DMAP), and 1-hydroxy-1*H*-benzotriazole. Subsequently, the α -nitrobenzyl ester group was selectively hydrolyzed with lithium hydroxide.^[20] The *N*-allyloxycarbonyl- β -nitrobenzyl aspartate was activated and coupled onto the dinucleotide 5'-phospho-2'-deoxyribocytidylylriboadenosine (pdCpA), and the aminoacylated dinucleotide was ligated to the suppressor tRNA_{CUA}.^[18] In vitro expression of the WT *ras* gene under control of the T7 promoter afforded about 20 $\mu\text{g mL}^{-1}$ of protein. The suppression efficiency for Nb-

Asp acylated tRNA_{CUA} at position 38 was approximately 60%. In vitro protein synthesis reactions containing the TAG mutant in the presence of the full-length unacylated suppressor tRNA_{CUA} resulted in less than 1% of the *ras* protein as compared with reactions which contain tRNA_{CUA} acylated with Nb-Asp.^[21] This control reaction demonstrates that the preparation of the caged *ras* protein is largely free of contaminating protein generated by readthrough of the amber codon by nonspecific tRNAs. Both the WT and mutant proteins were purified on a nickel resin to greater than 95% purity with an overall yield of approximately 50%.^[22]

Intrinsic GTPase activity was determined for both the WT and mutant proteins by measuring the rate of GTP hydrolysis in a single-turnover experiment using [γ -³²P]GTP.^[23] The reaction products were separated by chromatography on polyethyleneimine and quantified by phosphorimaging. There is no significant difference in the rate of catalysis k_{cat} between the WT and mutant *ras* proteins.^[24] Their intrinsic GTPase activities are unaffected by irradiation with light at a wavelength of 355 nm from a frequency-tripled neodymium-YAG laser (Table 1).^[25] In contrast to the WT *ras* protein, the caged mutant shows no p120–GAP-mediated GTPase activity,

Table 1. Intrinsic and p120–GAP-mediated GTPase activities of wild-type and mutant *ras* proteins before and after irradiation.

Protein	k_{cat} [$\text{s}^{-1} \times 10^4$] ^[a] (–GAP)	Specific activity [% GTP min ^{–1} $\times 10^3$] ^[b]		Ratio ^[d]
		(–GAP)	(+GAP) ^[c]	
Nb-Asp ^[e]	1.6 $\pm$ 0.02 %	7.6 $\pm$ 0.3 %	8.0 $\pm$ 0.08 %	1.1
Nb-Asp ^[f]	1.5 $\pm$ 0.2 %	6.9 $\pm$ 0.6 %	24 $\pm$ 2 %	3.5
WT ^[e]	1.7 $\pm$ 0.1 %	7.8 $\pm$ 0.2 %	57 $\pm$ 0.6 %	7.2
WT ^[f]	1.6 $\pm$ 0.4 %	7.2 $\pm$ 1 %	56 $\pm$ 3 %	7.8

[a] Reference [22, 23]. [b] The activity was calculated as the initial rate of conversion of GTP into GDP. [c] Reference [25]. [d] Ratio of activities in the presence and absence of p120–GAP.^[29] [e] Before irradiation. [f] After irradiation.

again under single-turnover conditions in the presence of a 100-fold excess of p120–GAP.^[26] These results show that the *o*-nitrobenzyl group efficiently blocks the productive association of *ras* and p120–GAP.

Upon irradiation, *o*-nitrobenzyl esters are known to undergo rapid photodecomposition to the free acid and nitrosobenzaldehyde.^[27] Photolysis of the caged *ras* protein restored roughly 50% of the GAP-dependent GTPase activity relative to WT *ras* (Table 1).^[25, 26] This conversion was also monitored by denaturing polyacrylamide gel electrophoresis of the [³⁵S]methionine-labeled protein (Figure 1). The caged mutant has slightly lower electrophoretic mobility than the WT protein. After photolysis to remove the *o*-nitrobenzyl ester group, approximately 50% of the mutant protein is converted into product with the same mobility as the WT *ras* protein. The similarity in the levels of the restored p120–GAP-mediated GTPase activity and the conversion into a product with WT *ras* protein gel mobility upon photolysis suggest that the uncaged protein has WT p120–GAP-dependent GTPase activity. Photolysis of the caged mutant for longer times did not result in greater conversion into the

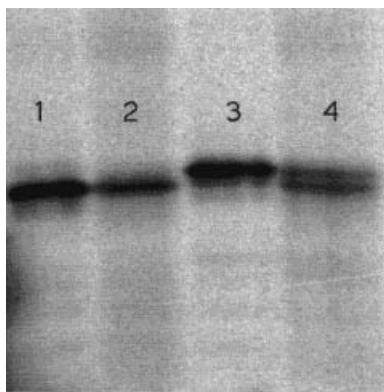


Figure 1. Autoradiogram of SDS polyacrylamide gel (16%) after purification and before and after irradiation of the [^{35} S]methionine-labeled protein products of in vitro translation reactions containing WT ras and Nb-Asp mutant. The caged protein (lane 3) has slightly lower electrophoretic mobility than the WT protein (lane 1). After photolysis to remove the *o*-nitrobenzyl ester group, about 50% of the mutant has shifted electrophoretic mobility (lane 4), while the mobility of the WT protein (lane 2) remains unaffected.

WT ras protein. This may be a consequence of a side reaction of the Nb-Asp with amino acids (300 μ M) present in the in vitro synthesis reaction, which results in the formation of an inactive amide side chain. Alternatively, ras may be modified by the *o*-nitrosobenzaldehyde by-product of the photolysis reaction.^[28]

In conclusion, these results show that installing Nb-Asp at position 38 of a ras protein generates a photocaged protein that retains full intrinsic catalytic activity, but is incapable of participating in signal transduction through its effector p120-GAP. After irradiation of the mutant, the WT protein is regenerated and its ability to interact with its effector protein is restored.

Received: December 3, 1997

Revised version: April 14, 1998 [Z112271E]

German version: *Angew. Chem.* **1998**, *110*, 2252–2255

Keywords: amino acids • mutagenesis • photochemistry • ras proteins • signal transduction

- [1] S. R. Adams, J. P. Y. Kao, G. Gryniewicz, A. Minta, R. Y. Tsien, *J. Am. Chem. Soc.* **1988**, *110*, 3212–3220; S. R. Adams, J. P. Y. Kao, R. Y. Tsien, *J. Am. Chem. Soc.* **1989**, *111*, 7957–7968; M. R. Blatt, G. Thiel, D. R. Trentham, *Nature* **1990**, *346*, 766–769; d) A. D. Turner, S. V. Pizzo, G. Rozakis, N. A. Porter, *J. Am. Chem. Soc.* **1988**, *110*, 244–250; N. A. Porter, K. A. Bush, K. S. Kinter, *J. Photochem. Photobiol. B* **1997**, *38*(1), 61–69; D. Mendel, J. A. Ellman, P. G. Schultz, *J. Am. Chem. Soc.* **1991**, *113*, 2758–2760.
- [2] G. Marriott, M. Heidecker, *Biochemistry* **1996**, *35*, 3170–3174; C. H. Self, S. Thompson, *Nature Medicine* **1996**, *2*, 817–820.
- [3] L. Weismuller, F. Wittinghofer, *Cell. Signalling* **1994**, *6*, 247–267.
- [4] M. Barbacid, *Annu. Rev. Biochem.* **1987**, *56*, 779–827.
- [5] J. Downward, *Curr. Opin. Genet. Dev.* **1992**, *2*, 13–18.
- [6] H. R. Bourne, D. A. Sanders, F. McCormick, *Nature* **1990**, *348*, 125–132.
- [7] K. Tanaka, M. Nakafuku, T. Satoh, M. S. Marshall, J. B. Gibbs, K. Matsumoto, Y. Kaziro, A. Tohe, *Cell* **1990**, *60*, 803–807; R. Ballester, T. Michaeli, K. Ferguson, H. P. Xu, F. McCormick, M. Wigler, *Cell* **1989**, *59*, 681–686; J. Downward, J. D. Graves, P. H. Warne, S. Rayter, D. A. Cantrell, *Nature* **1990**, *346*, 719–723; K. Zhang, J. E. DeClue, W. C. Vass, A. G. Papageorge, F. McCormick, D. R. Lowy, *Nature* **1990**, *346*, 754–756.
- [8] R. H. Medema, W. L. de Laat, G. A. Martin, F. McCormick, J. L. Bos, *Mol. Cell Biol.* **1992**, *12*(8), 3425–3430; D. R. Kaplan, D. K. Morrison, G. Wong, F. McCormick, L. T. Williams, *Cell* **1990**, *61*, 125–133; Y. Kaziro, H. Itoh, T. Kozasa, M. Nakafuku, T. Satoh, *Annu. Rev. Biochem.* **1991**, *60*, 349–400; M. Duchesne, F. Schweighoffer, F. Parker, F. Clerc, Y. Frobert, M. N. Thang, B. Tocque, *Science* **1993**, *259*, 525–528; J. McGlade, B. Brunkhorst, D. Anderson, G. Mbamalu, J. Settleman, S. Dedhar, M. Rozakis-Adcock, L. B. Chen, T. Pawson, *EMBO J.* **1993**, *12*, 3073–3081; G. A. Martin, A. Yatani, R. Clark, L. Conroy, P. Polakis, A. M. Brown, F. McCormick, *Science* **1992**, *255*, 192–194; A. Yatani, K. Okabe, P. Polakis, R. Halenbeck, F. McCormick, A. M. Brown, *Cell* **1990**, *61*, 769–776.
- [9] C. J. Noren, S. J. Anthony-Cahill, D. J. Suich, K. A. Noren, M. C. Griffith, P. G. Schultz, *Nucleic Acids Res.* **1989**, *18*, 83–88; S. A. Robertson, C. J. Noren, S. J. Anthony-Cahill, M. C. Griffith, P. G. Schultz, *Nucleic Acids Res.* **1989**, *17*, 9649–9660; J. A. Ellman, D. Mendel, S. J. Anthony-Cahill, C. J. Noren, P. G. Schultz, *Methods Enzymol.* **1991**, *202*, 301–336; J. S. Thorson, V. W. Cornish, J. E. Barrett, S. T. Cload, Y. Yano, P. G. Schultz, *A Biosynthetic Approach for the Incorporation of Unnatural Amino Acids into Proteins*, Humana Press, Clifton, NJ, in press.
- [10] B. M. Willumsen, A. G. Papageorge, H. Kung, E. Bekesi, T. Robins, M. Johnson, W. C. Vass, D. R. Lowy, *Mol. Cell Biol.* **1986**, *6*, 2646–2654; J. C. Stone, W. C. Vass, B. M. Willumsen, D. R. Lowy, *Mol. Cell Biol.* **1988**, *8*, 3565–3569; I. S. Sigal, J. B. Gibbs, J. S. D'Alonzo, E. M. Scolnick, *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 4725–4729.
- [11] K. Scheffzek, M. R. Ahmadian, W. Kabsch, L. Weismuller, A. Lautwein, F. Shmitz, A. Wittinghofer, *Science* **1997**, *277*, 333–338; I. Schlichting, S. C. Almo, G. Tapp, K. Wilson, K. Petratos, A. Lentfer, A. Wittinghofer, W. Kabsch, E. F. Pai, G. A. Petsko, R. S. Goody, *Nature* **1990**, *345*, 309–315.
- [12] H. R. Bourne, D. A. Sanders, F. McCormick, *Nature* **1991**, *349*, 117–127; C. Cales, J. F. Hancock, C. J. Marshall, A. Hall, *Nature* **1988**, *332*, 548–550.
- [13] M. S. A. Nur-E-Kamal, A. Sizeland, G. D'Abaco, H. Maruta, *J. Biol. Chem.* **1992**, *267*, 1415–1418; X. F. Zhang, J. Settleman, J. M. Kyriakis, E. Takeuchi-Suzuki, S. J. Elledge, M. S. Marshall, J. T. Bruder, U. R. Rapp, J. Avruch, *Nature* **1993**, *364*, 308–313.
- [14] H. Adari, D. R. Lowy, B. M. Willumsen, C. J. Der, F. McCormick, *Science* **1988**, *240*, 518–521.
- [15] P. H. Warne, P. R. Vician, J. Downward, *Nature* **1993**, *364*, 352–355;
- [16] P. Rodriguez-Vician, P. H. Warne, R. Dhand, B. Vanhaesebroeck, I. Gout, M. J. Fry, M. D. Waterfield, J. Downward, *Nature* **1994**, *370*, 527–532.
- [17] The crystal structure suggests that Asp33 could also be used to photocage the interaction between ras and p120-GAP. However, in vitro suppression efficiency with Nb-Asp at this position was less efficient than at position 38: suppression efficiencies were 20% and 60% for positions 33 and 38, respectively.
- [18] S. A. Robertson, J. A. Ellman, P. G. Schultz, *J. Am. Chem. Soc.* **1991**, *113*, 2722–2729; S. T. Cload, D. R. Liu, W. A. Froland, P. G. Schultz, *Chem. Biol.* **1996**, *3*, 1033–1038.
- [19] The construct used to generate the TAG mutant was constructed by polymerase chain reaction (PCR) of the full-length ras gene from the vector pGATrp (H. Chung, Ph.D. Thesis, University of California, Berkeley, **1993**) using a 5' primer that introduced an NdeI site at the start codon. The full length gene was inserted into an intermediate vector, then digested with NdeI/HindIII. The HindIII site is internal to the ras gene, so that a shortened version of ras consisting of the first 171 amino acids is generated. The shortened ras gene was inserted into the expression vector pAED4 between the NdeI and EcoRI sites using a HindIII/EcoRI linker that added a (His)₆ tag and the TAA and TGA stop codons.
- [20] J. M. Davey, A. H. Laird, J. S. Morley, *J. Chem. Soc. C* **1966**, 555–566.
- [21] Assayed by quantitating the incorporation of [^{35} S]methionine into full-length ras protein by phosphorimaging.
- [22] E. Hochuli, H. Dobeli, A. Schacher, *J. Chromatogr.* **1987**, *411*, 177–184.
- [23] Intrinsic GTPase activity was determined by incubating approximately 10 nM purified WT or mutant ras with 10 μ M [γ - ^{32} P]GTP (3000 Ci mmol⁻¹, Amersham) in 50 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (Hepes, pH 7.5) 100 mM NaCl, 1 mM MgCl₂,

10 mM ethylenediamine tetraacetate (EDTA), 1 mM 1,4-dithiothreitol (DTT), and 1 % bovine serum albumen (BSA) at 4 °C in a volume of 400 μ L. After 30 minutes this exchange reaction was stopped by the addition of MgCl_2 to give a final concentration of 25 mM and the enzyme-substrate (E·S) complex purified on a PD10 column. The purified E·S complex was divided into separate aliquots of 150 μ L, and rGTP was added to give a final concentration of 50 μ M. The reactions were incubated at 30 °C for various times before mixing 7.5- μ L samples with 7.5 μ L of stop solution (100 μ M rGTP, 100 μ M rGDP, 250 mM EDTA, 0.5 % sodium dodecylsulfate (SDS)). Conversion of GTP into GDP was monitored by chromatography on polyethylenimine (0.3 M KH_2PO_4 , 1 M LiCl_2 , pH 3.5).

- [24] For k_{cat} calculations based on monitoring the single-turnover experiment of the E·S complex in the presence of an excess of free unlabeled rGTP, the following relationship holds: $[P]/[E\cdot S]_0 = k_{\text{cat}}/(k_{\text{cat}} + k_{\text{off}}) \exp[-(k_{\text{cat}} + k_{\text{off}})t]$, where $[P]$ is the concentration of the GDP product, t is time, and k_{off} the off-rate for GTP in the E·S complex. This relationship is based on the following assumptions: The E·S complex can break down only to product or to free enzyme and free substrate; the observed reaction is strictly single-turnover, because once the labeled substrate has dissociated from the enzyme it will not appreciably reassociate because of competition by excess unlabeled substrate; and the product off-rate is not limiting because the E·P complex is broken down in the stop reaction.
- [25] Both WT and photocaged proteins were irradiated for up to five minutes with a frequency-tripled Spectra-Physics model GCR-150-10 laser (ca. 100 mJ at 355 nm, nominal pulse width of 7 ns). Longer photolysis times did not lead to greater conversion. Irradiation was performed in quartz cuvettes with stirring to ensure an even exposure. Reactions were chilled to 4 °C prior to irradiation to prevent overheating. The 500- μ L reactions contained 10 nM WT or mutant ras protein in 50 mM Hepes (pH 7.5), 1 mM MgCl_2 , 200 mM NaCl, 1 mM DTT, 0.1 % BSA, and 10 μ M semicarbazide·HCl to scavenge the nitrosobenzaldehyde by-product.
- [26] The p120-GAP assay was performed by isolation of the E·S complex as described in ref. [23], except that a greater than 100-fold excess of p120-GAP over the ras protein was added after dividing the E·S complex into separate reactions. p120-GAP was a gift from H. Chung and was prepared by overexpression from a derivative of pUC18 carrying the gene for bovine p120-GAP behind the Trp promoter as described in M. S. Marshall, W. S. Hill, A. S. Ng, U. S. Vogel, M. D. Schaber, E. Scolnick, R. A. F. Dixon, I. S. Sigal, J. B. Gibbs, *EMBO J.* **1989**, 8, 1105–1110.
- [27] H. Schupp, W. K. Wong, W. Schnabel, *J. Photochem.* **1987**, 36, 85–97.
- [28] Improved deprotection efficiencies have been reported when the *o*-nitrobenzyl group is substituted at the α -benzylic position because the photocleavage by-product of these compounds is the less reactive nitrosoketone. Attempts to improve the efficiency of the photocleavage reaction by using β -1-(3,4-methylenedioxy-6-nitrobenzyl)-ethyl aspartate resulted in lower yields of mutant protein.
- [29] Under saturating conditions, p120-GAP can catalyze the GTPase rate of ras by 10^5 -fold;^[30] however, catalysis in these experiments is limited by the ras protein, which is present in the reaction at a concentration of about 10 nM but has a k_d for p120-GAP of about 17 μ M.^[31]
- [30] P. Gideon, J. John, M. Frech, A. Lautwein, R. Clark, J. E. Scheffler, A. Wittinghofer, *Mol. Cell. Biol.* **1992**, 12, 2050–2056.
- [31] J. F. Eccleston, K. J. M. Moore, L. Morgan, R. H. Skinner, P. N. Lowe, *J. Biol. Chem.* **1993**, 268, 27012–27019.

One- and Two-Dimensional Electron Transfer Processes in Triarylamines with Multiple Redox Centers**

Christoph Lambert* and Gilbert Nöll

Intramolecular electron transfer (ET) processes have been studied extensively in inorganic binuclear transition metal complexes;^[1] organic donor-acceptor systems that are bridged by σ frameworks have been investigated in order to mimic biological ET processes.^[2] In contrast, much less is known about purely organic Robin/Day^[3] class II compounds with bridging π -electron systems and the electron transfer processes involved: Nelsen et al.^[4] studied a number of bis(hydrazine)phenylene radical cations and related species; Bonvoisin et al.^[5] investigated *m*-phenylene-bridged triarylamine systems. These radical cations are characterized by intervalence charge-transfer (IV-CT) bands in the NIR spectra which are associated with a photoinduced intramolecular electron transfer between two redox centers. As the coupling of redox centers over π -conjugated bridges is of central interest for the design of new optoelectronic materials,^[6] it was our aim to study basic intramolecular electron transfer processes in simple symmetrically substituted π systems. We chose π -bridged triarylamine derivatives since triarylamines in general are important hole carrier systems, which are widely used in organic optoelectronic devices.^[7]

4,4'-Bis(*N,N*-di-*p*-methoxyphenylamino)tolane (**2**) was synthesized by two Hagihara cross-coupling steps, and the corresponding trimer hexakis[4-(*N,N*-di-*p*-methoxyphenylamino)phenyl]benzene (**3**) was formed from **2** by catalysis with $[\text{Co}_2(\text{CO})_8]$ (Scheme 1).^[8] These derivatives should exhibit an intramolecular degenerate electron transfer in the singly and triply oxidized forms, respectively. Both neutral compounds are yellow, and their UV/Vis spectra in CH_2Cl_2 contain a strong absorption band at 373 nm (**2**) and 308 nm (**3**, with a shoulder at 330 nm). The cyclic voltammogram (CV)^[9] of **2** shows two waves at 200 and 340 mV (versus Fc/Fc^+) in CH_2Cl_2 (Figure 1) referring to two reversible oxidations. This corresponds to a comproportionation constant ($K_{\text{co}} = 10^{(\Delta E/0.059)}$, where ΔE is the difference of redox potentials for the two oxidative steps) of 236 and suggests **2** to be a class II derivative.^[1,3] In contrast, trimer **3** only shows one broad unresolved wave centered at 225 mV. This reversible oxidation process was calibrated by thin-layer coulometry with 2,5-bis(dicyanovinyl)furan as the reference, and it involves six electrons in total, leading to $\mathbf{3}^{6+}$.

UV/Vis/NIR spectroelectrochemical investigation^[10] of **2** shows that besides a band at 734 nm, which is characteristic for triarylamine radical cations,^[11] a second very intense band

[*] Dr. C. Lambert, Dipl.-Chem. G. Nöll
Institut für Organische Chemie der Universität
Universitätsstrasse 31, D-93040 Regensburg (Germany)
Fax: (+49) 941-943-4984
E-mail: christoph.lambert@chemie.uni-regensburg.de

[**] We are grateful to the Fonds der Chemischen Industrie (Liebig grant to C.L.) and to the Deutsche Forschungsgemeinschaft (Habilitationstipendium) for financial funding, and especially to Prof. J. Daub for his kind support at Regensburg. We thank C. Stadler for many helpful discussions.

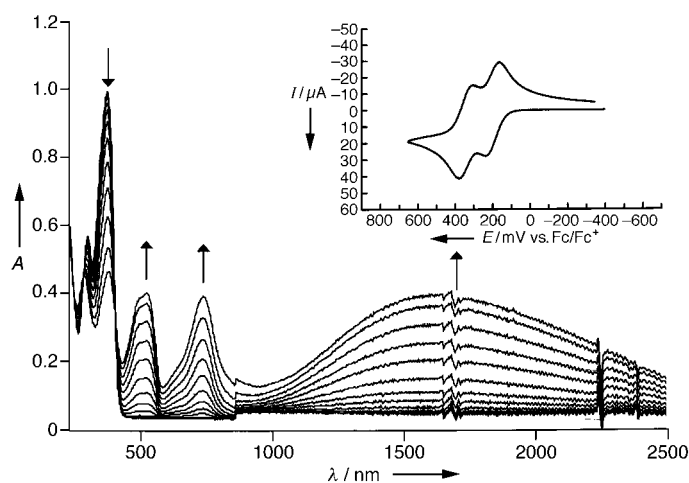
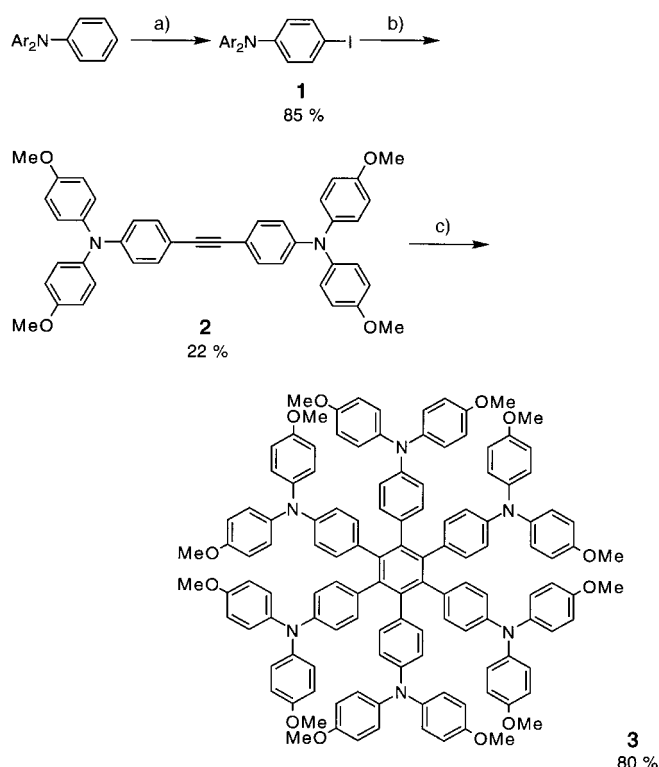


Figure 1. Spectroelectrochemistry of the oxidation of **2** to 2^+ . Inset: cyclic voltammogram of **2**.

($\epsilon_{\text{max}} = 22300 \text{ M}^{-1}\text{cm}^{-1}$) appears in the NIR spectrum at 1620 nm upon oxidation to the monocation 2^+ (6180 cm^{-1} , Figure 1). We attribute this band to a one-dimensional IV-CT. This band disappears when 2^+ is further oxidized to 2^{2+} , while the radical band at 734 nm rises continuously.^[11] Figure 2 shows both the absorbance of the radical band and the IV-CT band versus the applied potential. The absorbance of the IV-CT band is maximal at a potential when the radical band shows half the absorbance of the fully oxidized 2^{2+} . This proves that the IV-CT band is solely associated with 2^+ .

Spectroelectrochemistry of **3** also revealed, besides a radical band at 748 nm,^[11] an IV-CT band of low intensity

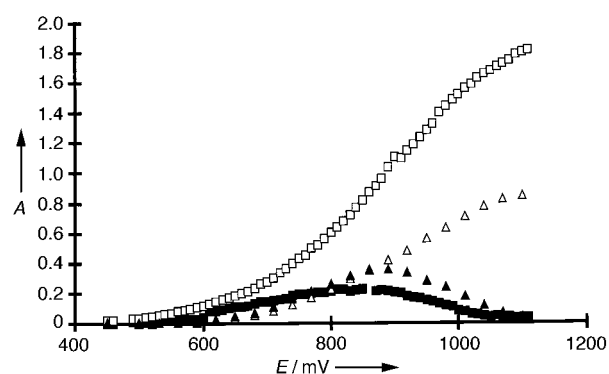
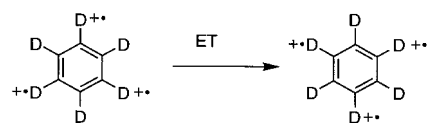


Figure 2. Plot of the absorbance of the radical band (**2**: Δ , **3**: $\square$) and the IV-CT band (**2**: $\blacktriangle$, **3**: $\blacksquare$) during oxidation versus potential (relative to Ag/AgCl); absorbance of the IV-CT band of **3** $\times 10$.

(in the order of $5000 \text{ M}^{-1}\text{cm}^{-1}$) at around 1390 nm (7200 cm^{-1}). A plot of the radical band and the IV-CT band against the potential again shows that the maximum of the IV-CT occurs at a potential when the radical band is at half the maximal intensity. Although 3^+ and 3^{5+} should exhibit IV-CT bands as well, we assign the observed band to be mainly due to the IV-CT in the trication 3^{3+} which should be the most intense. According to AM1-CI calculations^[12] the ground state of 3^{3+} is a ^4A state. There are two doubly degenerate (E) IV-charge transfers at 1.556 and 1.584 eV connected to the ^4A ground state by very small oscillator strengths ($f = 0.092$ and 0.181, respectively). The two-dimensional IV-CT is drawn schematically in Scheme 2 and refers to a classical concerted electron



Scheme 2. Concerted two-dimensional ET of 3^{3+} . D = 4-[N,N-bis-(4-methoxyphenyl)amino]phenyl.

transfer. There is a ^2E state only 0.0008 eV above the quartet ground state. This means that at ambient temperature both the ^4A and the ^2E state might be populated thermally. The ^2E state is connected to four excited ^2E and to four ^2A states lying between 1.556 and 1.586 eV. The oscillator strengths of these states amount in total to $f = 0.24$, which is comparable to the two excited ^4E states ($f = 0.27$). All these transitions may contribute to the observed IV-CT band of 3^{3+} .

To apply Hush's adiabatic line shape analysis^[1, 13, 14] to the observed IV-CT band of 2^+ we recorded UV/Vis/NIR spectra of chemically oxidized **2** (with $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in MeCN and SbCl_5 in all other solvents) in a number of different solvents at concentrations of about 10^{-4} – 10^{-5} M (Table 1) since the spectral data from the spectroelectrochemical experiment are influenced to some extent by ion pairing due to high salt concentrations.^[15]

According to Hush, the theoretical width at half-height of a Gaussian-shaped IV-CT band can be calculated from $\tilde{\nu}_{\text{max}}$ at the high-temperature limit (HTL) with Equation (1).^[13] As

$$\tilde{\nu}_{1/2}(\text{HTL}) = 47.94 \sqrt{\tilde{\nu}_{\text{max}}} \quad (1)$$

expected for class II compounds, the experimentally observed $\tilde{\nu}_{1/2}$ in polar solvents is somewhat broader (about 17 %) than

Table 1. Spectral data of **2**⁺ in different solvents.^[a]

	E_T^N	$\tilde{\nu}_{\max}$ [cm ⁻¹]	λ/λ_v [kcal mol ⁻¹]	$\epsilon_{\max}$ [M ⁻¹ cm ⁻¹]	V [kcal mol ⁻¹]	$\tilde{\nu}_{1/2}$ [cm ⁻¹]	$\tilde{\nu}_{1/2}(\text{HTL})$ [cm ⁻¹]	$g(\tilde{\nu}_v, T)$
2 ⁺ /CH ₂ Cl ₂	0.309	5710	16.3/4.5	22 300	3.1	3400	3620	0.94
2 ⁺ /PhCN	0.333	6490	18.5/4.5	–	–	4420	3860	1.15
2 ⁺ /EtCN	0.401	7370	21.1/4.5	–	–	5020	4120	1.22
2 ⁺ /DMF	0.404	7620	21.8/4.5	–	–	5140	4180	1.23
2 ⁺ /DMSO	0.444	7740	22.1/4.5	–	–	–	4220	–
2 ⁺ /MeCN	0.460	7990	22.8/4.5	14 100	3.4	4640	4290	1.08
[Fc-CC-Fc] ⁺ /MeCN ^[b]	0.460	7350	21.4/2.0	300–500	1.0	4000	4110	–

[a] E_T^N : normalized Dimroth–Reichardt solvent parameter. $\tilde{\nu}_{\max}$: absorption maximum. λ/λ_v : total/inner reorganization energy. $\epsilon_{\max}$: molar absorptivity. V : coupling energy. $\tilde{\nu}_{1/2}$: observed band width at half-height. $\tilde{\nu}_{1/2}(\text{HTL})$: theoretical band width at half-height at the high-temperature limit. $g(\tilde{\nu}_v, T)$: ratio of $\tilde{\nu}_{1/2}/\tilde{\nu}_{1/2}(\text{HTL})$. [b] Diferrocenylethyne.^[23]

the theoretical HTL width. However, $\tilde{\nu}_{1/2}$ decreases on going to less polar solvents until an even smaller value than $\tilde{\nu}_{1/2}(\text{HTL})$ is reached in CH₂Cl₂. The electronic coupling energy in CH₂Cl₂ and MeCN was calculated with Equation (2)^[1, 13, 14] from the IV-CT energy $\tilde{\nu}_{\max}$ (equivalent to the reorganization energy λ), from the observed width at half-height $\tilde{\nu}_{1/2}$, and from the molar absorptivity $\epsilon_{\max}$.^[16] For the distance d between the two redox centers we used the AM1 calculated N–N distance of 12.48 Å.^[17]

$$V = \frac{0.0206}{d} (\epsilon_{\max} \tilde{\nu}_{1/2} \tilde{\nu}_{\max})^{1/2} \quad (2)$$

The coupling energy V is 3.1 kcal mol⁻¹ in CH₂Cl₂ and 3.4 kcal mol⁻¹ in MeCN (Table 1), making the reaction strongly adiabatic. This is in reasonable agreement with the AM1-calculated^[5a] splitting energy of the HOMO and HOMO – 1 ($E_{\text{HOMO}} - E_{\text{HOMO}-1} = 2V$; $V_{\text{AM1}} = 3.8$ kcal mol⁻¹) of **2**, which refers in a first-order approximation to the coupling in **2**⁺. The electronic mixing coefficient α is an estimate for the electron delocalization: $\alpha = V/\tilde{\nu}_{\max}$.^[18] Thus, with $\alpha = 0.19$ in CH₂Cl₂ and 0.15 in MeCN the delocalization in **2**⁺ is much stronger than in diferrocenylethyne ($\alpha = 0.05$).^[18] A very crude partitioning of the reorganization energy λ in an outer (solvent, λ_s) and an inner (vibronic, λ_v) contribution was carried out by correlating the IV-CT energies in different solvents (Table 1) with the normalized E_T^N parameters.^[19] The intercept of a linear regression analysis is 1600 cm⁻¹ (4.6 kcal mol⁻¹), which is in good agreement with the AM1 calculated^[20] internal reorganization energy λ_v of 4.5 kcal mol⁻¹. For **3**³⁺, a similar internal reorganization energy per positive charge (4.8 kcal mol⁻¹) was calculated as one third of the total inner reorganization energy.^[20]

The rate constant for the adiabatic thermal ET process in MeCN was calculated with Equation (3).^[21] The nuclear frequency factor $\tilde{\nu}_v$ was estimated from the ratio $g(\tilde{\nu}_v, T)$ [Eq. (4)] of the observed IV-CT band width at half-height and

$$k_{\text{th}} = \nu_v \exp(-\Delta G^*/RT) \quad (3)$$

$$\tilde{\nu}_{1/2} = g(\tilde{\nu}_v, T) \tilde{\nu}_{1/2}(\text{HTL}) \quad (4)$$

the band width at the high-temperature limit (with the exception of the value for CH₂Cl₂ as solvent, we used an average of 1.17; Table 1).^[22] A value of 450 cm⁻¹ was obtained, which is similar to those observed for binuclear transition metal derivatives.^[1]

Since the magnitude of V (3.4 kcal mol⁻¹) is comparable to that of $\lambda/4$ we used Sutin's^[21] ΔG^* [= 2.8 kcal mol⁻¹ for **2**⁺ in

MeCN; see Eq. (5)] for the evaluation.

$$\Delta G^* = (\lambda/4 - V + V^2/\lambda) \quad (5)$$

This results in a very high rate constant $k_{\text{th}} = 1.2 \times 10^{11} \text{ s}^{-1}$ in MeCN and an even higher value in CH₂Cl₂ compared to transition metal compounds.^[1] Although the assumptions and the whole formalism employed are very approx-

imate, our study suggests that the ET rate in **2**⁺ is extremely high. This is due to the fact that electronic coupling V is high compared to the reorganization energy λ . This strong coupling results in a high molar absorptivity of the IV-CT band [Eq. (2)] which is much larger than in other inorganic and organic compounds ($\epsilon \approx 10^2 - 10^3 \text{ M}^{-1} \text{ cm}^{-1}$).^[1] As there are neither spin nor symmetry constraints on the excitation, the reason for the high ϵ value must be a strong overlap of the ground and excited state wavefunction. This is reasonable, as **2**⁺ has a rather low internal reorganization energy. For instance, in the case of diferrocenylethyne [Fc-CC-Fc]⁺ $\tilde{\nu}_{\max}$ in MeCN is similar (21.4 kcal mol⁻¹), but ϵ is very small (ca. 500 M⁻¹ cm⁻¹) because of a relatively small V (ca. 1 kcal mol⁻¹).^[23]

Since V is in a first-order approximation independent of the solvent polarity,^[24] Equation (5) suggests that there is a limit ratio of λ/V at which ΔG^* becomes zero and the system transforms to a class III compound with delocalized centers. This is the case for $\lambda = 2V$ (= 6.8 kcal mol⁻¹ in MeCN).^[25] Because the internal reorganization energy λ_v (ca. 4–5 kcal mol⁻¹) is even lower than $2V$, **2**⁺ should be more similar to a class III derivative in the gas phase or in nonpolar solvents when the total reorganization energy λ approaches λ_v . The fact that $\tilde{\nu}_{1/2}$ is smaller than $\tilde{\nu}_{1/2}(\text{HTL})$ in CH₂Cl₂ as well as the significantly higher ϵ values and electronic mixing coefficients α in CH₂Cl₂ ($\epsilon = 22\,300 \text{ M}^{-1} \text{ cm}^{-1}$, $\alpha = 0.19$) than in MeCN ($\epsilon = 14\,100 \text{ M}^{-1} \text{ cm}^{-1}$, $\alpha = 0.15$) support this assumption and places **2**⁺ in CH₂Cl₂ at the borderline between class II and class III.^[1, 26]

In conclusion, the symmetrically substituted aminotolane derivative **2**⁺ is characterized by a very intense, solvent dependent IV-CT band in the NIR spectrum. Whereas in most binuclear transition metal class II systems the charge is mainly localized on one metal atom,^[1] the charge in **2**⁺ is partially delocalized in one triphenylamine moiety. Since the reorganization terms will increase in value with increased localization of the charge perturbation upon excitation, the partial delocalization leads to both a small λ_v and a small λ_s relative to V . This makes the ET extremely fast. A trimeric system **3**³⁺ akin to **2**⁺ has been investigated which shows a degenerate two-dimensional IV-CT.

Received: February 18, 1998 [Z11490IE]
German version: *Angew. Chem.* **1998**, *110*, 2239–2242

Keywords: amines • cyclic voltammetry • electron transfer • mixed-valent compounds • semiempirical calculations

- [1] C. Creutz, *Progr. Inorg. Chem.* **1983**, 30, 1.
- [2] *Chem. Rev.* **1992**, 92, 369. This issue is devoted to ET processes in biologically relevant systems.
- [3] M. Robin, P. Day, *Adv. Inorg. Radiochem.* **1967**, 10, 247. Robin and Day distinguish between totally independent redox centers (class I), weakly or medium coupling (valence-trapped) redox centers (class II), and strongly coupling/completely delocalized centers (class III).
- [4] a) S. F. Nelsen, R. F. Ismagilov, D. R. Powell, *J. Am. Chem. Soc.* **1996**, 118, 6313; b) *J. Am. Chem. Soc.* **1997**, 119, 10213, and references therein; c) *J. Am. Chem. Soc.* **1998**, 120, 1924.
- [5] a) J. Bonvoisin, J.-P. Launay, M. Van der Auwaraer, F. C. De Schryver, *J. Phys. Chem.* **1994**, 98, 5052; corrigendum: *J. Phys. Chem.* **1996**, 100, 18006; b) J. Bonvoisin, J.-P. Launay, W. Verbouwe, M. Van der Auwaraer, F. C. De Schryver, *J. Phys. Chem.* **1996**, 100, 17079; c) J. Bonvoisin, J.-P. Launay, C. Rovira, J. Veciana, *Angew. Chem.* **1994**, 106, 2190; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2106.
- [6] A. Knorr, J. Daub, *Angew. Chem.* **1997**, 109, 2926; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2817, and references therein.
- [7] P. M. Borsenberger, D. S. Weiss, *Organic Photoreceptors for Imaging Systems*, Marcel Dekker, New York, **1993**.
- [8] Compounds **2** and **3** have been characterized by ^1H and ^{13}C NMR spectroscopy as well as microanalysis (**2**) or high-resolution mass spectrometry (**3**). After submitting this paper we became aware of a patent describing the synthesis of a compound similar to **3**: J. Shi, C. H. Chen, S. A. Van Slyke, C. W. Tang (Eastman Kodak), US-A 5554450, **1996** [*Chem. Abstr.* **1996**, 125, 312133p].
- [9] Cyclic voltammetry has been performed with a conventional three-electrode set-up with a Pt-disk electrode and a Ag/AgCl pseudo-reference electrode in 0.1M tetrabutylammonium hexafluorophosphate/ CH_2Cl_2 . Internal standard: ferrocene (Fc/Fc^+); scan rate: 250 mV s $^{-1}$.
- [10] The CV solutions were transferred to a spectroelectrochemical cell described in: J. Salbeck, I. Auerbach, J. Daub, *DECHEMA Monogr.* **1988**, 112, 177; J. Salbeck, *J. Electroanal. Chem.* **1992**, 340, 169; J. Salbeck, *Anal. Chem.* **1993**, 65, 2169.
- [11] a) F. A. Neugebauer, S. Bamberger, W. R. Groh, *Chem. Ber.* **1975**, 108, 2406; b) W. Schmidt, E. Steckhan, *Chem. Ber.* **1980**, 113, 577. The radical bands of 2^+ and 3^+ (ca. 740 nm) are at almost the same positions as those of 2^{2+} and 3^{6+} .
- [12] AM1-CI calculations were performed using the MOPAC 93 program package (Fujitsu). The geometry of 3^{3+} (methoxy substituents were omitted for simplicity) was optimized at the UHF level as a quartet state; the geometry was restricted to D_3 symmetry. This geometry was used for an CI calculation involving three doubly and three singly occupied orbitals (parameters: C.I. = (6,3), open(3,3)).
- [13] N. S. Hush, *Coord. Chem. Rev.* **1985**, 64, 135.
- [14] C. Creutz, M. D. Newton, N. Sutin, *J. Photochem. Photobiol. A* **1994**, 82, 47.
- [15] a) R. L. Blackburn, J. T. Hupp, *J. Phys. Chem.* **1990**, 94, 1788; b) R. L. Blackburn, J. T. Hupp, *Chem. Phys. Lett.* **1988**, 150, 399.
- [16] The molar absorptivity in CH_2Cl_2 was calculated from the spectroelectrochemical data since exact stoichiometric chemical oxidation was not possible. The molar absorptivity at the highest IV-CT absorbance during oxidation refers to a concentration $c(2^+) = c(2)_0\sqrt{K_{\text{CO}}}/(2 + \sqrt{K_{\text{CO}}})$ with $K_{\text{CO}} = 236$.
- [17] Using the N–N distance for d involves major uncertainties because the charge is partially delocalized into the phenyl rings, see reference [5a].
- [18] M. J. Powers, T. J. Meyer, *J. Am. Chem. Soc.* **1978**, 100, 4393.
- [19] S. F. Nelsen, Y. Kim, S. C. Blackstock, *J. Am. Chem. Soc.* **1989**, 111, 2045.
- [20] We used the method based on AM1-UHF calculations described in S. F. Nelsen, S. C. Blackstock, Y. Kim, *J. Am. Chem. Soc.* **1987**, 109, 677.
- [21] N. Sutin, *Progr. Inorg. Chem.* **1983**, 30, 441.
- [22] The nuclear frequency factor was evaluated numerically from $g(\nu_\nu, T) = 1.17$ with $g(\nu_\nu, T) = \left[\frac{h\nu_\nu}{2k_B T} \coth \frac{h\nu_\nu}{2k_B T} \right]^{1/2}$ at 298 K; see reference [13].
- [23] Taken from S. F. Nelsen, H. Chang, J. J. Wolff, J. Adams, *J. Am. Chem. Soc.* **1993**, 115, 12276; see also reference [18].
- [24] M. E. Gress, C. Creutz, C. O. Quicksall, *Inorg. Chem.* **1981**, 20, 1522.
- [25] N. S. Hush, *Chem. Phys.* **1975**, 10, 361.
- [26] G. E. McManis, R. M. Nielson, M. J. Weaver, *Inorg. Chem.* **1988**, 27, 1827.

Hexahelicenophanes and Their Racemization**

Herbert Meier,* Manfred Schwertel, and Dieter Schollmeyer

Dedicated to Professor Alan R. Katritzky on the occasion of his 70th birthday

Helicenes represent a fascinating class of compounds that exhibit exceptional properties.^[1–4] Since the first synthesis of [6]helicene by Newman and Lednicer,^[5] this area has developed rapidly, with the parent systems at the center of interest. The number of substituted [6]helicenes described in the literature remains relatively small, and bridged [6]helicenes are almost unknown.^[3, 6–8] We have now synthesized [6]helicenes whose terminal benzene rings are linked by polymethylenedioxy chains so that the influence of the cyclophane structure on the racemization can be studied.

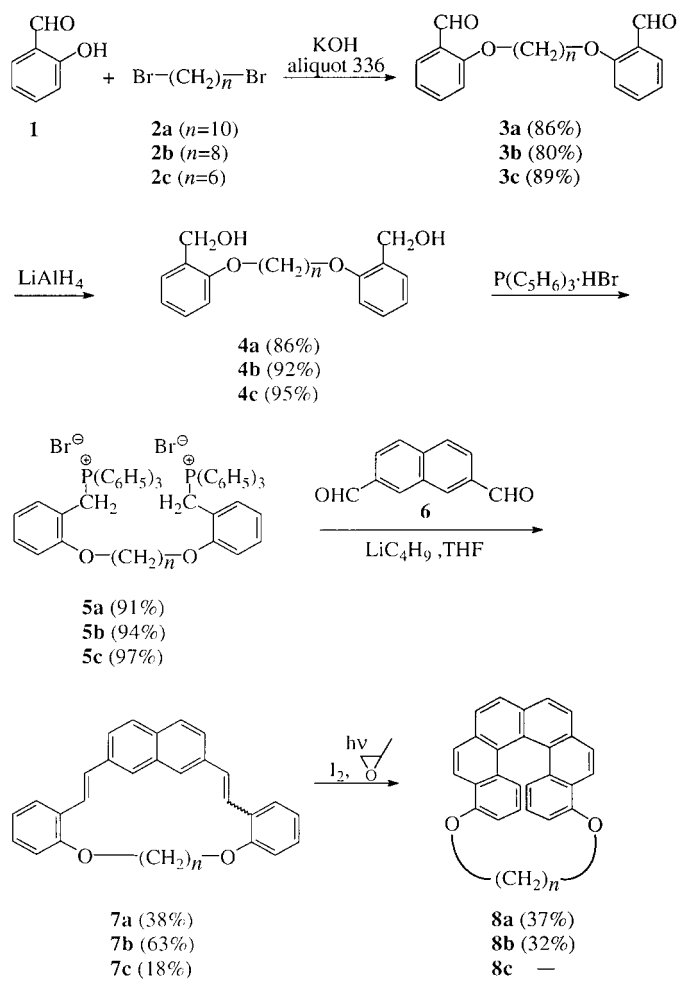
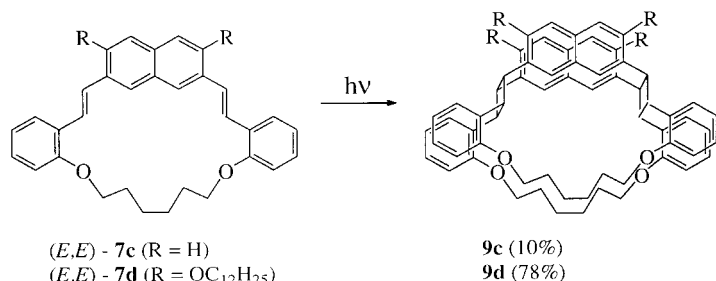
We first prepared the dialdehydes **3a–c** from salicylaldehyde (**1**) and α,ω -dibromoalkanes (**2a–c**) and then reduced them to the diols **4a–c** (Scheme 1). The transformation to the bisphosphonium salts **5a–c** and the subsequent twofold Wittig olefination, carried out in highly diluted solution with 2,7-naphthalenedicarbaldehyde (**6**), generated the macrocycles **7a–c**.^[9] The compounds **7a–c** were obtained as mixtures of *E,E* and *E,Z* isomers; however, the configuration does not play a role in the subsequent oxidative photocyclization. (The *E,Z* ratio from the cyclization process **5** + **6** $\rightarrow$ **7** decreases with decreasing chain length from 33% for **7a**, to 20% for **7b**, and almost 0% for **7c**). The twofold photocyclization in the presence of methyloxirane with iodine as an oxidizing agent^[10] yielded the bridged [6]helicenes **8a** and **8b**.^[11] In **7c** the short polymethylenedioxy chain did not permit the formation of the corresponding helicene.

Even in high dilution photodimerization of **7c** dominated completely and a totally different type of cyclophane **9c** was formed (Scheme 2). To enable a better investigation of the latter reaction, we improved the solubility of the cyclophane by the introduction of two dodecyloxy groups and optimized the reaction conditions for the photodimerization. Cyclophane **9d**^[12] was then obtained from **7d** in high yields. The dimerization reaction was also observed in competition to the photocyclization of **7b**, but to a smaller extent, while the dimerization of **7a** did not occur.

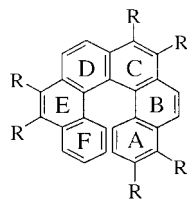
It was possible to enrich the enantiomers of **8a** and **8b** by chromatography on silica gel doped with the Newman reagent (*R*)-(–)-2-(2,4,5,7-tetranitro-9-fluorenylideneaminoxy)propionic acid ((*R*)-(–)-TAPA).^[13] The (*M*)-(–)-configuration forms weaker complexes with (*R*)-(–)-TAPA and was eluted first. The first-order kinetics for the racemization were determined by the measurement of the optical rotation $[\alpha]_D$ in 1,2,4-trichlorobenzene. Linear regression led to determination of the rate constant k_{rac} and the half-life $t_{1/2} = k_{\text{rac}}^{-1} \times$

[*] Prof. Dr. H. Meier, Dr. M. Schwertel, Dr. D. Schollmeyer
Institut für Organische Chemie der Universität
J. J. Becherweg 18–22, D-55099 Mainz (Germany)
Fax: (+49) 6131-395396
E-mail: hmeier@mail.uni-mainz.de

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


 Scheme 1. Synthesis of the hexahelicenophanes **8a** and **8b**.

 Scheme 2. Photodimerization of **7c** and **7d**.

In 2. The rate constants for the racemization reactions were determined at constant temperatures of 200, 180, 160, 150, 140, 130, and 120 °C, and by application of the Arrhenius equation, $\ln k_{\text{rac}} = f(1/T)$, the activation energy E_a could be calculated. In an analogous manner, application of the Eyring



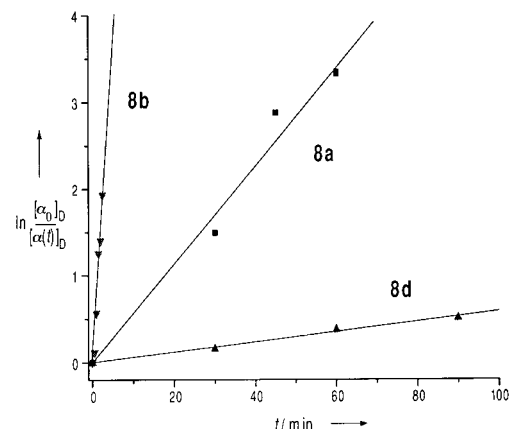
equation gave the $\Delta G^\ddagger$ values. Table 1 summarizes these parameters together with the results for $\Delta H^\ddagger$ and $\Delta S^\ddagger$. For comparison the data for the racemization of the unsubstituted [6]helicene **8d** were determined under the same conditions.

Figure 1 demonstrates impressively the influence of the bridges on the rate

 Table 1. Kinetic parameters for the racemization of the [6]helicenes **8a**, **8b**, and **8d** in 1,2,4 trichlorobenzene.^[a]

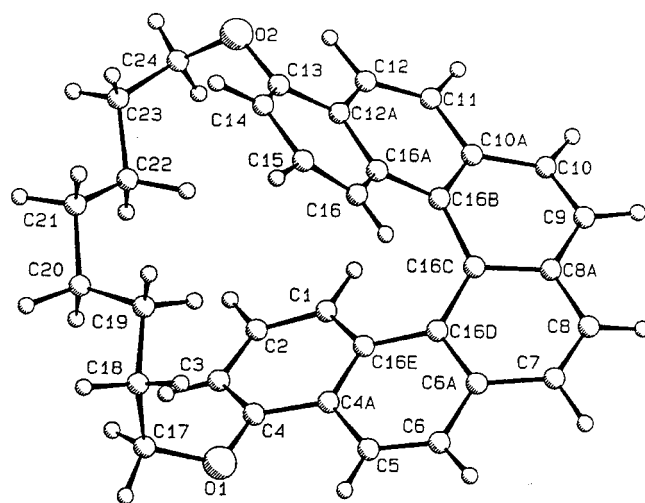
Compd	E_a [kJ mol ⁻¹]	$\ln A$	$\Delta G^\ddagger$ [kJ mol ⁻¹]	$\Delta H^\ddagger$ [kJ mol ⁻¹]	$\Delta S^\ddagger$ [J K ⁻¹ mol ⁻¹]	$t_{1/2}$ [min]
8d ^[14, 15]	148.1	27.9	156.3	144.2	-25.6	106
8a	143.7	29.0	147.7	139.8	-16.7	12
8b	116.7	24.7	137.3	112.8	-51.8	0.8

[a] The values for $\Delta G^\ddagger$, $\Delta H^\ddagger$, $\Delta S^\ddagger$, and $t_{1/2}$ refer to the reaction at 200 °C. The relative error in the determination of the parameters is $\pm 6\%$, but for $\Delta S^\ddagger$ it can be somewhat higher.


 Figure 1. Rate of racemization of the helicenophanes **8a** and **8b** in 1,2,3-trichlorobenzene at 200 °C relative to that of [6]helicene **8d**.

of racemization; k_{rac} increases drastically with chain length. However, this effect is not representative for alkoxy-substituted [6]helicenes; compound **8e** has a half-life $t_{1/2}$ which is more than twice as long as that of the unsubstituted **8d** under the conditions mentioned above.^[16] Normally, alkoxy substituents decelerate the racemization, and the acceleration for **8a** and **8b** is therefore a result of the cyclophane structure!

To interpret this unexpected effect, we performed an X-ray analysis of **8a** and **8b** (Figure 2). The helical structure of the compounds **8** becomes apparent from the increasing twist


 Figure 2. Molecular structure of (M)-(-)-**8b** in the solid state. The angles between neighboring planes of the benzene rings A–F (values for [6]helicene^[18] are given in parentheses) are: AB: 12.9° (9.8°); BC: 11.4° (15.2°); CD: 16.2° (14.4°); DE: 17.7° (15.2°); EF: 14.6° (11.5°).

angles along the (averaged) ring planes. The polymethylenedioxy chains clip the terminal benzene rings A and F together in such a way that the centers of the bridges lie on the (formal) C_2 axis. Due to crystal effects there are considerable deviations from C_2 symmetry. This statement is also valid for **8a**, whose crystal structure analysis gave very similar data.^[16]

The symmetry of the helices changes during the racemization from C_2 in the ground state to C_s in the transition state. This mechanism is in agreement with recent semi-empirical and ab initio quantum-mechanical calculations. The experimental $\Delta H^\ddagger$ values of [6]helicenes are reproduced best by the AM1 method.^[19, 20] Figure 2 shows the strong steric interference of the polymethylenedioxy chains with the terminal rings A and F, especially in the range of the carbon atoms C-3 and C-14. This effect increases the energy of the C_2 ground states and is more pronounced for the shorter chain in **8b** than for the longer chain in **8a**. Figure 3 shows schematically that the bridge can turn aside into the C_s transition state,^[21] thus decreasing the energy of the steric interaction.

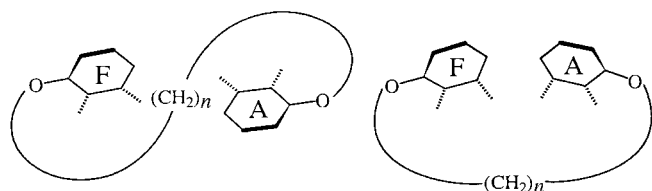


Figure 3. Schematic representation of the bridges between the terminal rings A and F in the C_2 -symmetric ground state (left) and the C_s -symmetric transition state (right) of the racemization of **8a** and **8b**.

The drastic lowering of the racemization barrier in going from **8d** to **8a** to **8b** is due to the differences between the steric energies (included in the enthalpy term) of the ground and transition states of the cyclophanes. Moreover, the high negative activation entropy $\Delta S^\ddagger$ of **8b** should be noted. The shorter bridge is less flexible and has a lower probability for the turn.

Received: February 4, 1998 [Z114371E]

German version: *Angew. Chem.* **1998**, *110*, 2224–2226

Keywords: cyclophanes • helical structures • kinetics • racemization

- 2H), 7.76 (d, 2H), 7.88 (s, 2H) (aromatic H); ^{13}C NMR (CDCl_3): δ = 27.2, 29.8, 30.2, 30.2 (CH_2), 68.1 (OCH_2), 125.2, 128.8 (olefinic CH), 111.7, 120.5, 124.6, 125.4, 127.9, 128.5, 130.2 (aromatic CH), 126.0, 132.5, 134.0, 136.1, 156.9 (aromatic C_q); **7b**: M.p. 266 °C; *E,E* configuration: ^1H NMR (CDCl_3): δ = 1.61 (m, 4H, CH_2), 1.87 (m, 4H, CH_2), 1.91 (m, 4H, CH_2), 4.03 (t, 4H, OCH_2), 7.33 (AB, ^3J = 16.6 Hz, 2H, olefinic H), 7.74 (AB, ^3J = 16.6 Hz, 2H, olefinic H), 6.86 (d, 2H), 6.96 (t, 2H), 7.22 (t, 2H), 7.45 (d, 2H), 7.64 (d, 2H), 7.75 (d, 2H), 8.08 (s, 2H) (aromatic H); the ^{13}C NMR data correspond largely to that of **7a**. **7c**: M.p. 260 °C, pure *E,E* configuration, ^1H NMR (CDCl_3): δ = 1.89 (m, 4H, CH_2), 2.00 (m, 4H, CH_2), 4.04 (t, 4H, OCH_2), 7.14 (AB, ^3J = 16.5 Hz, 4H), 8.01 (AB, ^3J = 16.5 Hz, 4H) (olefinic H), 6.91 (d, 2H), 6.99 (t, 2H), 7.24 (t, 2H), 7.37 (d, 2H), 7.70 (d, 2H), 7.74 (d, 2H), 8.29 (s, 2H) (aromatic H); the ^{13}C NMR data correspond largely to that of **7a**.
- [10] L. Liu, B. Yang, T. J. Katz, M. K. Pointdexter, *J. Org. Chem.* **1991**, *56*, 3769–3775.
- [11] **8a**: M.p. 252 °C; ^1H NMR (CDCl_3): δ = 1.41 (m, 12H, CH_2), 1.67 (m, 2H, CH_2), 1.99 (m, 2H, CH_2), 4.33 (m, 2H, OCH_2), 4.50 (m, 2H, OCH_2), 6.48 (t, 2H, 2-H), 6.64 (d, 2H, 3-H), 6.90 (d, 2H, 1-H), 7.85 (d, 2H, 6-H), 7.92 (d, 2H, 7-H), 7.97 (d, 2H, 8-H), 8.32 (d, 2H, 5-H); ^{13}C NMR (CDCl_3): δ = 25.0, 28.9, 29.0, 29.1 (CH_2), 67.0 (OCH_2), 107.2 (C-3), 120.7 (C-1), 121.5 (C-5), 123.8 (C-4a), 123.9 (C-2), 124.5 (C-16c), 124.8 (C-6), 126.4 (C-8), 126.6 (C-7), 127.7 (C-16b), 130.8 (C-16a), 131.9 (C-6a), 132.6 (C-8a), 153.9 (C-4); FD-MS: m/z (%) = 498 (100) [M^+]. **8b**: M.p. 243 °C; ^1H NMR (CDCl_3): δ = 1.12 (m, 4H, CH_2), 1.31 (m, 4H, CH_2), 1.70 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 4.23 (m, 2H, OCH_2), 4.56 (m, 2H, OCH_2), 6.48 (t, 2H, 2-H), 6.70 (m, 4H, 1-H, 3-H), 7.82 (d, 2H, 6-H), 7.90 (d, 2H, 7-H), 7.95 (d, 2H, 8-H), 8.20 (d, 2H, 5-H); the ^{13}C NMR data correspond largely to that of **8a**; FD-MS: m/z (%) = 470 (100) [M^+].
- [12] **9d**: M.p. 225 °C; ^1H NMR (CDCl_3): δ = 0.89 (t, 12H, CH_3), 1.29–2.16 (m, 96H, CH_2), 3.69 (t, 8H, OCH_2), 3.77 (t, 8H, OCH_2), 4.96 (AA'BB', 8H), 5.24 (AA'BB', 8H) (CH, four-membered ring), 6.21 (s, 4H), 6.64 (d, 4H), 6.82 (t, 4H), 7.06 (t, 4H), 7.31 (d, 4H), 7.80 (s, 4H) (aromatic H); ^{13}C NMR (CDCl_3): δ = 14.2–32.0 (CH_2), 68.1, 68.2 (OCH_2), 37.5, 41.5 (CH, four-membered ring), 103.6, 110.7, 119.5, 126.5, 128.0, 130.1 (aromatic CH), 124.4, 126.4, 130.7, 133.1, 155.7, 157.0 (aromatic C_q); FD-MS: m/z (%) = 1630 (33) [M^+], 815 (100) [M^{2+}]. The less soluble compound **9c** gives corresponding ^1H NMR and MS data.
- [13] See F. Mikeš, G. Boshart, E. Gil-Av, *J. Chromatogr.* **1997**, *122*, 205–221, and references therein.
- [14] In naphthalene the parameters $\Delta G^\ddagger$ = 154.7 kJ mol $^{-1}$, $\Delta S^\ddagger$ = –28.0 J mol $^{-1}$ K $^{-1}$, and $\Delta H^\ddagger$ = 141.3 kJ mol $^{-1}$ (T = 205 °C) were determined.^[15]
- [15] R. H. Martin, M. J. Marchant, *Tetrahedron Lett.* **1972**, *13*, 3707–3708; R. H. Martin and M. J. Marchant, *Tetrahedron* **1974**, *30*, 347–349.
- [16] M. Schwertel, Dissertation, Universität Mainz **1997**.
- [17] Crystal structure of **8b**: Enraf-Nonius CAD4 diffractometer, $\text{Cu}_K\alpha$ radiation: λ = 154 pm, T = 22 °C, scan-type $\omega/2\theta$, scan range $1.5 \leq \theta \leq 75.0^\circ$, $0 \leq h \leq 22$, $0 \leq k \leq 15$, $0 \leq l \leq 13$, reflections: measured 4962, unique 4962 (R_{sigma} = 0.0178), observed 4855 ($|F|/|F| > 4.0$), Lorentz and polarization correction, structure solution: SIR-92, refinement: SHELXL-93, 348 refined parameters, weighting scheme: $W = 1/[\sigma^2 F_o^2 + (0.0860 P)^2 + 0.32 P]$ with $P = (\text{Max}(F_o^2, 0) + 2 F_c^2)/3$, hydrogen atoms were located from difference Fourier maps and refined isotropically assuming riding motion, other atoms were refined anisotropically; ωR_2 = 0.1229 (R^1 = 0.0423 for observed reflections, 0.0431 for all reflections), goodness of fit S = 1.032, extinction g = 0.0050(4), largest peak in difference Fourier synthesis –0.18, 0.33 e Å $^{-3}$, $\text{C}_{34}\text{H}_{30}\text{O}_2$, M_r = 470.58, orthorhombic, space group $Pna2_1$, a = 18.1447(4), b = 12.3799(3), c = 10.8228(3) Å, V = 2431.1(1) Å ^{3} , Z = 4, $F(000)$ = 1000, ρ_{calcd} = 1.286 g cm $^{-3}$, crystal dimensions: 0.320 × 0.512 × 0.512 mm ^{3} . Crystallographic data (without structure factors) for the structures reported in this publication have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-408279. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [18] C. de Rango, G. Tsoucaris, J. P. Declercq, G. Germain, J. P. Putzeys, *Cryst. Struct. Commun.* **1973**, *2*, 189–192; J. Navaza, G. Tsoucaris, G.

Le Bas, A. Navaza, C. de Rango, *Bull. Soc. Chim. Belg.* **1979**, 88, 863–870.

[19] S. Grimme, S. D. Peyerimhoff, *Chem. Phys.* **1996**, 204, 411–417.

[20] R. H. Janke, G. Haupe, E.-U. Würthwein, J. H. Borkent, *J. Am. Chem. Soc.* **1996**, 118, 6031–6035.

[21] Force field calculations (PC Model 4.0, Serena Software)^[16] are in accordance with models.

Nonclassical Metal Carbonyls: Appropriate Definitions with a Theoretical Justification**

Anthony J. Lupinetti, Gernot Frenking*, and Steven H. Strauss*

There is a growing class of metal carbonyl compounds with unusually high $\bar{\nu}(\text{CO})$ values.^[1–5] Examples are (average values for $\bar{\nu}(\text{CO})$ in parentheses; for free CO: $\bar{\nu}(\text{CO}) = 2143 \text{ cm}^{-1}$) $[\text{Cu}(\text{CO})_2][\text{AsF}_6]$ (2171 cm^{-1}),^[6] $[\text{Ag}(\text{CO})_2][\text{Nb}(\text{OTeF}_5)_6]$ (2208 cm^{-1}),^[7] $[\text{Au}(\text{CO})_2][\text{Sb}_2\text{F}_{11}]$ (2236 cm^{-1}),^[8] $[\text{Hg}(\text{CO})_2][\text{Sb}_2\text{F}_{11}]_2$ (2280 cm^{-1}),^[9] and $[\text{Ir}(\text{CO})_6][\text{Sb}_2\text{F}_{11}]_3$ (2268 cm^{-1}).^[10] There is a consensus that these and other high $\bar{\nu}(\text{CO})$ values are due to greatly diminished π backbonding for late transition metal $[\text{M}(\text{CO})_n]^{m+}$ species.^[2–5, 11–20] For the vast majority of metal carbonyl complexes (i.e., *classical* metal carbonyl complexes), the effect of π backbonding to lower $\bar{\nu}(\text{CO})$ below 2143 cm^{-1} more than compensates for the factors that tend to raise $\bar{\nu}(\text{CO})$ above 2143 cm^{-1} , such as σ bonding and/or the positive charge on the metal center.^[2–5] Nevertheless, a $\bar{\nu}(\text{CO})$ value greater than 2143 cm^{-1} can occur for two distinguishable situations: 1) negligible or relatively minor $\text{M} \rightarrow \text{CO}$ π backbonding (i.e., *nonclassical* behavior) or 2) π backbonding that is *significant* (i.e., *classical* behavior) but *insufficient* to lower $\bar{\nu}(\text{CO})$ below 2143 cm^{-1} .^[2] The two situations are illustrated in Figure 1,^[2] which was adapted from theoretical results in the literature.^[19, 20]

According to this model, two different complexes with different bonding characteristics can have the same unusually high $\bar{\nu}(\text{CO})$ value. A related distinction between classical and nonclassical behavior, based on new theoretical results, will be discussed below. Nevertheless, it is often convenient to use a definition based on a simple experimental observable, so that the experimentalist can decide in “real time” whether to further modify a new metal complex for a particular application. Therefore, some workers have referred to *all*

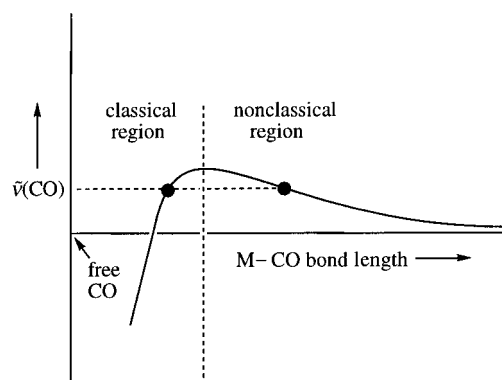


Figure 1. Separation of classical and nonclassical metal carbonyls based on their position relative to the $\bar{\nu}(\text{CO})$ vs. $\text{M}-\text{C}$ curve maximum. The circles represent equilibrium geometries for a hypothetical classical metal carbonyl (left circle, $\partial(\bar{\nu}(\text{CO}))/\partial((\text{M}-\text{C})) > 0$) and for a hypothetical nonclassical metal carbonyl (right circle, $\partial(\bar{\nu}(\text{CO}))/\partial((\text{M}-\text{C})) < 0$). Note that both complexes have the same $\bar{\nu}(\text{CO})$ value, which is greater than 2143 cm^{-1} . The difference in $\text{M}-\text{C}$ values for the two complexes is not to scale.

metal carbonyl complexes with $\bar{\nu}(\text{CO})_{\text{av}} > 2143 \text{ cm}^{-1}$ as nonclassical, a definition that can be simply applied once vibrational spectra of a new compound are recorded ($\bar{\nu}(\text{CO})_{\text{av}}$ is the average over all $\text{C}-\text{O}$ stretching normal modes, weighted according to their degeneracies).

Aubke, Willner, and co-workers have recently argued that “as smooth correlations between the formal charge on the metal and the bonding characteristics in the CO ligands emerge, it becomes increasingly obvious that any arbitrary subdivision using vague terms like “classical” and “nonclassical (σ -only)” carbonyl complexes as proposed sometime ago for the thermally unstable $[\text{Ag}(\text{CO})_n]^+$ ($n = 1, 2$) species is incorrect, inappropriate, and unnecessary. The first metal carbonyl derivative $[\text{Pt}(\text{CO})_2\text{Cl}_2]$ reported in 1868 with an average $\bar{\nu}_{\text{CO}}$ value of 2175 cm^{-1} [well above that (2143 cm^{-1}) for free CO] would be assigned “nonclassical,” which is in our view absurd.”^[10] It is historically ironic, but hardly absurd, that the very first carbonyl complex has an average $\bar{\nu}(\text{CO})$ value higher than that of free CO, while more than 95 % of the metal carbonyls which were subsequently studied have average $\bar{\nu}(\text{CO})$ values less than 2143 cm^{-1} . Since the ordering of metal carbonyls as classical or nonclassical is not a historical classification, it is irrelevant if the first carbonyl complex ever synthesized belongs to one or the other category.

Herein we present computational evidence that the metal–carbon bonds in the d^{10} $D_{\infty h}$ dicarbonyl species $[\text{Rh}(\text{CO})_2]^-$, $[\text{Pd}(\text{CO})_2]$, $[\text{Cu}(\text{CO})_2]^+$, and $[\text{Au}(\text{CO})_2]^+$ are fundamentally different than the metal–carbon bonds in the isoelectronic, isoleptic, and isostructural species $[\text{Ag}(\text{CO})_2]^+$, $[\text{Zn}(\text{CO})_2]^{2+}$, $[\text{Cd}(\text{CO})_2]^{2+}$, and $[\text{Hg}(\text{CO})_2]^{2+}$. Based on this fundamental difference, two categories of metal carbonyls are clearly warranted (no matter what they are called). It is our hope that the distinction we now report will cause chemists to think in new ways and, most importantly, to discover new chemistry. Note that there is spectroscopic and/or structural data for four of the eight $D_{\infty h}$ dicarbonyl species we have studied: $[\text{Cu}(\text{CO})_2]^+$,^[6] $[\text{Ag}(\text{CO})_2]^+$,^[7] $[\text{Au}(\text{CO})_2]^+$,^[8] and $[\text{Hg}(\text{CO})_2]^{2+}$.^[9]

[*] Prof. Dr. G. Frenking
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
Fax: (+49) 6421-282-189
E-mail: Frenking@ps1515.chemie.uni-marburg.de
Prof. S. H. Strauss, A. J. Lupinetti
Department of Chemistry, Colorado State University
Fort Collins, CO 80523 (USA)
Fax: (+1) 970-491-1801
E-mail: Strauss@chem.colostate.edu

[**] This work was supported by the U.S. NSF (CHE-9628769), the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. We acknowledge the excellent service and generous allotment of computer time of the HRZ Marburg.

Our approach was to monitor the effect of two F[−] ions placed 3 Å away from the metal centers of the dicarbonyl complexes listed above. The pair of F[−] ions was added to each D_{∞h} [M(CO)₂]ⁿ complex so that the M⋯F[−] vectors were orthogonal to the M–C vectors, and the entire [M(CO)₂(F)₂]^{n−2} fragment was planar (D_{2h} symmetry; Figure 2). The hard base F[−] was selected to model the weak

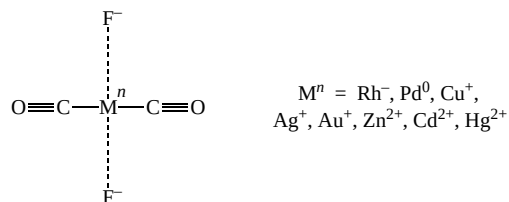


Figure 2. Calculated geometry for the D_{2h}-symmetric complexes [M(CO)₂(F)₂]^{n−2}.

M⋯F[−] interactions that exist in crystals of [Ag(CO)₂][B(OTeF₅)₄]^[7, 21] and [Hg(CO)₂][Sb₂F₁₁]₂^[9] and that are presumed to exist in other late transition metal dicarbonyl species such as [Cu(CO)₂][AsF₆][−] and [Au(CO)₂][Sb₂F₁₁]₂[−]. Note that one of the three unique [Ag(CO)₂]⁺ ions in [Ag(CO)₂][B(OTeF₅)₄] interacts with two fluorine atoms from different B(OTeF₅)₄[−] ions such that the centrosymmetric [Ag(CO)₂(F)₂] moiety is planar with an Ag⋯F distance of 3.02(1) Å and an F–Ag–C angle of 70.4(9)° (the sum of van der Waals radii for silver and fluorine is about 3.2 Å).^[7, 21] It does not matter that some of the [M(CO)₂(F)₂] moieties in this study are unknown species at the time of this writing; our objective was to create a set of homologous [M(CO)₂]ⁿ and [M(CO)₂(F)₂]^{n−2} complexes and to study the effect of changing the metal on the M–C and C–O bond lengths.

The geometry optimizations and frequency calculations were carried out in the gas phase at the MP2 level of theory. For each metal atom, the quasi-relativistic, small-core, effective-core potential (ECP) developed by Stoll and Preuss with a (311111/22111/411) valence shell basis set was used.^[22, 23] A 6-31G(d) basis set was used for C, O, and F atoms. The calculations were carried out using the program package Gaussian 94.^[24] All bond lengths were optimized except for the M⋯F[−] distances, which were fixed at either 3 Å or ∞ (for infinite M⋯F[−] distances the fluoride-free [M(CO)₂]ⁿ species were studied). The M⋯F[−] distances were intentionally fixed at exactly 3 Å for all of the [M(CO)₂(F)₂]^{n−2} species so that all of the [M(CO)₂]ⁿ species would be subject to the same perturbation by the two F[−] ions. It was not our intention to calculate the equilibrium M⋯F[−] distances for the different complexes.

The calculated bond lengths and wavenumbers are listed in Table 1, the changes in the C–O and M–C bond lengths in Table 2. The C–O bond length increased in all cases when the two F[−] ions were added to the metal dicarbonyl complexes. However, the same ligand-field perturbation *decreased* the M–C bond length for [Rh(CO)₂][−], [Pd(CO)₂], [Cu(CO)₂]⁺,

Table 1. Calculated distances and symmetric carbon–oxygen stretching frequencies for D_{2h} [M(CO)₂(F)₂]^{n−2} species.^[a]

M	M–F [Å]	M–C [Å]	C–O [Å]	$\tilde{\nu}_{\text{sym}}(\text{CO})$ [cm ^{−1}]
Rh [−]	∞	1.901	1.182	2019
Rh [−]	3	1.797	1.241	1817
Pd ⁰	∞	1.942	1.156	2112
Pd ⁰	3	1.924	1.167	2046
Cu ⁺	∞	1.884	1.142	2196
Cu ⁺	3	1.850	1.148	2164
Ag ⁺	∞	2.160	1.142	2184
Ag ⁺	3	2.196	1.147	2152
Au ⁺	∞	2.007	1.142	2201
Au ⁺	3	1.983	1.148	2164
Zn ²⁺	∞	2.011	1.140	2187
Zn ²⁺	3	2.046	1.142	2182
Cd ²⁺	∞	2.228	1.140	2185
Cd ²⁺	3	2.365	1.143	2176
Hg ²⁺	∞	2.126	1.139	2195
Hg ²⁺	3	2.725	1.148	2138

[a] Calculated values of the free CO molecule: $\tilde{\nu}_{\text{sym}}(\text{CO}) = 2118 \text{ cm}^{-1}$, C–O = 1.151 Å.

Table 2. Summary of the results of the calculations on [M(CO)₂]ⁿ and [M(CO)₂(F)₂]^{n−2}.^[a]

Group 9	Group 10	Group 11	Group 12
		Cu ⁺	Zn ²⁺
		Δ(C–O) = 0.006 Å	Δ(C–O) = 0.002 Å
		Δ(M–C) = −0.034 Å	Δ(M–C) = 0.035 Å
Rh [−]	Pd ⁰	Ag ⁺	Cd ²⁺
Δ(C–O) = 0.059 Å	Δ(C–O) = 0.011 Å	Δ(C–O) = 0.005 Å	Δ(C–O) = 0.003 Å
Δ(M–C) = −0.104 Å	Δ(M–C) = −0.018 Å	Δ(M–C) = 0.036 Å	Δ(M–C) = 0.136 Å
		Au ⁺	Hg ²⁺
		Δ(C–O) = 0.006 Å	Δ(C–O) = 0.009 Å
		Δ(M–C) = −0.024 Å	Δ(M–C) = 0.599 Å

[a] Δ(C–O) and Δ(M–C) are the differences of the C–O and M–C bond lengths between [M(CO)₂(F)₂]^{n−2} (M⋯F[−] = 3 Å) and [M(CO)₂]ⁿ (M⋯F[−] = ∞).

and [Au(CO)₂]⁺ but *increased* the M–C bond length for the other four complexes. The decreases in M–C bond lengths for the rhodium(−I), palladium(0), copper(I), and gold(I) complexes are indicative of metal carbonyl complexes with significant π backbonding. The presence of the F[−] ions leads to a less positive (or more negative) effective charge on the metal centers, which should weaken the M←CO σ bonds (as well as decrease the M⋯CO electrostatic attraction^[20]) but should strengthen the M→CO π bonds (i.e., the F[−] ions induce a significant amount of *additional* π backbonding between the metal ion and the CO ligands). The decrease in the M–C distance strongly suggests that the M–CO bonds in the species [Rh(CO)₂(F)₂]^{3−}, [Pd(CO)₂(F)₂]^{2−}, [Cu(CO)₂(F)₂][−], and [Au(CO)₂(F)₂][−] are *stronger* than in the parent dicarbonyl complexes [Rh(CO)₂][−], [Pd(CO)₂], [Cu(CO)₂]⁺, and [Au(CO)₂]⁺, respectively. Therefore, for these four d¹⁰ metal dicarbonyl complexes, the fluoride-ion perturbation resulted in an increase in M→CO π backbonding that more than offset the decrease in M←CO σ bonding or the change in the M⋯CO electrostatic interaction.

In contrast, the M–C bond lengths for the silver(I), zinc(II), cadmium(II), and mercury(II) species *increased* as the M⋯F distance decreased from ∞ to 3 Å, indicating that the M–C bonds in these [M(CO)₂(F)₂]^{n−2} species are probably *weaker* than in the corresponding parent dicarbonyl cations. As

above, the presence of the F^- ions lowered the effective charge on the Ag^+ , Zn^{2+} , Cd^{2+} , and Hg^{2+} ions. However, for these metal ions the increase in π backbonding, if any, did not offset the weakening of the $M \leftarrow CO$ σ bonds. Therefore, the set of eight parent dicarbonyl complexes $[M(CO)_2]^n$ in Table 2 should be divided into two distinct categories depending on whether $\Delta(M-C)$ is negative (classical behavior; Rh^- , Pd^0 , Cu^+ , and Au^+) or positive (nonclassical behavior; Ag^+ , Zn^{2+} , Cd^{2+} , and Hg^{2+}).

Let us compare the related complexes $[Cu(CO)_2]^+$ and $[Ag(CO)_2]^+$ with and without the pair of F^- ions at 3 Å. In the case of the copper(i) complex, $\Delta(C-O) = 1.148 \text{ Å} - 1.142 \text{ Å} = 0.006 \text{ Å}$ and $\Delta(M-C) = 1.850 \text{ Å} - 1.884 \text{ Å} = -0.034 \text{ Å}$; in the case of the silver(i) complex, $\Delta(C-O) = 1.147 \text{ Å} - 1.142 \text{ Å} = 0.005 \text{ Å}$ and $\Delta(M-C) = 2.196 \text{ Å} - 2.160 \text{ Å} = 0.036 \text{ Å}$. The virtual equivalence of the $\Delta(C-O)$ values for these two systems provides no clue that the metal-carbon bonds respond so differently to the same chemical perturbation. Based on the $\Delta(M-C)$ values, it certainly seems appropriate to place the parent complexes in different categories, classical for $[Cu(CO)_2]^+$ and nonclassical for $[Ag(CO)_2]^+$. Note that $[Cu(CO)_2]^+$ is classical by the $\Delta(M-C)$ definition even though the calculated value of $\tilde{\nu}_{sym}(CO)$, at 2195 cm^{-1} , is much higher than the calculated value for free CO, 2118 cm^{-1} (the experimental values for $\tilde{\nu}_{sym}(CO)$ and $\tilde{\nu}_{asym}(CO)$ for $[Cu(CO)_2][AsF_6]$ are 2177 and 2164 cm^{-1} , respectively^[6]). This observation provides additional justification for the concept shown graphically in Figure 1.

It is important to note that our results should only be used to interpret the magnitude of *changes* in the amounts of σ and π bonding for a given system, not the absolute amounts of σ and π bonding in a given complex. The fact that $\Delta(M-C)$ is negative for $[Cu(CO)_2]^+$ and positive for $[Ag(CO)_2]^+$ means that these two complexes should be categorized as classical and nonclassical metal carbonyl complexes, respectively. Our results do not indicate that there is zero π backbonding in $[Ag(CO)_2]^+$, only that charge and σ effects outweigh any π effects. The behavior of $[Cu(CO)_2]^+$ (classical) and $[Ag(CO)_2]^+$ (nonclassical), as probed by the fluoride-ion perturbation, is consistent with other theoretical^[20] and experimental^[25] results.

Finally, let us compare the four d^{10} complexes of the fifth period $[Rh(CO)_2]^-$, $[Pd(CO)_2]$, $[Ag(CO)_2]^+$, and $[Cd(CO)_2]^{2+}$. The monotonic trends in the C–O distances at $M \cdots F = \infty$ (1.182, 1.156, 1.142, and 1.140 Å, respectively), $\tilde{\nu}_{sym}(CO)$ at $M \cdots F = \infty$ (2019, 2112, 2184, and 2185 cm^{-1} , respectively), $\Delta(C-O)$ (0.059, 0.011, 0.005, and 0.003 Å , respectively), and $\Delta\tilde{\nu}_{sym}(CO)$ (–202, –66, –32, and -9 cm^{-1} , respectively) mask the more significant result that $\Delta(M-C)$ is *negative* for $[Rh(CO)_2]^-$ and $[Pd(CO)_2]$ but *positive* for $[Ag(CO)_2]^+$ and $[Cd(CO)_2]^{2+}$. The “smooth correlation” in the C–O bond lengths and $\tilde{\nu}(CO)$ values is smooth only because weakening the $M \leftarrow CO$ σ bond and strengthening the $M \rightarrow CO$ π bond *both* cause the C–O distance to increase and $\tilde{\nu}(CO)$ to decrease regardless of whether the complex is classical or nonclassical.

The distinction between classical and nonclassical metal carbonyls based on $\Delta(M-C)$ is unequivocal, nonarbitrary, and chemically relevant. In the former category, the change in

$M \rightarrow CO$ π backbonding due to the fluoride-ion perturbation has a larger effect on the $M-C$ bond than the offsetting but less significant change in $M \leftarrow CO$ σ bonding or the change in the ionic component of the $M-CO$ bond. In the latter category, the opposite is true. However, this appropriate definition will be difficult (at least) for the experimentalist to apply routinely. For this very important practical reason, neither we nor other chemists should object to the continued use of the definition that nonclassical metal carbonyls exhibit $\tilde{\nu}(CO)_{av} > 2143 \text{ cm}^{-1}$. The $\tilde{\nu}(CO)$ definition, although arbitrary and equivocal, is appropriate in a very important way. A $\tilde{\nu}(CO)_{av}$ value $> 2143 \text{ cm}^{-1}$ should put the chemist on alert that the compound under study deserves very careful scrutiny; if nothing else, it is “in the range” where unusual (i.e., not usual = not classical = nonclassical) behavior such as $\Delta(M-C) > 0$ can occur.

Other definitions^[2] of “nonclassical metal carbonyl” can and undoubtedly will be conceived and tested by other researchers. It is expected that further experimental and theoretical work will lead to new surprises, new insights, and new debates about the metal-carbon bonds in metal carbonyls with $\tilde{\nu}(CO)_{av}$ values $> 2143 \text{ cm}^{-1}$.

Received: November 3, 1997 [Z11114IE]
German version: *Angew. Chem.* **1998**, *110*, 2229–2232

Keywords: ab initio calculations • carbonyl complexes • pi interactions • transition metals

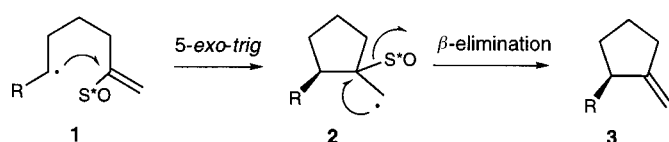
- [1] F. Aubke, *Abstract INORG-205, 215th American Chemical Society National Meeting*, Dallas, TX, 1998.
- [2] S. H. Strauss, *Chemtracts:Inorg. Chem.* **1997**, *10*, 77–103.
- [3] J. E. Ellis, W. Beck, *Angew. Chem.* **1995**, *107*, 2695–2697; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2489–2491.
- [4] L. Weber, *Angew. Chem.* **1994**, *106*, 1131–1133; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1077–1078.
- [5] F. Aubke, C. Wang, *Coord. Chem. Rev.* **1994**, *137*, 483–524.
- [6] J. J. Rack, J. D. Webb, S. H. Strauss, *Inorg. Chem.* **1996**, *35*, 277–278.
- [7] P. K. Hurlburt, J. J. Rack, J. S. Luck, S. F. Dec, J. D. Webb, O. P. Anderson, S. H. Strauss, *J. Am. Chem. Soc.* **1994**, *116*, 10003–10014.
- [8] H. Willner, J. Schaeb, G. Hwang, F. Mistry, R. Jones, J. Trotter, F. Aubke, *J. Am. Chem. Soc.* **1992**, *114*, 8972–8980.
- [9] H. Willner, M. Bodenbinder, C. Wang, F. Aubke, *J. Chem. Soc. Chem. Commun.* **1994**, 1189–1190.
- [10] C. Bach, H. Willner, C. Wang, S. J. Rettig, J. Trotter, F. Aubke, *Angew. Chem.* **1996**, *108*, 2104–2106; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1974–1976.
- [11] C. D. Desjardins, D. B. Edwards, J. Passmore, *Can. J. Chem.* **1979**, *57*, 2714–2715.
- [12] M. Pasquali, C. Floriani, A. Gaetani-Manfredotti, *Inorg. Chem.* **1981**, *20*, 3382–3388.
- [13] F. Calderazzo, *J. Organomet. Chem.* **1990**, *400*, 303–320.
- [14] L. A. Barnes, M. Rosi, C. W. Bauschlicher, *J. Chem. Phys.* **1990**, *93*, 609–624.
- [15] A. Veldkamp, G. Frenking, *Organometallics* **1993**, *12*, 4613–4622.
- [16] E. I. Solomon, P. M. Jones, J. A. May, *Chem. Rev.* **1993**, *93*, 2623–2644.
- [17] M. A. Lynn, B. E. Bursten, *Inorg. Chim. Acta* **1995**, *229*, 437–443.
- [18] A. S. Goldman, K. Krogh-Jespersen, *J. Am. Chem. Soc.* **1996**, *118*, 12159–12166.
- [19] D. E. Sherwood, M. B. Hall, *Inorg. Chem.* **1983**, *22*, 93–100.
- [20] A. J. Lupinetti, S. Fau, G. Frenking, and S. H. Strauss, *J. Phys. Chem.* **1997**, *101*, 9551.
- [21] P. K. Hurlburt, J. J. Rack, S. F. Dec, O. P. Anderson, S. H. Strauss, *Inorg. Chem.* **1993**, *32*, 373–374.
- [22] M. Dolg, U. Wedig, H. Stoll, H. Preuss, *J. Chem. Phys.* **1987**, *86*, 866–872.

- [23] D. Andrae, U. Häußermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, 77, 123–141.
- [24] Gaussian 94: M. J. Frish, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomberts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. DeFrees, I. Baker, J. J. P. Stewart, Head-Gordon, M., C. Gonzalez, Pople, J. A., Eds., Gaussian Inc.: Pittsburgh, PA, **1995**.
- [25] J. J. Rack, S. H. Strauss, *Catal. Today* **1997**, 36, 99.

Radical Cyclization/ β -Elimination Tandem Reactions: Enantiopure Sulfoxides as Temporary Chiral Auxiliaries**

Emmanuel Lacôte, Bénédicte Delouvrié, Louis Fensterbank, and Max Malacria*

Owing to their compatibility with a large number of interesting functionalities and their occasionally high efficiency, diastereoselective radical cyclizations now represent a strategy of choice in the field of asymmetric synthesis.^[1, 2] Notably, the addition of a carbon-centered (alkyl or vinyl) radical to an alkene moiety bearing a chiral auxiliary has been well studied, and generally higher diastereoselectivities are obtained when the addition occurs in the position α to the chiral auxiliary.^[3] Nonetheless, good to excellent β -diastereoselectivities have also been observed,^[4] the use of Lewis acids being critical in the case of chiral acrylates^[5] and oxazolidinones amides.^[6] Continuing our interest in chiral sulfur-based auxiliaries (sulfoxides^[4c] and sulfinimines^[7]), we have proposed the tandem reaction depicted in Scheme 1 as a new means for the preparation of enantiomerically enriched five-membered rings. We anticipated a highly diastereoselec-



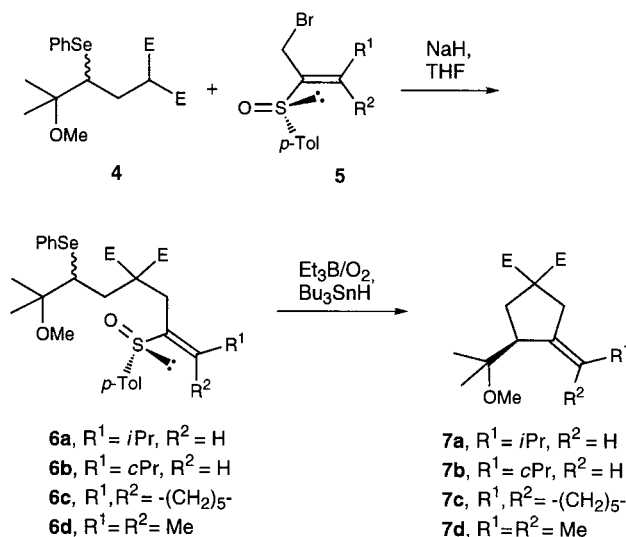
Scheme 1. Proposed new tandem reaction. S*O = homochiral sulfoxide auxiliary

[*] Prof. Dr. M. Malacria, E. Lacôte, B. Delouvrié, Dr. L. Fensterbank
Laboratoire de Chimie Organique de Synthèse, associé au CNRS
Université Pierre et Marie Curie
4, place Jussieu, Tour 44–54, Case 229
F-75252 Paris Cedex 05 (France)
Fax: (+33) 1-44-27-73-60
E-mail: malacria@ccr.jussieu.fr

[**] Acknowledgment is made to the Ministère de l'Éducation Nationale and the CNRS. The authors thank Professor Philippe Renaud (Université de Fribourg), Dr. Pierre Mangeney, and Professor Alexandre Alexakis (Université Pierre et Marie Curie) for helpful discussions, Dr. Karin Schein for experimental assistance, Dr. Serge Thorimbert (Université Pierre et Marie Curie) for assistance with chiral GC analysis, and Dr. René Thouvenot (Université Pierre et Marie Curie) for ³¹P NMR measurements.

tive radical cyclization (with an a priori quite favorable α -selectivity), followed by the well-documented elimination of β -sulfinyl radicals.^[8]

This approach, which relies on the easy introduction and the low cost of the homochiral sulfoxide unit, was first tested with **6a**, which is easily prepared by coupling of malonate **4**^[9] and the known enantiopure *E* allylic bromide **5a** (Scheme 2).^[10] Under low-temperature radical cyclization



Scheme 2. Synthesis of the precursors **6** and the subsequent radical tandem reactions. E = CO₂Me

conditions (Et₃B/O₂),^[11] **6a** underwent an exclusive *anti*-Michael 5-*exo*-*trig* radical cyclization to afford the cyclopentyl derivative **7a** in 60 % yield (Table 1, entry 1). The substitution

Table 1. Results of the tandem reaction (yields and stereoselectivity)

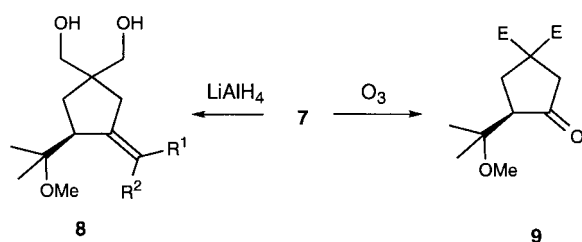
Entry	Precursor	T [°C]	Lewis acid	Product, yield [%] ^[a]	ee [%], ^[12] abs. config. ^[b]
1	6a	–78	–	7a , 60	54, <i>S</i>
2	6b	–78	–	7b , 52 ^[c]	48, <i>S</i>
3	6b	0	–	7b , 90	42, <i>S</i>
4	6b	0	MAD	7b , 46	64, <i>R</i>
5	6c	–40	–	7c , 62	88, <i>S</i>
6	6c	0	–	7c , 77	86, <i>S</i>
7	6d	–78	–	7d , 72	> 96, <i>S</i>
8	6d	–40	–	7d , 70	> 96, <i>S</i>
9	6d	0	–	7d , 93	> 96, <i>S</i>
10	6d	0	Et ₂ AlCl	7d , 63	60, <i>S</i>
11	6d	0	MAD	7d , 52	92, <i>R</i>

[a] See the Experimental section. [b] The absolute configuration of **7d** was determined by a CD measurement.^[16] Ozonolysis of **7a–c** afforded ketone **9** with positive specific rotations as found for **7d**, which also suggests a mainly *S* configuration for **7a–c**. [c] Starting material (38 %) was recovered.

of the vinyl sulfoxide at the β -position is sufficient here to preclude the 6-*endo*-*trig* mode of cyclization. Moreover, no cyclopentyl derivative incorporating the sulfoxide moiety was observed, which confirmed the efficiency of the β -elimination of the sulfoxide auxiliary. The promising stereoselectivity of this sequence (54 % ee) was equally interesting.^[12]

A similar result in terms of yield and stereoselectivity was obtained with **6b** (Table 1, entry 2). No sulfoxide adduct with cleavage of the cyclopropyl ring was isolated in this reaction, which suggests that the β -elimination of the sulfoxide moiety is faster than the rearrangement of the traditional radical clock, the α -cyclopropyl radical. This result is not surprising in view of the estimated rate of about 10^9 s^{-1} for the β -elimination of the arylsulfinyl radical;^[13] the generally recognized rate for the opening of related α -cyclopropyl radicals is 5.10^7 s^{-1} .^[14] When the reaction was run at 0°C , the yield of cyclization adduct **7b** dramatically increased (90%, Table 1, entry 3), but at the expense optical purity.

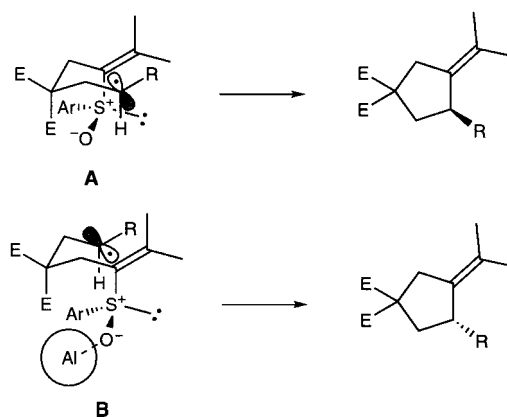
We thus decided to examine the behavior of terminally disubstituted vinyl sulfoxides. We anticipated that the addition of a substituent *cis* to the sulfoxide moiety would create additional allylic strain,^[15] and thus freeze the reactive conformations and boost stereoselectivity. This proved correct, since terminally disubstituted vinyl sulfoxides **6c** and **6d** afforded much higher stereoselectivities (up to 96% *ee*; Table 1, entries 5 and 7). In both cases, no significant decrease in stereoselectivity was observed when the reaction was carried out at 0°C , and the chemical yield was greatly improved. The high enantiomeric purity of **7d** led us to ozonolyze this compound to provide ketone **9**. A CD measurement on this product was performed to determine the absolute configuration of the stereogenic center. An intense positive Cotton effect was observed, from which the *S* configuration was inferred for **7d** (Scheme 3).^[16]



Scheme 3. Derivatizations of the cyclization products **7**. See Scheme 2 for E, R¹, and R².

With a view to reverse the stereochemical outcome of the reaction, the effect of a Lewis acid was investigated next.^[14d] While the use of Et₂AlCl promisingly diminished the optical yield (Table 1, entry 10), the addition of the very bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) to the reaction medium proved very rewarding, as the *R* enantiomer of **7d** was obtained with 92% *ee* (Table 1, entry 11). This confirmed the versatility of this process.^[12] Interestingly, the same effect of inversion was still observed, although to a lesser extent, with the conformationally less constrained cyclopropyl precursor **6b** (Table 1, entry 4).

The stereoselectivities obtained with **6c** and **6d** may be rationalized by the following pseudo-chair transition state models (Scheme 4). When no Lewis acid is present the radical cyclization takes place through transition state **A**, in which the sulfoxide moiety in the lowest energy conformer is present with the lone pair electrons *s-cis* to the vinyl moiety.^[15] The attack takes place *syn* to the sulfur–oxygen bond and *anti* to



Scheme 4. Transition state models.

the *p*-tolyl group; the bulky alkyl group is thus forced into a pseudo-equatorial position. In the presence of the very bulky MAD Lewis acid, which complexes to the oxygen atom of the sulfoxide group, the radical cyclization would occur as depicted in transition state **B**, *syn* to the bulky *p*-tolyl group. This a priori more difficult approach could partly explain the lower yield observed with MAD. This model also applies to a large extent to monosubstituted alkenes. However, these less rigid systems easily assume other reactive conformations, which decreases the overall selectivity of the process.

In conclusion, a new radical cyclization/ β -elimination tandem reaction has been designed which affords alkylidene-cyclopentyl derivatives in high optical purities. The absolute configuration of the products can be controlled simply by the presence or the absence of the MAD Lewis acid in the reaction mixture. The efficient β -elimination of the chiral sulfoxide auxiliary augurs well for the synthesis of useful enantiopure cyclopropyl and cyclobutyl derivatives. This and applications to the synthesis of compounds of biological relevance are currently under active investigation in our laboratory.

Experimental Section

General procedure for the cyclization: To a solution of vinyl sulfoxide **6d** (530 mg, 0.89 mmol) in toluene (18 μL) at 0°C were added under argon *n*-tributyltin hydride (360 μL , 1.3 μmol , 1.5 equiv) and triethylborane (4.5 mL, 4.5 mmol, 5 equiv). Air was injected through the solution every 30 min. After 1.5 h the same quantities of tributyltin hydride and triethylborane were added, and air was again injected. The reaction mixture was stirred at 0°C for 3 h, diluted with diethyl ether (50 mL), and washed twice with brine. The organic layer was dried over MgSO₄, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography to afford 248 mg of **7d** (93%) as a yellow oil. *R*_f = 0.30 (petroleum ether:diethyl ether, 80:20); ¹H NMR (400 MHz, CDCl₃): δ = 3.72 (s, 3H), 3.67 (s, 3H), 3.10 (s, 3H), 2.94 (d, *J* = 14.7 Hz, 1H), 2.82–2.85 (m, 2H), 2.48 (dd, *J* = 13.9, 8.7 Hz, 1H), 2.38 (dd, *J* = 13.9, 4.2 Hz, 1H), 1.66 (s, 3H), 1.64 (d, *J* = 2 Hz, 3H), 1.15 (s, 3H), 1.04 (s, 3H); ¹³C NMR (50 MHz, CDCl₃): δ = 173.4, 172.6, 133.6, 126.5, 78.7, 59.1, 52.7, 52.6, 49.2, 48.9, 39.3, 34.7, 23.5, 22.9, 22.7, 21.7; IR (film) $\tilde{\nu}$ = 2920, 1730, 1070, 730 cm⁻¹; elemental analysis for C₁₆H₂₆O₅: found (calcd): C 64.50 (64.41), H 8.83 (8.78); [α]_D²⁵ = –34.0° (*c* = 1.32, CHCl₃).

Received: March 6, 1998,

Revised version: April 14, 1998 [Z11562IE]

German version: *Angew. Chem.* **1998**, *110*, 2219–2221

Keywords: asymmetric synthesis • cyclizations • domino reactions • Lewis acids • radicals

- [1] B. Giese, B. Kopping, T. Göbel, J. Dickhaut, G. Thoma, K. J. Kulicke, F. Trach, *Org. React. (N.Y.)* **1996**, *48*, 301–856.
- [2] D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1996**.
- [3] a) N. A. Porter, B. Lacher, V. H.-T. Chang, D. R. Magnin, *J. Am. Chem. Soc.* **1989**, *111*, 8309–8310; b) N. A. Porter, D. M. Scott, B. Lacher, B. Giese, H. G. Zeitz, H. J. Lindner, *J. Am. Chem. Soc.* **1989**, *111*, 8311–8312; c) D. M. Scott, A. T. McPhail, N. A. Porter, *Tetrahedron Lett.* **1990**, *31*, 1679–1682; d) N. A. Porter, D. M. Scott, I. J. Rosenstein, B. Giese, A. Veit, H. G. Zeitz, *J. Am. Chem. Soc.* **1991**, *113*, 1791–1799.
- [4] a) J. G. Stack, D. P. Curran, S. V. Geib, J. Rebek, Jr., P. Ballester, *J. Am. Chem. Soc.* **1992**, *114*, 7007–7018; b) K. Rück, H. Kunz, *Synlett* **1992**, 343–344; c) M. Zahouily, M. Journet, M. Malacria, *Synlett* **1994**, 366–368; d) M. Nase, Y. Watanabe, Y. Ueno, T. Toru, *J. Org. Chem.* **1997**, *62*, 7794–7800.
- [5] a) Review: P. Renaud, M. Gerster, *Angew. Chem.* **1998**, *110*, in press; *Angew. Chem. Int. Ed.* **1998**, *37*, in press; b) M. Nishida, E. Ueyama, H. Hayashi, Y. Ohtake, Y. Yamaura, E. Yanaginuma, O. Yonemitsu, A. Nishida, N. Kawahara, *J. Am. Chem. Soc.* **1994**, *116*, 6455–6456; c) M. Nishida, A. Nishida, N. Kawahara, *J. Org. Chem.* **1996**, *61*, 3574–3575.
- [6] M. P. Sibi, C. P. Jasperse, J. Ji, *J. Am. Chem. Soc.* **1995**, *117*, 10779–10780.
- [7] E. Lacôte, M. Malacria, *C. R. Acad. Sci. Fr., Ser. IIc* **1998**, 191–194.
- [8] a) T. E. Boothe, J. L. Greene, Jr., P. B. Shevlin, M. R. Willcott III, R. R. Inners, A. Cornelis, *J. Am. Chem. Soc.* **1978**, *100*, 3874–3879; b) G. A. Russell, H. Tashtoush, P. Ngovivatchai, *J. Am. Chem. Soc.* **1984**, *106*, 4622–4623; other representative addition–elimination sequences with vinyl sulfones: c) J. R. McCarthy, E. W. Huber, T.-B. Le, F. M. Laskovics, D. P. Matthews, *Tetrahedron* **1996**, *52*, 45–58; d) S. Caddick, C. L. Shering, S. N. Wadman, *Tetrahedron Lett.* **1997**, *38*, 6249–6250; e) F. Aldabbagh, W. R. Bowman, *Tetrahedron Lett.* **1997**, *38*, 3793–3794; vinylsulfimides: f) A. J. Clark, S. Rooke, T. J. Sparey, P. C. Taylor, *Tetrahedron Lett.* **1996**, *37*, 909–912; vinyltrifluoromethylsulfones: g) J. Xiang, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 11986–11987.
- [9] Malonate **4** was obtained in 50–60% yield by the addition of phenylselenenyl chloride in methanol onto prenyl dimethylmalonate: D. G. Garratt, A. Kabo, *Can. J. Chem.* **1980**, *58*, 1030–1041.
- [10] Allyl bromides **5a**, **5c**, and **5d**: E. Bonfand, P. Gosselin, C. Maignan, *Tetrahedron: Asymmetry* **1993**, *4*, 1667–1676. Bromide **5b** was prepared by the same procedure.
- [11] K. Nozaki, K. Oshima, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549.
- [12] The determination of the enantiomeric excesses was performed on the diols **8** with the chiral phosphorus derivatives method of Alexakis and Mangeney: A. Alexakis, J. C. Frutos, S. Mutti, P. Mangeney, *J. Org. Chem.* **1994**, *59*, 3326–3334.
- [13] P. J. Wagner, J. H. Sedon, M. J. Lindstrom, *J. Am. Chem. Soc.* **1978**, *100*, 2579–2580.
- [14] M. Newcomb, *Tetrahedron* **1993**, *49*, 1151–1176.
- [15] Review: R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841–1860.
- [16] CD measurements on related chiral cyclopentanones: a) C. Djerassi, R. Records, C. Ouannes, J. Jacques, *Bull. Soc. Chim. Fr.* **1966**, 2378–2381; b) P. Sundararaman, G. Barth, C. Djerassi, *J. Am. Chem. Soc.* **1981**, *103*, 5004–5007; c) D. Stien, R. Samy, R. Nougier, D. Crich, M. P. Bertrand, *J. Org. Chem.* **1997**, *62*, 275–286. The ketone from **7d** displays the following specific rotation: $[\alpha]_D^{25} = +127.3$ ($c = 0.6$, CH_2Cl_2).

Regioselective Synthesis of *trans*-1 Fullerene Bis-Adducts Directed by a Crown Ether Tether: Alkali Metal Cation Modulated Redox Properties of Fullerene–Crown Ether Conjugates**

Jean-Pascal Bourgeois, Luis Echegoyen,*
Monia Fibbioli, Ernö Pretsch,* and
François Diederich*

Since the introduction of the tether-directed remote functionalization of fullerenes,^[1–3] a variety of bis(cyclopropanated) [60]fullerene derivatives have been synthesized both regio- and stereoselectively^[2] by macrocyclization of the carbon sphere by a double Bingel addition.^[4] This reaction has provided ready access to bis(methano)fullerenes with *cis*-2, *cis*-3, *e*, *trans*-4, and *trans*-3 addition patterns (Figure 1).^[5]

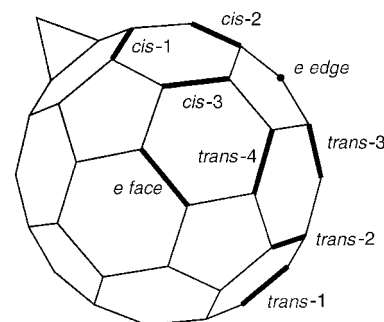


Figure 1. Position notation for bis-adducts of C_{60} .

However, it has proven quite challenging to develop extended tethers with a suitable degree of conformational homogeneity that would span the carbon sphere and direct the second addend into the *trans*-2 and, in particular, the *trans*-1 positions on the opposite pole.^[6] Among the up to eight regioisomeric C_{60} bis-adducts isolated from various sequential (nontethered) double additions,^[7, 8] the *trans*-1 derivative is almost always the least abundant for both kinetic and statistical reasons. Thus, the stepwise Bingel reaction with diethyl 2-bromomalonate, reported by Hirsch and co-workers,^[5, 7] gave the *trans*-1 bis-adduct in only 0.8–2% yield after tedious regioisomer separation. Regioselective access to a *trans*-1 bis-adduct was achieved by Kräutler et al. in a most elegant topochemical reaction in which anthracenes are added by cycloaddition to the two poles of the fullerene.^[9]

[*] Prof. Dr. L. Echegoyen
Department of Chemistry, University of Miami
Coral Gables, FL 33124 (USA)
Fax: (+1) 305-284-4571
E-mail: lechegoyen@unmiami.ir.miami.edu
Prof. Dr. E. Pretsch, Prof. Dr. F. Diederich,
Dipl.-Chem. J.-P. Bourgeois, Dipl.-Chem. M. Fibbioli
Laboratorium für Organische Chemie, ETH-Zentrum
Universitätsstrasse 16, CH-8092 Zürich (Switzerland)
Fax: (+41) 1-632-1109
E-mail: diederich@org.chem.ethz.ch

[**] This work was supported by the Swiss National Science Foundation, the US National Science Foundation (CHE-9313018), and a NIH Fogarty Fellowship (1 F06 TW-02231–01 to L.E.).

for K^+ , with close to Nernstian response to all monovalent ions investigated. The potentiometric selectivity coefficients, $\log K_{K,J}^{\text{pot}}$, were determined by the separate solution method^[19] with $J = Rb^+$: -0.7 ± 0.2 , NH_4^+ : -0.9 ± 0.2 , Na^+ : -1.7 ± 0.2 , Cs^+ : -2.3 ± 0.4 , H^+ : -2.4 ± 0.3 , Li^+ : -2.7 ± 0.3 , Mg^{2+} : < -3.5 , Ca^{2+} : < -4.0 , Sr^{2+} : < -4.3 . The selectivity sequence observed clearly deviates from that of a membrane based on an ion exchanger (Hofmeister series)^[18a] and clearly demonstrates that $(\pm)\text{-1}$ acts as an ionophore. Effective complex formation constants, K_{IL}^{eff} (I: alkali metal ion, L: ligand), in the same solvent polymeric phase were obtained by comparing the responses of two membranes, one with the H^+ -selective ionophore ETH 2439 (see Experimental Section) and NaTFPB, and the other with these components and $(\pm)\text{-1}$.^[18b] If a 1:1 stoichiometry is assumed, the $\log K_{IL}^{\text{eff}}$ values for the following alkali metal ions I were found to be: K^+ : 5.4 ± 0.2 , Na^+ : 4.0 ± 0.2 , Cs^+ : 3.3 ± 0.5 , Li^+ : 2.9 ± 0.3 . The values for K^+ , Na^+ , and Li^+ are lower by 3.9, 2.7, and 3.8 orders of magnitude, respectively, than for valinomycin as ligand in the same membrane matrix.^[18b, c]

To analyze the effect of cation complexation on the redox properties of the fullerene–crown ether conjugates $(\pm)\text{-1}$ – $(\pm)\text{-3}$, cyclic voltammetric (CV) studies were performed in CH_3CN/CH_2Cl_2 (1/1).^[20] The CV of $(\pm)\text{-1}$ is shown in Figure 2, both in the presence of one equivalent of

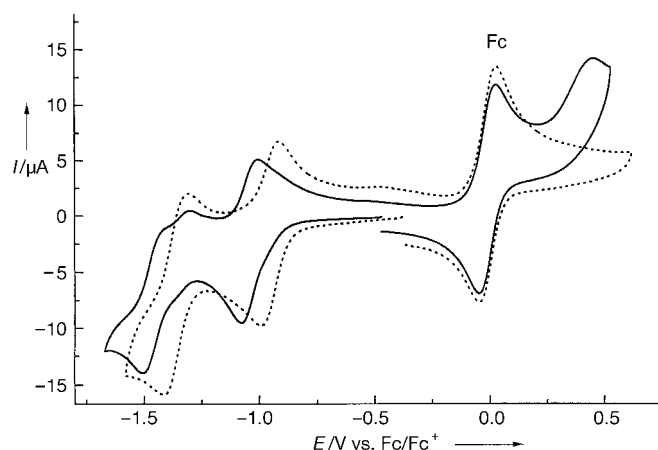


Figure 2. Cyclic voltammograms for $(\pm)\text{-1}$ recorded at 100 mVs^{-1} on a glassy carbon working mini-electrode; solid line: solution of free $(\pm)\text{-1}$ with one equivalent of [2.2.2]cryptand present; dotted line: solution of $(\pm)\text{-1}$ with ten equivalents of KPF_6 .

[2.2.2]cryptand and in the presence of ten equivalents of KPF_6 . The cryptand was added to try to ensure that the species observed initially was uncomplexed, since peaks corresponding to the Na^+ and K^+ complexes were observed in the FAB mass spectrum of free $(\pm)\text{-1}$. The first fullerene-based reduction process of uncomplexed $(\pm)\text{-1}$ is quasireversible ($\Delta E_{pp} = 70 \text{ mV}$) and occurs at $E_{1/2} = -1.04 \text{ V}$ versus ferrocene/ferrocenium (Fc/Fc^+ ; Table 1). The second fullerene-based reduction process is somewhat more complicated, and exhibits what appear to be two closely spaced waves. Because of these observations, we did not attempt to quantify $E_{1/2}$ for this process.

A closer examination of this voltammogram suggests that the first wave exhibits a shoulder at more positive potentials,

Table 1. Redox potentials [V vs Fc/Fc^+] for $(\pm)\text{-1}$ – $(\pm)\text{-3}$ and **11**.^[a]

	+ [2.2.2]cryptand ^[b]		+ KPF_6 ^[c]	
	$E_{1/2}^1$	$E_{1/2}^2$	$E_{1/2}^1$	$E_{1/2}^2$
$(\pm)\text{-1}$	-1.04 (70)	-1.51 ^[d]	-0.95 (79)	-1.36 (104)
$(\pm)\text{-2}$	-1.02 (79)	-1.48 ^[d]	-0.97 (75)	-1.43 ^[d]
$(\pm)\text{-3}$	-1.05 (83)	-1.47 ^[d]	-1.01 (77)	-1.46 ^[d]
11	-0.94 (77)	-1.36 (80)	-0.95 (85)	-1.36 (93)

[a] In CH_3CN/CH_2Cl_2 (1/1) in the presence of $0.1 \text{ M } Bu_4NPF_6$. Fc/Fc^+ was used as the internal reference, and measurements were made with a glassy carbon working mini-electrode. Values for ΔE_{pp} [mV] are given in parenthesis. [b] One equivalent of [2.2.2]cryptand. [c] Ten equivalents of KPF_6 . [d] Only the cathodic potential is given.

although it is not as clearly resolved as in the second reduction. The chemically irreversible oxidation at about $+0.4 \text{ V}$ corresponds to the added cryptand. Addition of KPF_6 results in a large anodic shift of the reduction processes, with the first one shifting to -0.95 V versus Fc/Fc^+ ; this is a shift in potential of 90 mV relative to that of the uncomplexed compound and is attributed to the electrostatic effect of K^+ bound in close proximity to the carbon sphere. The shifted couples due to complexation of K^+ correspond well with the small shoulders previously mentioned. The second redox process has $\Delta E_{pp} = 100 \text{ mV}$ and $E_{1/2} = -1.36 \text{ V}$ versus Fc/Fc^+ . Addition of ten equivalents of [2.2.2]cryptand reversed the voltammetric response to the original voltammogram, observed in the absence of KPF_6 , which indicates that the K^+ binding process with $(\pm)\text{-1}$ is reversible.

Very similar results were obtained from the CV studies of $(\pm)\text{-2}$ and $(\pm)\text{-3}$, but the observed anodic shifts for the first redox couple upon complexation with K^+ were smaller (50 mV for $(\pm)\text{-2}$ and 40 mV for $(\pm)\text{-3}$, Table 1). The reduction of the anodic shift from 90 mV (in $(\pm)\text{-1}$) to 40 mV (in $(\pm)\text{-3}$) can be readily explained with an increasing averaged distance, evidenced by molecular modeling,^[11] between the cation bound to the crown ether and the fullerene sphere as the addition pattern changes from *trans*-1, to *trans*-2, and to *trans*-3.

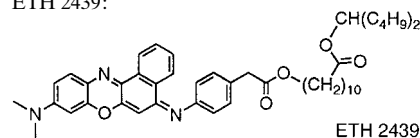
This investigation demonstrates that a significant perturbation of the electronic structure of the fullerene occurs only when the bound cation is positioned closely and tightly on the fullerene surface as seen in $(\pm)\text{-1}$ and, to a lesser extent, in $(\pm)\text{-2}$ and $(\pm)\text{-3}$. In previous fullerene–crown ether conjugates, the ionophore moiety was positioned at a much greater distance from the fullerene surface and, correspondingly, significant cation-mediated electrochemical effects were not detected. The Bingel macrocyclization reaction should also provide a highly effective method for positioning other organic chromophores^[2c] such as porphyrins in sufficiently close proximity to the fullerene sphere to induce profound changes in the photophysical and redox properties of the carbon allotrope.

Experimental Section

Membrane preparation and EMF (electromotive force) measurements: Ion-selective electrode (ISE) membranes were prepared by dissolving the carrier(s) and NaTFPB, together with DOS and PVC (2/1 w/w), in THF (1.5 mL), pouring this solution into a glass ring ($\varnothing = 26 \text{ mm}$) on a glass plate, and allowing the solvent to evaporate overnight. The three

membrane compositions were (concentrations [mmol kg⁻¹] in parentheses): (±)-1 (6.3), ETH 2439 (6.6), and NaTFPB (3.1); (±)-1 (7.4) and NaTFPB (3.7); ETH 2439 (6.6) and NaTFPB (3.3). Three 6-mm discs were punched from each membrane and mounted in Philips electrode bodies (IS-561, Glasbläseerei Möller, Zürich). The internal filling solution was 0.01 M KCl for the ISE membrane based on (±)-1 as only carrier, and 0.1 M KCl buffered to pH 3.9 with 5 × 10⁻³ M AcOH/AcOK for the other two. Before measurements, the ISEs were equilibrated with the respective internal filling solution overnight. The pH values were determined with Metrohm glass and reference electrodes. All EMF measurements were performed at room temperature (21.5 ± 0.5 °C) in stirred solutions.

ETH 2439:



Selectivity coefficients, $K_{H,J}^{pot}$, were obtained on 0.1 M chloride solutions with the separate solution method.^[19] Effective complex formation constants, K_{IL}^{eff} were calculated by Equation (1) from the $K_{H,J}^{pot}$ values of two ISEs based on ETH 2439 (measured at pH 11.0), one with and the other without ligand (±)-1 (L).^[18b] A 1:1 stoichiometry of the complex IL was assumed, and L_T

$$K_{IL}^{eff} = \frac{1}{L_T - R_T} \frac{K_{H,J}^{pot}(\text{with L})}{K_{H,J}^{pot}(\text{without L})} \quad (1)$$

and R_T are the total concentrations of (±)-1 and NaTFPB, respectively. The standard deviations given were calculated from the results obtained with three ISEs from the same membrane. A measuring station of our own design, with an adapted LabView program, was used for EMF measurements.

Received: March 11, 1998 [Z11571 IE]

German version: *Angew. Chem.* **1998**, *110*, 2203–2207

Keywords: cyclic voltammetry • electrochemistry • fullerenes • ionophores

- [1] a) L. Isaacs, R. F. Haldimann, F. Diederich, *Angew. Chem.* **1994**, *106*, 2434–2437; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2339–2342; b) L. Isaacs, P. Seiler, F. Diederich, *Angew. Chem.* **1995**, *107*, 1636–1639; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1466–1469; c) L. Isaacs, F. Diederich, R. F. Haldimann, *Helv. Chim. Acta* **1997**, *80*, 317–342; d) F. Cardullo, P. Seiler, L. Isaacs, J.-F. Nierengarten, R. F. Haldimann, F. Diederich, T. Mordasini-Denti, W. Thiel, C. Boudon, J.-P. Gisselbrecht, M. Gross, *Helv. Chim. Acta* **1997**, *80*, 343–371.
- [2] a) J.-F. Nierengarten, V. Gramlich, F. Cardullo, F. Diederich, *Angew. Chem.* **1996**, *108*, 2242–2244; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2101–2103; b) J.-F. Nierengarten, T. Habicher, R. Kessinger, F. Cardullo, F. Diederich, V. Gramlich, J.-P. Gisselbrecht, C. Boudon, M. Gross, *Helv. Chim. Acta* **1997**, *80*, 2238–2276; c) P. R. Ashton, F. Diederich, M. Gómez-López, J.-F. Nierengarten, J. A. Preece, F. M. Raymo, J. F. Stoddart, *Angew. Chem.* **1997**, *109*, 1611–1614; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1448–1451.
- [3] a) L.-L. Shiu, K.-M. Chien, T.-Y. Liu, T.-I. Lin, G.-R. Her, T.-Y. Luh, *J. Chem. Soc. Chem. Commun.* **1995**, 1159–1160; b) G.-X. Dong, J.-S. Li, T.-H. Chan, *J. Chem. Soc. Chem. Commun.* **1995**, 1725–1726; c) E. Nakamura, H. Isobe, H. Tokuyama, M. Sawamura, *Chem. Commun.* **1996**, 1747–1748; d) C. K.-F. Shen, K.-M. Chien, C.-G. Juo, G.-R. Her, T.-Y. Luh, *J. Org. Chem.* **1996**, *61*, 9242–9244; e) M. Taki, S. Sugita, Y. Nakamura, E. Kasashima, E. Yashima, Y. Okamoto, J. Nishimura, *J. Am. Chem. Soc.* **1997**, *119*, 926–932; f) H. Isobe, H. Tokuyama, M. Sawamura, E. Nakamura, *J. Org. Chem.* **1997**, *62*, 5034–5041; g) C. K.-F. Shen, H.-H. Yu, C.-G. Juo, K.-M. Chien, G.-R. Her, T.-Y. Luh, *Chem. Eur. J.* **1997**, *3*, 744–748.
- [4] C. Bingel, *Chem. Ber.* **1993**, *126*, 1957–1959.
- [5] A. Hirsch, I. Lamparth, H. R. Karfunkel, *Angew. Chem.* **1994**, *106*, 453–455; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 437–438.
- [6] The tether-directed synthesis of a *trans*-1 bis(Diels–Alder) adduct of C₆₀ has been proposed in a Concepts Article, but no characterization of the product was reported: Y. Rubin, *Chem. Eur. J.* **1997**, *3*, 1009–1016.
- [7] F. Djojo, A. Herzog, I. Lamparth, F. Hampel, A. Hirsch, *Chem. Eur. J.* **1996**, *2*, 1537–1547.
- [8] Q. Lu, D. I. Schuster, S. R. Wilson, *J. Org. Chem.* **1996**, *61*, 4764–4768.
- [9] B. Kräutler, T. Müller, J. Maynollo, K. Gruber, C. Kratky, P. Ochsenbein, D. Schwarzenbach, H.-B. Bürgi, *Angew. Chem.* **1996**, *108*, 1294–1296; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1204–1206.
- [10] a) F. Diederich, U. Jonas, V. Gramlich, A. Herrmann, H. Ringsdorf, C. Thilgen, *Helv. Chim. Acta* **1993**, *76*, 2445–2453; b) J. Osterodt, M. Nieger, P.-M. Windscheif, F. Vögtle, *Chem. Ber.* **1993**, *126*, 2331–2336; c) F. Arias, Q. Xie, Y. Wu, Q. Lu, S. R. Wilson, L. Echegoyen, *J. Am. Chem. Soc.* **1994**, *116*, 6388–6394; d) S. N. Davey, D. A. Leigh, A. E. Moody, L. W. Tetler, F. A. Wade, *J. Chem. Soc. Chem. Commun.* **1994**, 397–398; e) A. Gügel, A. Kraus, J. Spickermann, P. Belik, K. Müllen, *Angew. Chem.* **1994**, *106*, 601–603; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 559–561; f) A. Kraus, A. Gügel, P. Belik, M. Walter, K. Müllen, *Tetrahedron* **1995**, *51*, 9927–9940; g) U. Jonas, F. Cardullo, P. Belik, F. Diederich, A. Gügel, E. Harth, A. Herrmann, L. Isaacs, K. Müllen, H. Ringsdorf, C. Thilgen, P. Uhlmann, A. Vasella, C. A. A. Waldruff, M. Walter, *Chem. Eur. J.* **1995**, *1*, 243–251; h) F. Arias, L. Echegoyen, S. R. Wilson, Q. Lu, Q. Lu, *J. Am. Chem. Soc.* **1995**, *117*, 1422–1427; i) D. A. Leigh, A. E. Moody, F. A. Wade, T. A. King, D. West, G. S. Bahra, *Langmuir* **1995**, *11*, 2334–2336; j) F. Arias, L. A. Godínez, S. R. Wilson, A. E. Kaifer, L. Echegoyen, *J. Am. Chem. Soc.* **1996**, *118*, 6086–6087; k) J. Osterodt, A. Zett, F. Vögtle, *Tetrahedron* **1996**, *52*, 4949–4962; l) F. Arias, P. Bolas, Y. Zuo, O. Domínguez, M. Gómez-Kaifer, L. Echegoyen in *Recent Advances in the Chemistry and Physics of Fullerenes and Related Materials*, Vol. 3 (Eds.: K. M. Kadish, R. S. Ruoff), The Electrochemical Society Inc., Pennington, NJ, **1996**, pp. 165–176; m) A. Ikeda, C. Fukuhara, S. Shinkai, *Chem. Lett.* **1997**, 407–408; n) S. Wang, R. M. Leblanc, F. Arias, L. Echegoyen, *Langmuir* **1997**, *13*, 1672–1676; o) P. S. Baran, R. R. Monaco, A. U. Khan, D. I. Schuster, S. R. Wilson, *J. Am. Chem. Soc.* **1997**, *119*, 8363–8364; p) M. Kawaguchi, A. Ikeda, S. Shinkai, *J. Chem. Soc., Perkin Trans. 1* **1998**, *2*, 179–184.
- [11] Force field simulations were carried out with the CVFF force field in the program Insight II 95.0 of Discover 2.9.7 (Biosym Technologies, San Diego, **1997**). The calculations predicted that the relative stabilities of the products formed by addition of bis-malonate **4** to C₆₀ would be in the order *trans*-1 > *trans*-2 > *trans*-3.
- [12] A. Reitz, M. A. Avery, M. S. Verlander, M. Goodman, *J. Org. Chem.* **1981**, *46*, 4859–4863.
- [13] a) C. J. Pedersen, *Org. Synth. Coll. Vol.* **6**, **1972**, 395–400; b) R. N. Greene, *Tetrahedron Lett.* **1972**, 1793–1796.
- [14] All new compounds were fully characterized by ¹H, ¹³C NMR, and IR spectroscopy and FAB mass spectrometry. UV/Vis spectra were measured for fullerene derivatives, and elemental analyses were obtained for the non-fullerene derivatives.
- [15] W. E. Smith, *J. Org. Chem.* **1972**, *37*, 3972–3973.
- [16] J. C. Duff, *J. Chem. Soc.* **1941**, 547–550.
- [17] F. Wada, H. Hirayama, H. Namiki, K. Kikukawa, T. Matsuda, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1473–1474.
- [18] a) E. Bakker, P. Bühlmann, E. Pretsch, *Chem. Rev.* **1997**, *97*, 3083–3132; b) E. Bakker, E. Pretsch, *Anal. Chem.* **1998**, *70*, 295–302; c) E. Bakker, M. Willer, M. Lerchi, K. Seiler, E. Pretsch, *Anal. Chem.* **1994**, *66*, 516–521.
- [19] G. G. Guilbault, R. A. Durst, M. S. Frant, H. Freiser, E. H. Hansen, T. S. Light, E. Pungor, G. Rechnitz, N. M. Rice, T. J. Rohm, W. Simon, J. D. R. Thomas, *Pure Appl. Chem.* **1976**, *48*, 129–132.
- [20] Electrochemical experiments were performed in dry CH₃CN/CH₂Cl₂ (1/1, 5 mL) containing 0.1 mM Bu₄NPF₆, typically with 0.5 mM compound, all under an argon atmosphere. The solvent mixture was selected mainly for solubility reasons. [2.2.2]Cryptand and KPF₆ were added directly to the cell as solids. An EG & G Princeton Applied Research model 263A Potentiostat/Galvanostat was used to obtain the measurements. A glassy carbon mini-electrode was used as the working electrode, a Ag/AgCl electrode from Bioanalytical Systems was used as the reference, and 0.5 mM Fc was added as an internal potential standard. A Pt wire served as the counter-electrode. A typical scan was run at a rate of 100 mV s⁻¹, and no compensation for solution resistance was applied.

SSZ-23: An Odd Zeolite with Pore Openings of Seven and Nine Tetrahedral Atoms**

Miguel A. Camblor, María-José Díaz-Cabañas, Joaquin Perez-Pariente, Simon J. Teat, William Clegg, Ian J. Shannon, Philip Lightfoot, Paul A. Wright, and Russell E. Morris*

Millions of years of nature and four decades of synthetic effort have resulted in more than sixty known thermally stable aluminosilicate zeolites.^[1] Their ordered microporous architecture enables small molecules to be discriminated on the basis of their size and shape: a property that is used extensively in separation processes and catalysis. We have found that SSZ-23 is the first aluminosilicate zeolite to possess pores bounded by nine tetrahedral atoms. This surprising result fundamentally alters the expected shape-selective influence in molecular sieving and hydrocarbon transformations, which unleashes great potential for new and improved separation and catalytic processes.

Solid-state chemists describe inorganic oxides consisting of infinite ionic arrays in terms of constituent building units: tetrahedra, octahedra, chains, rings, sheets, and blocks. This not only permits rationalization of their structural chemistry but also acts as a spur for the synthesis of new materials that may have related but distinct architectures and composition and, as a result, different and desirable properties. Microporous framework solids exhibit a particularly rich diversity of structure and applications, and each discovery of a novel material provides fresh insight, revealing a predicted (but until then unobserved) member of a structural series or a framework with completely new and unexpected features. Recent examples in the latter category include the aluminophosphate VPI-5 with a pore constrained by a ring of eighteen

tetrahedra (eighteen-membered ring, 18MR),^[2] aluminosilicates with interconnected channels bound by both 10MRs and 12MRs,^[3] and aluminosilicates with two independent multi-dimensional channel systems^[4] or with pore openings bounded by 14MRs.^[5] Each new example has stimulated great interest because of the promise it holds for improved catalytic and molecular sieving properties. The group of Zones at Chevron has been particularly active during this period in the synthesis of new zeolites by use of custom-made, structure-directing templates.

Among the wealth of new materials discovered, the zeolite SSZ-23, patented in 1987, was found to have catalytic properties for the reaction of methanol to hydrocarbons that correspond to those of a medium-pore zeolite.^[6] Conventional wisdom suggested that it must have channel openings to the internal acid sites bounded by 10MRs (rather than 8MR or 12MRs, the other possible pore openings), but because of the small crystallite size, structure solution was not possible. We will show that SSZ-23 is, in fact, the first aluminosilicate with 9MR pore openings, and the first microporous solid to contain both 7MR and 9MR openings—in this respect it is truly an odd zeolite.

Our unexpected discovery was made possible by the rapid development of the extremely powerful field of microcrystalline X-ray diffraction (diffraction on very small single crystals) accomplished at synchrotron radiation sources. For reasons of crystallographic complexity, it is unlikely that the structure could have been solved in any other way. The power of this crystallographic method is such that the position of the organic template cation was revealed, showing that its orientation alternates in adjacent cages. Not only does our study explain the observed catalytic and sorption behavior, but a whole new range of structural possibilities for aluminosilicates is suggested, as yet unconsidered because of preconceptions of the expected building blocks. Now that 9MRs have been observed in thermally stable and strongly acidic solids, new catalytic applications will certainly follow.

Initially, a sample of aluminosilicate SSZ-23 was prepared according to published methods as a very fine microcrystalline powder, and was found to have a powder X-ray diffraction pattern as reported in the literature.^[6] In separate experiments, pure silica SSZ-23 was synthesized at near neutral pH with *N,N,N*-trimethyl-1-adamantammonium (TMAda⁺) cations as structure-directing agents and F[−] anions as mineralizers. Chemical analysis suggests the following formula for the unit cell: [(C₁₃H₂₄N⁺)_{4.1}F[−]_{3.3}(OH)_{0.8}(H₂O)_{1.6}][SiO₂]₆₄ (found: N 1.20, C 13.50, H 2.16, F 1.31; calculated for [C₁₃H₂₄N⁺F[−](H₂O)_{0.5}]₄[SiO₂]₆₄ N 1.19, C 13.24, H 2.14, F 1.61). The weight loss up to 800°C was 19.7% instead of the calculated 18.8%. Thus, F[−] ions seem to be present in slightly smaller concentrations than required to balance the positive charge of the organic cation. In the above experimental formula we have included OH[−] to achieve charge balance. However, in view of the ²⁹Si MAS NMR spectrum, it appears more realistic to consider the presence of a small amount (2.7%) of connectivity defects in the form of SiOH/SiO[−] couples (which gives the required 0.8 additional negative charges per unit cell). The zeolite was stable during thermal removal of the template in air, and N₂ adsorption isotherms at

[*] Dr. R. E. Morris, Dr. I. J. Shannon, Dr. P. Lightfoot, Dr. P. A. Wright
School of Chemistry, University of St. Andrews
St. Andrews, KY16 9ST (UK)
Fax: (+44) 1334-463-808
E-mail: rem1@st-andrews.ac.uk

Dr. M. A. Camblor, M.-J. Díaz-Cabañas
Instituto de Tecnología Química
Universidad Politécnica de Valencia
Avda. Los Naranjos s/n, E-46071 Valencia (Spain)

Dr. J. Perez-Pariente
Instituto de Catalysis y Petrolequímica
CSIC, Campus Universidad Autónoma, Cantoblanco,
E-28049 Madrid (Spain)

Dr. S. J. Teat, Prof. W. Clegg
Department of Chemistry, University of Newcastle
Newcastle upon Tyne, NE1 7RU (UK)

and
CCLRC Daresbury Laboratory, Warrington, WA4 4AD (UK)

[**] R.E.M. and I.J.S. thank the Royal Society of Edinburgh for the provision of SOEID and BP Research Fellowships respectively. M.A.C. and M.J.D.-C. gratefully acknowledge the CICYT for financial support (Spain, MAT97-0723). M.A.C. also thanks Dr. H. Koller for providing a copy of reference [11] before publication. P.A.W., P.L., and J.P.-P. thank the British Council and CSIC Madrid. We would also like to thank the EPSRC and CCLRC for access to facilities and for financial support. The abbreviation 7MR (for example) is used to describe a ring which contains seven tetrahedral atoms such as silicon or aluminium and seven bridging oxygen atoms.

77 K of calcined SSZ-23 reveal a microporous volume of $0.20 \text{ cm}^3 \text{ g}^{-1}$ (by the *T*-plot method; 0.226 as measured at $p/p_0 = 0.30$). The Horvath–Kawazoe formalism^[7] applied to the Ar isotherm at 87.3 K gives an average micropore diameter of 5.7 Å.

Attempts to solve the structure from high-quality synchrotron X-ray powder diffraction data with simulated annealing and Monte Carlo computational techniques were all unsuccessful. Small crystals of SSZ-23 were then examined at the Synchrotron Radiation Source, Daresbury (UK). The need to use synchrotron X-ray radiation for this study is demonstrated by the recent work of Zones and co-workers, in which a SSZ-42 zeolite crystal of four times the volume of the SSZ-23 crystal produced data that was too weak, when collected on a similar instrument in the laboratory, to yield a refined structural model of suitable quality.^[8]

In broad structural terms, the tetrahedral framework of SSZ-23 can be thought of as two-dimensional arrays of cages, with molecular access between the cages in the planes of the arrays restricted by the 7MR and 9MR pore openings. A more detailed structural consideration shows that the smallest characteristic subunit of SSZ-23 consists of three 4MRs and four 5MRs (Figure 1). These are linked together, through



Figure 1. Two of the characteristic subunits of SSZ-23 (see text for further details). The diagram also shows the location of the partially occupied fluorine sites inside the small cages. Si atoms are shown as grey spheres, O atoms as clear spheres, and F atoms as black spheres.

4MRs and 6MRs, to form slightly puckered layers parallel to the (101) face of the unit cell. These layers are then linked together by 4MRs to give the three-dimensional structure shown in Figure 2. This “pillaring” of layers produces channels running parallel to the [001] direction that are bounded at their narrowest points by 7MR windows. Parallel to the [101] direction are the channels bounded by 9MR windows, slightly offset against each other (Figures 3 and 4). Cages are located at the intersection of the 7MR and 9MR channels. The TMA⁺ template cations inside the cages were located by difference Fourier techniques (Figure 5).

Unusually for zeolites, the cages have no symmetry; the template molecules are aligned parallel to the long axis of the cages. Careful examination of the difference Fourier map

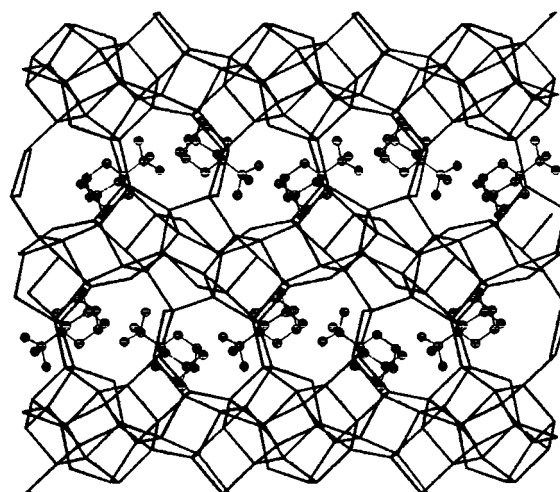


Figure 2. The structure of SSZ-23 viewed parallel to the [001] direction, showing the 7MR windows and the orientation of the TMA⁺ cation. For clarity, the framework structure is shown as single lines joining the Si atoms; O atoms, which would be placed near the centers of the lines, have been omitted.

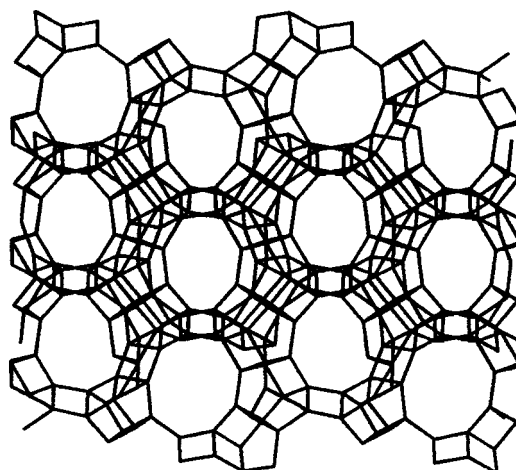


Figure 3. The framework structure of SSZ-23 viewed parallel to the [101] direction, showing the channels bounded by the 9MR windows. For clarity, the template molecule has been omitted and the framework is depicted in the same fashion as in Figure 2.

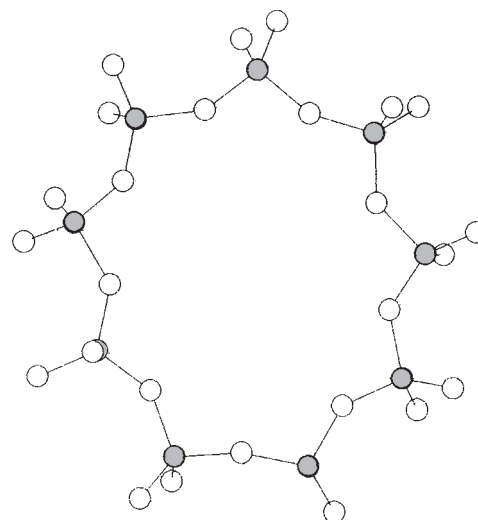


Figure 4. Detail of one of the 9MRs from SSZ-23. The Si atoms are depicted as grey spheres, and the O atoms as white spheres.

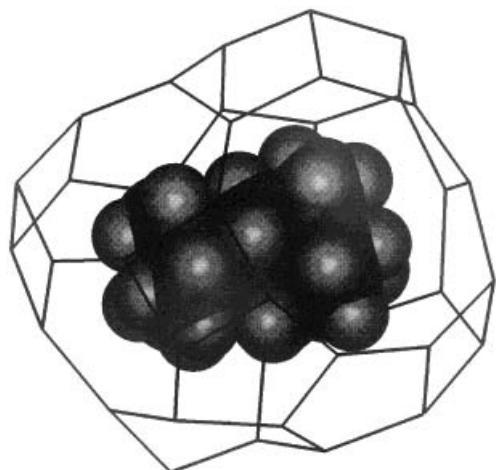


Figure 5. The TMAda⁺ templating cation, depicted as a space-filling model, inside the cage formed by the intersection of the 9MR and 7MR channels.

revealed three regions of residual electron density within the small structural subunits shown in Figure 1. These are attributed to the charge-balancing fluoride ions detected in the chemical analysis. They are bonded to silicon atoms, increasing the silicon coordination to fivefold with bond lengths (Si(7)–F(3) 1.96(3), Si(12)–F(1) 1.937(14), Si(13)–F(2) 1.95(2) Å) that are consistent with both the ²⁹Si MAS NMR spectra and other reports of fluoride-containing zeolites and silica polymorphs for which a preference for the F[−] ions to reside in small cages has been seen. The total refined occupancy of the three F[−] ion sites is also in reasonable agreement with the expected value from the chemical analysis. A preliminary Rietveld refinement of our structural model against powder X-ray diffraction data from the aluminosilicate SSZ-23 sample confirms that the framework structures of the two materials are identical.

The ²⁹Si MAS NMR spectrum of the as-synthesized material consists of two very broad bands ($\delta \approx -108$ and -114 ; Figure 6). Both bands can be assigned to Si(4Si) sites, and show some resolution of crystallographically independent sites. In fact, a simulation of the spectrum using the Si–O–Si angles derived in this work and the equation of Thomas et al.^[9] and neglecting the influence of F[−] gives the same two broad bands with about the same intensities when pure Gaussian lines with full width at half maxima of 2 ppm are used. The low resolution of this spectrum is probably a consequence of considerable line broadening due to heteronuclear coupling of ²⁹Si with ¹H and ¹⁹F nuclei. In this spectrum there is also a broad shoulder at $\delta \approx -102$ (2.7% relative intensity) and a very broad hump in the region $\delta = -130$ to -150 (4% relative intensity). The former is probably due to the presence of a very small number of connectivity defects, in agreement with the lower than expected F[−] ion content. The latter appears in the region expected for pentacoordinated Si atoms: SiO₄F units in the clathrasil framework structure nonasil (NON)^[10] resonate at about $\delta = -144$ (Si–F ca. 1.8–1.9 Å), while in TPAF-silicalite a broad hump very similar to the one shown here appears in the region $\delta = -115$ to -135 .^[11] This feature has been assigned to

pentacoordinated Si atoms bonded to F[−] ions that rapidly exchange at room temperature between different Si sites. Our ²⁹Si NMR spectra and X-ray diffraction results seem to confirm this assignment.

The ²⁹Si NMR spectrum of the calcined material shows enhanced resolution, and no resonances around $\delta = -100$ that could be assigned to SiOH connectivity defects, which indicates that they are annealed upon heating. There is also no evidence of pentacoordinated Si atoms, which indicates that the F[−] ions leave the material, probably as HF, during calcination. All resonances appear in the Si(4Si) region and, despite a significant overlap of the peaks, at least nine different sites (seven lines plus two shoulders) can be distinguished. The resolution of crystallographic sites is a consequence of the lack of connectivity defects, the high degree of local order of the material, and the absence of heteronuclear coupling of ²⁹Si with ¹H or ¹⁹F nuclei. By the use of the equation of Thomas et al.,^[9] the average Si–O–Si angle for every Si site is shown to fall in the range of 140.8 to 159.8°. Furthermore, the experimental ²⁹Si MAS NMR spectrum is in reasonable agreement with the spectrum calculated from the values obtained from a preliminary Rietveld refinement of the powder diffraction data of the calcined material.

The SSZ-23 structure type is an intriguing addition to the family of high-silica zeolites, and can be prepared with or without aluminium in the framework. Light is shed on the role of fluoride as a mineralizer in silicate crystallization by its inclusion in the framework structure attached to pentacoordinated silicon atoms. The presence of 7MRs and 9MRs in a stable solid acid is unexpected. Among the known zeolite topologies, rings with an odd number of tetrahedra are rare (with the exception of the more frequent 5MR), while even-numbered rings are ubiquitous (4MR, 6MR, 8MR, 10MR,

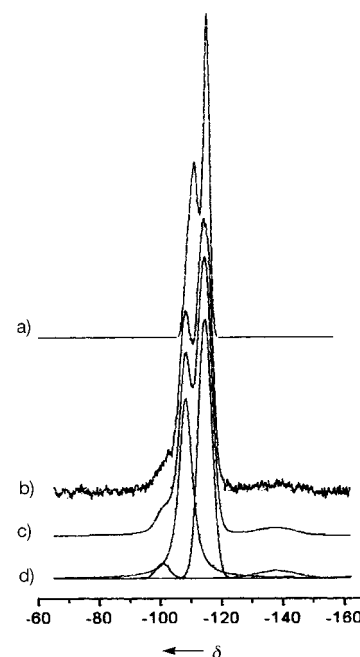


Figure 6. ²⁹Si MAS NMR spectra of as-synthesized SSZ-23: a) Simulation using the Si–O–Si angles obtained in this work and the equation of Thomas et al.^[9] b) Experimental spectrum. c) Simulation with all deconvoluted components. d) Individual deconvoluted components.

Table 1. Fractional coordinates and equivalent isotropic displacement parameters U_{equiv} for SSZ-23.^[a]

Atom	x	y	z	$U_{\text{equiv}} [\text{\AA}^2]$	Atom	x	y	z	$U_{\text{eq}} [\text{\AA}^2]$
Si(1)	0.59105(15)	0.16686(9)	0.20389(14)	0.0097(4)	O(18)	0.6618(5)	0.1137(3)	0.1752(5)	0.0302(14)
Si(2)	0.6351(2)	0.16809(9)	0.44152(15)	0.0127(4)	O(19)	0.4741(4)	0.1588(2)	0.1421(4)	0.0230(13)
Si(3)	0.69632(15)	0.57232(9)	−0.03740(15)	0.0107(4)	O(20)	0.5929(4)	0.3488(2)	0.4575(4)	0.0209(12)
Si(4)	0.66614(15)	0.49124(9)	0.13311(14)	0.0094(4)	O(21)	0.5313(4)	0.0435(3)	0.5938(4)	0.0231(13)
Si(5)	0.6625(2)	0.29875(9)	0.21813(15)	0.0112(4)	O(22)	0.2550(4)	0.4651(3)	0.4069(4)	0.0271(14)
Si(6)	0.6889(2)	0.30373(9)	0.44861(15)	0.0112(4)	O(23)	0.7727(4)	0.5288(3)	−0.0852(5)	0.0308(15)
Si(7)	0.5039(2)	0.40460(10)	0.1951(2)	0.0148(4)	O(24)	0.6977(5)	0.5644(3)	0.4059(4)	0.0300(15)
Si(8)	0.4663(2)	0.09638(9)	0.52554(15)	0.0118(4)	O(25)	0.1585(5)	0.5697(2)	0.4003(4)	0.0263(13)
Si(9)	0.7777(2)	0.55142(9)	0.33339(15)	0.0117(4)	O(26)	0.7033(4)	0.2962(3)	0.3361(4)	0.0226(13)
Si(10)	0.36884(14)	0.00001(9)	0.37794(14)	0.0082(4)	O(27)	0.5580(4)	0.3389(2)	0.1887(4)	0.0208(12)
Si(11)	0.1541(2)	0.50214(9)	0.35464(14)	0.0119(4)	O(28)	0.8602(4)	0.4980(3)	0.3767(4)	0.0244(13)
Si(12)	0.8221(2)	0.38557(9)	0.1683(2)	0.0133(4)	O(29)	0.0522(5)	0.4660(3)	0.3707(5)	0.036(2)
Si(13)	0.5381(2)	0.41447(10)	0.4240(2)	0.0203(5)	O(30)	0.3415(5)	0.0086(3)	0.2609(4)	0.0292(14)
Si(14)	0.8892(2)	0.37328(9)	0.55406(15)	0.0108(4)	O(31)	0.7965(4)	0.3253(2)	0.5173(4)	0.0219(12)
Si(15)	0.3487(2)	0.46238(10)	0.5030(2)	0.0159(5)	O(32)	0.6054(4)	0.4709(3)	0.4705(5)	0.037(2)
Si(16)	0.9363(2)	0.44089(10)	0.3693(2)	0.0164(5)	N(1)	0.2428(8)	0.7703(5)	0.1550(11)	0.081(4)
O(1)	0.6380(4)	0.5326(2)	0.0329(4)	0.0136(11)	C(1)	0.3457(7)	0.7267(4)	0.1737(7)	0.034(2)
O(2)	0.5926(4)	0.1660(3)	0.3221(4)	0.0242(13)	C(2)	0.5292(15)	0.7219(12)	0.1601(26)	0.171(13)
O(3)	0.9008(5)	0.4015(3)	0.2708(4)	0.035(2)	C(3)	0.3687(15)	0.7103(9)	0.2776(11)	0.116(7)
O(4)	0.6618(4)	0.2360(2)	0.4841(4)	0.0190(12)	C(4)	0.4504(11)	0.6122(6)	0.2391(12)	0.078(4)
O(5)	0.5436(4)	0.1450(2)	0.4930(4)	0.0220(13)	C(5)	0.4773(16)	0.6709(7)	0.2948(12)	0.097(6)
O(6)	0.7546(4)	0.3237(2)	0.1668(4)	0.0179(12)	C(6)	0.2674(14)	0.8296(6)	0.2124(12)	0.105(6)
O(7)	0.7534(4)	0.4429(2)	0.1182(4)	0.0218(12)	C(7)	0.5595(13)	0.7035(8)	0.2696(20)	0.137(10)
O(8)	0.6365(4)	0.2305(2)	0.1751(4)	0.0157(11)	C(8)	0.3194(13)	0.6723(6)	0.1102(15)	0.130(9)
O(9)	0.4366(4)	0.4154(3)	0.4794(4)	0.0233(13)	C(9)	0.4313(10)	0.7629(7)	0.1453(15)	0.100(6)
O(10)	0.9431(4)	0.3958(3)	0.4641(4)	0.0204(12)	C(10)	0.4250(16)	0.6300(8)	0.1223(20)	0.149(12)
O(11)	0.3965(4)	0.1321(2)	0.5894(4)	0.0132(11)	C(11)	0.1602(12)	0.7437(10)	0.1979(23)	0.205(15)
O(12)	0.5605(4)	0.4591(2)	0.1489(4)	0.0208(12)	C(12)	0.5153(23)	0.6654(12)	0.1113(18)	0.158(13)
O(13)	0.6119(4)	0.6022(2)	−0.1252(4)	0.0188(12)	C(13)	0.2111(18)	0.7845(10)	0.0455(15)	0.188(14)
O(14)	0.7357(4)	0.1251(3)	0.4725(4)	0.0260(13)	F(1) ^[b]	0.7395(11)	0.4040(7)	0.2683(10)	0.025
O(15)	0.4869(4)	0.4187(3)	0.3065(4)	0.0268(13)	F(2) ^[b]	0.6632(13)	0.4191(8)	0.3659(13)	0.025
O(16)	0.3942(4)	0.0661(2)	0.4285(4)	0.0187(12)	F(3) ^[b]	0.6473(27)	0.4140(16)	0.2743(26)	0.025
O(17)	0.7114(4)	0.5353(2)	0.2244(4)	0.0219(13)					

[a] Numbers in parentheses represent the estimated standard deviations on the last digit or digits. The fluorine displacement parameters are fixed. [b] The fluoride ion site occupancies, SOF, for F(1)–F(3) are 0.317(10), 0.262(10), and 0.131(10).

12MR). In the very few cases in which 3MRs, 7MRs, or 9MRs are known, their presence is associated with either Zn^{2+} or Be^{2+} sites in the tetrahedral building units or to a very specific templating effect. Thus, the LOV, VSV, and RSN structure types represent the only zeolite-type materials to possess a fully connected three-dimensional network of tetrahedra with 3MR and 9MRs, and all of them have Zn^{2+} or Be^{2+} sites in the structure.^[1] On the other hand, ZSM-18 (MEI) is the only known zeolite with 7MRs.^[12]

With our knowledge of the structural features, we can now explain previous catalytic studies that showed that SSZ-23 produced *para*-xylene selectively during the conversion of methanol into aromatic hydrocarbons.^[6] The initial interpretation was that the structure possessed 10MR pore openings. In addition, adsorption data showed that *n*-hexane was adsorbed much more readily than 3-methylpentane and 2,2-dimethylbutane, in strong contrast to ZSM-5. With the knowledge of the structure, we see that these data are explained by the 9MR pore openings, which have free diameters of $5.4 \times 3.8 \text{ \AA}$. The 7MRs are considerably smaller, with free diameters of $3.5 \times 2.5 \text{ \AA}$. An immediate application of such 9MR zeolites would be in the isomerization of xylenes, because *para*-xylene is a mainstay of the fabric industry through its conversion into terephthalic acid. Further work is in progress to investigate further the shape-selective properties of 9MR structures. We also wish to emphasize that it is

unlikely that any technique other than microcrystalline diffraction could have yielded the structure. The low symmetry and large unit cell result in sixteen tetrahedral cation sites in the asymmetric unit, making *ab initio* solution from powder data improbable. Moreover, the lack of a suitable projection axis means that high-resolution electron microscopy could not have yielded crucial information, and model building approaches would have been hampered by the absence of accepted secondary building units as starting points. Indeed, SSZ-23 had already remained unsolved for a decade before the advent of both improved synthetic methods using fluoride ions and the extremely powerful technique of microcrystalline diffraction.

Experimental Section

Synthesis of purely siliceous SSZ-23: Tetraethylorthosilicate (10.42 g) was hydrolyzed in an aqueous solution of TMAOH (32.56 g of a 0.767 M solution). The ethanol produced, together with some water, was allowed to evaporate completely (within the limit of detection of ^1H NMR spectroscopy) at room temperature under stirring. Then, HF (1.033 g, 48% aq) diluted in water (0.91 g) was added, and the white slurry formed was placed into Teflon-lined 60-mL stainless steel autoclaves. The reaction mixture (1.0 SiO_2 :0.50 TMAOH:0.50 HF:15 H_2O) was heated at 150°C under rotation (60 r min^{-1}) for 30 d. The solid product was recovered by filtration (80% yield, based on SiO_2), washed with distilled water, and dried at 100°C .

Single-crystal X-ray diffraction: A small single fragment ($20 \times 20 \times 5 \text{ \mu m}^3$) of a twinned crystal of pure silica SSZ-23 was used. X-ray diffraction data

were collected at 160 K with a Bruker AXS SMART CCD area-detector diffractometer on the high-flux single-crystal diffraction station 9.8 at CCLRC Daresbury Laboratory Synchrotron Radiation Source, with a wavelength of 0.6849 Å selected by a horizontally focusing silicon (111) monochromator and vertically focused by a cylindrically bent palladium-coated zerodur mirror.^[13] The data set covered more than a hemisphere of reciprocal space with several series of exposures, each series with a different crystal orientation and each exposure taken over 0.2° rotation. Corrections were made for the decay of the synchrotron beam intensity as part of standard interframe scaling procedures.^[14] The SSZ-23 sample was examined in the as-synthesized form and therefore included the template and charge-balancing fluoride ions. The crystal structure of SSZ-23 was solved with the direct methods program SHELXS-97^[14] and refined with a full-matrix least-squares technique with the program SHELXL-97.^[14] The final cycle of least-squares refinement included anisotropic displacement parameters for silicon, oxygen, carbon, and nitrogen atoms, and fractional occupancies for the fluorine atoms. The hydrogen atoms of the template molecule were placed in chemically sensible positions, and their positions were recalculated after each cycle of refinement. A total of 22014 integrated intensities were measured ($1.79 < \theta < 28.27^\circ$), of which 8314 were unique and 4665 observed ($F^2 > 2\sigma(F^2)$). The large proportion of unobserved reflections is due to the small size of the crystal. Final refinement of the 571 least-squares parameters converged to $wR(F^2_{\text{obs}}) = 0.1657$, $wR(F^2_{\text{all data}}) = 0.2028$, $R(F_{\text{obs}}) = 0.0811$, $S(F^2_{\text{all data}}) = 0.992$; max. residual electron density = 0.744 e Å⁻³. Refinement on F^2 was carried out against all data; the observed criterion $F^2 > 2\sigma(F^2)$ was used only for the calculation of $wR(F^2_{\text{obs}})$ and $R(F_{\text{obs}})$ and is not relevant to the choice of reflections for refinement. The final unit cell was refined to $a = 12.9594(3)$, $b = 21.7919(6)$, $c = 13.5980(4)$ Å, and $\beta = 101.855(2)^\circ$, $V = 3758.3(2)$ Å³ at $T = 160$ K, space group $P2_1/n$, $\rho_{\text{calc}} = 2.13$ g cm⁻³. Details of the final atomic coordinates, equivalent isotropic displacement parameters, and fluoride ion occupancies are given in Table 1. Further details of the crystal structure investigation may be obtained from the Fachinformationzentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de) on quoting the depository number CSD-408348.

Received: February 27, 1998 [Z 11528IE]
German version: *Angew. Chem.* **1998**, *110*, 2234–2239

Keywords: heterogeneous catalysis • microporosity • synchrotron radiation • zeolites

- [1] W. M. Meier, D. H. Olson, C. Baerlocher, *Atlas of Zeolite Structure Types*, Elsevier, New York, **1996**.
- [2] M. E. Davis, C. Saldarriaga, C. Montes, J. M. Garces, C. Crowder, *Nature* **1988**, *331*, 698–699.
- [3] M. D. Shannon, J. L. Casci, P. A. Cox, S. J. Andrews, *Nature* **1991**, *353*, 417–420.
- [4] M. E. Leonowicz, J. A. Lawton, S. L. Lawton, M. K. Rubin, *Science* **1994**, *264*, 1910–1913.
- [5] C. C. Freyhardt, M. Tsapatsis, R. F. Lobo, K. J. Balkus, M. E. Davis, *Nature* **1996**, *381*, 295–298.
- [6] a) S. I. Zones, R. A. van Nordstrand, D. S. Santilli, D. M. Wilson, L. Yuen, L. D. Scampavia in *Zeolites: Facts, Figures, Future* (Eds.: P. A. Jacobs, R. A. van Santen) Elsevier, Amsterdam, **1989**, pp. 299–309; b) S. I. Zones, *Eur. Pat. Appl.* 231 018, **1987** [*Chem. Abstr.* **1987**, *107*, 179456f]; c) the pattern was indexed with the program TREOR90 and gave the space group symmetry $P2_1/n$, with unit-cell dimensions $a = 13.13(1)$, $b = 21.78(1)$, $c = 13.75(1)$ Å, and $\beta = 102.61(6)^\circ$.
- [7] G. Horvath, K. Kawazoe, *J. Chem. Eng. Jpn.* **1983**, *16*, 470–475.
- [8] C. Y. Chen, L. W. Finger, R. C. Medrud, P. A. Crozier, I. Y. Chan, T. V. Harris, S. I. Zones, *Chem. Commun.* **1997**, 1775–1776.
- [9] J. M. Thomas, J. Klinowski, S. Ramdas, B. K. Hunter, D. T. B. Tennakoon, *Chem. Phys. Lett.* **1983**, *102*, 158–161.
- [10] G. van de Goor, C. C. Freyhardt, P. Behrens, *Z. Anorg. Allg. Chem.* **1995**, *621*, 311–314.
- [11] H. Koller, A. Wölker, H. Eckert, C. Panz, P. Behrens, *Angew. Chem.* **1997**, *109*, 2939–2940; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2823–2825.

- [12] M. E. Davis, R. F. Lobo, *Chem. Mater.* **1992**, *4*, 756–768.
- [13] R. J. Cernik, W. Clegg, C. R. A. Catlow, G. Bushnell-Wye, J. V. Flaherty, G. N. Greaves, I. Burrows, D. J. Taylor, S. J. Teat, M. Hamichi, *J. Synchrotron Rad.* **1997**, *4*, 279–268.
- [14] G. M. Sheldrick, Programs SADABS and SHELX-97, Göttingen, **1997**.

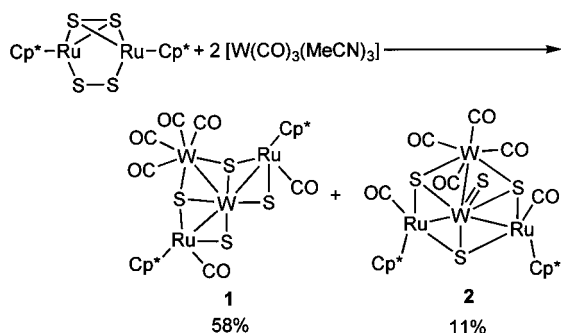
Formation of Isomeric Tetrathiotungstate Clusters $[\{\text{Cp}^*\text{Ru}(\text{CO})\}_2(\text{WS}_4)\{\text{W}(\text{CO})_4\}]$ by the Reaction of $[\text{Cp}^*\text{Ru}_2\text{S}_4]$ with $[\text{W}(\text{CO})_3(\text{MeCN})_3]$

Masahiro Yuki, Masaaki Okazaki, Shinji Inomata, and Hiroshi Ogino*

Dinuclear transition metal sulfur complexes of the type $[\text{Cp}^*_2\text{M}_2\text{S}_4]$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) are excellent starting materials for the formation of multinuclear transition metal sulfur clusters.^[1] However, surprisingly little is known about reactivity of the iron-^[2] or ruthenium-containing complexes.^[3] In 1994 our group reported the reactions of $[\text{Cp}^*_2\text{Fe}_2\text{S}_4]$ with iron and ruthenium carbonyl complexes to give *closo*- $[\text{Cp}^*_2(\text{CO})_3\text{Fe}_2\text{MS}_2]$ clusters ($\text{M} = \text{Fe}, \text{Ru}$).^[2] Rauchfuss et al. reported that the ruthenium analogue $[\text{Cp}^*_2\text{Ru}_2\text{S}_4]$ ^[4] reacts with $[\text{Cp}^*\text{Ru}(\text{MeCN})_3](\text{PF}_6)$ and $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{PF}_6)_2$ to give $[\text{Cp}^*_3\text{Ru}_3\text{S}_4](\text{PF}_6)^{[3a]}$ and $[\text{Cp}^*_3\text{RhRu}_2\text{S}_4(\text{MeCN})](\text{PF}_6)_2^{[3c]}$ respectively. To examine whether this cluster construction methodology can be applied generally, the thermal reaction of $[\text{Cp}^*_2\text{Ru}_2\text{S}_4]$ with $[\text{W}(\text{CO})_3(\text{MeCN})_3]$ was investigated, and is described here. In the reaction, there was a dramatic redistribution of CO and S ligands between the W and Ru centers to give geometric isomers of tetrathiotungstate clusters $[\{\text{Cp}^*\text{Ru}(\text{CO})\}_2(\text{WS}_4)\{\text{W}(\text{CO})_4\}]$. Furthermore, we observed thermal and photochemical interconversion between the two isomers.

A solution of $[\text{Cp}^*_2\text{Ru}_2\text{S}_4]$ in toluene was added to a solution of $[\text{W}(\text{CO})_3(\text{MeCN})_3]$ ^[5] (2 equiv) in acetonitrile (Scheme 1). The mixture was heated at 50 °C with stirring for 40 minutes. Evaporation of the volatile components and subsequent flash chromatographic separation of the residue over silica gel gave the two red-brown clusters **1** and **2** in 58 % and 11 % yield. Elemental analysis and mass spectrometry data indicated that **1** and **2** have the same formula $\text{Cp}^*_2\text{Ru}_2\text{W}_2\text{S}_4(\text{CO})_6$,^[6] which is consistent with a cubane-type mixed metal–sulfur cluster $[(\text{Cp}^*\text{Ru})_2(\text{W}(\text{CO})_3)_2(\mu_3\text{-S})_4]$. However, X-ray diffraction study disclosed that this is not the case.^[7] Cluster **1** was unequivocally determined to be $[\{\text{Cp}^*\text{Ru}(\text{CO})\}_2\{\text{W}(\mu_3\text{-S})_2(\mu_2\text{-S})_2\}\{\text{W}(\text{CO})_4\}]$ (Figure 1). Interestingly, according to the crystal structure of **1**, redistribution of CO and S ligands

[*] Prof. H. Ogino, M. Yuki, Dr. M. Okazaki, Dr. S. Inomata
Department of Chemistry, Graduate School of Science
Tohoku University
Sendai 980–8578 (Japan)
Fax: (+81) 22-217-6543
E-mail: ogino@agnus.chem.tohoku.ac.jp



Scheme 1. Synthesis of **1** and **2** in toluene/acetonitrile (50 °C, 40 min).

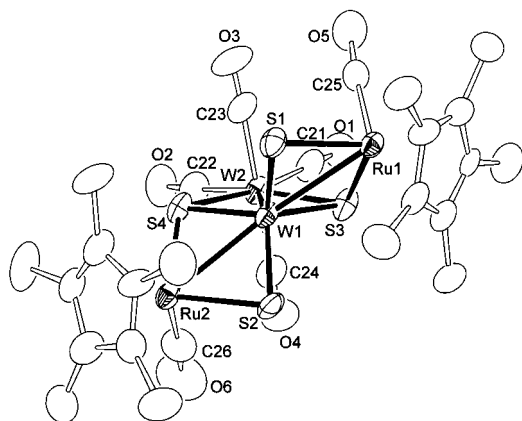


Figure 1. Structure of **1** (ellipsoids at the 50% probability level). Selected bond lengths [Å] and angles [°]: W1–W2 2.9053(7), W1–Ru1 2.874(2), W1–Ru2 2.869(2), W1–S1 2.212(3), W1–S2 2.196(3), W1–S3 2.268(4), W1–S4 2.272(3), W2–S3 2.551(3), W2–S4 2.553(3), Ru1–S1 2.403(4), Ru1–S3 2.387(3), Ru2–S2 2.395(3), Ru2–S4 2.384(4), O3...O5 3.18(2), O4...O6 3.19(2), W2–W1–Ru1 98.82(3), W2–W1–Ru2 98.98(3), Ru1–W1–Ru2 162.08(4), S1–W1–S2 111.8(1), S1–W1–S3 106.5(1), S1–W1–S4 109.1(1), S2–W1–S3 107.6(1), S2–W1–S4 106.9(1), S3–W1–S4 115.0(1).

takes place between Ru and W centers without the loss of any ligands. The W1 atom, with four S ligands, adopts a slightly distorted tetrahedral geometry with S–W–S angles of 106.5(1)–115.0(1)°. The WS₄ fragment is bound to one W atom by two S atoms and to two Ru atoms by four S atoms, two of which bridge one Ru and two W atoms in a μ_3 fashion; the other S atoms are bound to one Ru and one W atom in a μ_2 fashion. The Ru1 and Ru2 atoms each bear a Cp* and a CO ligand. The W2 atom, with four CO ligands and two S ligands, has a distorted octahedral geometry. The three metal–metal bond lengths (W1–W2 2.9053(7), W1–Ru1 2.874(2), and W1–Ru2 2.869(2) Å) lie in the normal range expected for metal–metal single bonds. The W–S bond lengths in W^{VI}(=S)₄ of 2.196(3)–2.272(3) Å are similar to those in tetrathiotungstate clusters previously reported, and confirm the unsaturated bonding character. In contrast, the bonds of the two μ_3 -S atoms (S3, S4) to the octahedral W2 atom (2.551(3), 2.553(3) Å) are 0.28 Å longer than those to the tetrahedral W1 atom. This reflects the dative bond character of the former bonds. The NMR spectroscopic data of **1** are consistent with the crystal structure (Figure 1).

The structure of [(Cp*₂Ru(CO))₂][W(μ_3 -S)₃(=S)][W(CO)₄] (**2**) is shown in Figure 2. Redistribution of CO and S ligands

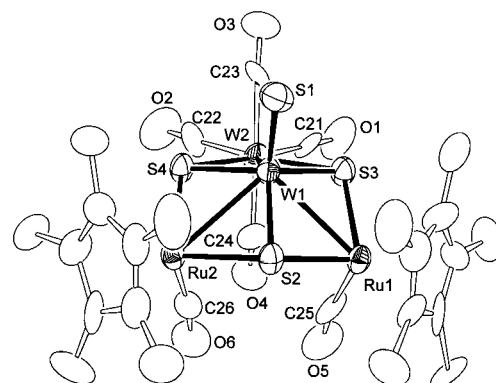


Figure 2. Structure of **2** (ellipsoids at the 50% probability level). Selected bond lengths [Å] and angles [°]: W1–W2 2.997(1), W1–Ru1 2.900(2), W1–Ru2 2.892(2), W1–S1 2.125(7), W1–S2 2.261(6), W1–S3 2.274(6), W1–S4 2.276(5), W2–S3 2.558(6), W2–S4 2.566(6), Ru1–S2 2.394(6), Ru1–S3 2.421(6), Ru2–S2 2.373(6), Ru2–S4 2.408(6), O4...O5 3.07(3), O4...O6 3.09(3), O5...O6 3.14(3), W2–W1–Ru1 95.45(5), W2–W1–Ru2 95.69(5), Ru1–W1–Ru2 94.55(6), S1–W1–S2 109.9(2), S1–W1–S3 110.2(3), S1–W1–S4 110.4(3), S2–W1–S3 107.4(2), S2–W1–S4 106.8(2), S3–W1–S4 112.0(2).

between the Ru and W centers was again observed, without the loss of any ligands. Unlike **1**, **2** has a terminal S ligand. The WS₄ fragment is bound to one W atom by two S atoms and to two Ru atoms by three S atoms, two of which bridge one Ru and two W atoms in a μ_3 fashion; the third S atom is bound to two Ru atoms and one W atom also in a μ_3 fashion. Three metal–metal bonds (W1–W2 2.997(1), W1–Ru1 2.900(2), and W1–Ru2 2.892(2) Å) are somewhat longer than those in **1**. The elongation of the metal–metal bonds is attributable to the large steric repulsion between CO ligands on W2 and the two Ru atoms in **2** (O4...O5 3.07(3), O4...O6 3.09(3), and O5...O6 3.14(3) Å). All spectroscopic data indicate that the molecular structure of **2** in the crystal is maintained in solution.

Investigations of the reactivity of **1** and **2** revealed that isomerization between **1** and **2** occurred both thermally and photochemically in solution [Eq. (1)]. When a solution of **1** in



[D₆]benzene was irradiated, the amount of **1** decreased while the amount of **2** increased. Cluster **1** disappeared completely after one hour of irradiation, and **2** was formed in approximately 50% yield with the deposition of an unidentified brown precipitate. Thermolysis of a solution of **2** in [D₆]benzene at 80 °C for two hours caused **2** to disappear completely to yield **1** in approximately 90% yield. The difference in thermodynamic stability between **1** and **2** may be due to steric reasons: The steric crowding between CO ligands on W and the two Ru atoms is less severe in cluster **1** than in **2**.

The tetrathiometalates [MS₄]²⁻ have been employed as building blocks for the synthesis of transition metal clusters for the last three decades. However, there are still few examples of [MS₄]²⁻ coordinated to organometallic fragments.^[8] Our system is the first example in which the [MS₄]²⁻ unit combines with three organometallic moieties. The

mechanism and general scope of application of this reaction are now under investigation.

Experimental Section

1 and 2: A solution of $[\text{Cp}^*_2\text{Ru}_2\text{S}_4]$ (161 mg, 0.268 mmol) in toluene (15 mL) was added to a solution of $[\text{W}(\text{CO})_5(\text{MeCN})_3]$ in acetonitrile, which was prepared by refluxing a solution of $[\text{W}(\text{CO})_6]$ (189 mg, 0.536 mmol) in acetonitrile (5 mL). The mixture was heated with stirring at 50 °C for 40 min. The volatile components were removed under reduced pressure, and the residue was extracted with toluene/hexane (1/1, 10 mL). Compounds **1** and **2** were obtained from the extracted solution and the insoluble material as follows: the extracted solution was subjected to flash column chromatography (silica gel, eluent toluene/hexane (1/1)). A red-brown fraction was concentrated to give **1** in 58% yield. An analytically pure sample was obtained by recrystallization from dichloromethane/hexane. The insoluble dark brown residue was dissolved in dichloromethane and subjected to flash column chromatography (silica gel, eluent dichloromethane). The red-brown fraction was collected, and the solution was concentrated to give red-brown **2** in 11% yield. Analytically pure **2** was obtained by recrystallization from toluene/hexane.

1: Elemental analysis calcd for $\text{C}_{26}\text{H}_{30}\text{O}_6\text{Ru}_2\text{S}_4\text{W}_2$: C 27.48, H 2.66; found C 27.83, H 2.74; MS (FAB, Xe, *m*-nitrobenzyl alcohol matrix): m/z : 1138 $[M^+]$; IR (KBr): $\tilde{\nu}_{\text{max}}[\text{cm}^{-1}]$ = 2031, 1975, 1959, 1921, 1848 ν_{CO} ; ^1H NMR ($[\text{D}_6]$ benzene): δ = 1.68 (s, 30H, Cp*), ^{13}C NMR ($[\text{D}_6]$ benzene): δ = 207.8, 204.3, 200.5 (CO), 100.5 (C_5Me_5), 10.2 (C_5Me_5); UV/Vis (toluene): $\lambda_{\text{max}}[\text{nm}]$ ($\epsilon[\text{cm}^{-1}\text{M}^{-1}]$) = 314 (1.7×10^4), 349 (1.5×10^4), 408 (1.2×10^4), 480 (sh), 535 (sh).

2: Elemental analysis calcd for $\text{C}_{26}\text{H}_{30}\text{O}_6\text{Ru}_2\text{S}_4\text{W}_2$: C 27.48, H 2.66; found C 27.71, H 2.95; MS (FAB, Xe, *m*-nitrobenzyl alcohol matrix): m/z : 1138 $[M^+]$; IR (KBr): $\tilde{\nu}_{\text{max}}[\text{cm}^{-1}]$ = 2019, 1975, 1905(sh), 1882 ν_{CO} ; ^1H NMR ($[\text{D}_6]$ benzene): δ = 1.59 (s, 30H, Cp*), ^{13}C NMR ($[\text{D}_2]$ dichloromethane): δ = 209.7, 208.1, 205.3, 196.2 (CO), 100.4 (C_5Me_5), 10.3 (C_5Me_5); UV/Vis (toluene): $\lambda_{\text{max}}[\text{nm}]$ ($\epsilon[\text{cm}^{-1}\text{M}^{-1}]$) = 325 (2.4×10^4), 429 (1.1×10^4), 510 (8.2×10^3), 682 (2.3×10^3).

Received: February 13, 1998 [Z11478IE]
German version: *Angew. Chem.* **1998**, *110*, 2232–2234

Keywords: clusters • isomerizations • ruthenium • sulfur • tungsten

- [1] J. Wachter, *Angew. Chem.* **1989**, *101*, 1645–1658; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1613–1626, and references therein.
- [2] T. Mitsui, S. Inomata, H. Ogino, *Inorg. Chem.* **1994**, *33*, 4934–4936.
- [3] a) E. J. Houser, H. Krautscheid, T. B. Rauchfuss, S. R. Wilson, *J. Chem. Soc. Chem. Commun.* **1994**, 1283–1284; b) Q. Feng, T. B. Rauchfuss, S. R. Wilson, *J. Am. Chem. Soc.* **1995**, *117*, 4702–4703; c) A. Venturelli, T. B. Rauchfuss, A. K. Verma, *Inorg. Chem.* **1997**, *36*, 1360–1365.
- [4] T. B. Rauchfuss, D. P. S. Rodgers, S. R. Wilson, *J. Am. Chem. Soc.* **1986**, *108*, 3114–3115.
- [5] D. P. Tate, W. R. Knipple, J. M. Augl, *Inorg. Chem.* **1962**, *1*, 433–434.
- [6] Only one example of structurally characterized geometric isomers is known for sulfur clusters: a) P. Braunstein, J. M. Jud, A. Tiripicchio, M. Tiripicchio-Camellini, E. Sappa, *Angew. Chem.* **1982**, *94*, 318–319; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 307–308; b) P. D. Williams, M. D. Curtis, D. N. Duffy, W. M. Butler, *Organometallics* **1983**, *2*, 165–167.
- [7] Crystal data for **1**: $\text{C}_{26}\text{H}_{30}\text{O}_6\text{Ru}_2\text{S}_4\text{W}_2$, M_r = 1136.60, crystal dimensions $0.50 \times 0.40 \times 0.25 \text{ mm}^3$, a = 22.41(1), b = 13.432(6), c = 11.148(3) Å, β = 90.07(3)°, V = 3355(2) Å³, T = 293 K, monoclinic, space group $P2_1/n$ (no. 14), Z = 4, ρ_{calcd} = 2.249 g cm^{−3}, ρ_{found} = 2.23 g cm^{−3}, $F(000)$ = 2136, μ = 80.08 cm^{−1}, Rigaku AFC6S diffractometer, MoK α radiation (λ = 0.71069 Å), graphite monochromator, scan mode $\omega - 2\theta$, $2\theta_{\text{max}}$ = 55.0°, 8247 measured reflections, Lorentz-polarization and absorption correction (transmission factors: 0.7316–1.0000), 4762 observed reflections with ($I > 3\sigma(I)$), Patterson methods (DIRDIF92 PATTY), full-matrix least-squares refinement, 361 parameters, H atoms not located, R = 0.045 and R_w = 0.065 ($w = 1/(\sigma^2 F_o)$), max. residual electron

density 1.09 e Å^{−3}. Crystal data for **2**: $\text{C}_{28}\text{H}_{34}\text{Cl}_4\text{O}_6\text{Ru}_2\text{S}_4\text{W}_2$, M_r = 1306.47, crystal dimensions $0.30 \times 0.20 \times 0.15 \text{ mm}^3$, a = 15.642(8), b = 11.132(6), c = 23.463(4) Å, β = 96.64(2)°, V = 4058(2) Å³, T = 293 K, monoclinic, space group $P2_1/c$ (no. 14), Z = 4, ρ_{calcd} = 2.138 g cm^{−3}, ρ_{found} = 2.1 g cm^{−3}, $F(000)$ = 2472, μ = 68.92 cm^{−1}, Rigaku AFC6S diffractometer, MoK α radiation (λ = 0.71069 Å) graphite monochromator, scan mode $\omega - 2\theta$, $2\theta_{\text{max}}$ = 55.0°, 10167 measured reflections, Lorentz-polarization, decay (27.4%) and absorption correction (transmission factors: 0.7988–1.0000), 3634 observed reflections with ($I > 3\sigma(I)$), Patterson methods (DIRDIF92 PATTY), full-matrix least-squares refinement, 415 parameters, H atoms not located, R = 0.056 and R_w = 0.075 ($w = 1/(\sigma^2 F_o)$), max. residual electron density 2.12 e Å^{−3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101083. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [8] a) K. E. Howard, T. B. Rauchfuss, S. R. Wilson, *Inorg. Chem.* **1988**, *27*, 3561–3567; b) P. A. Shapley, Z. Gebeyehu, N. Zhang, S. R. Wilson, *ibid.* **1993**, *32*, 5646–5651; c) S. Ogo, T. Suzuki, K. Isobe, *ibid.* **1995**, *34*, 1304–1305; d) B. Zhuang, P. Yu, L. Huang, L. He, J. Lu, *Polyhedron* **1994**, *13*, 125–131; e) W. J. Evans, M. A. Ansari, J. W. Ziller, S. I. Khan, *Organometallics* **1995**, *14*, 3–4; f) J. Ruiz, V. Rodríguez, G. López, P. A. Chaloner, P. B. Hitchcock, *J. Organomet. Chem.* **1995**, *493*, 77–82; g) Y. Mizobe, M. Hosomizu, Y. Kubota, M. Hidai, *J. Organomet. Chem.* **1996**, *507*, 179–185.

$[\text{Re}_5(\mu\text{-H})_4(\text{CO})_{20}]^-$ and $[\text{Re}_5(\mu\text{-H})_5(\text{CO})_{20}]$, Two Isolobal Analogues of Cyclopentane

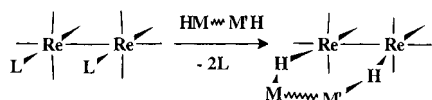
Mirka Bergamo, Tiziana Beringhelli, Giuseppe D'Alfonso,* Pierluigi Mercandelli, Massimo Moret,* and Angelo Sironi

The $\text{ReH}(\text{CO})_4$ fragment, isoelectronic with d⁸ $\text{M}(\text{CO})_4$, can be considered isolobal with (singlet) methylene,^[1] as far as the formation of metal–metal interactions is concerned, since its frontier orbitals allow the interaction with two metal centers. The known $[\text{ReH}(\text{CO})_4]_n$ oligomers ($n = 2–4$)^[2] are therefore isolobal analogues of the corresponding $(\text{CH}_2)_n$ species: $[\text{Re}_2(\mu\text{-H})_2(\text{CO})_8]$ is an ethylene-like molecule,^[2b] and the triangular and square-planar clusters $[\text{Re}_3(\mu\text{-H})_3(\text{CO})_{12}]$ and $[\text{Re}_4(\mu\text{-H})_4(\text{CO})_{16}]$ “correspond” to cyclopropane and cyclobutane, respectively. Interestingly, until now no organometallic analogue of the most stable $(\text{CH}_2)_n$ oligomers (i.e., those with $n = 5$ or 6) was known. The pentanuclear cyclic clusters $[\text{Re}_5(\mu\text{-H})_5(\text{CO})_{20}]^{n-}$ ($n = 0, 1$) reported here fill this gap, at least partially.

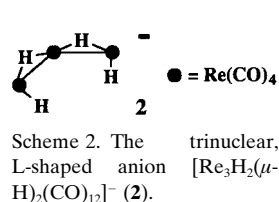
We recently exploited the σ -donor capability of transition metal hydrides^[3–5] in the synthesis of open-chain tri- and

- [*] Prof. G. D'Alfonso, Dr. M. Bergamo, Prof. T. Beringhelli
Dipartimento di Chimica Inorganica,
Metallorganica e Analitica e Centro CNR CSSMTBO
Via Venezian 21, I-20133 Milano (Italy)
Fax: (+39) 2-2362748
E-mail: dalf@csmtbo.mi.cnr.it
Dr. M. Moret, Dr. P. Mercandelli, Prof. A. Sironi
Dipartimento di Chimica Strutturale e
Stereochemica Inorganica e Centro CNR CSSMTBO,
Via Venezian 21, I-20133 Milano (Italy)

tetranuclear clusters,^[6,7] by allowing hydrido–carbonyl rhenates to react with $[\text{Re}_2(\text{CO})_9\text{L}]$, where L is a very labile ligand such as THF or H_2O (the otherwise labile MeCN ligand is not labile enough to be substituted by neutral^[8] or anionic^[6] hydride complexes). Recently the di-substituted complex 1,2-*eq,eq*- $[\text{Re}_2(\text{CO})_8(\text{THF})_2]$ (**1**) was obtained by the reaction of $[\text{Re}_2(\mu\text{-H})_2(\text{CO})_8]$ with diazomethane.^[9] The success of this reaction suggests that ring clusters could be obtained, as shown in Scheme 1, by reaction with complexes that contain two terminal hydride groups and are therefore able to act as bidentate “ligands”. We have prepared one such species, the



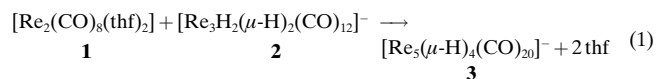
Scheme 1. Synthesis of ring clusters.



Scheme 2. The trinuclear, L-shaped anion $[\text{Re}_3\text{H}_2(\mu\text{-H})_2(\text{CO})_{12}]^-$ (**2**).

trinuclear L-shaped anion $[\text{Re}_3\text{H}_2(\mu\text{-H})_2(\text{CO})_{12}]^-$ (**2**, Scheme 2), by addition of $[\text{ReH}_2(\text{CO})_4]^-$ to $[\text{Re}_2(\mu\text{-H})_2(\text{CO})_8]$ in a reaction analogous to the previously reported addition of $[\text{Re}(\text{CO})_5]^-$ to $[\text{Re}_2(\mu\text{-H})_2(\text{CO})_8]$.^[6] The

treatment of **1** with a stoichiometric amount of **2** afforded the novel cyclic pentanuclear cluster anion $[\text{Re}_5(\mu\text{-H})_4(\text{CO})_{20}]^-$ (**3**) in high yield as determined spectroscopically [Eq. (1)].



The addition of stoichiometric amounts of $\text{CF}_3\text{SO}_3\text{H}$ to anion **3** in CH_2Cl_2 gave the neutral derivative $[\text{Re}_5(\mu\text{-H})_5(\text{CO})_{20}]$ (**4**) in quantitative yield, as shown by IR and NMR spectroscopy.

The metal frameworks of clusters **3**^[10] and **4**^[13] (80 valence electrons) exhibit an uncommon cyclopentane-like geometry, unprecedented among purely hydrido–carbonyl clusters (Figures 1 and 2). Previous examples of carbonyl compounds with a pentacyclic arrangement of the metal atoms have extra ligands bridging the metal atoms across the ring that contribute to the stabilization of the metallic core; see for example the $\text{Ru}_5(\mu_5\text{-C}_2)$ clusters^[14a–d] and, particularly significant to the present study, the isoelectronic $[\text{Mn}_5(\mu_5\text{-In})(\text{CO})_{20}]^{2-}$ anion.^[14e]

The Re_5 ring in anion **3** and in the two crystallographically independent molecules **4a** and **4b** is built up of five octahedral $\text{Re}(\text{CO})_4$ units with local idealized C_{2v} symmetry. Their relative conformations can be described as *e/s/s/e* (*e* = eclipsed, *s* = staggered) starting from Re1-Re2 ; the eclipsed Re-H-Re interactions are longer than the staggered ones (see Figures 1 and 2).

The local steric arrangement of the CO groups and the results of potential energy calculations on atom pairs^[15] suggest that all the Re-H vectors, in both **3** and **4**, point *inside* the metal ring. This feature was first observed for two of the

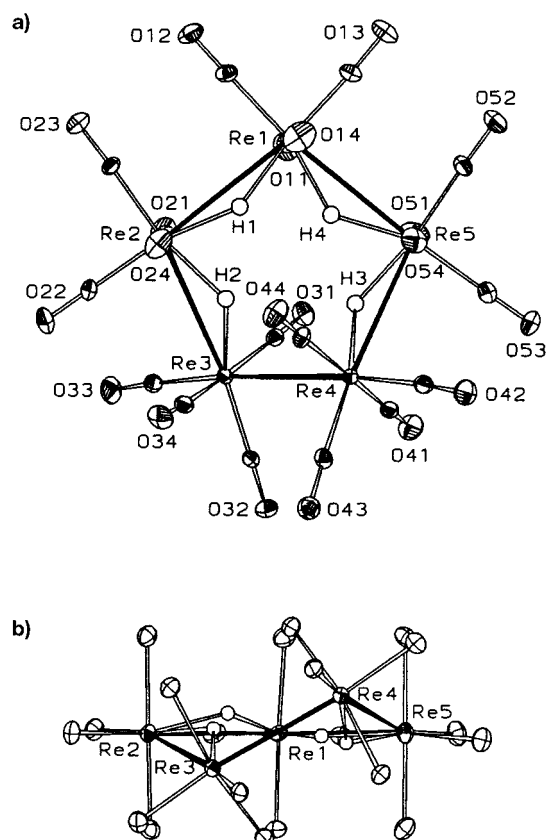


Figure 1. Ortep drawing of anion **3**. a) Top view. b) The same anion viewed along the Re2-Re1-Re5 bisector. Metal–metal bond lengths [Å]: Re1-Re2 3.455(1), Re2-Re3 3.280(1), Re3-Re4 3.086(1), Re4-Re5 3.302(1), Re5-Re1 3.416(1).

$\text{Re}(\mu\text{-H})\text{Re}$ interactions in $[\text{Re}_4(\mu\text{-H})_4(\text{CO})_{16}]$.^[2a] Here *all* the $\mu\text{-H}$ bridges can lie simultaneously inside the Re_5 moiety because the metallacycle is puckered and not strictly planar as in the cyclobutane analogue.^[2a]

Analysis of the ring conformation with the puckering coordinates of Rao et al.^[16] gave a twisted conformation on the Re3-Re4 bond for **3** (Figure 1b), with a puckering amplitude $\tau_m = 48.0^\circ$ and a pseudorotation parameter $P = 252.5^\circ$ (calculated from the endocyclic torsion angles and with the bond Re1-Re2 taken as the reference). The resulting anion possesses idealized C_2 symmetry with the twofold axis passing through Re1 and the middle of the unbridged Re3-Re4 edge. The λ conformation of the Re_5 ring is shown in Figure 1b.

One of the two independent molecules in **4** (**4a**) exhibits features similar to **3** (twisted conformation on the Re3-Re4 edge, $\tau_m = 47.2^\circ$, $P = 255.9^\circ$), even though all the Re-Re edges are bridged by hydrogen and longer than in **3** (Re1-Re2 and Re1-Re5 are particularly long; the former is the longest among pure hydrido–carbonyl rhenium complexes). In contrast, in **4b** (Figure 2), the Re_5 ring has an almost envelope conformation on Re4 (Figure 2b) with $\tau_m = 49.8^\circ$ and $P = 262.6^\circ$.^[17] A conformational change such as this is associated with rotation about the Re2-Re3 edge. The molecule **4b** has an average C-Re2-Re3-C torsion angle of $32(3)^\circ$, which is closer to staggered (45°) than eclipsed (0°).

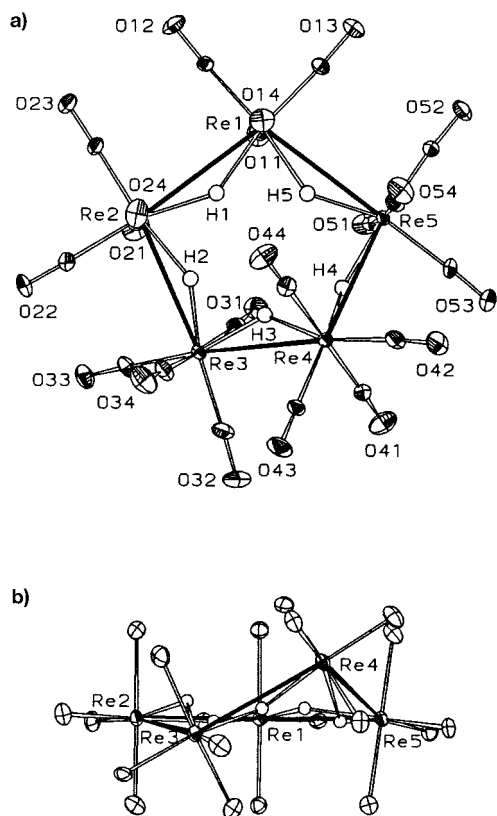


Figure 2. Ortep drawing of **4b**. a) Top view. b) The same molecule viewed along the Re2–Re1–Re5 bisector, to show the envelope conformation. Metal–metal bond lengths (the values for **4a** are given in square brackets) [Å]: Re1–Re2 3.4967(5) [3.4934(5)], Re2–Re3 3.3537(5) [3.3663(5)], Re3–Re4 3.3546(6) [3.3308(6)], Re4–Re5 3.3406(5) [3.3286(5)], Re5–Re1 3.4620(6) [3.4696(6)] (mean Re–Re bond length 3.402 in **4b**, 3.398 in **4a**).

The presence of two significantly different conformations in the same crystal, which are both on the pseudorotation path for pentaatomic rings (the puckering amplitude is almost the same in all the three species **3**, **4a**, and **4b**), stems from the high flexibility of these molecules, so that packing forces are sufficient to drive these clusters into different conformations. In agreement with this, only two sharp resonances for carbonyl groups (axial and equatorial CO groups) were observed in the ^{13}C NMR spectra of **3** and **4** in solution, even at 193 K. For **3**, this also implies fast scrambling of the four H ligands over the five Re–Re bonds.

In spite of the octahedral coordination at the Re centers, the puckering amplitude of these rhenium species is comparable with that observed for organic five-membered rings of tetrahedral carbon atoms.^[16] The puckering features therefore make these clusters even more akin to the purely organic cycloalkanes, and further demonstrate that isolobality may lead to more than a purely formal relationship.

Experimental Section

The addition of $[\text{Re}_2(\mu\text{-H})_2(\text{CO})_8]$ (143 mg, 0.240 mmol) to a solution of $[\text{NEt}_4][\text{ReH}_2(\text{CO})_4]$ (103 mg, 0.240 mmol) in THF at 273 K afforded the trinuclear anion **2** instantaneously, as shown by IR spectroscopy. The solvent was removed under vacuum, and the residue was treated with Et_2O (ca. 10 mL) and filtered. Addition of *n*-hexane gave a yellow precipitate of spectroscopically pure **2** (160 mg, 0.156 mmol, 65% yield). IR (THF): $\nu(\text{CO}) = 2098\text{w}$, 2067m , 2031w , 2002vs , 1989s , 1970ms , 1929m cm^{-1} ;

^1H NMR ($[\text{D}]_8\text{THF}$, 193 K): $\delta = -5.82(2)$, $-16.10(2)$. The $[\text{PPh}_4]^+$ salt was prepared in the same way.

A sample of $[\text{NEt}_4]\textbf{2}$ (88 mg, 0.0856 mmol) dissolved in THF was treated at 273 K with a solution of **1** (2 mL, ca. 0.045 M) in THF. The solution was allowed to warm up to room temperature, and was then evaporated to dryness. The residue was dissolved in CH_2Cl_2 , and IR spectroscopy showed the fast formation of **3**, which was complete within 10 min. Workup with $\text{Et}_2\text{O}/n$ -hexane afforded 85 mg of spectroscopically pure $[\text{NEt}_4]\textbf{3}$ (61% yield). IR (CH_2Cl_2): $\nu(\text{CO}) = 2115\text{vw}$, 2092m , 2053mw , 2028vs , 2005s , 1994sh , 1953ms , 1885mw cm^{-1} ; ^1H NMR ($[\text{D}]_8\text{THF}$, 193 K): $\delta = -15.74$; ^{13}C NMR ($[\text{D}]_8\text{THF}$, 193 K): $\delta = 192.1(1)$, $187.8(1)$.

A sample of $[\text{NEt}_4]\textbf{3}$ (30 mg, 0.018 mmol) in CD_2Cl_2 was treated with $\text{CF}_3\text{SO}_3\text{H}$ (1.8 μL , 0.020 mmol) at 193 K. The solution changed from yellow-orange to colorless, and IR spectroscopy showed that **4** had formed quantitatively. The solution was filtered through Florosil, concentrated and recrystallized from $\text{CH}_2\text{Cl}_2/n$ -hexane to give colorless crystals of **4**. IR (THF): $\nu(\text{CO}) = 2107\text{m}$, 2094w , 2038vs , 2013s , 1968mw cm^{-1} ; ^1H NMR ($[\text{D}]_8\text{THF}$, 193 K): $\delta = -17.22$; ^{13}C NMR ($[\text{D}]_8\text{THF}$, 193 K): $\delta = 182.5(1)$, $180.8(1)$.

Received: February 27, 1998 [Z11530IE]

German version: *Angew. Chem.* **1998**, *110*, 2201–2203

Keywords: carbonyl complexes • clusters • hydrides • isolobal relationship • rhenium

- [1] R. Hoffmann, *Angew. Chem.* **1982**, *94*, 725; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 711.
- [2] a) N. Masciocchi, A. Sironi, G. D'Alfonso, *J. Am. Chem. Soc.* **1990**, *112*, 9395; b) M. J. Bennet, W. A. G. Graham, J. K. Hoyano, W. L. Hutcheon, *J. Am. Chem. Soc.* **1972**, *94*, 6232; c) D. K. Huggins, W. Fellmann, J. M. Smith, H. D. Kaesz, *J. Am. Chem. Soc.* **1964**, *86*, 4841.
- [3] R. H. Crabtree, *Angew. Chem.* **1993**, *105*, 828; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 789.
- [4] L. M. Venanzi, *Coord. Chem. Rev.* **1982**, *43*, 251.
- [5] See also: M. Bergamo, T. Beringhelli, G. D'Alfonso, G. Ciani, M. Moret, A. Sironi, *Inorg. Chim. Acta* **1997**, *259*, 291, and references therein.
- [6] M. Bergamo, T. Beringhelli, G. D'Alfonso, G. Ciani, M. Moret, A. Sironi, *Organometallics* **1996**, *15*, 3876.
- [7] M. Bergamo, T. Beringhelli, G. D'Alfonso, P. Mercandelli, M. Moret, A. Sironi, *Organometallics* **1997**, *16*, 4129.
- [8] A. Albiniati, R. M. Bullock, B. J. Rappoli, T. F. Koetzle, *Inorg. Chem.* **1991**, *30*, 1414.
- [9] L. Carlucci, G. D'Alfonso, D. M. Proserpio, unpublished results.
- [10] a) Crystal data for **3**: $\text{C}_{28}\text{H}_{24}\text{N}_6\text{O}_{20}\text{Re}_5$, $M_r = 1625.48$, monoclinic, space group $P2_1/c$ (no. 14), $a = 9.880(4)$, $b = 19.548(8)$, $c = 21.580(9)$ Å, $\beta = 101.10(1)^\circ$, $V = 4090(3)$ Å³ (by least-squares refinement on diffractometer angles of centered reflections with $0 < \theta < 23^\circ$), $Z = 4$, $T = 293$ K, graphite-monochromatized $\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, $\rho_{\text{calcd}} = 2.640$ Mg m⁻³, $F(000) = 2936$, yellow crystal $0.45 \times 0.27 \times 0.22$ mm, $\mu(\text{MoK}\alpha) = 14.818$ mm⁻¹, absorption correction with SADABS, relative transmission 0.646–1.000, SMART diffractometer, ω scan, frame width 0.3° , maximum time per frame 20 s, $\theta = 1.9$ – 27.0° , $-12 < h < 12$, $-23 < k < 24$, $-26 < l < 26$, 33719 reflections of which 8132 were independent ($R_{\text{int}} = 0.0297$), no crystal decay, solution by direct methods (SIR96)^[11] and subsequent Fourier syntheses, anisotropic full-matrix least squares on F_o^2 (SHELX97^[12]), hydrogen atoms refined with a riding model, data/parameters = 8132/487, $\text{GOF}(F_o^2) = 0.995$, $R1 = 0.0386$ and $wR2 = 0.0653$ for all data, $R1 = 0.0267$ and $wR2 = 0.0622$ for reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0363P)^2 + 1.8818P]$ where $P = (F_o^2 + 2F_c^2)/3$, max./min. residual electron density 1.863/–1.588 e Å⁻³. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101153. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [11] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435.

- [12] G. M. Sheldrick, SHELXL-97: Program for structure refinement, Göttingen, 1997.
- [13] Crystal data for **4**: $\text{C}_{20}\text{H}_{30}\text{O}_{20}\text{Re}_5$, $M_r = 1496.24$, triclinic, space group $P\bar{1}$ (no. 2), $a = 9.316(1)$, $b = 18.511(2)$, $c = 19.431(2)$ Å, $\alpha = 77.12(1)$, $\beta = 88.17(1)$, $\gamma = 85.69(1)^\circ$, $V = 3256.9(6)$ Å³ (by least-squares refinement on diffractometer angles of centered reflections with $0 < \theta < 23^\circ$), $Z = 4$, $T = 293$ K, graphite-monochromatized $\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, $\rho_{\text{calcd}} = 3.051$ Mg m⁻³, $F(000) = 2640$, colorless crystal $0.28 \times 0.08 \times 0.06$ mm, $\mu(\text{MoK}\alpha) = 18.592$ mm⁻¹, absorption correction with SADABS, relative transmission 0.480–1.000, SMART diffractometer, ω scan, frame width 0.3° , maximum time per frame 40 s, $\theta = 2.2$ – 28.3° , $-12 < h < 12$, $-24 < k < 24$, $-25 < l < 25$, 37916 reflections of which 14444 were independent ($R_{\text{int}} = 0.0379$), crystal decay 1.1%, solution by direct methods (SIR96)^[11] and subsequent Fourier syntheses, anisotropic full-matrix least squares on F_o^2 (SHELX97),^[12] hydrogen atoms refined with a riding model, data/parameters = 14444/811, $\text{GOF}(F_o^2) = 0.789$, $R1 = 0.0445$ and $wR2 = 0.0446$ for all data, $R1 = 0.0240$ and $wR2 = 0.0427$ for reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0128P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$, max./min. residual electron density 1.080/–1.208 e Å⁻³.^[10b]
- [14] a) C. J. Adams, M. I. Bruce, B. W. Skelton, A. H. White, *J. Chem. Soc. Chem. Commun.* **1992**, 26; b) C. J. Adams, M. I. Bruce, B. W. Skelton, A. H. White, *Chem. Commun.* **1996**, 969; c) C. J. Adams, M. I. Bruce, B. W. Skelton, A. H. White, *Chem. Commun.* **1996**, 975; d) C. J. Adams, M. I. Bruce, B. W. Skelton, A. H. White, *J. Organomet. Chem.* **1996**, 506, 191; e) M. Schollenberger, B. Nuber, M. L. Ziegler, *Angew. Chem.* **1992**, 104, 329; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 350.
- [15] A. G. Orpen, *J. Chem. Soc. Dalton Trans.* **1980**, 2509.
- [16] S. T. Rao, E. Westhof, M. Sundaralingam, *Acta Crystallogr. Sect. A* **1981**, 37, 421.
- [17] For comparison: $[\text{Mn}_5(\mu_5\text{-In})(\text{CO})_{20}]^{[14e]}$ yields puckering values of $\tau_m = 46.9^\circ$ and $P = 99.2^\circ$, which correspond to an envelope conformation.

Photoluminescent Rigid Molecular Rods with Cumulenic C_n ($n = 3, 4$) Spacers: Modulation of Electronic Interaction**

Bo Hong* and Jeffrey V. Ortega

Rigid molecular rods with linear structures, molecular wires, are currently studied as important components for the construction of functional nanoscale photonic and electronic devices.^[1,2] With the incorporation of photoactive and/or redox-active metal centers, these molecular assemblies may present interesting properties based on long range electron/energy transfer and electronic communication between the two remote ends of the wires.^[2–5] To ensure the directionality and also to construct multicomponent supramolecular systems with well-defined structures, rigid spacers must be used to afford restricted conformational mobility and a controllable distance between structural subunits. In addition,

spacers (for example, polyphenyls,^[6] alkenes,^[7] or alkynes^[5,8]) can also be selected to serve as electron-conducting active components to promote long-range electronic coupling between terminal subunits or (for example, saturated hydrocarbons^[9]) to serve as passive connecting components.

Systems with unsaturated sp carbon chains (C_n) between two subunits constitute one of the most fundamental classes of one-dimensional molecular wires, however, intense studies in numerous laboratories have focused on the systems with alkynes or acetylenyl bridges.^[2,5,8] We report here the photoluminescent and redox-active systems with Ru and Os centers spanned by allene (C_3) or cumulene (C_4) bridges, and the preliminary data on the unique molecular photophysical and redox properties of these new rigid rodlike supramolecular systems. The unique structures of the allene and cumulene bridges permit the tuning of electronic communication between the end subunits. In the C_3 chain the two terminal $p\pi$ orbitals will be rotated by 90° , while in the C_4 chain the terminal $p\pi$ orbitals remain conjugated (Figure 1).

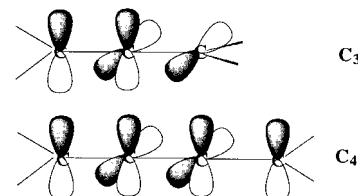


Figure 1. Comparison of the $p\pi$ orbitals in the C_3 and C_4 bridges.

As a result, the electronic coupling across the sp carbon chain can be readily controlled by changing the number of carbon atoms.

The C_n -bridged tetratopic spacers, namely, 1,1',3,3'-tetrakis(diphenylphosphanyl)allene (C_3P_4), 1,1',4,4'-tetrakis(diphenylphosphanyl)cumulene (C_4P_4), and the ligand 1,1'-bis(diphenylphosphanyl)ethene ($\text{C}_2\text{P}_2\text{e}$) are prepared according to the literature methods.^[10–12] The use of the phosphane group in the spacer here has two advantages. First, it serves as a linker group between the C_n bridge and the metal-based subunits ($\text{M}(\text{bpy})_2$ ($\text{M} = \text{Ru}$ and Os ; $\text{bpy} = 2,2'$ -bipyridine)). Second, the incorporation of phosphane ligands in polypyridyl-osmium(II) complexes can enhance the lifetime of the $^3\text{MLCT}$ state;^[13–15] the replacement of one of the σ -donating polypyridyl ligands with phosphane can result in the increase in the energy of the $^3\text{MLCT}$ excited state and the decrease of the rate of nonradiative decay.

The PF_6^- salts of the C_n -bridged ruthenium(II) and osmium(II) complexes are synthesized by treatment of C_nP_4 ($n = 3$ or 4), in a refluxing tetrahydrofuran/ethylene glycol mixture, with $[\text{M}(\text{bpy})_2\text{Cl}_2]$ ($\text{M} = \text{Ru}$ or Os , Table 1). Mono- or bimetallic complexes, $\text{MC}_2\text{P}_2\text{e}$, MC_nP_4 ($n = 3$ or 4), and $\text{MC}_n\text{P}_4\text{M}$ ($n = 3$ or 4), are obtained by using different metal-to-ligand ratios. All new complexes have been fully characterized by $^31\text{P}\{\text{H}\}$ NMR spectroscopy, fast atom bombardment mass spectrometry (FAB-MS), and elemental analysis. Specifically, many of the fragment ions observed in FAB-MS only involve sequential loss of counteranions (PF_6^-) and PPh_2 units, and the inner sphere metal–ligand coordination was left intact, thus making peak identification straightforward.

[*] Prof. B. Hong, J. V. Ortega
Department of Chemistry
University of California, Irvine
Irvine, CA 92697-2025 (USA)
Fax: (+1) 714-824-3168
E-mail: bhong@uci.edu

[**] This work was supported by the University of California, Irvine, UCI's Physical Sciences Committee on Research, and the US National Science Foundation CAREER Award (CHE-9733546). J.V.O. acknowledges support from the Graduate and Professional Opportunity Program from the US Department of Education.

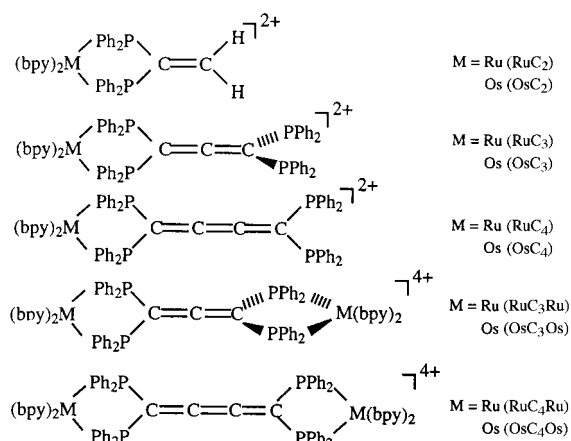


Table 1. Analytical data for the complexes.^[a]

RuC ₂ P ₂ e: Yield 95 %. ³¹ P{ ¹ H} NMR: δ = 18.21. FAB/MS: <i>m/z</i> (%): 955 (100) [<i>M</i> ⁺ – PF ₆], 809 (11) [<i>M</i> ⁺ – 2PF ₆]. Elemental analysis calcd for C ₄₆ H ₃₈ N ₄ P ₂ Ru(PF ₆) ₂ : C 50.24, N 5.10, H 3.48; found: C 50.05, N 4.50, H 5.03.
OsC ₂ P ₂ e: Yield 63 %. ³¹ P{ ¹ H} NMR: δ = –23.32. FAB/MS: <i>m/z</i> (%): 1045 (100) [<i>M</i> ⁺ – PF ₆], 900 (50) [<i>M</i> ⁺ – 2PF ₆]. Elemental analysis calcd for C ₄₆ H ₃₈ N ₄ P ₂ Os(PF ₆) ₂ : C 46.47, N 4.71, H 3.22; found: C 47.41, N 5.06, H 3.85.
RuC ₃ P ₄ : Yield 80 %. ³¹ P{ ¹ H} NMR: δ = 2.34, –30.22. FAB/MS: <i>m/z</i> (%): 1167 (22) [<i>M</i> ⁺ – PF ₆ – PPh ₂ + O], 1151 (17) [<i>M</i> ⁺ – PF ₆ – PPh ₂], 1021 (100) [<i>M</i> ⁺ – 2PF ₆ – PPh ₂ + O], 1005 (27) [<i>M</i> ⁺ – 2PF ₆ – PPh ₂]. Elemental analysis calcd for C ₅₁ H ₅₆ N ₄ P ₄ Ru(PF ₆) ₂ · 2H ₂ O: C 56.25, N 3.70, H 3.99; found: C 56.00, N 4.10, H 4.52.
OsC ₃ P ₄ : Yield 89 %. ³¹ P{ ¹ H} NMR: δ = –30.49, –37.37. FAB/MS: <i>m/z</i> (%): 1425 (44) [<i>M</i> ⁺ – PF ₆], 1280 (26) [<i>M</i> ⁺ – 2PF ₆], 1241 (81) [<i>M</i> ⁺ – PF ₆ – PPh ₂], 1095 (100) [<i>M</i> ⁺ – 2PF ₆ – PPh ₂]. Elemental analysis calcd for C ₅₁ H ₅₆ N ₄ P ₄ Os(PF ₆) ₂ · 2H ₂ O: C 53.12, N 3.49, H 3.77; found: C 52.80, N 3.97, H 3.94.
RuC ₄ P ₄ : Yield 48 %. ³¹ P{ ¹ H} NMR: δ = 13.91, 5.95. FAB/MS: <i>m/z</i> (%): 1512 (10) [<i>M</i> ⁺], 1381 (100) [<i>M</i> ⁺ – PF ₆ + 2O], 1365 (30) [<i>M</i> ⁺ – PF ₆ + O], 1349 (45) [<i>M</i> ⁺ – PF ₆]. Elemental analysis calcd for C ₅₂ H ₅₆ N ₄ P ₄ Ru(PF ₆) ₂ : C 57.95, N 3.75, H 3.78; found: C 57.75, N 3.78, H 3.76.
OsC ₄ P ₄ : Yield 56 %. ³¹ P{ ¹ H} NMR: δ = –26.99, –30.74. FAB/MS: <i>m/z</i> (%): 1618 (100) [<i>M</i> ⁺ + 2O], 1601 (55) [<i>M</i> ⁺ + O], 1585 (75) [<i>M</i> ⁺], 1471 (55) [<i>M</i> ⁺ – PF ₆ – 2O], 1455 (75) [<i>M</i> ⁺ – PF ₆ + O], 1437 (15) [<i>M</i> ⁺ – PF ₆]. Elemental analysis calcd for C ₅₂ H ₅₆ N ₄ P ₄ Os(PF ₆) ₂ : C 54.69, N 3.54, H 3.57; found: C, 54.74; N, 3.85; H, 3.91.
RuC ₃ P ₄ Ru: Yield 61 %. ³¹ P{ ¹ H} NMR: δ = 140.87. FAB/MS: <i>m/z</i> (%): 1765 (100) [<i>M</i> ⁺ – 3PF ₆ + O], 1620 (17) [<i>M</i> ⁺ – 4PF ₆ + O], 1435 (10) [<i>M</i> ⁺ – 4PF ₆ – PPh ₂ + O], 1417 (15) [<i>M</i> ⁺ – 4PF ₆ – PPh ₂]. Elemental analysis calcd for C ₇₁ H ₇₂ N ₈ P ₄ Ru ₂ (PF ₆) ₄ : C 50.06, N 5.13, H 3.32; found: C 50.69, N 5.60, H 3.72.
OsC ₃ P ₄ Os: Yield 85 %. ³¹ P{ ¹ H} NMR: δ = 83.64. FAB/MS: <i>m/z</i> (%): 2088(6) [<i>M</i> ⁺ – 2PF ₆ + O], 1943 (100) [<i>M</i> ⁺ – 3PF ₆ + O], 1797 (39) [<i>M</i> ⁺ – 4PF ₆ + O], 1280 (67) [<i>M</i> ⁺ – 4PF ₆]. Elemental analysis calcd for C ₇₁ H ₇₂ N ₈ P ₄ Os ₂ (PF ₆) ₄ : C 46.28, N 4.75, H 3.07; found: C 46.45, N 4.98, H 3.55.
RuC ₄ P ₄ Ru: Yield: 57 %. ³¹ P{ ¹ H} NMR: δ = –2.24. FAB/MS: <i>m/z</i> (%): 1936 (45) [<i>M</i> ⁺ – 2PF ₆ + 2O], 1920 (20) [<i>M</i> ⁺ – 2PF ₆ + O], 1904 (10) [<i>M</i> ⁺ – 2PF ₆], 1775 (20) [<i>M</i> ⁺ – 3PF ₆ + O], 1759 (30) [<i>M</i> ⁺ – 3PF ₆], 1630 (35) [<i>M</i> ⁺ – 4PF ₆ + O], 1614 (25) [<i>M</i> ⁺ – 4PF ₆], 1427 (100) [<i>M</i> ⁺ – 4PF ₆ – PPh ₂]. Elemental analysis calcd for C ₇₂ H ₇₂ N ₈ P ₄ Ru ₂ (PF ₆) ₄ : C 50.33, N 5.10, H 3.30; found: C 50.56, N 5.25, H 3.26.
OsC ₄ P ₄ Os: Yield 27 %. ³¹ P{ ¹ H} NMR: δ = –5.11. FAB/MS: <i>m/z</i> (%): 2101 (15) [<i>M</i> ⁺ – 2PF ₆ + O], 1997 (75) [<i>M</i> ⁺ – 3PF ₆ + 3F], 1937 (40) [<i>M</i> ⁺ – 3PF ₆], 1856 (100) [<i>M</i> ⁺ – 4PF ₆ + 4O], 1808 (45) [<i>M</i> ⁺ – 4PF ₆ + O], 1792 (20) [<i>M</i> ⁺ – 4PF ₆]. Elemental analysis calcd for C ₇₂ H ₇₂ N ₈ P ₄ Os ₂ (PF ₆) ₄ : C 46.55, N 4.72, H 3.05; found: C 46.70, N 4.92, H 3.01.

[a] ³¹P{¹H} NMR spectra were recorded in [D₃]MeCN, 202 MHz at 22 °C. The FAB-MS were recorded with *m*-nitrobenzyl alcohol as the matrix.

The redox properties of complexes with C₂, C₃, and C₄ carbon chains have been probed by cyclic voltammetry and the data of metal-based oxidations are included in Table 2. Several unique and interesting features exist when we compare these metal-based redox waves:

1) Each of the monomeric complexes exhibits a single reversible one-electron process for which the *i*_p^a/*i*_p^c value is approximately unity, and corresponds to the M^{II}/M^{III} redox couple (M = Ru or Os).

2) The C_{*n*}-bridged spacers have profound influence on the metal-based oxidations in all mono- and homobimetallic complexes. As the carbon chain length increases, the M^{II}/M^{III} redox potential continuously shift to significantly less positive values (Table 2). In other words, the oxidation of the M^{II} centers (M = Ru or Os) become more thermodynamically

Table 2. Electrochemical and photophysical data for the complexes.^[a]

Complex	<i>E</i> _{1/2} (M ^{II} /M ^{III}), Δ <i>E</i> _p ^[b]	λ _{EM} , nm	τ _{EM} , ns (± 15 %)
RuC ₂ P ₂ e	+1.70 (1e [–] , 80)	530	25
RuC ₃ P ₄	+1.55 (1e [–] , 70)	535	40
RuC ₄ P ₄	+1.07 (1e [–] , 82)	540	15
OsC ₂ P ₂ e	+1.35 (1e [–] , 76)	600	190
OsC ₃ P ₄	+1.12 (1e [–] , 74)	570	350
OsC ₄ P ₄	+0.80 (1e [–] , 62)	590	410
RuC ₃ P ₄ Ru	+1.07 (2e [–] , 96)	560	45
RuC ₄ P ₄ Ru	+1.01 (1e [–] , 69), +1.43 (1e [–] , 63)	595	820
OsC ₃ P ₄ Os	+0.77 (2e [–] , 100)	575	520
OsC ₄ P ₄ Os	+0.72 (1e [–] , 78), +1.35 (1e [–] , 76)	660	480

[a] In deoxygenated acetonitrile at 25 °C. [b] Versus SCE.

favorable with longer chains as the rigid spacers. This may suggest that the π-acidity of the polyphosphane spacers becomes significantly weaker when the cumulenenic carbon chain length is increased. As a result, the observed *E*_{1/2}(M^{II}/M^{III}) values of MC₂P₂e (M = Ru, +1.70 V; Os, +1.35 V) and MC₃P₄ (M = Ru, +1.55 V; Os, +1.12 V) are significantly higher than those of the metal-based redox waves in [M(bpy)₃](PF₆)₂ (M = Ru, +1.29 V;^[4] Os, +0.81^[13b,15]), while those of MC₄P₄ (M = Ru, +1.07 V; Os, +0.80 V) have shifted to lower or approximately the same value. The electrochemical studies of Os^{II} complexes with mono- and bidentate phosphanes, such as dppm (*E*_{1/2} = +1.27 V versus the saturated calomel electrode (SCE) in [Os(bpy)₂-(dppm)]²⁺; dppm = Ph₂PCH₂PPh₂),^[13b] have shown that the change from pyridyl-type ligands to the more π-accepting phosphanes cause an increase in *E*_{1/2}(Os^{II}/M^{III}). This shift was ascribed, in large part, to the stabilization of the dπ levels by enhanced back-bonding to the phosphane.^[13b,15]

3) While the homobimetallic complexes MC₃P₄M (M = Ru or Os) feature two overlapping one-electron processes, the corresponding MC₄P₄M (M = Ru or Os) complexes have two consecutive one-electron processes (Figure 2). This is ascribed to the difference in the electronic communication between the two terminal subunits resulting from the change of spacer group.

For the binuclear complexes that can undergo multistep charge-transfer [Eq. (1)] the equilibrium constant *K*_c for the

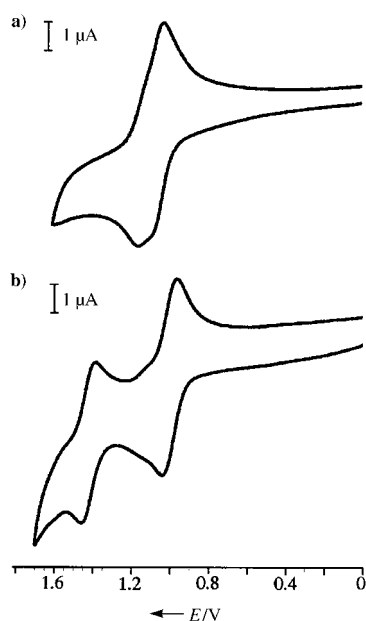
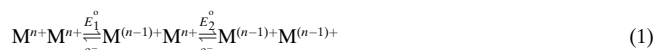


Figure 2. Cyclic voltammogram of a) $\text{RuC}_3\text{P}_4\text{Ru}$ and b) $\text{RuC}_4\text{P}_4\text{Ru}$. Electrolyte: 0.1 M $\text{Ni}(\text{Bu}_4\text{PF}_6)$, Pt disk (1.0 mm) working electrode, Ag/AgCl reference electrode, Pt wire counter-electrode, scan rate 100 mV s^{-1} .

comproportionation reaction is defined as shown in Equation (2), with $\Delta E^\circ = E_1^\circ - E_2^\circ$ in mV and at 298 K.^[16] Here



$$K_c = \frac{[\text{M}^{(n-1)+}\text{M}^{(n-1)+}]}{[\text{M}^{n+}\text{M}^{n+}][\text{M}^{(n-1)+}\text{M}^{(n-1)+}]} = \exp[(E_1^\circ - E_2^\circ)/25.69] \quad (2)$$

$\text{M}^{n+}\text{M}^{n+}$, for example, represent the discrete binuclear complexes. Stationary cyclic voltammetry has been applied previously to determine the ΔE° value by estimation from $\Delta E_{1/2}$.^[16a] From $\Delta E_{1/2}$ a quantitative measure of the energetics for the comproportionation reactions can be achieved and K_c values range from four in the uncoupled Robin and Day Class I systems to 10^{13} in the strongly coupled Class III systems.^[14b,17] For our homobimetallic complexes $\text{MC}_4\text{P}_4\text{M}$ ($\text{M} = \text{Ru}$ or Os), the calculated K_c values are 1.3×10^7 for $\text{M} = \text{Ru}$ ($\Delta E_{1/2} = 420 \text{ mV}$) and 4.5×10^{10} for $\text{M} = \text{Os}$ ($\Delta E_{1/2} = 630 \text{ mV}$). Such K_c values are comparable or larger than those reported for species with strong electronic interaction between the two redox centers spanned by rigid spacers such as pyrazine.^[14b,16b,17] In addition, the $\text{OsC}_4\text{P}_4\text{Os}$ complex has a much greater K_c value than that of the corresponding $\text{RuC}_4\text{P}_4\text{Ru}$ complex.

Previously Creutz^[17] discussed the remarkable changes in the electronic coupling through a given bridge that can be accomplished by changing the nature of M^{II} and M^{III} and that the increase in the $\text{M}-\text{M}$ interaction reflects the increasing ability of M^{II} to interact with the bridging ligand (spacer). More specifically, the increasing $\text{M}-\text{M}$ interaction in our Ru^{II} and Os^{II} series can be ascribed to the increasing $\text{M}-\text{L}$ interaction by virtue of $d\pi-\text{L}\pi^*$ mixing (L represents the spacer). Other representative examples include the interaction between two $\text{Ru}(\text{NH}_3)_5$ units ($\Delta E_{1/2} = 390 \text{ mV}$) and $\text{Os}(\text{NH}_3)_5$ units ($\Delta E_{1/2} = 760 \text{ mV}$) bridged by pyrazine.^[17]

When a molecule contains two noninteracting metal centers, it is expected that the current–potential response in

stationary cyclic voltammetry will be the same as a single-step charge transfer from a monomeric center.^[14b,16,18] The observed metal-based oxidations of $\text{MC}_3\text{P}_4\text{M}$ ($\text{M} = \text{Ru}$ or Os) correspond to two overlapping one-electron processes. This indicates that the electronic interaction between the two metal centers spanned by a C_3P_4 spacer is rather weak, giving apparently simultaneous one-electron oxidation of the two metal centers. Hence, by fine tuning of the number of carbon atoms in the rigid rodlike C_n chains, we can control the electronic interaction (or communication) between the two terminal redox centers.

As shown in Table 2, the monometallic complexes $\text{RuC}_2\text{P}_2\text{e}$ ($\tau_{\text{EM}} = 25 \text{ ns}$) and RuC_nP_4 ($\tau_{\text{em}} = 40$ and 15 ns for $n = 3$ and 4 , respectively) have, relative to $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$ ($\lambda_{\text{em}} = 582 \text{ nm}$, $\tau = 960 \text{ ns}$ ^[14]), short-lived triplet excited states. This observation is presumably due to the mixing between the charge transfer band and the (higher energy) metal-centered excited states.^[19] In contrast, $\text{OsC}_2\text{P}_2\text{e}$ ($\tau = 190 \text{ ns}$) and OsC_nP_4 ($\tau = 350$ and 410 ns for $n = 3$ and 4 , respectively) exhibit much longer lived $^3\text{MLCT}$ excited states when compared with the corresponding osmium complex $[\text{Os}(\text{bpy})_3](\text{PF}_6)_2$ ($\lambda_{\text{EM}} = 746 \text{ nm}$, $\tau = 60 \text{ ns}$). This change in Os-based excited states is consistent with that predicted by the energy gap law:^[13b] the replacement of one of the σ -donating polypyridyl ligands with phosphane can result in a decrease in the rate of nonradiative decay due to an increase of the energy gap between the emitting MLCT excited state (largely triplet in character) and the singlet ground state. Correspondingly, emissions from monomeric complexes with phosphanes shift significantly toward high energy. Typically, such a blue shift is expected when a stronger ligand (such as polyphosphane) is used to replace a relatively weak ligand (such as bpy). Homobimetallic complexes $\text{MC}_n\text{P}_4\text{M}$ ($\text{M} = \text{Ru}$ and Os) have red-shifted emission maxima (Table 2) relative to the corresponding monomeric species MC_nP_4 , indicative of a lower triplet energy in bimetallic complexes. Lowering of the triplet energy may inhibit mixing between the MLCT triplet and the higher energy metal- or ligand-centered excited states. Such decoupling of the states will also result in the prolongation of triplet lifetimes and is largely responsible for the observed longer lifetimes in homobimetallic species. Typically, Ru^{II} complexes with polyphosphanes have electronic absorption in the visible region with λ_{max} around $380\text{--}450 \text{ nm}$, while Os^{II} complexes absorb with λ_{max} around $450\text{--}500 \text{ nm}$. These are assigned to MLCT bands from the terminal $\text{Ru}^{\text{II}}/\text{Os}^{\text{II}}$ -polypyridyl units. A representative comparison between the absorption and emission spectra is shown in Figure 3, using data for $\text{RuC}_4\text{P}_4\text{Ru}$.

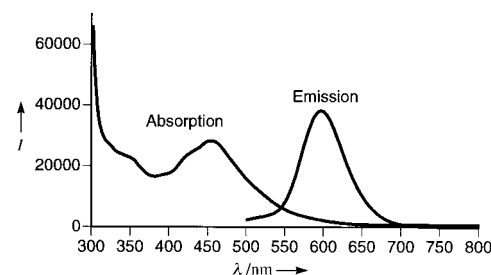


Figure 3. Comparison of the absorption and emission spectra of $\text{RuC}_4\text{P}_4\text{Ru}$ in deoxygenated acetonitrile at 25°C . An excitation wavelength of 480 nm was used for the measurement of the steady-state emission.

In conclusion, we have shown that rigid spacers with C_n ($n=3, 4$) sp carbon chains are suitable novel types of molecular building blocks in the construction of molecular rods. Compounds containing these types of spacers exhibit interesting photophysical properties and tunable electronic communication between the terminal sites upon change of the carbon chain length. Currently we are investigating the application of such spacers, including the ones with longer chain lengths, in the construction of functional supramolecular systems capable of performing, for example, directional intramolecular electron/energy transfer.

Experimental Section

All reactions were carried out in a nitrogen atmosphere unless otherwise noted.

General procedure for the monomeric complexes MC_2P_2e and MC_nP_4 ($n=3, 4$): A solution of $[M(bpy)_2Cl_2]$ ($M=Ru$ or Os) (1.0 equiv) in ethylene glycol (20 mL) was added dropwise to a refluxing solution of C_3P_4 , C_4P_4 , or C_2P_2e (typically, 2.2–3.0 equiv) in THF. The resulting mixture was heated under reflux for 15 h. An excess of NH_4PF_6 was then added and the mixture was heated under reflux for up to 60 h to ensure the completion of reaction. The solution was cooled to room temperature, and the THF portion of the reaction mixture was removed by rotary evaporation. The resulting ethylene glycol solution was added dropwise to a saturated solution of KPF_6 in H_2O . The precipitate was collected by vacuum filtration, washed with H_2O (3×20 mL) and diethyl ether (3×20 mL), then dried in vacuo. The product was then purified by column chromatography (basic alumina, acetonitrile/toluene (60/40) eluent).

General procedure for the synthesis of the homobimetallic complexes MC_nP_4M ($M=Ru$ or Os , $n=3$ or 4): A hot solution of C_nP_4 (1.0 equiv, $n=3$ or 4) in THF was added dropwise to a hot solution of $[M(bpy)_2Cl_2]$ ($M=Ru$ or Os) (2.2 equiv) in ethylene glycol (20 mL) at approximately $120^\circ C$. The resulting mixture was refluxed for 15 h, then allowed to cool to room temperature. An excess of NH_4PF_6 was added and the mixture was then refluxed for up to 60 h to ensure the completion of reaction. The mixture was again cooled to room temperature, and the THF portion of the solvent mixture was removed by rotary evaporation. The resulting ethylene glycol solution was added slowly to a saturated solution of KPF_6 in H_2O . The precipitate was collected by vacuum filtration, washed with H_2O (3×20 mL) and diethyl ether (3×20 mL), and dried in vacuo. The homobimetallic product was isolated by column chromatography as the second fraction, using basic alumina and acetonitrile as eluent, from the corresponding monometallic complex.

Received: February 2, 1998

Revised version: March 19, 1998 [Z114241E]

German version: *Angew. Chem.* **1998**, *110*, 2210–2214

Keywords: cumulenes • cyclic voltammetry • metal–metal interactions • P ligands • photoluminescence

- [1] J.-M. Lehn, *Supramolecular Chemistry: Concept and Perspectives*, VCH, Weinheim, **1995**.
- [2] Some recent leading papers: a) M. Brady, W. Weng, Y. Zhou, J. W. Seyler, A. J. Amoroso, A. M. Arif, M. Böhme, G. Frenking, J. A. Gladysz, *J. Am. Chem. Soc.* **1997**, *119*, 775; b) K. Wärnmark, J. A. Thomas, O. Heyke, J.-M. Lehn, *Chem. Commun.* **1996**, 701; c) R. W. Lass, P. Steinert, J. Wolf, H. Werner, *Chem. Eur. J.* **1996**, *2*, 19; d) N. L. Narvor, L. Toupet, C. Lapinte, *J. Am. Chem. Soc.* **1995**, *117*, 7129; e) M. D. Ward, *Chem. Soc. Rev.* **1995**, 121; f) R. J. Lagow, J. J. Kampa, H.-C. Wei, S. L. Battle, Laude, J. W., C. J. Harper, R. Bau, R. C. Stevens, J. F. Haw, E. Munson, *Science* **1995**, *267*, 362.
- [3] V. Balzani, F. Scandola, *Supramolecular Photochemistry*, Harwood, Chichester, **1991**.

- [4] V. Balzani, A. Juris, M. Venturi, S. Campagna, S. Serroni, *Chem. Rev.* **1996**, *96*, 759.
- [5] a) A. Harriman, R. Ziessel, *Chem. Commun.* **1996**, 1707; b) V. Grossshenny, A. Harriman, R. Ziessel, *Angew. Chem.* **1995**, *107*, 1211; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1100; c) V. Grossshenny, A. Harriman; F. M. Remero; R. Ziessel, *J. Phys. Chem.* **1996**, *100*, 17472.
- [6] F. Barigelli, L. Flamigni, V. Balzani, J. P. Collin, J. P. Sauvage, A. Sour, E. C. Constable, A. M. W. Cargill Thompson, *J. Am. Chem. Soc.* **1994**, *116*, 7692; *J. Chem. Soc. Chem. Commun.* **1993**, 942.
- [7] A. C. Benniston, V. Goulle, A. Harriman, J.-M. Lehn, *J. Phys. Chem.* **1994**, *98*, 7798.
- [8] V. S.-Y. Lin, S. G. DiMaggio, M. J. Therien, *Science* **1994**, *264*, 1105.
- [9] a) A. D. Padden-Row, *Acc. Chem. Res.* **1994**, *27*, 18; b) G. L. Closs, J. R. Miller, *Science* **1988**, *240*, 440; c) T. A. Perkins, B. T. Hauser, J. R. Eyler, K. S. Schanze, *J. Phys. Chem.* **1990**, *94*, 8745; d) A. D. Joran; B. A. Leland, G. G. Geller, J. J. Hopfield, P. B. Dervan, *J. Am. Chem. Soc.* **1984**, *106*, 6090.
- [10] H. Schmidbaur, S. Manhart, A. Schier, *Chem. Ber.* **1993**, *126*, 2389.
- [11] H. Schmidbaur, T. Pollok, *Angew. Chem.* **1986**, *98*, 365; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 348.
- [12] I. J. Colquhoun; W. McFarlane, *J. Chem. Soc. Dalton Trans.* **1982**, 1915.
- [13] a) E. M. Kober, J. V. Caspar, B. P. Sullivan, T. J. Meyer, *Inorg. Chem.* **1988**, *27*, 4587; b) S. R. Johnson, T. D. Westmoreland, J. V. Caspar, K. R. Barqawi, T. J. Meyer, *Inorg. Chem.* **1988**, *27*, 3195.
- [14] a) R. G. Brewer, G. E. Jensen, K. J. Brewer, *Inorg. Chem.* **1994**, *33*, 124; b) M. M. Richter, K. J. Brewer, *Inorg. Chem.* **1993**, *32*, 2827.
- [15] P.-W. Wang, M. A. Fox, *Inorg. Chem.* **1995**, *34*, 36.
- [16] a) D. E. Richardson, H. Taube, *Inorg. Chem.* **1981**, *20*, 1278; b) D. E. Richardson, H. Taube, *Coord. Chem. Rev.* **1984**, *60*, 107; c) F. Salaymeh, S. Berhane, R. Yusof, R. de la Rosa, E. Y. Fung, R. Matamoros, K. W. Lau, Q. Zheng, E. M. Kober, J. C. Curtis, *Inorg. Chem.* **1993**, *32*, 3895.
- [17] a) C. Creutz, *Prog. Inorg. Chem.* **1983**, *30*, 1; b) M. B. Robin, P. Day, *Adv. Inorg. Radiochem.* **1967**, *10*, 247.
- [18] J. B. Flanagan, S. Margel, A. J. Bard, F. C. Anson, *J. Am. Chem. Soc.* **1978**, *100*, 4248.
- [19] P. S. Braterman, A. Harriman, G. A. Heath, L. J. Yellowlees, *J. Chem. Soc. Dalton Trans.* **1983**, 1801.

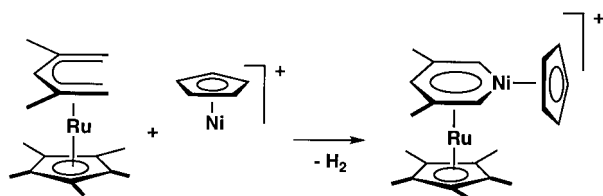
The First Homoleptic Metallabenzene Sandwich Complex**

Ulli Englert, Frank Podewils, Ingo Schiffrers, and Albrecht Salzer*

In connection with our previous studies on the reactivity of “half-open” metallocenes, we have found examples for the insertion of organometallic fragments into the “open” side of pentadienyl ligands, leading to the formation of metallacyclic six-membered ring ligands (Scheme 1).^[1, 2] Using Wade’s rules, this can be regarded as the expansion of an *arachno* to a *nido* structure. The metallabenzenes thus formed (exchange of CH for an isolobal metal fragment) are one of the rarest, but nevertheless most interesting representatives of metallacycles of the transition elements.^[3] They are considered to be

[*] Prof. Dr. A. Salzer, Priv.-Doz. Dr. U. Englert, Dipl.-Chem. F. Podewils, I. Schiffrers
Institut für Anorganische Chemie der Technischen Hochschule
D-52056 Aachen (Germany)
Fax: (+49) 241-8888-288
E-mail: albrecht.salzer@ac.rwth-aachen.de

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

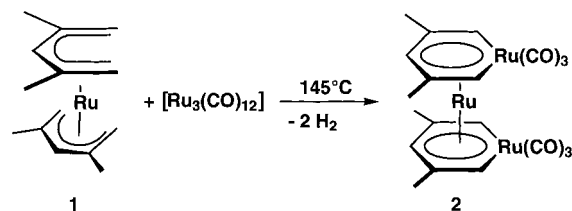


Scheme 1.

intermediates in the alkyne oligomerization,^[4] but are also of fundamental interest with respect to their possible aromatic character.^[4–6]

In contrast, heterocycles of the main group elements such as [C₅H₅BR][–] or C₅H₅P, which are formed by isolobal exchange of CH by BR[–] or P, have been well known and investigated over the last 30 years. They are eminently suitable as ligands for metal–sandwich complexes.

After having developed a new, very efficient route to the “open” ruthenocene (C₇H₁₁)₂Ru (**1**),^[7] we have also investigated the possible insertion of unsaturated metal fragments into **1**. Surprisingly, the thermolysis of **1** in the presence of Ru₃(CO)₁₂ does not lead to simple, but to double insertion of two Ru(CO)₃ units into all four terminal C–H bonds in *endo* position (Scheme 2). To our knowledge, **2** is the first sandwich



Scheme 2.

complex comprising two metallacyclic ligands. A formal dissection of **2** shows that (CO)₃Ru[–] is isolobal to CH and BH[–]; the organometallic ligand [C₅H₅Ru(CO)₃][–] can therefore also possibly be considered as an equivalent of boratabenzene [C₅H₅BH][–].

Complex **2** is lemon-yellow and air-stable, decomposes at temperatures above 170°C, and can be sublimed at 90°C under high vacuum without decomposition. The carbon atoms directly coordinated to ruthenium show a typical low-field shift (δ = 128.3), which is however less pronounced than in previous examples.^[2] The mass spectrum shows characteristic peaks corresponding to the consecutive loss of all six CO groups as well as the formation of tetramethylruthenocene.

Large prismatic crystals of **2** can be grown from benzene within hours. The single-crystal X-ray diffraction study^[8] confirms the structure of a bis(metallabenzene) sandwich complex (Figure 1). The two rings show an exact *syn*-ecliptical conformation, but are not completely coplanar, but tilted by 18° towards each other; the two Ru(CO)₃ units are both bent away from the plane formed by the five carbon atoms by approximately 15°. Similar values have been found for other ruthenabenzenes. Various explanations have been put forward for this phenomenon, among them the optimization of Ru–C and Ru–Ru bond lengths^[1] as well as steric repulsion^[4] but the latter is clearly not the case for **2**.

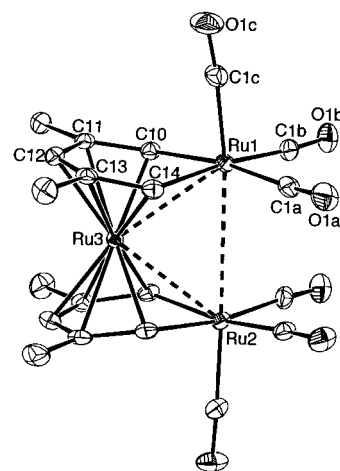


Figure 1. Structure of **2** in the solid state (PLATON^[9]). Selected bond lengths [Å]: Ru1–Ru3 2.831(2), Ru2–Ru3 2.812(2), Ru1–Ru3 3.382(2), Ru1–C10 2.076(3), Ru1–C14 2.062(3), Ru1–C1a 1.965(3), Ru1–C1b 1.939(3), Ru1–C1c 1.863(3).

The *syn*-ecliptical arrangement of the ring ligands appears surprising at first, considering that “open” metallocenes show a preference for the *gauche*-ecliptic conformation^[10] and other heterosubstituted bis(arene) complexes preferentially show *anti*-ecliptic conformations or are disordered in the solid state with a low barrier of rotation.^[11] Comparable exceptions are distiba- and dibismaferrocene, for which a bonding interaction of the two heteroatoms has been postulated.^[12] Preliminary results of an extended-Hückel MO calculation make it likely that all three ruthenium atoms in **2** are linked through a multicenter bond.^[13] The distance between the two ring ruthenium atoms is 3.38 Å and therefore only 20% longer than the bond to the central ruthenium atom (ca. 2.82 Å). It is considerably shorter than the sum of the van der Waals radii and the distance between the two heteroatoms in the distiba- and dibismaferrocenes (3.58–3.69 Å). The C–C bond lengths within the metallacycle are very similar (1.39–1.43 Å), while the Ru–C bond lengths are somewhat longer than in previous examples.^[1, 4] The Ru–C bond to the equatorial carbonyl groups is significantly longer than that to the axial ligand. This is plausible, as the *trans* configuration of carbonyl- and pentadienylidene ligand should result in a mutual bond weakening. The *syn*-ecliptical conformation appears to persist in solution, as **2** shows five CO absorptions in the IR spectrum in agreement with symmetry class C_{2v}.

Complex **2** can be protonated to a hydride species that can be isolated as a solid (δ (¹H) = –16.1) and is reversibly oxidized to a monocation (+0.8 V against SCE). All properties of **2** therefore point to a pronounced similarity to classical metallocenes. Current investigations will show, whether this also applies to its reactions (metalation, ring transfer etc.).

The possible aromaticity of metallabenzenes has been extensively discussed by R. Hoffmann^[5] and J. Blecke.^[6] Compound **2** shows structural properties typical for this class of compounds, such as approximate ring planarity and delocalized bonding within the ring.

We had postulated in a previous publication that “bis-(metallabenzene) complexes or even tripledecker compounds with a central metallabenzene ring should be stable”.^[2] The

first part of this statement has now been verified, possibly a consequence of the previously observed property of metal-labenzenes to form more stable metal- π bonds than classical arenes.^[3] An additional intra-ring interaction of the two ring metals, as observed for the first time in **2**, could make a further contribution to the stabilization of multidecker structures.

Experimental Section

2: A solution of bis(dimethylpentadienyl)ruthenium (**1**) (0.29 g, 1.0 mmol) in nonane (35 mL) was refluxed with $\text{Ru}_3(\text{CO})_{12}$ (1.28 g, 2.0 mmol) overnight. The solvent was evaporated under reduced pressure and the residue was taken up in hexane and purified by chromatography on silica gel. The yellow fraction was collected and recrystallized from benzene or toluene, yield 0.11 g (17%). ^{13}C NMR (125.7 MHz, CD_2Cl_2): δ = 198.9 (CO), 193.9 (CO), 128.3 (C1), 111.3 (C2), 94.4 (C3), 25.5 (CH_3); ^1H NMR (500 MHz, CD_2Cl_2): δ = 6.23 (t, ^4J = 1.5 Hz, 2H), 5.62 (d, ^4J = 1.5 Hz, 4H), 1.72 (s, 12H, CH_3); IR (cm^{-1} , hexane): $\tilde{\nu}$ = 2074 m, 2049 m, 2010 s, 1995 w, 1980 m.

Received: March 13, 1998 [Z11585IE]

German version: *Angew. Chem.* **1998**, *110*, 2196–2197

Keywords: aromaticity • carbonyl complexes • metallacycles • metal–metal interactions • sandwich complexes

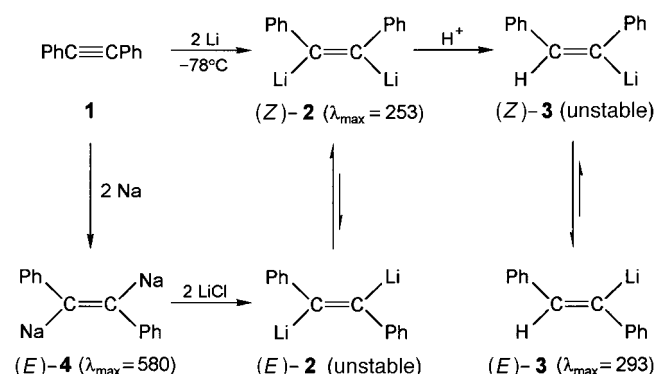
- [1] H. W. Bosch, U. Hund, D. Nietlispach, A. Salzer, *Organometallics* **1992**, *11*, 2087–2098.
- [2] U. Bertling, U. Englert, A. Salzer, *Angew. Chem.* **1994**, *106*, 1026–1028, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1003–1005.
- [3] J. R. Bleeker, R. Behm, Y.-F. Xie, M. Y. Chiang, K. D. Robinson, A. M. Beatty, *Organometallics* **1997**, *16*, 606–623.
- [4] W. Lin, S. R. Wilson, G. Girolami, *Organometallics* **1997**, *16*, 2356–2361.
- [5] D. L. Thorn, R. Hoffmann, *Nouv. J. Chem.* **1979**, *3*, 39–45.
- [6] J. R. Bleeker, *Acc. Chem. Res.* **1991**, *24*, 271–277.
- [7] A. Salzer, F. Podewils, A. Bauer in: *Synthetic Methods of Organometallic and Inorganic Chemistry*, Vol. 9 (Eds.: W. A. Herrmann, R. Beckhaus), Thieme, Stuttgart, in press.
- [8] a) Crystal structure analysis: $\text{C}_{20}\text{H}_{18}\text{O}_6\text{Ru}_3$, ENRAF-Nonius CAD4; $\text{MoK}\alpha$ radiation, λ = 0.71073 Å, graphite monochromator; intensity collection with ω - 2θ range at 203 K. Fragment of a yellow platelet $0.6 \times 0.4 \times 0.3$ mm, triclinic, space group $P\bar{1}$ (no. 2); a = 8.563(3), b = 9.103(3), c = 15.607(3) Å, α = 105.55(2), β = 98.25(3), γ = 109.03(3)°, V = 1071.8(7) Å³, Z = 2, ρ_{calc} = 2.037 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 20.81 cm⁻¹, $F(000)$ = 636; 4790 reflections registered with $3 < \theta < 26^\circ$, absorption correction by the Gauss-method^[14] with transmission coefficients between 0.477 and 0.588, 4082 symmetry-independent reflections with $I > \sigma(I)$ in structure solution^[15] and refinement^[16] for 263 parameters; all hydrogen atoms were refined isotropically, R = 0.023, R_w = 0.045, $w^{-1} = \sigma^2(F_o)$. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101246. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] A. L. Spek, PLATON 94, Utrecht, **1994**.
- [10] R. D. Ernst, *Chem. Rev.* **1988**, *88*, 1255–1291.
- [11] a) G. E. Herberich, H. Ohst, *Adv. Organomet. Chem.* **1986**, *25*, 199–236; a) C. Elschenbroich, M. Nowotny, B. Metz, W. Massa, J. Graulich, *Angew. Chem.* **1991**, *103*, 601–604, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 547–550.
- [12] A. J. Ashe III, S. Al-Ahmad, *Adv. Organomet. Chem.* **1996**, *39*, 325–353.
- [13] B. Ganter, unpublished results.
- [14] P. Coppens, L. Leiserowitz, D. Rabinovich, *Acta Crystallogr.* **1965**, *18*, 1035–1038.
- [15] G. M. Sheldrick, SHELXS-86, Göttingen, **1988**.
- [16] B. A. Frenz und ENRAF-Nonius, SDP, version 5.0, **1989**.

Mechanism of Reduction of Diphenylacetylene by Metallic Lithium

Adalbert Maercker, Michael Kemmer, Hsien C. Wang, Da-Hai Dong, and Michael Szwarc*

The reduction of a cold (-78°C) solution of diphenylacetylene (tolane, **1**) in THF by metallic sodium or lithium was reported previously.^[1] When the solution is kept for five hours in contact with a sodium mirror, **1** is reduced quantitatively to the disodium adduct (*E*)-**4**. Its absorption at long wavelength (λ_{max} = 580 nm, ϵ = 6.4×10^4) implies a conjugated *trans* structure of the adduct. Since steric hindrance prevents the conjugation in the *cis* isomer, its absorption is expected in the near-UV range.

The protonation of (*E*)-**4** by methanol at -78°C yields *trans*-stilbene as well as dibenzyl and regenerates some previously reduced **1**. No *cis*-stilbene was detected. In contrast, prolonged contact of a cold (-78°C) solution of **1** in THF with the silvery surface of metallic lithium yields a red precipitate. The reduction is quantitative after ten hours of contact, as evident by the titration analysis yielding a ratio of $\text{Li}:\textbf{1} = 2:1$. Since the reduction takes place on the surface of the metal, the addition of the second lithium atom is favored over any other outcome. The addition of MeOH to the red slurry at -78°C yields pure *cis*-stilbene as the only product, whereas *cis*-PhCD=CDPh is formed on addition of MeOD. In view of these observations, the *cis* structure (*Z*)-**2** is proposed for the initially formed dilithium adduct.



The addition of a cold solution of LiCl in THF to the cold solution of (*E*)-**4** yields again the red precipitate that forms *cis*-stilbene on protonation by MeOH. Apparently, the *trans*-disodium adduct (*E*)-**4** is converted into the *cis*-dilithium adduct upon substitution of sodium by lithium. Although the mechanism of this conversion is unknown, we might conclude that the *cis*-dilithium adduct (*Z*)-**2** is more stable than its *trans* isomer (*E*)-**2**.

[*] Prof. M. Szwarc, Dr. H. C. Wang, D.-H. Dong
Loker Hydrocarbon Research Institute
University of Southern California
University Park, Los Angeles, CA 90089–1661 (USA)
Fax: (+1) 619-259-6022
Prof. A. Maercker, Dr. M. Kemmer
Institut für Organische Chemie der Universität Siegen (Germany)

The red precipitate dissolves on warming its slurry to 25 °C. Monoprotection by THF^[1] produces the easily isomerized^[2] vinyl carbanion (Z)-3, which is rapidly converted into (E)-3 (absorbing at $\lambda_{\text{max}} = 293 \text{ nm}$). *trans*-Stilbene is formed on addition of MeOH, and *trans*-PhCD=CHPh when MeOD is added.

Reactions of radical anions and carbanions are profoundly affected by the nature of cations and solvents.^[3–6] The reduction of 1 in other solvents could be instructive, especially in diethyl ether. Then the undesired protonation by the solvent might be avoided. Indeed, no deuterated products were produced when the solution of (Z)-2 in perdeuterated diethyl ether was kept at 25 °C for 24 hours.

A cold (–78 °C) solution of 1 in diethyl ether is reduced quantitatively to the soluble adduct (Z)-2 when kept in contact with the silvery surface of lithium for ten hours. The shape of the spectrum of (Z)-2 ($\lambda_{\text{max}} = 253 \text{ nm}$, $\epsilon = 1.6 \times 10^4$) remains unaltered in the course of the reduction despite its rising intensity. This observation complies with the known high degree of disproportionation of lithium salts of radical anions in diethyl ether.^[7]

The strikingly different spectra of the dilithium adduct in diethyl ether and that of the disodium adduct in THF indicate their greatly diverse structures, which is unaccountable by the modification of their solvation or ionicity. Compound (E)-4 seems to be a conjugated *trans* adduct, and (Z)-2 a non-conjugated *cis* adduct. The results of their protonation and deuteration support this conjecture. Pure *cis*-stilbene is produced on addition of MeOH to a cold solution of (Z)-2, and *cis*-PhCD=CDPh is formed on addition of MeOD. In contrast, *trans*-stilbene is the product of protonation of (E)-4.

Cis-stilbene is still formed on protonation of a solution of (Z)-2 in diethyl ether that is rapidly warmed to 25 °C. However, some slow reaction sets up at this temperature, as indicated by fading of the peak at 253 nm and the rising absorption at 278 nm (Figure 1). Monitoring these changes at 278 nm reveals the zero-order kinetics of this reaction (Figure 2). At ambient temperature this “253–278” conversion is completed within 24 hours. Thereafter, the addition of

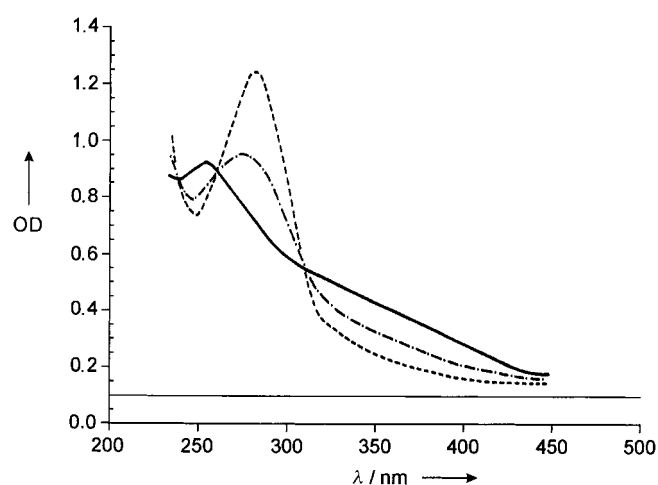


Figure 1. UV/Vis spectra (OD = optical density) of the initial *cis*-dilithium adduct (Z)-2 ($\lambda_{\text{max}} = 253 \text{ nm}$) and the product of its conversion (E)-5 ($\lambda_{\text{max}} = 278 \text{ nm}$): solution kept for 0 (—), 2 (---), and 10 h (– · – ·) at room temperature. Note the isosbestic points at 257 and 310 nm.

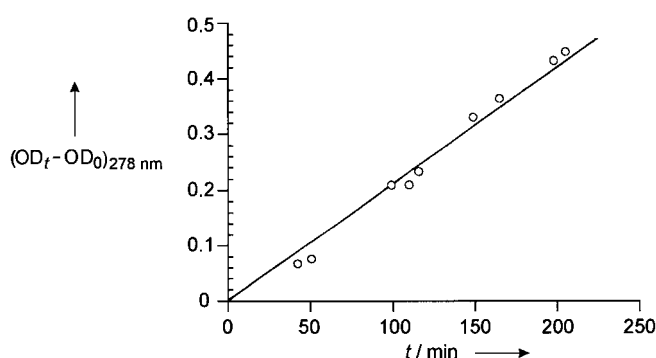


Figure 2. Plot of $(OD_t - OD_0)$ versus time t for the dilithium adduct of diphenylacetylene in diethyl ether monitored at 278 nm: zero-order kinetics.

MeOH produces *trans*-stilbene, but surprisingly *trans*-PhCD=CHC₆H₄D is formed on addition of MeOD. The aromatic deuterium atom of this deuterated *trans*-stilbene is located in the *ortho* position (as shown by NMR spectroscopy), and the deuterated phenyl group is linked to the vinylic CH group. The latter conclusion is derived from the mass spectrum of the benzaldehyde formed by ozonolysis of the deuterated stilbene. Only peaks for C₆H₅CDO and C₆H₄DCHO are observed, but none for C₆H₄DCDO.

Although long-lived intermediates are not formed in the above process, as demonstrated by the isosbestic points at 257 and 310 nm, its zero-order kinetics implies that some intermediate present in minute concentration but regenerated by the reaction participates in the overall process. Two questions arise:

1) Why is *cis*-(Z)-2 the most stable isomer of the dilithium adduct while, in contrast, *trans*-(E)-4 is the stable isomer of the disodium adduct?

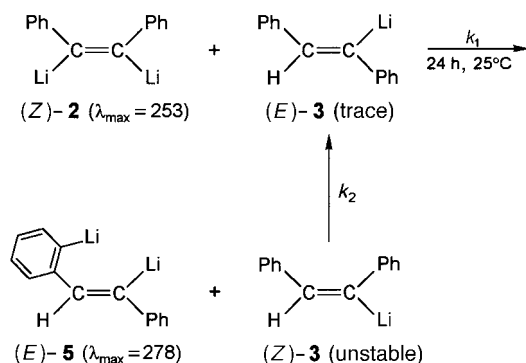
2) What is the mechanism of the 253–278 conversion that leads to the zero-order kinetics? Moreover, why does the addition of MeOD to the finally converted adduct lead to deuteration of a specific phenyl group?

The authors of reference [1] believed at the time of publication that the *trans*-dilithium adduct (E)-2 should be more stable than its *cis* isomer (Z)-2 because the conjugation stabilizing the *trans* adduct is lost for the *cis* isomer due to the steric hindrance. However, recent ab initio computations^[8] revealed the double-bridged structure of vicinal dilithium adducts, which is contrast to that of the disodium adduct. The bridging allows each lithium atom to interact with both phenyl groups, thus providing even larger stabilization than the conjugation. The *cis* isomers are therefore still more stable than the *trans* isomers, even for monophenylated dilithioethenes,^[9, 10] although the *trans* form seems to be preferred for the aliphatic dilithioethenes.^[11, 12] Indeed, dialkylacetylenes yield exclusively the *trans*-dilithioalkenes on reduction by metallic lithium.^[13] However, a direct *cis*–*trans* isomerization is precluded in the latter systems.^[14]

The mechanism of the (Z)-2 → (E)-5 rearrangement, presented below, was proposed in the thesis of one of us.^[10] It accounts for all the reported observations. The presence of a minute amount of moisture or any protonating agent in the solution of (Z)-2 yields a tiny amount of monolithiated *trans*-

stilbene (*E*)-**3**. Its lithiation by (*Z*)-**2** then produces *ortho*-lithiated (*E*)-**5**, which absorbs at 278 nm and is the final product of the 253–278 conversion.

The proposed mechanism accounts for the formation of the *trans*-stilbene carrying two deuterium atoms, one vinylic and one aromatic, upon addition of MeOD. The monolithium adduct (*E*)-**3**, but not (*Z*)-**3**, is lithiated by (*Z*)-**2** since the agostic effect^[15] of its vinylic lithium atom activates its *ortho* proton. The lack of activation of the (*Z*)-**3** protons accounts



for its inertness. The isomerization of (*Z*)-**3** to (*E*)-**3** regenerates the latter and allows for the repetition of the process.

The 253–278 conversion is expected to accelerate on addition of the independently prepared intermediate (*E*)-**3** to the solution of the primary dilithium adduct (*Z*)-**2** in diethyl ether. This has been experimentally verified.^[10] A solution of (*E*)-**3** (5 mmol), prepared by allowing lithium to react with α -chloro-*trans*-stilbene in diethyl ether, was added to one of two aliquots (6 mmol each) of the primary solution of the dilithium adduct (*Z*)-**2** in diethyl ether. After both aliquots had been kept at 20 °C for four hours, the analysis showed 10 % conversion in the aliquot containing the added (*E*)-**3**, but only 2 % in the other.

The intermediate (*E*)-**3** is continually formed through the isomerization of (*Z*)-**3** and destroyed by its reaction with (*Z*)-**2**. It is plausible to assume that its minute concentration is stationary, that is, $d[(E)\text{-}3]/dt = k_2[(Z)\text{-}3] - k_1[(Z)\text{-}2] \cdot [(E)\text{-}3] = 0$. Hence, $[(E)\text{-}3] = k_2[(Z)\text{-}3]/k_1[(Z)\text{-}2]$, and the rate of the 253–278 conversion, equal to $k_1[(Z)\text{-}2] \cdot [(E)\text{-}3]$, is $k_2[(Z)\text{-}3]$; that is it is constant for a constant concentration of (*Z*)-**3** but increases with increasing concentration of (*Z*)-**3**. The observed zero-order kinetics of the conversion is therefore accounted for at low concentrations of (*E*)-**3**.

Experimental Section

High-vacuum technique was used during this study. The oxides coating the chunks of lithium are stripped away by keeping the metal for a few hours in a solution of anthracene in diethyl ether. Shaking and decanting removed the anthracene and the stripped residues (see reference [16] for details of this operation to leave the chunks with a silvery surface). The stilbenes were isolated by evaporation of the solvents, and the residues were then recrystallized.

Received: January 26, 1997 [Z11409IE]
German version: *Angew. Chem.* **1998**, *110*, 2216–2218

Keywords: agostic interactions • kinetics • lithium • rearrangements • reductions

- [1] G. Levin, J. Jagur-Grodzinski, M. Szwarc, *J. Am. Chem. Soc.* **1970**, *92*, 2268–2275.
- [2] R. Knorr, E. Lattke, *Tetrahedron Lett.* **1977**, 3969–3972.
- [3] *Ions and Ion-Pairs in Organic Reactions* (Ed.: M. Szwarc), Wiley, New York, **1972**.
- [4] T. E. Hogen-Esch, *Adv. Phys. Org. Chem.* **1977**, *15*, 153–266.
- [5] J. W. Bausch, P. S. Gregory, G. A. Olah, G. K. S. Prakash, P. von R. Schleyer, G. A. Segal, *J. Am. Chem. Soc.* **1989**, *111*, 3633–3640.
- [6] C. Lambert, P. von R. Schleyer, *Angew. Chem.* **1994**, *106*, 1187–1199; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1129–1140.
- [7] G. Levin, B. E. Holloway, M. Szwarc, *J. Am. Chem. Soc.* **1976**, *98*, 5706–5709.
- [8] Y. Apeloig, T. Clark, A. J. Kos, E. D. Jemmis, P. von R. Schleyer, *Israel J. Chem.* **1980**, *20*, 43–50.
- [9] A. Maercker, U. Girreser, *Angew. Chem.* **1990**, *102*, 718–720; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 667–669.
- [10] M. Kemmer, *Darstellung von vicinalen Dilitioalkenen, Stabilitäten und Folgereaktionen*, Shaker, **1997**.
- [11] P. von R. Schleyer, E. Kaufmann, A. J. Kos, T. Clark, J. A. Pople, *Angew. Chem.* **1986**, *98*, 164–165; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 169–170.
- [12] E. E. Bolton, W. D. Laidig, P. von R. Schleyer, H. F. Schaefer III, *J. Am. Chem. Soc.* **1994**, *116*, 9602–9612, and references therein.
- [13] A. Maercker, U. Girreser, *Tetrahedron* **1994**, *50*, 8019–8034.
- [14] A. Maercker, T. Graule, W. Demuth, *Angew. Chem.* **1987**, *99*, 1075–1076; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1032–1034.
- [15] W. Bauer, M. Feigel, G. Müller, P. von R. Schleyer, *J. Am. Chem. Soc.* **1988**, *110*, 6033–6046.
- [16] M. Szwarc, *Carbanions, Living Polymers, and Electron Transfer Processes*, Wiley-Interscience, New York, **1968**, pp. 151–188.

Rearrangement of 5-Substituted 5-Aminopentadienals**

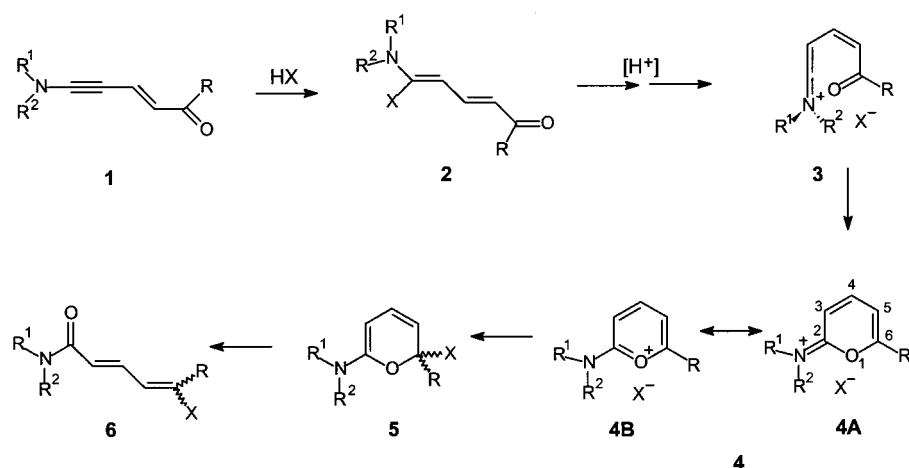
Fabian Fischer, Daniel Berger, and Markus Neuenschwander*

Dedicated to Professor Klaus Hafner on the occasion of his 70th birthday

As typical “push–pull” (PP) acetylenes,^[1] dialkylamino-propinals react easily with carboxylic acids and HCl to give 3-X-substituted 3-aminopropenals, which nearly quantitatively rearrange to 3-acyloxy- and 3-chloroacrylicamides.^[2,3] Similarly, PP-enynes of type **1** are expected to add acids, while the hereby formed 5-substituted 5-aminopenta-2,4-dien-1-als **2** could be prone to a vinylogous rearrangement to give 5-substituted pentadienecarboxamides **6** after extrusion of X[−] (**2**→**3**), ring closure (**3**→**4**), addition of X[−] (**4**→**5**), and ring opening (**5**→**6**). Whereas simple PP-enynes **1** remained unknown for a long time,^[4] they have been made available recently by two synthetic sequences.^[5,6] As a result, reactions of **1** with acids may be investigated in more detail now.

[*] Prof. Dr. M. Neuenschwander, Dr. F. Fischer, Dr. D. Berger
Departement für Chemie und Biochemie der Universität
Freiestrasse 3, CH-3012 Bern (Switzerland)
Fax: (+41)31-631-3426

[**] Aminoacrylic Compounds, Part 31. This work has been supported by the Swiss National Foundation (project no. 20–50331.97). Part 30: reference [7].



- a $R^1 = R^2 = \text{Me}$, $R = \text{H}$; b $R^1, R^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$, $R = \text{H}$; c $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R = \text{H}$;
 d $R^1 = R^2 = \text{Me}$, $R = \text{Me}$; e $R^1, R^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$, $R = \text{Me}$; f $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R = \text{Me}$;
 g $R^1, R^2 = \text{CH}=\text{CH}-\text{N}-\text{CH}=\text{CH}$, $R = \text{H}$

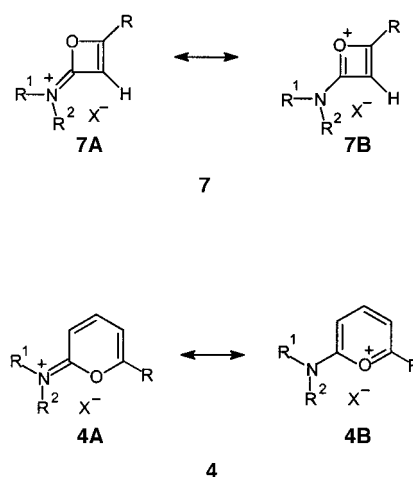
In fact, PP-enynes react with carboxylic acids (e.g. HOAc^[7]) and hydrogen halides HF, HCl,^[7] HBr, and HI to give *trans*-addition products **2**^[8] with high yields; these may be isolated ($X = \text{OAc}$, Cl, F)^[9] or spectroscopically identified in most cases. Qualitatively, reaction rates for $\mathbf{1} + \text{HX} \rightarrow \mathbf{2}$ increase with acidity of HX. For example, additions of HF or HOAc are considerably slower than those of HCl, HBr, or HI, whereas uncatalyzed additions of phenol are very slow (50% conversion after two to four days).

In most cases, compounds **2** rearrange to form 2-aminopyrylium salts **4** with high yields in the presence of acids, and the reaction rates of conversions $\mathbf{2} \rightarrow \mathbf{4}$ are strongly influenced by the ability of X to act as a leaving group. Thus, reactions of 5-substituted 5-aminopentadienals **2** bearing good leaving groups ($X = \text{Cl}$, Br, I) are so fast that it is not easy to isolate the corresponding addition products **2** for $X = \text{Br}$, I. The consequence is that salts **4** are conveniently available in a simple one-pot procedure by treating PP-enynes **1** with 1.05 molar equivalents of HCl, HBr, or HI.^[9, 10] On the other hand, compounds **2** bearing comparably bad leaving groups ($X = \text{F}$, OAc) only react in the presence of a large excess of acid. These results favor acid-catalyzed cleavage of the leaving group X ($\mathbf{2} \rightarrow \mathbf{3}$) to be the rate-determining step in the reaction $\mathbf{2} \rightarrow \mathbf{4}$.

2-Aminopyrylium halides **4** ($X = \text{F}$, Cl, Br, I) are quite unreactive^[11] and are not prone to spontaneous ring openings to form 5-halopentadienecarboxamides **6**. In that respect, compounds **2** ($X = \text{Cl}$) are very different from 3-amino-3-chloroacroleins, which rearrange to 3-chloroacrylicamides^[2, 3] at 0 °C in the presence of traces of acid; the sequence proceeds over oxetene immonium salts **7** as intermediates, according to mechanistic investigations.^[12] We believe that the different behavior is related to the considerable difference in energy between intermediates **7** and **4**: Oxetene immonium salts **7** are highly strained molecules without any resonance stabilization (**7B**^[13]), while 2-aminopyrylium salts **4** are essentially strain-

free compounds whose energy decreases due to π delocalization (**4B**^[13]). This reasonably explains why salts **4** with weakly nucleophilic counterions X^- are not prone to an easy ring opening of the type $\mathbf{4} \rightarrow \mathbf{6}$. In the following we will show that the "aminopentadienal rearrangement"^[14] may take place at low temperatures (0–20 °C) in the presence of stronger nucleophiles.^[15]

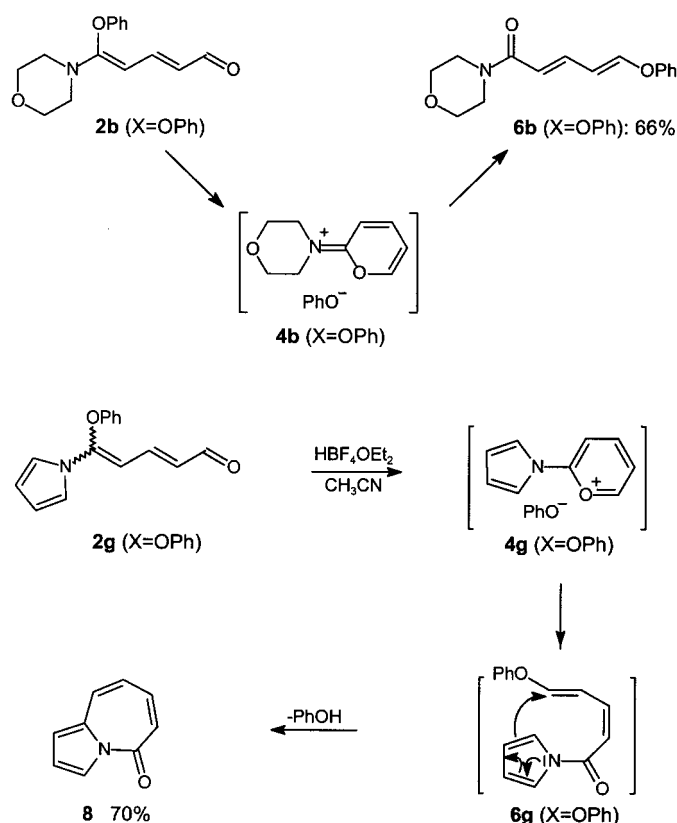
5-Morpholinopent-2-en-4-in-1-al (**1b**) nearly quantitatively adds acetic acid to give **2b** ($X = \text{OAc}$), which rearranges to the corresponding 2-aminopyrylium acetate **4b** ($X = \text{OAc}$, ca. 90% yield) only in an excess of HOAc



(ca. 25 molar equiv). In the absence of a further nucleophile, no ring opening $\mathbf{4b} \rightarrow \mathbf{6b}$ ($X = \text{OAc}$) is observed. However, if Et_3N is added to a solution of **4b** ($X = \text{OAc}$) in CH_2Cl_2 , then **6b** ($X = \text{OAc}$) may be isolated in moderate yields (23%).^[16] Similarly, **4b** ($X = \text{OAc}$) as well as **4b** ($X = \text{F}$) rearrange in an excess of EtOH to give **6b** ($X = \text{OEt}$, 33%).

For realizing faster aminopentadienal rearrangements^[14] $\mathbf{2} \rightarrow \mathbf{4} \rightarrow \mathbf{6}$, salts **4** with more nucleophilic counterions X^- are needed. For example, phenol adds very slowly in the reaction $\mathbf{1b} \rightarrow \mathbf{2b}$ ($X = \text{OPh}$). According to ^1H NMR spectroscopy (300 MHz, CDCl_3 , 20 °C), a maximum concentration of **2b** ($X = \text{OPh}$) is observed after about four days. Quite surprisingly, 2-aminopyrylium phenolate **4b** ($X = \text{OPh}$) is not directly observed by NMR spectroscopy because nucleophilic attack of phenol $\mathbf{4b} \rightarrow \mathbf{5b}$ is too fast. Considering the low reaction rate of the addition of phenol to **1b**, the overall yield of 66% for the isolated morpholinamide **6b** ($X = \text{OPh}$) is remarkable.

Finally, a quite spectacular rearrangement sequence is observed for (*Z/E*)-**2g** ($X = \text{OPh}$) in the presence of HBF_4 : Ring closure ($\mathbf{2g} \rightarrow \mathbf{4g}$, $X = \text{OPh}$) followed by ring opening ($\mathbf{4g} \rightarrow \mathbf{6g}$) and final addition/elimination ($\mathbf{6g} \rightarrow \mathbf{8} + \text{PhOH}$) gives the well-known^[17] 3a-aza-azulen-4-one **8**.



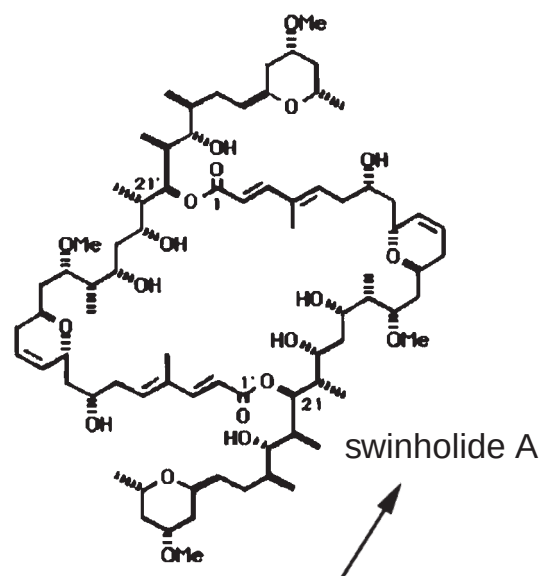
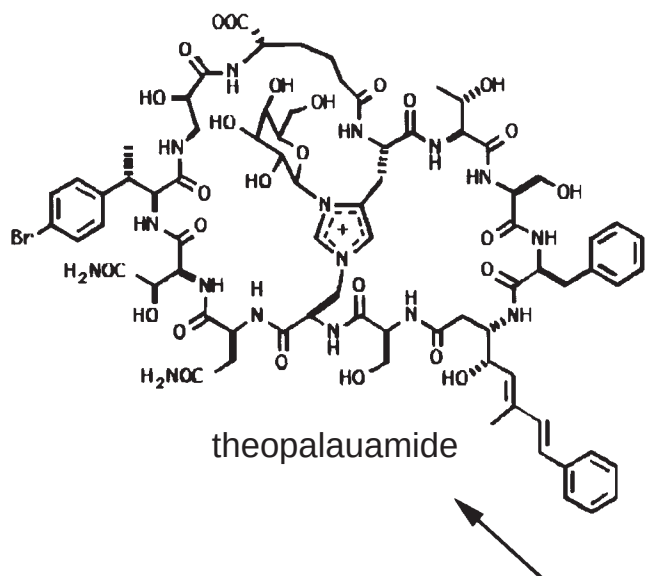
These results show that PP-enynes **1** react with a variety of acids, while the hereby formed addition products **2** easily rearrange in most cases (X=Cl, Br, I) to give 2-aminopyrylium salts **4**. On the other hand, the postulated ring-opening reaction **4** → **6** only proceeds in the presence of nucleophilic counterions.

Received: February 16, 1998 [Z11485IE]
German version: *Angew. Chem.* **1998**, *110*, 2214–2216

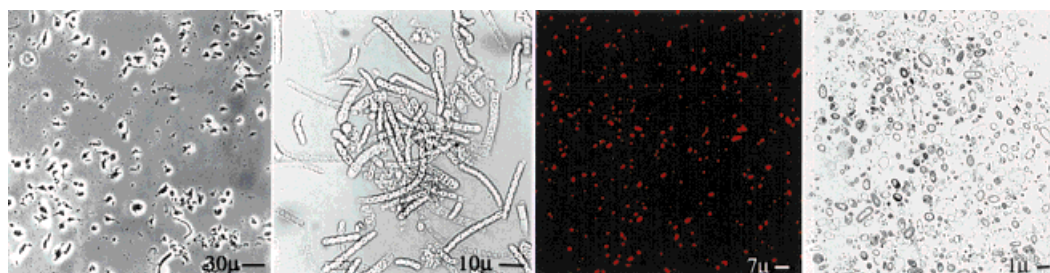
Keywords: aminopentadienals • donor–acceptor systems • enynes • pyrylium salts • rearrangements

- [1] Important syntheses: a) K. Hafner, M. Neuenschwander, *Angew. Chem.* **1968**, *80*, 443–444; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 459–460; b) M. E. Kuehne, P. J. Sheeran, *J. Org. Chem.* **1968**, *33*, 4406–4413; c) G. Himbert, M. Regitz, *Synthesis* **1972**, 571–573; d) G. Himbert, *Angew. Chem.* **1979**, *91*, 432–433; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 405; e) T. Sasaki, A. Kojima, *J. Chem. Soc. C* **1970**, 476–480.
- [2] a) M. Neuenschwander, K. Hafner, *Angew. Chem.* **1968**, *80*, 444; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 460; b) H. J. Gais, K. Hafner, M. Neuenschwander, *Helv. Chim. Acta* **1969**, *52*, 2641–2657.
- [3] W. Steglich, G. Höfle, W. König, F. Weygand, *Chem. Ber.* **1968**, *101*, 308–322.

- [4] For the synthesis of two highly substituted PP-enynes of type **1**, see Y. Sato, Y. Kobayashi, M. Sugiura, H. Shirai, *J. Org. Chem.* **1978**, *43*, 199–202; G. Himbert, W. Brunn, *Liebigs Ann. Chem.* **1985**, 2206–2216.
- [5] Three PP-enynes **1** have been prepared in a surprisingly simple way by aldol condensation of PP-acetylenes^[1] with ketones: I. G. Ostroumov, E. Yu. Khakunova, A. E. Tsil'ko, I. A. Maretina, A. A. Petrov, *Zh. Org. Khim.* **1990**, *26*, 2508–2510; *J. Org. Chem. USSR (Engl. Transl.)* **1990**, *26*, 2172–2173.
- [6] Compared with the aldol condensation of PP-acetylenes described in ref. [6], Pd⁰-catalyzed coupling of trialkylsilyl- or trialkylstannylamines with 3-iodopropenal or 4-iodobut-3-en-2-one has a much broader scope and makes aldehydes **1a–c** and **1g** (R = H) available as well: a) A. Bartlome, U. Stämpfli, M. Neuenschwander, *Chimia* **1991**, *45*, 346–349; b) D. Berger, Dissertation, Universität Bern, **1995**; c) D. Berger, A. Bartlome, M. Neuenschwander, *Helv. Chim. Acta* **1996**, *79*, 179–191; d) F. Fischer, Dissertation, Universität Bern, **1998**.
- [7] D. Berger, M. Neuenschwander, *Helv. Chim. Acta* **1996**, *79*, 192–202.
- [8] Mechanistic considerations (for a discussions see ref. [7]) suggest that reactions of acids with **1** should give Z/E mixtures of **2**, which could isomerize to the thermodynamically favored Z isomer due to a pronounced π delocalization of **2** (or of protonated **2**).
- [9] For illustrations of the ¹H NMR, ¹³C NMR, IR, UV, and mass spectra of **1**, **2**, **4**, and **6** as well as discussions of NMR spectra see ref. [6b,d].
- [10] The following 2-aminopyrylium salts **4**^[9] have been isolated (yield): X = Cl: **4a** (64%), **4b** (75%), **4c** (84%), **4d** (63%), **4e** (82%), **4f** (69%); X = Br: **4a** (47%); X = I: **4a** (49%); X = BF₄: **4b** (99%). The following 2-aminopyrylium salts **4** have been identified in solution^[9] (NMR yields based on pyrazine as a reference): **4b** (X = OAc, 90%), **4b** (X = F, 81%), **4g** (X = OCOC₂H₅, BF₄, ca. 40%).
- [11] Similarly, 2,4-bis(dialkylamino)pyrylium salts are relatively stable towards nucleophiles: R. Spitzner, R. Radeglia, W. Schroth, *Tetrahedron Lett.* **1985**, *26*, 3967–3970.
- [12] A. Niederhauser, G. Bart, M. Neuenschwander, *Helv. Chim. Acta* **1973**, *56*, 2427–2449.
- [13] It should be noted that the energy of **7** is supposed to increase due to the contribution of the “antiaromatic” 4 π resonance form **7B**, whereas the contribution of the “aromatic” 6 π resonance form **4B** is thought to lower the energy of **4**.
- [14] The term “pentadienal rearrangement” goes back to Roedig, who showed that perchloropentadienals are subject to a 1,5-O-shift at high temperatures: a) A. Roedig, G. Märkl, S. Schödel, *Angew. Chem.* **1957**, *69*, 240; *Liebigs Ann. Chem.* **1962**, *659*, 1–16. b) A. Roedig, G. Märkl, F. Frank, R. Kohlaupt, M. Schlosser, *Chem. Ber.* **1967**, *100*, 2730–2741.
- [15] Alternatively, the reactivity of pyrylium salts **4** may be increased by replacing dialkylamino groups by weaker π donors: Thus, 5-ethoxypent-2-en-4-in-1-al is available by Pd⁰-induced coupling of 1-trimethylstannyl-2-ethoxyethyne with 3-iodopropenal (60%) and adds HCl to give 5-chloro-5-ethoxypenta-2,4-dien-1-al. After storage of a solution of this compound in CDCl₃ for 30 days at –30°C, ethyl 5-chloropentadienoate is isolated in 50% yield: C. Bacilieri, Diplomarbeit, Universität Bern, **1995**.
- [16] Apparently, Et₃N may induce a ring opening by nucleophilic attack at C(6) of **4b** [**4b** (X = OAc) → **6b** (X = Et₃N⁺)], so that even weak nucleophiles such as AcO[–] may displace Et₃N in an addition–elimination sequence. It seems that Et₃N is an attractive nucleophilic auxiliary for inducing ring openings of easily available 2-aminopyrylium salts of type **4** (X = Cl, OAc). Experiments in view of generalizing this method are planned.
- [17] a) W. Flitsch, B. Mütter, U. Wolf, *Chem. Ber.* **1973**, *106*, 1993–2000; b) W. Flitsch, F. Kappenberg, H. Schmitt, *ibid.* **1978**, *111*, 2407–2422.



Micrographs of
purified cell types.
Associated
chemistry
shown above



Sponge
cells



Filamentous
bacteria



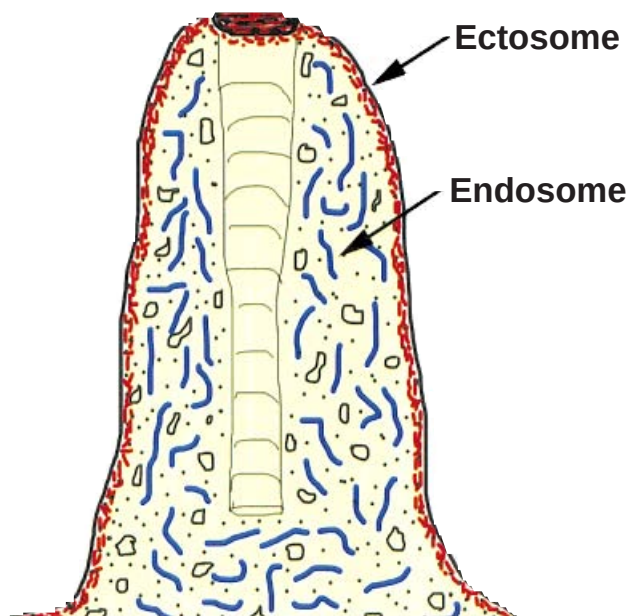
Unicellular
cyanobacteria



Unicellular
bacteria



Underwater photo of
the lithistid sponge
Theonella swinhoei



Schematic cross section showing
location of bacterial symbionts
and sponge cells in *T. swinhoei*
(legend shown in center panel)

Lithistid Sponges: Star Performers or Hosts to the Stars

Carole A. Bewley and D. John Faulkner*

The lithistid sponges are almost unique among marine invertebrates because they contain so many different classes of compounds. After defining the term “lithistid”, we review the chemistry of the lithistid sponges and illustrate most of the important compounds that have been reported. We then describe the strategies that we have employed in

the structural elucidation of cyclic peptides. Whereas most natural product studies end when the structure has been elucidated, we were intrigued by the fact that many lithistid metabolites resembled secondary metabolites from microorganisms and decided to investigate the source of two bioactive metabolites at the cellular level. Using

the sponge *Theonella swinhoei*, we were able to separate three types of microorganisms from the sponge cells and analyze the metabolites from each cell type, even after the cells had been fixed. Although there had been speculation that both swinholid A and the bicyclic peptides were produced by cyanobacteria (blue-green algae), our

1. Introduction

Lithistid sponges are renowned among marine organisms for their ability to produce a diverse array of biologically active metabolites. Representative compounds include polyketides, cyclic peptides, alkaloids, pigments, and novel sterols. This extreme diversity of metabolites defied simple chemotaxonomic rationalization until we demonstrated that symbiotic microorganisms were responsible for the production of some representative compounds.^[1] In this review we will present a summary of the chemistry attributed to lithistid sponges and outline our research on the chemical relationships between a lithistid sponge and its symbionts.

2. What is a Lithistid Sponge?

The sponge order Lithistida (Porifera, Demospongiae) is an artificial assemblage of species of diverse origins that are

grouped together because they have skeletons consisting in large part of fused or interlocked spicules called desmas.^[2] The rigid skeleton of fused desmas dictates the shape of the lithistid sponge and also serves to divide the sponge into external (ectosome) and internal (endosome) tissues. From the viewpoint that the lithistid sponges have diverse origins, one might predict the lack of a chemotaxonomic theme among the metabolites. However, one would not expect the dominance of biologically active compounds in sponges that are so well physically protected by a shield of fused siliceous spicules. Lithistid sponges have a quite ancient lineage, being well represented in the Cambrian fossil record. In modern times lithistid sponges are predominantly found in deeper waters, which presents the collector with considerable logistical problems, and which has resulted in chemical investigations being concentrated on those genera that can be found at normal scuba depths. A summary of the taxonomic classification of lithistid sponges^[3] is shown in Figure 1.

3. Chemistry of the Lithistid Sponges

The underlying chemotaxonomic theme of the chemistry of lithistid sponges is that there is no theme. Almost every class of compound is represented in a seemingly random manner. However, the incidence of biologically active compounds with unusual structures is very high and this may indeed be the underlying theme.

[*] Prof. D. J. Faulkner

Scripps Institution of Oceanography
University of California at San Diego
La Jolla, CA 92093-0212 (USA)
Fax (+1) 619-534-2997
E-mail: jfaulkner@ucsd.edu

Dr. C. A. Bewley
Laboratory of Chemical Physics, NIDDK
National Institutes of Health, Bldg. 5, Room B135
Bethesda, MD 20892 (USA)
E-mail: bewley@speck.niddk.nih.gov

Phylum Porifera

Class Demospongiae

Subclass Tetractinomorpha

Order Lithistida

Family Theonellidae

Genera *Discodermia*, *Jereicopsis*,
Racodiscula, *Theonella*

Family Phymatellidae

Genera *Neosiphonia*, *Reidisporgia*

Family Phymaraphinidae

Genus *Kaliapsis*

Family Corallistidae

Genera *Callipelta*, *Corallistes*,
Homophymia, *Macandrewia*

Family Neopeltidae

Genus *Neopelta*

Family Pleromidae

Genus *Pleroma*

Family Dorydermidae

Genus *Anaderma*

Family Scleritodermidae

Genera *Aciculites*, *Amphibleptula*,
Microscleroderma, *Scleritoderma*,
Tabropane

Family Siphonidiidae

Genera *Gastrophanella*, *Leiodermatium*,
Siphonidium

Family Desmantidae

Genus *Desmanthus*

Family Petromicidae

Genus *Petromica*

Family Vetulinidae

Genus *Vetulina*

Figure 1. Current classification of extant lithistid sponges.^[3]

3.1. Sterols

Even the earliest studies of lithistid sponges resulted in the isolation of unusual compounds. In 1981, Djerassi and co-workers identified the 4-methylene sterols conicasterol (**1**) and theonellasterol (**2**) as the major sterols from *Theonella conica* and *T. swinhoei*.^[4] Two years later, the same research group reported the isolation of pulchrasterol (**3**) and other Δ^7 sterols from the New Zealand deep water lithistid sponge *Aciculites pulchra*.^[5] The Δ^7 sterols are not normal sponge sterols and are normally associated with starfish and sea cucumbers.^[6] The 4-methylene sterols appear to be unique to *Theonella*, although 4-methylsterols are often found in dinoflagellates.^[6, 7] Subsequently, the corresponding 3-keto-4-methylene sterols, theonellasterone (**4**) and conicasterone (**5**), were isolated from *T. swinhoei*, together with the Diels–Alder adducts, bisconicasterone (**6**) and bistheonellasterone (**7**), and nine minor oxygenated 4-methylene sterols.^[8–10] Interestingly, the 3-keto-4-methylene sterols **4** and **5** were obtained as crystals from the tissues of the sponge.^[8] More recently, it has been found that in *Jereicopsis graphidiophora*^[11] and *Microscleroderma spirophora*^[12] the normal 3β -hydroxysterols are replaced by 3β -methoxysterols, which include the bisenol ether **8**.^[12]

3.2. Macrolides and Acetogenins

The isolation and identification of swinholide A (**9**) provided natural product chemists with a very valuable lesson in the art of structural elucidation. Swinholide A, which is a potent cytotoxic agent from *T. swinhoei*, was first reported to be a monomeric 22-membered lactone,^[13] while misakinolide A from *Theonella* sp. was first identified as a monomeric

D. John Faulkner received his B.Sc. and Ph.D. degrees from Imperial College, London, where he studied synthetic organic chemistry under the guidance of Sir Derek Barton. After receiving postdoctoral training from R. B. Woodward at Harvard University and W. S. Johnson at Stanford University, he joined the faculty of the Scripps Institution of Oceanography, University of California, San Diego, where he is now Professor of Marine Chemistry. At the urging of his colleagues to “do something more marine”, he turned his attention to marine natural products chemistry and has never regretted making the change in research emphasis. His research interests include the structural elucidation of marine natural products, their biomedical potential, and their role in the life cycles of the marine environment.

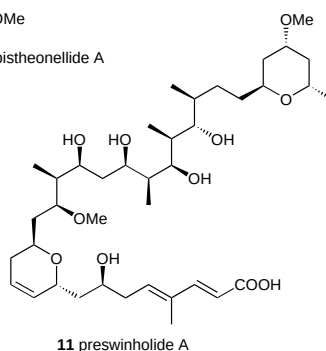
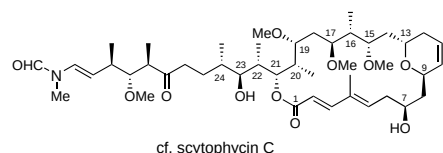
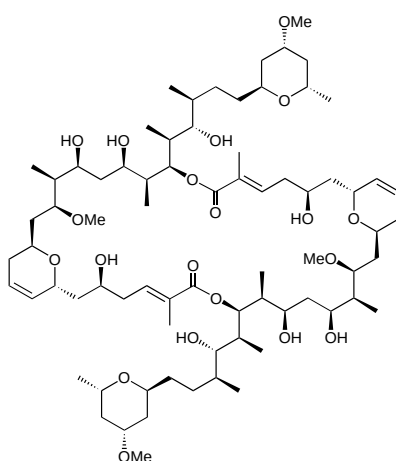
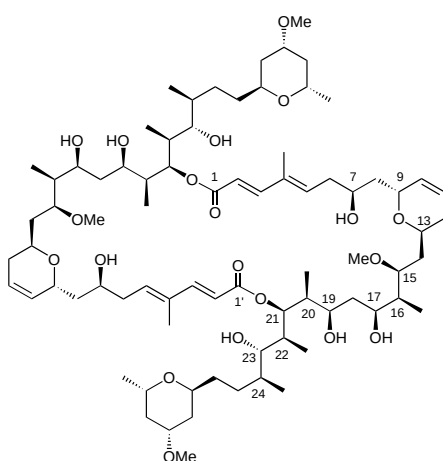
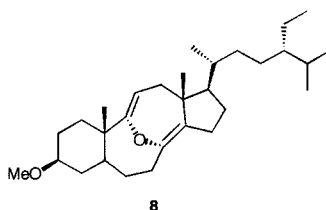
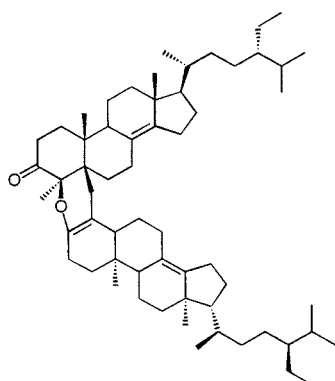
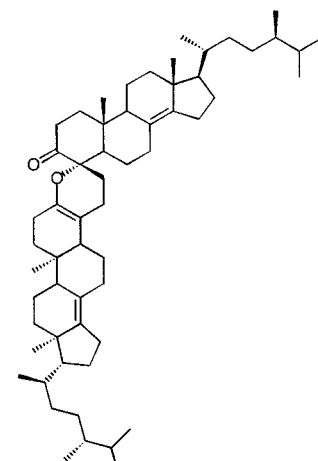
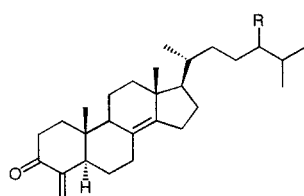
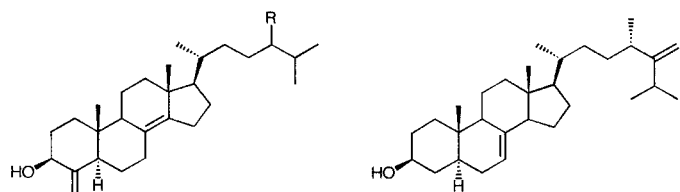


D. J. Faulkner



C. A. Bewley

Carole Ann Bewley, born October 27, 1963, received her B.Sc in Chemistry from San Diego State University in 1985. After working as a research associate at the Salk Institute for Biological Studies in the group of Professor Jean Rivier, she joined the graduate program at Scripps Institution of Oceanography, University of California, San Diego, and completed her doctoral studies in 1995 under the supervision of Professor D. John Faulkner. She is currently a Cancer Research Institute postdoctoral fellow at the National Institutes of Health in the laboratory of Dr. G. Marius Clore.

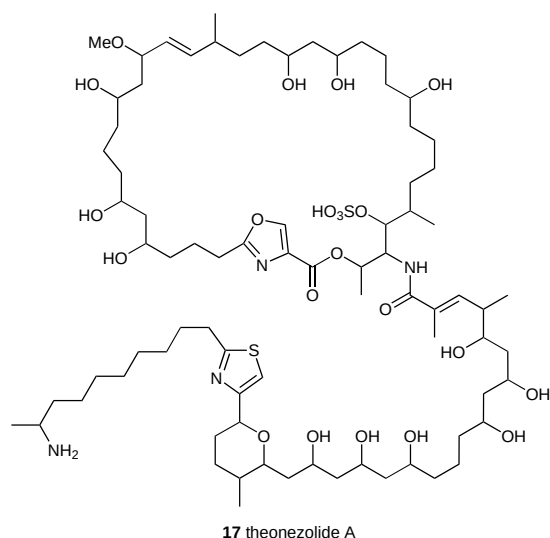
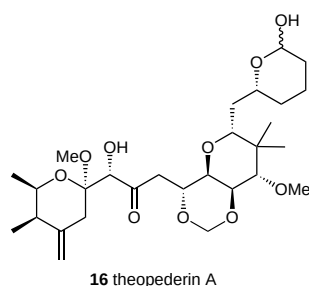
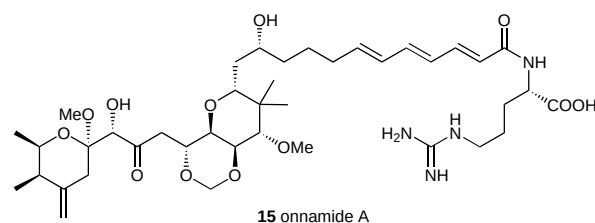
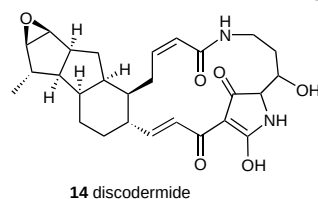
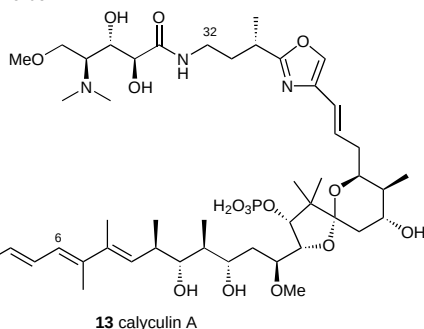
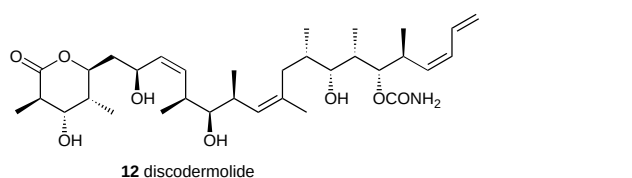


20-membered lactone that lacked a disubstituted olefin in the lactone ring.^[14] Both compounds gave the correct elemental analytical results and misakinolide A even gave a strong $[M^+ + H]$ peak for the monomer in the mass spectrum. The symmetrical dimeric structures of both swinholid A and misakinolide A first became apparent during the structural elucidation of bistheonellides A (10) and B from *Theonella* sp., when it was discovered that bistheonellide A (10), which was spectroscopically identical to misakinolide A,^[15, 16] gave an unsymmetrical tribenzoate as one of its esterification products and a “dimeric” molecular ion in the mass spectrum. The dimeric 44-membered ring structure and absolute stereochemistry of swinholid A (9) were established unambiguously by X-ray crystallographic analysis.^[17] Since then, a number of dimeric macrolides of the swinholid^[18, 19] and bistheonellide^[20] families, together with preswinholide A (11),^[21] the monomer of swinholid A (9), have been reported. Of these compounds, swinholid A (9) was shown to be the most cytotoxic^[22] and has, therefore, been the target of both conformational^[23] and synthetic studies that culminated in two excellent total syntheses.^[24, 25]

The X-ray structure of discodermolide (12), an immunosuppressive and cytotoxic agent from *Discodermia dissoluta*, revealed a novel “polypropionate” structure.^[26] Owing to its unusual and potentially useful biological profile, which includes the ability to stabilize microtubules more potently than taxol,^[27] and the real or perceived difficulty in obtaining large supplies of the drug from natural sources, discodermolide (12) has become a popular target for synthetic programs.^[28, 29] The calyculins, exemplified by calyculin A (13),^[30] are a family of eight potent antitumor agents from *D. calyx* that inhibit protein phosphatases 1 and 2A. Calyculins B, E,

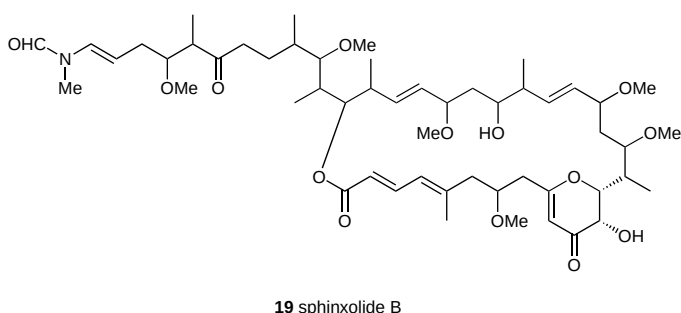
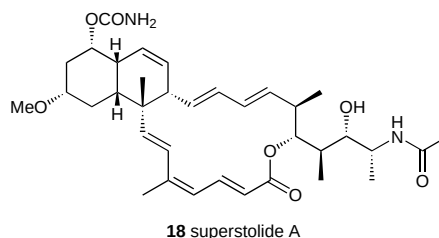
and F are geometrical isomers of calyculin A (13) with respect to the C2–C3 and C6–C7 bonds while calyculins C, D, G, and H are a homologous series with a methyl group at C-32.^[31–34] *D. polydiscus* contained the cytotoxic and antifungal macrocyclic lactam discodermide (14).^[35]

In 1988, onnamide A (15) was isolated from an Okinawan species of *Theonella*.^[36] Onnamide A (15), whose structure strikingly resembled that of the insect toxin pederin,^[37] was shown to possess antiviral properties and was subsequently synthesized by Hong and Kishi.^[38] An additional nine compounds in the onnamide series were subsequently reported together with their cytotoxicities against the P388 cell line.^[39, 40] The theopederins, exemplified by theopederin A (16), are cytotoxins from *Theonella* sp. that



have slightly simpler structures.^[41] The most complex of the macrolides from *Theonella* sp. are the cytotoxic theonezolides A (**17**), B, and C, for which there is limited stereochemical data.^[42, 43]

Neosiphonia superstes is a deep water lithistid sponge that was obtained by dredging. It is the source of superstolides A (**18**)^[44] and its 24,25-dehydro derivative superstolide B,^[45] as well as sphinxolides B (**19**), C, and D,^[46] all of which are potent cytotoxic macrolides. Sphinxolide itself was originally ob-

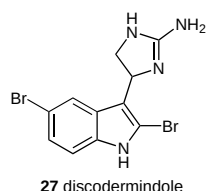
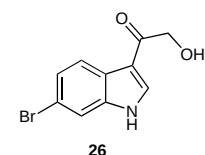
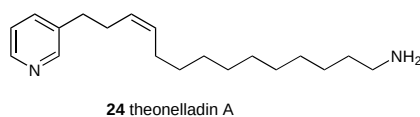
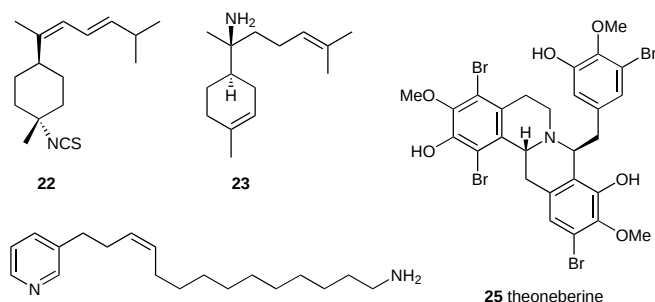
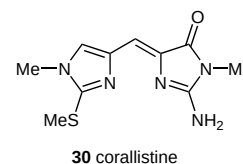
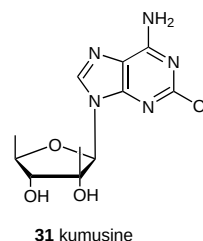
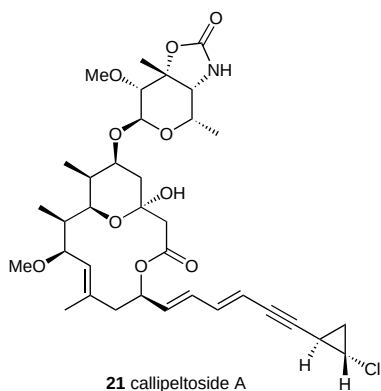
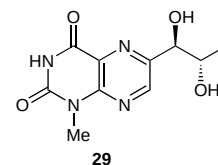
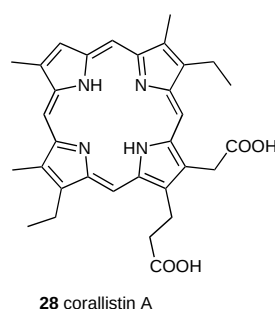
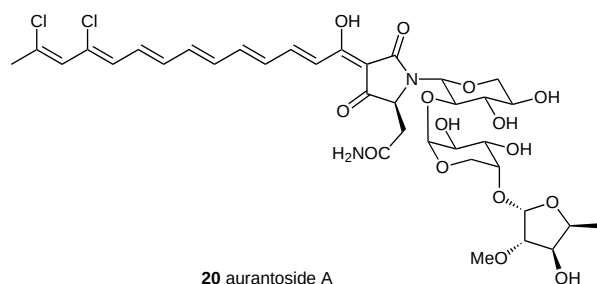


tained from an unidentified Pacific nudibranch (sea slug) which had evidently consumed a sponge that contained the macrolide.^[47] The sphinxolides B (**19**) and D were also found, together with two related cytotoxic macrolides, reidispongolides A and B, from *Reidispongia coerulea*, which was also dredged from a depth of 500 m in the same region south of New Caledonia.^[48]

There are two examples of lithistid sponges that contain chlorinated acetogenins with added sugar substituents. Aurantiosides A (**20**) and B are cytotoxic orange pigments from a Japanese *Theonella* sp.^[49] A New Caledonian species of *Callipelta* contains callipeltosides A (**21**), B, and C, which are most unusual cytotoxic macrolides that contain a chlorocyclopropane group.^[50,51]

3.3. Alkaloids and Other Nitrogenous Bases

Seven bisabolene sesquiterpenes exemplified by theonellin isocyanate (**22**) from *Theonella swinhoei* from Okinawa^[52] and aminobisabolene (**23**) from an Okinawan *Theonella* sp.^[53] were among the earliest nitrogenous metabolites to be attributed to lithistid sponges. Theonelladin A (**24**) is one of four antineoplastic (tumor inhibiting) pyridine alkaloids from an Okinawan specimen of *T. swinhoei*.^[54] Examples of both of the preceding classes of alkaloids are commonly found in non-lithistid sponges. One of the most unusual natural products from *Theonella* sp. is the mildly antimicrobial and cytotoxic isoquinoline alkaloid theoneberine (**25**),^[55] which



resembles a terrestrial alkaloid. The relatively simple metabolites ethyl 6-bromo-3-indolcarboxylate and 3-hydroxyacetal-6-bromoindole (**26**) were isolated from the deep water lithistid *Pleroma menoui*^[56] while *D. polydiscus* contained the moderately cytotoxic brominated indole derivative discodermindole (**27**).^[57]

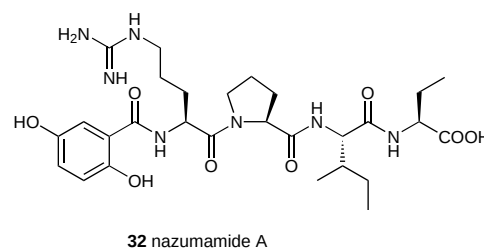
The natural function of five cytotoxic porphyrin pigments, exemplified by corallistin A (**28**), from a New Caledonian species of *Corallistes* is something of a mystery since there is almost no light at the depth of 300 m. from which the sponge was collected.^[58, 59] Other *Corallistes* species contain pteridines, such as 1-methylpteridine-2,4-dione from *C. fulvodesmus* and the 6-dihydroxypropyl derivative **29** from *C. undulatus*,^[60] and corallistine (**30**) also from *C. fulvodesmus*.^[61] Finally, there is the chlorinated nucleoside kumusine (**31**) that was isolated from a *Theonella* sp. and shows moderate immunosuppressive activity and cytotoxicity.^[62]

3.4. Peptides

In 1993, Fusetani and Matsunaga wrote an excellent review of “Bioactive Sponge Peptides” that included detailed accounts of the peptides from lithistid sponges.^[63] Rather than duplicate their review, we will simply emphasize the broad range of peptide structures found in lithistid sponges and provide an update to the information in that review. The most remarkable features of the peptides from lithistid sponges are the unusual range of bioactivities and the almost ubiquitous inclusion of nonstandard as well as D-amino acids.

3.4.1. Linear Peptides

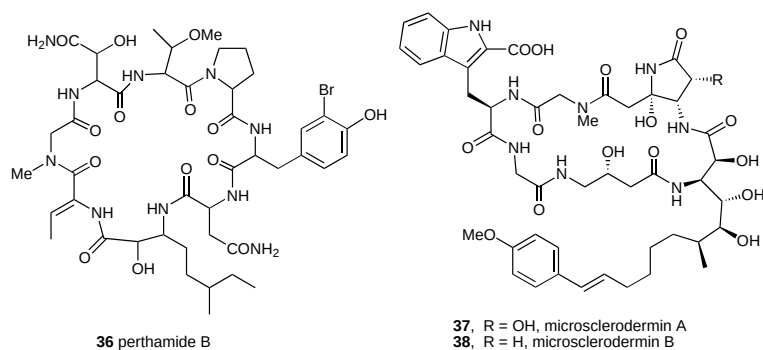
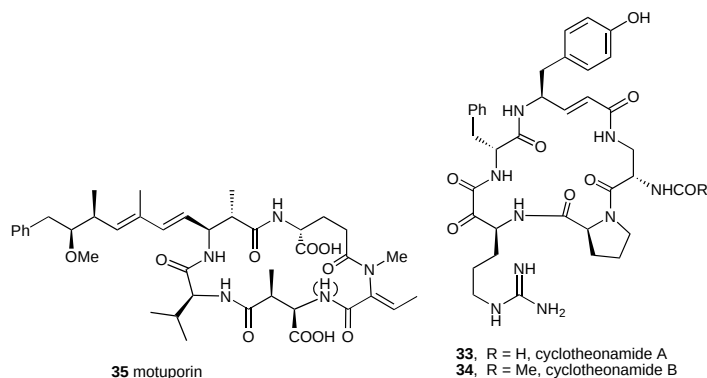
The same *Theonella* sp. that produced the cyclotheonamides (see Section 3.4.2) also contained the thrombin inhibitor nazumamide A (**32**), which is a relatively simple tetrapeptide in which the N-terminus is capped as a 2,5-dihydroxybenzamide group.^[64] In contrast, polytheonamides



A–C from *T. swinhoei* are highly cytotoxic linear 48-residue peptides that are characterized by an unusually high number of *tert*-leucine residues.^[65]

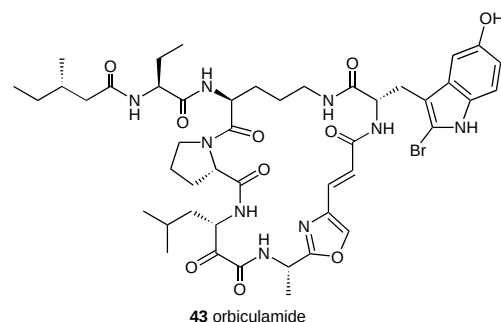
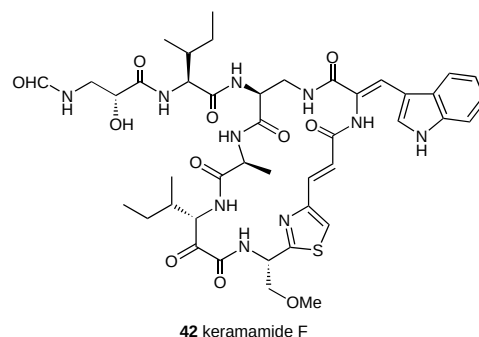
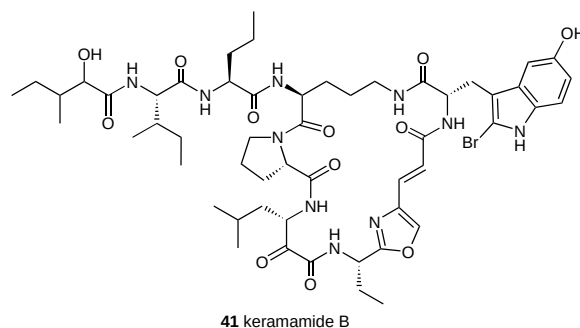
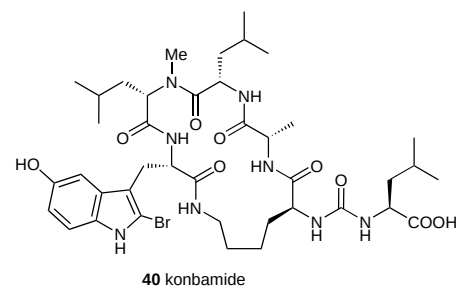
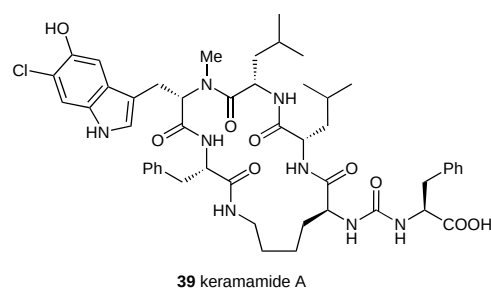
3.4.2. Cyclic Peptides

Two of the more spectacular cyclic peptides to be found in lithistid sponges are cyclotheonamides A (**33**) and B (**34**) from a Japanese species of *Theonella*, which were described in 1990 as potent thrombin inhibitors.^[66] The presence of



the α -ketoamide functionality in the cyclotheonamides attracted the attention of those working on FK506 and cyclosporin, and cyclotheonamide was soon synthesized, which resulted in the reassignment of the stereochemistry.^[67] This synthesis was followed by a number of studies to define the molecular basis for the mechanism of action of the cyclotheonamides as serine protease inhibitors,^[68] additional synthetic studies,^[69] and the structural elucidation of three more analogues, cyclotheonamides C–E.^[70] Motuporin (**35**) is a potent inhibitor of protein phosphatase 1 and cytotoxin that was isolated from a specimen of *T. swinhoei* from Papua New Guinea.^[71] The structure of the pentapeptide motuporin (**35**) differs from that of the cyanobacterial metabolite nodularin^[72] by the substitution of (*S*)-arginine by (*S*)-valine. The cytotoxic octapeptide perthamide B (**36**), which weakly inhibits the binding of interleukin-1 β to EL4.1.6 cells is a cyclic octapeptide from an Australian *Theonella* sp.^[73] A deep water *Microscleroderma* species from New Caledonia contained two antifungal cyclic peptides, microsclerodermins A (**37**) and B (**38**), which possess a very complex β -amino acid moiety.^[74]

The sarcoplasmic reticulum Ca²⁺-ATPase inhibitor keramamide A (**39**), which was isolated from an Okinawan *Theonella* sp., is a cyclic hexapeptide that contains an unusual urea functionality in the side chain.^[75] Konbamide (**40**), which is a calmodulin antagonist, is a very similar cyclic hexapeptide with one urea group that was isolated by the same research group from a different specimen of *Theonella* sp. from Okinawa. The proposed structure of konbamide (**40**) has recently been questioned as a consequence of the results from a synthetic study.^[76] Although from the same sponge, the structures of keramamides B (**41**) and C–H are quite different from that of keramamide A (**39**), with all containing an



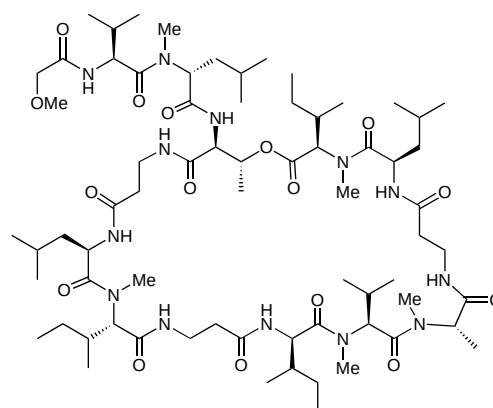
α -ketoamide functionality and either an oxazole (keramamides B (**41**), C, D, and E) or a thiazole (keramamides F (**42**), G and H) moiety in the cyclic peptide ring system.^[77–79] Orbiculamide (**43**) is a cytotoxic peptide from a Japanese

Theonella sp. that is closely related to keramamide D.^[80] The structures of the discobahamins A and B obtained from a deep water specimen of *Discodermia* sp. collected off the Bahamas differ from that of keramamide D only in the nature of the side chain.^[81]

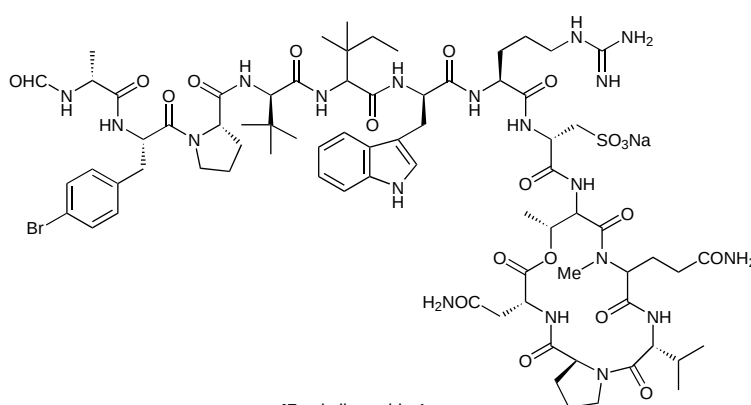
3.4.3. Cyclic Depsipeptides

In 1984, Fusetani's group described discodermin A as an antimicrobial cyclic tetradecapeptide lactone from *Discodermia kiiensis*.^[82] Subsequent papers reported the structures of discodermins B–H,^[83–86] but in the process the structures of discodermins A (44) and B–D were revised.^[86] The range of biological activities of this series of compounds has also been expanded: discodermin A (44) inhibited the tumor promotion activity of okadaic acid,^[87] discodermins A–D are potent inhibitors of phospholipase A₂,^[88] and all the members of the series are cytotoxic. Discokioldes A (45) and B–D are cytotoxic depsipeptides from *D. kiiensis* that have a unique oxazole-containing β -hydroxy acid forming the side chain.^[89]

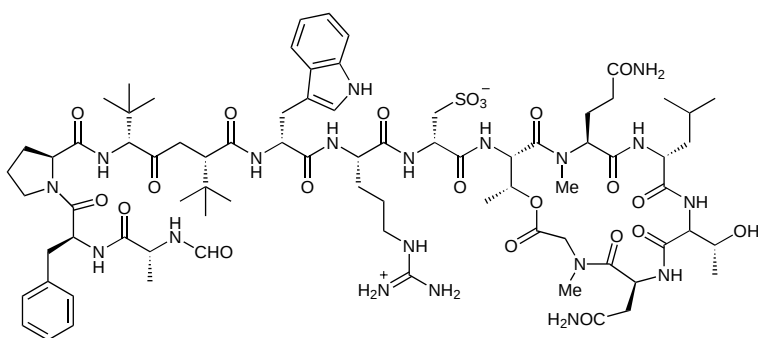
In 1986, Kitagawa's group described the isolation of the theonellapeptolides, which inhibited cell division in fertilized sea urchin eggs, and showed that theonellapeptolide Id (46) was a cyclic depsipeptide.^[90] Shortly after, Nakamura



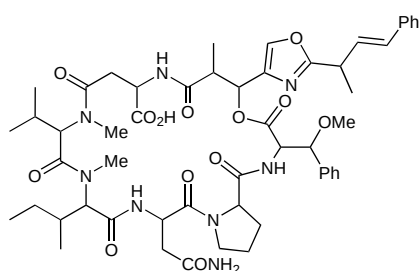
46 theonellapeptolide Id



47 polydiscamide A



44 discodermin A



45 discokioldes A

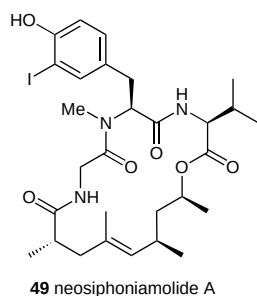
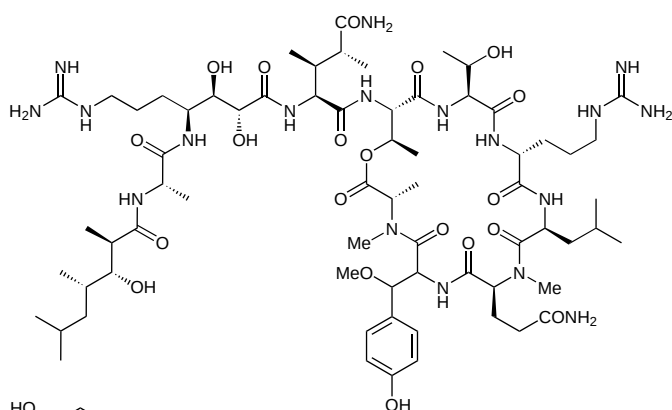
described as cytotoxic tridecapeptide lactones from *T. swinhoei*.^[92–95] Polydiscamide A (47), which was isolated from *D. polydiscus*, is also a cytotoxic tridecapeptide cyclic lactone albeit with a smaller ring size.^[96]

Recently, Minale's group has reported a series of cyclic depsipeptides from a New Caledonian species of *Callipelta*. The structural elucidations of callipeltins A (48) B, and C, which possess anti-HIV, antifungal, and cytotoxicity activities, revealed a side chain that terminated with an unusual polypropionate moiety.^[97, 98] Along with the sphinxolides reviewed above, *Neosiphonia superstes* contained the small cyclic depsipeptide neosiphoniamolide A (49), which is remarkably similar in structure to the geodiamolides and jaspamide that had previously been isolated from nonlithistid sponges.^[99]

3.4.4. Bicyclic Peptides

The 1989 paper by Matsunaga et al. on the structural elucidation of the antifungal bicyclic peptide theonellamide F (50) from a Japanese species of *Theonella* was a landmark paper in the history of marine natural products chemistry because it presented an elegant solution to a structural problem that was a degree of difficulty beyond the research of the time.^[100] This paper inspired us to examine a Philippine specimen of *Theonella*

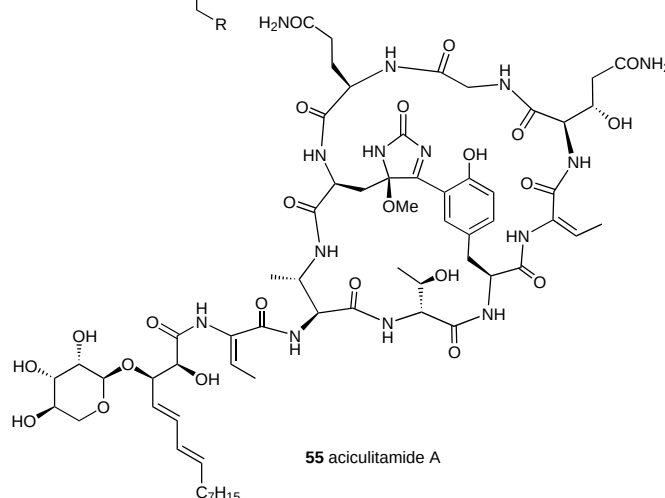
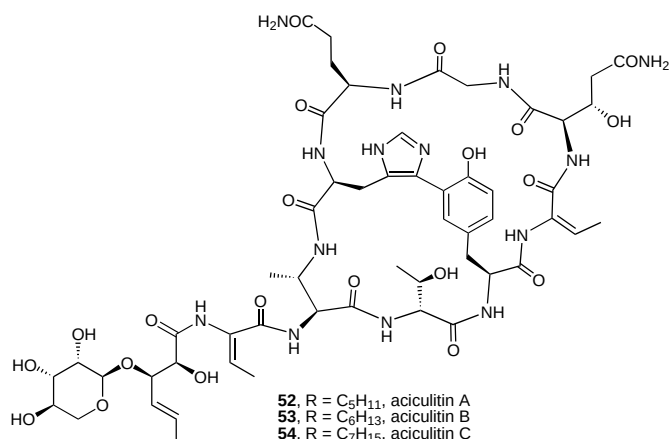
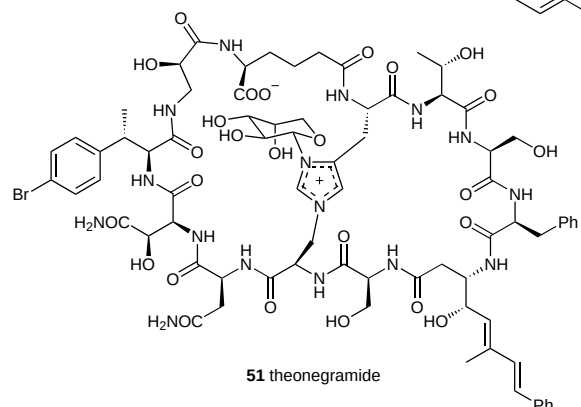
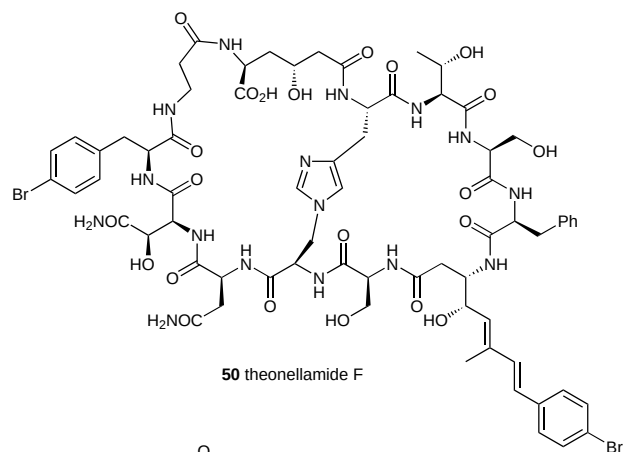
et al. reported the same compound as theonellamine B from an Okinawan species of *Theonella* and recorded its activity as a Na⁺,K⁺-ATPase inhibitor.^[91] In due course, five more theonellapeptolides (Ia, Ib, Ic, Ie, and IId) were



swinhoei, from which we isolated theonegramide (**51**), the first example of a glycopeptide from a lithistid sponge.^[101] Matsunaga and Fusetani have subsequently reported the structures of the cytotoxic bicyclic peptides theonellamides B and C and the cytotoxic glycopeptides theonellamides A, D, and E.^[102] The structural elucidation of the cytotoxic and antifungal bicyclic lipoglycopeptides aciculitins A–C (**52**–**54**) and the artifacts aciculitamides A (**55**) and B from *Aciculites orientalis* is undoubtedly the most complex problem that has been tackled in our laboratory and is featured below.^[103]

4. Structural Elucidation of Cyclic Peptides from Lithistid Sponges

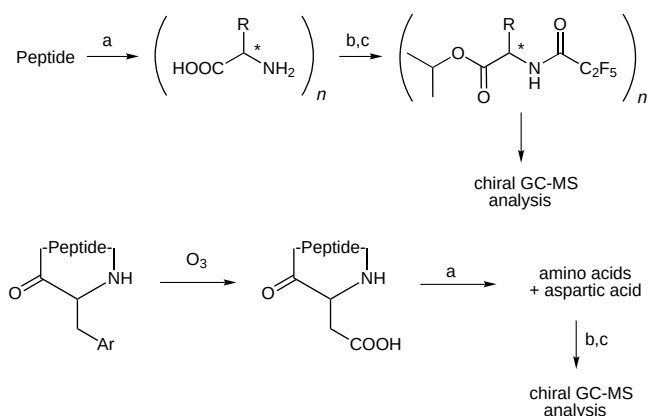
The majority of the techniques used in the structural elucidation of cyclic peptides, depsipeptides, and glycopeptides are standard and are quite familiar to marine natural products chemists. However, there are still some lessons to be learned and improvements to be made. We regard our preferred isolation method as one such improvement. When we extracted *A. orientalis* with methanol, we obtained a crude extract that showed strong antifungal activity but gave very poor NMR spectra. As the purification proceeded, with methanol as the eluent in most chromatographic procedures, the antifungal activity decreased and the spectra improved until the artifacts, aciculitamides A (**55**) and B, were isolated. Both compounds contained a methoxy group that had resulted from addition of the solvent to an autoxidation product. When we obtained a new collection of the sponge, we devised an extraction procedure that avoided the use of methanol and have since found that it gives superior results in most cases.¹⁰³ The sponge is diced and lyophilized, then extracted sequentially with hexane and ethyl acetate at room



temperature. After removal of residual organic solvents, the sponge is then extracted with water:acetonitrile (1:1) at room temperature until the extracts no longer show antifungal activity and/or a positive color reaction for the peptide on thin-layer chromatography. The acetonitrile is evaporated on a rotatory evaporator and the remaining water lyophilized to obtain a powder that is of much higher purity than a corresponding methanol extract.

An attractive feature of the peptides from lithistid sponges is the presence of unusual amino acids. The identification of unusual amino acids can usually be accomplished from the ^1H and ^{13}C NMR data together with the COSY, TOCSY, HMBC, and HMQC nmr experiments. Problems arise when the amino acids are not joined through standard peptide bonds, but instead with unusual linkages such as those between histidine and alanine in theonellamide F (**50**) and theonegramide (**51**) and between histidine and tyrosine in the aciculitins (**52–54**). In such cases, and particularly for aciculitamide A (**55**), a combination of HMBC and ROESY data must be used to establish the location of nonpeptidal bonding between the residues. The sequence in which individual amino acids are linked through peptide or lactone bonds is determined by C–H correlations through two and three bonds. However, in some bicyclic peptides the required correlation data may be missing when the molecule either adopts a conformation in which the dihedral angles are inappropriate for scalar coupling or is undergoing motion that is fast on the NMR time scale. This occurred in the aciculitins (**52–54**) when no long-range coupling was observed across the peptide bonds adjacent to the bicyclic ring junctions. The solution was provided by a ROESY experiment that indicated the proximity of hydrogen atoms on adjacent amino acid residues.^[103]

The peptides from lithistid sponges often contain both D- and L-amino acids, which makes the determination of the absolute configuration of each individual amino acid an essential part of every structural elucidation. We selected mass spectrometry coupled to gas chromatography on a chiral phase as the method of choice for the determination of the absolute configuration of the amino acids that resulted from acid hydrolysis of the peptides since it requires the least amount of material and, more importantly, the identity of the peaks can be confirmed by MS (Scheme 1, top). The method depends on having reference standards for both D- and L-amino acids and thus determination of the absolute configuration of unusual amino acids can be problematic. There are two potential solutions. One can often obtain standards of unusual amino acids through the generosity of colleagues who have isolated or synthesized the required compounds or by in house synthesis. Alternatively, one can chemically modify the peptide prior to hydrolysis to convert the unusual amino acid residue into one of the standard amino acids, and then determine the absolute configuration of the newly formed amino acid. For example, aromatic amino acids that are substituted on the aromatic rings can be converted by ozonolysis into aspartic acid residues, which are then analyzed by GC-MS on a chiral phase (Scheme 1, bottom). In the aciculitins (**52–54**) the two aromatic residues, histidine and tyrosine, were differentiated by varying the ozonolysis reaction time to take advantage of the fact that the hetero-



Scheme 1. Determination of the absolute configuration of amino acids in a peptide. Top: Hydrolysis of a peptide and derivatization of the resulting amino acids for chiral GC-MS analysis. Bottom: Ozonolysis of a peptide containing a substituted aromatic amino acid to obtain a peptide containing aspartic acid, which is then analyzed using GC-MS with a chiral phase. a) 5N HCl, 100 °C, 16 h; b) CH_3COCl , isopropyl alcohol, 100 °C, 45 min; c) $(\text{C}_2\text{F}_5\text{CO})_2\text{O}$, CH_2Cl_2 , 100 °C, 45 min.

aromatic ring is oxidized more rapidly than the phenolic ring. We have examined the possibility of determining the absolute configuration of an individual amino acid residue by using molecular modeling and ROESY data but we do not recommend this method for small peptides unless the peptide has a nearly rigid ring system.

5. Many Lithistid Metabolites Resemble Compounds from Other Sources!

While recognizing that the degree of similarity between chemical structures is a subjective matter, Table 1 illustrates some of the more obvious similarities between lithistid metabolites and natural products from other sources. There is a small possibility that theonellin isocyanate (**22**) and theonelladin A (**24**) were incorrectly attributed to *T. swinhoei* and were in fact biosynthesized by other sponges. This may arise if the taxonomist identifies only one specimen selected from a mixed collection or if the lithistid sponge has absorbed the compound from seawater or from another sponge during the collection process. In other cases, we know that certain lithistid metabolites have been found in other sponges: for example, we have isolated swinholide A (**9**) from an *Ircinia* sp. from the Philippines. However, even when we eliminate the problematic examples, we are still confronted by Kitagawa's observation^[17] that part of the structure of swinholide A (**9**) bears a striking resemblance to a portion of scytophycin C from the filamentous cyanophyte *Scytonema pseudohofmannii*,^[104] even down to the level of having identical absolute configurations at all of the twelve stereocenters that are common to both molecules. This degree of similarity cannot be ignored.

In 1984, Fusetani and co-workers were the first to observe that discodermin A (**44**) contained amino acids that previously had been found only in peptides from bacteria and speculated, without any real evidence, that the peptides might be of bacterial origin.^[82] By 1993 and perhaps earlier, that

Table 1. Some compounds from lithistid sponges that are similar to compounds from other sources.

Species	Compound	Related compound	Source of related compound
<i>Theonella</i> sp.	theonellasterol (2)	3-methylsterols	dinoflagellates ^[7]
<i>T. swinhoei</i>	swinholid (9)	scytophycin C	cyanobacterium (<i>Scytonema pseudohofmanni</i>) ^[104]
<i>Theonella</i> sp.	onnamide A (15)	pederin	blister beetle (<i>Paederus</i> spp.) ^[37]
<i>Theonella</i> sp.	theopederin A (16)	pederin	blister beetle (<i>Paederus</i> spp.) ^[37]
<i>Neosiphonia superstes</i>	sphinxolide B (19)	scytophycin C	cyanobacterium (<i>Scytonema pseudohofmanni</i>) ^[104]
<i>Neosiphonia superstes</i>	sphinxolide B (19)	rhizopodin	myxobacterium (<i>Myxococcus stipitatus</i>) ^[105]
<i>Reidisporgia coerulea</i>	reidispongioides (cf. 19)	halichondramide	sponge (<i>Halichondria</i> sp.) ^[106]
<i>T. swinhoei</i>	theonellin isothiocyanate (22)	3-isocyanotheonellin	sponge (<i>Halichondria</i> cf. <i>lendenfeldi</i>) ^[107]
<i>T. swinhoei</i>	theonelladin A (24)	niphatesines	sponge (<i>Niphates</i> sp.) ^[108]
<i>Corallistes</i> sp.	corallistin A (28)	chlorophylls	plants and algae
<i>T. swinhoei</i>	motuporin (35)	nodularin	cyanobacterium (<i>Nodularia spumigena</i>) ^[109]
<i>Theonella</i> sp.	keramamide A (39)	ferintoic acid	cyanobacterium (<i>Microcystis aeruginosa</i>) ^[110]
<i>Neosiphonia superstes</i>	neosiphoniamolide A (49)	chondramides	myxobacterium (<i>Chondromyces crocatus</i>) ^[111]
<i>Neosiphonia superstes</i>	neosiphoniamolide A (49)	geodiamolide	sponge (<i>Geodia</i> sp.) ^[112]
<i>Discodermia dissoluta</i>	discodermide (14)	alteramide A	marine bacterium (<i>Alteromonas</i> sp.) ^[113]
<i>Discodermia dissoluta</i>	discodermide (14)	ikarugamycin	soil bacterium (<i>Streptomyces</i> sp.) ^[114]

hypothesis had undergone a subtle change that resulted in many authors attributing the metabolites in lithistid sponges to cyanobacterial symbionts.^[115] Two factors influenced this change. The first was the similarities between cyanobacterial metabolites and certain compounds from lithistid sponges, as discussed above. The second was the presence of filamentous bacterial symbionts in lithistid sponges that, when viewed by scanning electron microscopy, physically resemble the filamentous cyanobacterial symbiont *Oscillatoria spongeliae* found in the sponge *Dysidea herbacea*.

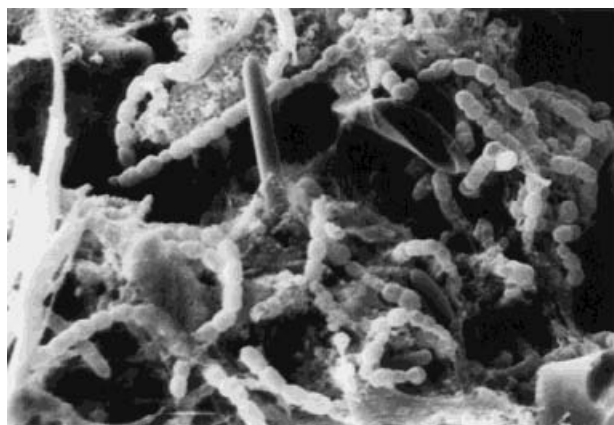


Figure 2. Scanning electron micrographs of *Theonella swinhoei*; filamentous bacteria in the interior of the sponge are visible.

Not all lithistid sponges have filamentous microorganisms interspersed among the interior tissues. We performed an analysis of lithistid sponges in our collection and found that the presence of filamentous microorganisms (Figure 2) correlated with antifungal activity of a crude extract of the sponge and, where the metabolites were known, with the presence of peptides containing aromatic β -amino acids (Table 2). Aromatic and aliphatic β -amino acids were well known as constituents of cyclic peptides from cyanobacteria (Table 3), but we could not accept the hypothesis that the filaments were cyanobacteria because photosynthetic organisms such as cyanobacteria do not prosper in the absence of light and lithistid sponges are often found at great depths, in caves and

in other shaded environments. Furthermore, the filaments are found only in the interior of the sponge where they are situated within a skeleton of fused siliceous desmas that exclude light (Figure 2). This does not mean that all lithistid sponges are devoid of cyanobacteria: shallow water lithistid sponges have symbiotic unicellular cyanobacteria within the outer tissues but they were considered insufficient in density to account for the relatively high yields of cyclic peptides obtained from lithistid sponges. In order to solve this conundrum, we decided to investigate the cellular location of metabolites in a shallow water specimen of *Theonella swinhoei* from Palau.

6. Cellular Location of Swinholid A and Cyclic Peptides Isolated from *Theonella Swinhoei*

6.1. Background

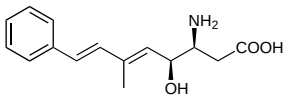
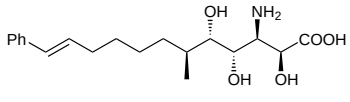
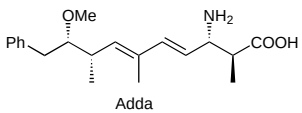
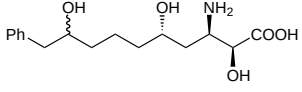
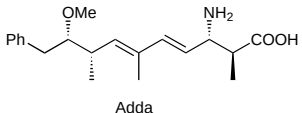
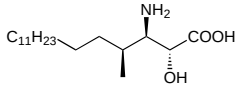
There are several techniques that can be used to determine the cellular location of metabolites in sponges. In 1983, we reported that the brominated metabolites aerothionin (**56**) and homoaerothionin (**57**) of *Aplysina fistularis* were located in sponge cells called spherulous cells and not in bacteria. The cellular location of bromine was detected with an energy dispersive X-ray analyzer in conjunction with transmission electron microscopy.^[118] One might also use preferential staining to detect chemicals in cells observed by light microscopy. These methods rely on direct observation of a specific chemical class but do not allow the identity of the individual chemicals to be determined.

A significant breakthrough in cellular localization studies came when we found that metabolites could be recovered in good yield from cells that had been fixed with formalin or glutaraldehyde. This enabled us to separate the cell types in *Dysidea herbacea* by disrupting the sponge into individual cells, fixing the cells, and then separating the cyanobacterial cells from all other cell types by using a cell sorter to detect and separate those cells that contained fluorescent photosynthetic pigments. The fluorescent cell fraction contained better than 99% filamentous cyanobacteria, as judged by

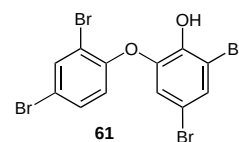
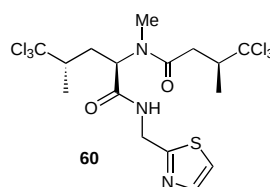
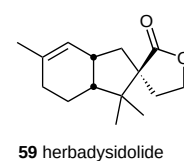
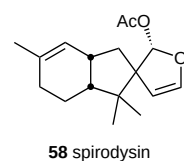
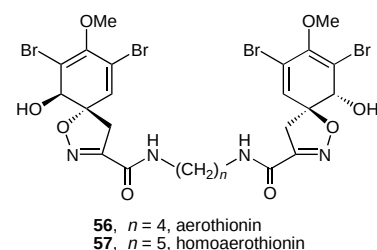
Table 2. Correlations between the presence of symbiotic filamentous bacteria, antifungal activity, and secondary metabolites.

Collection number	Identification	Collection site	Filamentous bacteria	Antifungal	Presence of β -amino acids	Chemistry
NCI-007	<i>Theonella swinhoei</i>	Negros Island	+	+	+	theonegramide (51)
NCI-013	<i>Aciculites orientalis</i>	Negros island	–	+	–	aciculitins (52 – 54)
NCI-036	<i>T. swinhoei</i>	Negros island	+	+	+	theonegramide (51)
NCI-141	<i>T. swinhoei</i>	Siquijor	+	+	+	theonegramide (51)
NCI-154	<i>Theonella</i> sp.	Siquijor	–	+	–	aurantosides (cf. 20)
NCI-1010	<i>Theonella</i> sp.	Siquijor	+	+	+	theonegramide (51)
NCI-1919	<i>Theonella</i> sp.	Siquijor	+	+	+	theonegramide (51)
NCI-1933	<i>Scleroderma</i> sp.	Cuyo Island	–	–	–	unknown
NCI-1934	<i>Discodermia</i> sp.	Cuyo Island	+	+	+	unknown peptide
NCI-1935	<i>Discodermia</i> sp.	Cuyo island	+	+	+	unknown peptide
93-085	<i>T. swinhoei</i>	Palau	+	+	+	theopalauamide (62), swinholide A (9)
93-087	<i>T. swinhoei</i>	Palau	+	+	+	theopalauamide (62), swinholide A (9)
95-001	<i>T. swinhoei</i>	Palau	+	+	+	theopalauamide (62), swinholide A (9)
R-1385	<i>Corallistes</i> sp.	New Caledonia	–	–	–	corallistins (cf. 28)
R-1401	<i>Corallistes</i> sp.	New Caledonia	–	–	–	pyrroles
R-1407	<i>Reidispongia coerulea</i>	New Caledonia	–	–	–	reidispongiolides (cf. 19)
R-1408	<i>Neosiphonia superstes</i>	New Caledonia	–	–	–	sphinxolides (cf. 19)
R-1466	<i>Microscleroderma</i> sp.	New Caledonia	+	+	+	microsclerodermins (37 , 38)
L1978-279	<i>T. conica</i>	Red Sea	–	–	–	sterols (cf. 1)
L1979-541	<i>T. swinhoei</i>	Red Sea	+	?	+	swinholide A (9)

Table 3. β -Amino acids found in peptides from lithistid sponges and cyanophytes.

β -Amino acid	Source
	theonegramide (51) <i>Theonella swinhoei</i> sponge ^[101]
	microsclerodermin (37 and 38) <i>Microscleroderma</i> sp. sponge ^[74]
	motuporin (35) <i>Theonella swinhoei</i> sponge ^[71]
	scytonemin A <i>Scytonema</i> sp. U-3-3 cyanobacterium ^[116]
	nodularin <i>Nodularia spumigena</i> cyanobacterium ^[72]
	calophycin <i>Calothrix fusca</i> EU-10-1 cyanobacterium ^[117]

Adda = (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid.



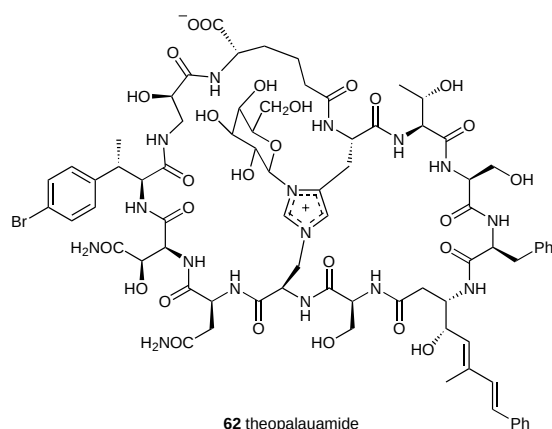
light, fluorescence, and electron microscopy. After washing the cells repeatedly to remove all traces of fixative, the cells were disrupted in methanol and the contents analyzed by GC-MS or NMR spectroscopy. In a specimen of *D. herbacea* from the Great Barrier Reef that contained a very high proportion of cyanobacterial cells, the sesquiterpenes spirodysin (**58**) and herbadysidolide (**59**) were found in the cell fraction containing mainly sponge cells and some non-photosynthetic bacteria, while the chlorinated amino acid derivative 13-demethylisodysidenin (**60**) was extracted from the filamentous cyanobacterium *Oscillatoria spongeliae*.^[119] A specimen of *D. herbacea* from Palau contained the brominated biphenyl ether **61** that was located in the cyanobacterial cells and not in the sponge cells. However, examination of sponge sections by polarized light microscopy revealed crystals of the bromin-

ated biphenyl ether **61** situated just below the surface of the sponge. This suggested that the cyanobacterium had been actively excreting the brominated metabolite, which crystallized on exposure to seawater.^[120]

In order to examine the cellular location of the metabolites from *T. swinhoei* we could not use the techniques outlined above because there were no specific reagents to stain for swinholide A (**9**) or cyclic peptides and we could not use fluorescence spectroscopy to separate the cells on a cell sorter. This led to experimenting with techniques to separate cell types on the basis of density.

6.2. Metabolites of a Palauan Specimen of *T. swinhoei*

An important step in any investigation of the localization of metabolites in a sponge is to identify and record the spectral characteristics of the metabolites in the sponge. Three specimens of *T. swinhoei* were collected in Palau, Western Caroline Islands, and were immediately subjected to cell separation procedures. Representative samples of the sponges were frozen for chemical studies, which showed that the chemical constitutions of the three sponges were identical. The freeze-dried sponges were extracted as described above. The hexane and dichloromethane extracts contained large amounts of theonellasterol (**2**), while the ethyl acetate extract contained appreciable quantities of swinholide A (**9**). The aqueous acetonitrile extract contained what initially appeared to be a single cyclic peptide but has now been resolved into two interconverting cyclic peptides.^[122] The major bicyclic peptide theopalauamide (**62**), which was earlier called P951,^[121] is



closely related to theonegramide (**51**, previously isolated from a specimen of *T. swinhoei* from Negros Island in the Philippines)^[101] and differs only by the replacement of the sugar D-arabinose by D-galactose.^[122] Although we were able to identify the new sugar in a straightforward manner, confirmation that the structure of the peptide was identical in both compounds was both tricky and time-consuming. Details of the structural elucidation of theopalauamide (**62**) and the interconverting isomer have been reported.^[122]

6.3. Cellular Location Studies

In retrospect, one of the greatest advantages of working with the lithistid sponge *T. swinhoei* was that the presence of the layer of fused desmas that separates the ectosome from the endosome enabled us to simply and cleanly separate the true unicellular cyanobacterium *Aphanocapsa feldmanni*, that occurs only in the ectosome, from the filamentous bacterium that was found only in the endosome. Sponge cells and unicellular eubacteria were found in both ectosome and endosome. After the gross dissection to separate ectosomal and endosomal tissues of three replicate sponges, each tissue sample was dissociated using an Omega 1000 juicer.^[123] The tissues collected on the filter were suspended in a mixture of 1.25% glutaraldehyde and 1.9% formaldehyde in filtered (0.2-μm) seawater (pH 8.15). After passing the suspension through a 42-μm nylon filter, the resulting cell suspensions were separated by differential centrifugation to obtain cell pellets, each 1 mL in volume, of sponge cells, filamentous bacteria, unicellular bacteria and, from the ectosome, unicellular cyanobacteria (see Frontispiece). Each of the pellets, which were prepared in triplicate, was washed three times by resuspension in sterile filtered seawater followed by centrifugation.^[121]

Each pellet was examined by transmission electron microscopy and by two methods of chemical analysis. For the chemical analyses, the pellets were extracted with methanol and the resulting extracts dried under nitrogen and redissolved in CDCl₃. Extracts of the sponge cells and cyanobacteria were completely soluble in CDCl₃ but extracts of the filamentous bacteria and unicellular bacteria were incompletely dissolved so that the insoluble material from these fractions had to be dried under nitrogen and dissolved in [D₆]DMSO. Each fraction was examined by ¹H NMR spectroscopy using a 500 MHz spectrometer and required 512 scans to produce satisfactory spectra. The spectra were compared with spectra of solutions (1 mM) of authentic swinholide A (**9**) and theopalauamide (**62**) recorded on the same instrument using 128 scans. The resulting spectra (Figure 3) clearly indicated that swinholide A (**9**) was present only in the lightest fraction that contained a mixed population of heterotrophic unicellular bacteria and that theopalauamide (**62**) was localized in the filamentous bacteria. These results were confirmed by HPLC analyses (Figure 4), which also confirmed that the sponge cell fractions and the ectosomal fractions of *A. feldmanni* were devoid of the bioactive metabolites. The three replicates for each cell type gave identical results and thus fortified the validity of the experimental data. The semi-quantitative manner in which the study was performed allows us to predict that the quantities of the bioactive compounds produced by the symbionts is not trivial.

7. Conclusions

Although we have demonstrated that the bioactive metabolites swinholide A (**9**) and theopalauamide (**62**) are localized in symbiotic unicellular bacteria and filamentous bacteria,

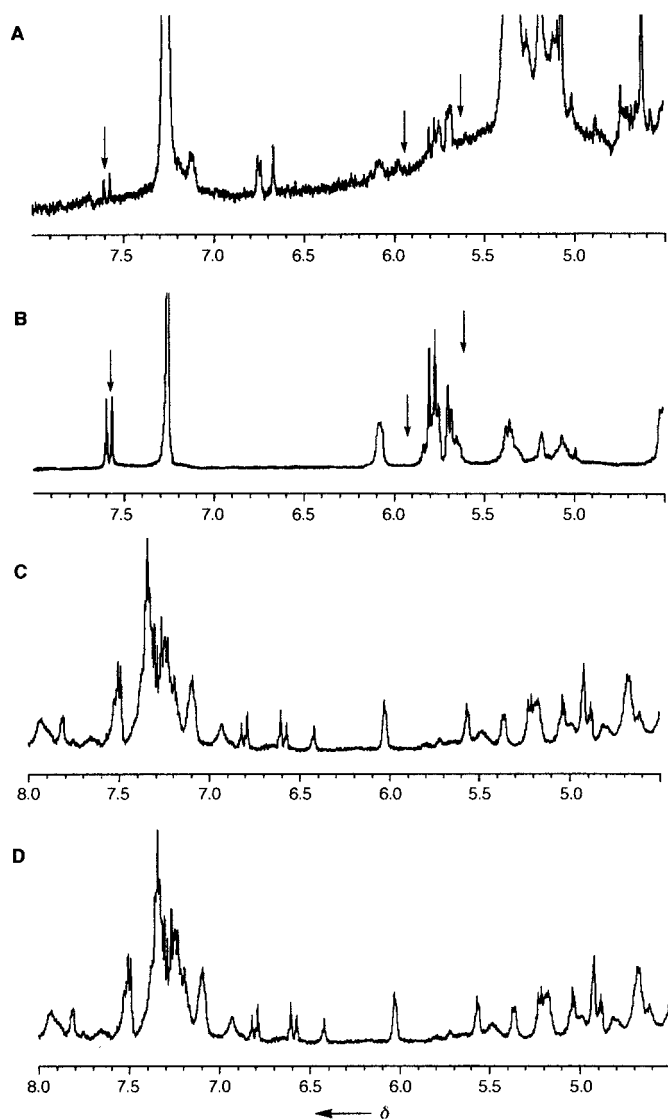


Figure 3. ^1H NMR spectra of an extract of purified unicellular eubacteria (A), an authentic sample of swinholid A (**9**, B), an extract from purified filamentous non-photosynthetic bacteria (C), and an authentic sample of 1 mM theopalauamide (**62**, D). Spectra were recorded on a 500 MHz spectrometer (Varian Unity). Spectra of cell extracts were recorded with 512 scans and the standards with 128 scans.

respectively, and are presumably produced by the symbionts, we would caution against making generalized statements about the biosynthetic origin of other metabolites until additional studies suggest a trend. The statistical correlation between the presence of cyclic peptides that contain aromatic β -amino acids and the presence of filamentous bacteria appears strong enough to suggest a real correlation but this remains to be confirmed. However, we cannot propose that all peptides from lithistid sponges are produced by filamentous bacteria because we could not detect filaments in some sponges that produce peptides devoid of aromatic β -amino acids.

One of the more curious discoveries of this research, as determined by transmission electron microscopy, is that the filamentous bacteria that were earlier presumed to be cyanobacteria are in fact non-photosynthetic and lack the

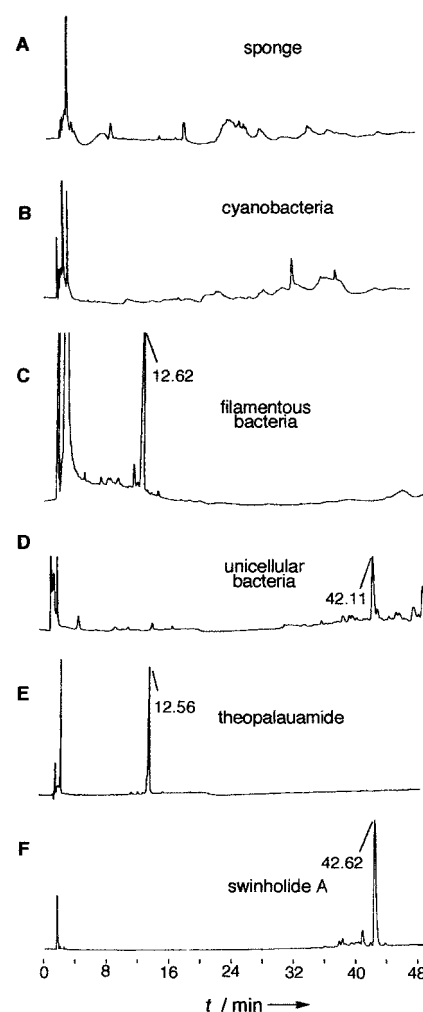


Figure 4. HPLC traces of extracts from purified sponge cells (A), purified unicellular cyanobacterial cells (B), purified filamentous non-photosynthetic bacteria (C), and the mixed population of unicellular heterotrophic eubacteria (D). HPLC traces of authentic standards of theopalauamide (**62**) and swinholid A (**9**) are shown in (E) and (F), respectively. Co-injections of swinholid A and the unicellular eubacterial extract, and theopalauamide and the filamentous bacterial extract, gave single peaks eluting from the HPLC column (data not shown).

cellular constituents (thylakoids) necessary for photosynthesis. We have compared the transmission electron micrographs of the filamentous bacteria from the Palauan *T. swinhoei* with micrographs showing the ultrastructure of other filamentous non-photosynthetic prokaryotes and have noted a strong resemblance to filamentous gliding bacteria of the Family *Beggiatoaceae*. However, we do not have any definitive evidence that the filamentous symbionts are *Beggiatoa*-like, and their taxonomic classification remains to be determined by molecular techniques used in phylogenetic studies. While there are no published reports of chemistry from *Beggiatoa*, it is interesting to note that chemical studies of other distant non-photosynthetic gliding bacteria (myxobacteria) have resulted in the isolation of some metabolites that are similar to those described from lithistid sponges.^[124]

The research described above may have a damaging impact on the validity of applying chemotaxonomy to sponges. In principle, one cannot place any faith in chemotaxonomic

relationships between sponges if the metabolites are not biosynthesized by the sponge. Yet it is possible that the associations between symbiotic bacteria and host sponges are so stable and long-lasting that the metabolites produced by the symbionts are truly representative of the host sponge. In that case, we can treat any sponge that has unique symbionts as a single entity for chemotaxonomic purposes. The evolution of secondary metabolites is a subject for speculation because individual compounds do not leave a fossil record. A simple application of Darwin's principles leads to the suggestion that secondary metabolites evolved from primary metabolites by means of a series of random mutations that served to produce, in a step-wise manner, new metabolites that increased the fitness (ability to survive) of the producing organism.^[125] If symbionts evolve to produce metabolites that increase the fitness of the host and the association is stable, then the host may also be considered to have evolved accordingly. Thus the application of chemotaxonomy to lithistid sponges depends on the stability of the host–symbiont relationships. From that viewpoint, the isolation of swinholid A (**9**) from an *Ircinia* sp. from the Philippines, and the absence of swinholides in all samples of *T. swinhoei* thus far examined from the Philippines, are problematic and suggest that the symbiotic association between the producing bacterium and *T. swinhoei* is less stable or less well evolved. On the other hand, the fact that all specimens of *T. swinhoei* from the Indo-Pacific that we have examined to date contained very similar bicyclic peptides, exemplified by theopalauamide (**62**) and theonegramide (**51**), together with large populations of filamentous bacteria, provides some evidence of stability in host–symbiont relationships (see Table 2), but more data is required.

Our research has raised as many questions as it has answered. We do not know the identity of the filamentous bacteria in which theopalauamide (**62**) was localized. The situation is even worse for swinholid A (**9**), which was localized to a cell fraction containing a mixture of unicellular bacteria. The obvious solution to this problem is to culture the individual bacteria and determine which isolate contains swinholid A (**9**). We are aware of at least one unsuccessful attempt to culture symbiotic bacteria from *T. swinhoei* that produces swinholid A, but we are not really surprised that the desired symbiont could not be cultured. It seems quite logical to expect that a microorganism that has adapted to life as a symbiont will not readily accept routine culture conditions.

The good news for marine natural product chemists is that there are probably many more populations of lithistid sponges that contain new biologically active metabolites. Each specimen must be carefully sampled and compounds purified, for one cannot assume that every specimen of a particular species of lithistid sponge will contain exactly the same array of metabolites. We anticipate that the lithistid sponges will remain in the forefront of chemical studies and will provide some of the best experimental systems for future studies of symbiosis in sponges.

Received: June 3 1998 [A 2321E]

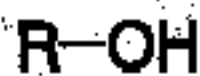
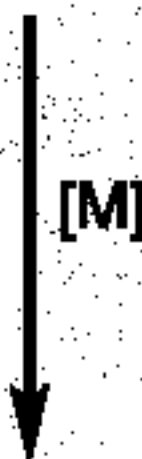
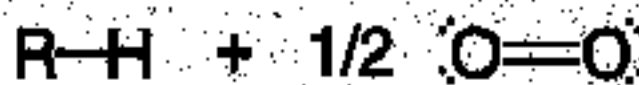
German version: *Angew. Chem.* **1998**, *110*, 2280–2297

- [1] C. A. Bewley, Dissertation, University of California, San Diego, **1995**.
- [2] P. R. Bergquist, *Sponges*, University of California Press, Berkeley, CA, **1978**, pp. 140.
- [3] M. Kelly-Borges, S. A. Pomponi, *Mol. Mar. Biol. Biotechnol.* **1994**, *3*, 87–103.
- [4] E. Kho, D. K. Imagawa, M. Rohmer, Y. Kashman, C. Djerassi, *J. Org. Chem.* **1981**, *46*, 1836–1839.
- [5] B. V. Crist, X. Li, P. R. Bergquist, C. Djerassi, *J. Org. Chem.* **1983**, *48*, 4472–4479.
- [6] F. J. Schmitz in *Marine Natural Products: Chemical and Biological Perspectives, Vol. 1* (Ed.: P. J. Scheuer), Academic Press, New York, **1978**, pp. 241–297.
- [7] Y. Shimizu, M. Alam, A. Kobayashi, *J. Am. Chem. Soc.* **1976**, *98*, 1059.
- [8] M. Kobayashi, K. Kawazoe, T. Katori, I. Kitagawa, *Chem. Pharm. Bull.* **1992**, *40*, 1773–1778.
- [9] Y. Inouye, Y. Sugo, T. Kusumi, N. Fusetani, *Chem. Lett.* **1994**, 419–420.
- [10] Y. Sugo, Y. Inouye, N. Nakayama, *Steroids* **1995**, *60*, 738–742.
- [11] M. V. D'Auria, L. Gomez Paloma, L. Minale, R. Riccio, C. Debitus, C. Lévi, *J. Nat. Prod.* **1992**, *55*, 311–320.
- [12] V. Costantino, E. Fattorusso, A. Mangoni, M. Aknin, E. M. Gaydou, *Steroids* **1994**, *59*, 181–184.
- [13] S. Carmely, Y. Kashman, *Tetrahedron Lett.* **1985**, *26*, 511–514.
- [14] R. Sakai, T. Higa, Y. Kashman, *Chem. Lett.* **1986**, 1499–1502.
- [15] Y. Kato, N. Fusetani, S. Matsunaga, K. Hashimoto, R. Sakai, T. Higa, Y. Kashman, *Tetrahedron Lett.* **1987**, *28*, 6225–6228.
- [16] The name misakinolide A appears to have been dropped in favor of bistheonellide A.
- [17] I. Kitagawa, M. Kobayashi, T. Katori, M. Yamashita, J. Tanaka, M. Doi, T. Ishida, *J. Am. Chem. Soc.* **1990**, *112*, 3710–3712.
- [18] M. Kobayashi, J. Tanaka, T. Katori, I. Kitagawa, *Chem. Pharm. Bull.* **1990**, *38*, 2960–2966.
- [19] S. Tsukamoto, M. Ishibashi, T. Sasaki, J. Kobayashi, *J. Chem. Soc. Perkin Trans. 1* **1991**, 3185–3188; **1993**, 1273 (corrigendum).
- [20] J. Kobayashi, S. Tsukamoto, A. Tanabe, T. Sasaki, M. Ishibashi, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2379–2383.
- [21] J. S. Todd, K. A. Alvi, P. Crews, *Tetrahedron Lett.* **1992**, *33*, 441–445.
- [22] M. Kobayashi, K. Kawazoe, T. Okamoto, T. Sasaki, I. Kitagawa, *Chem. Pharm. Bull.* **1994**, *42*, 19–26.
- [23] M. Doi, T. Ishida, M. Kobayashi, I. Kitagawa, *J. Org. Chem.* **1991**, *56*, 3629–3632.
- [24] I. Paterson, K.-S. Yeung, R. A. Ward, J. G. Cumming, J. D. Smith, *J. Am. Chem. Soc.* **1994**, *116*, 9391–9392; I. Paterson, J. G. Cumming, R. A. Ward, *Tetrahedron* **1995**, *51*, 9393–9412; I. Paterson, J. D. Smith, R. A. Ward, *Tetrahedron* **1995**, *51*, 9413–9436; I. Paterson, R. A. Ward, J. D. Smith, J. G. Cumming, K.-S. Yeung, *Tetrahedron* **1995**, *51*, 9437–9466; I. Paterson, K.-S. Yeung, R. A. Ward, J. D. Smith, J. G. Cumming, S. Lamboley, *Tetrahedron* **1995**, *51*, 9467–9486.
- [25] K. C. Nicolau, K. Ajito, A. P. Patron, H. Khatuya, P. K. Richter, P. Beritano, *J. Am. Chem. Soc.* **1996**, *118*, 3059–3060.
- [26] S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, *J. Org. Chem.* **1990**, *55*, 4912.
- [27] E. ter Haar, R. J. Kowalski, E. Hamel, C. M. Lin, R. E. Longley, S. P. Gunasekera, H. S. Rosenkranz, B. W. Day, *Biochemistry* **1996**, *35*, 243–250.
- [28] J. B. Nerenberg, D. T. Hung, P. K. Somers, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 12621–12622.
- [29] A. B. Smith III, Y. Qiu, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **1995**, *117*, 12011–12012.
- [30] Isolation: Y. Kato, N. Fusetani, S. Matsunaga, K. Hashimoto, S. Fujita, T. Furuya, *J. Am. Chem. Soc.* **1986**, *108*, 2780–2781; Synthesis: D. A. Evans, J. R. Gage, J. L. Leighton, *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453; N. Tanimoto, S. W. Gerritz, A. Sawabe, T. Noda, S. A. Filla, S. Masamune, *Angew. Chem.* **1994**, *106*, 674–677; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 673–675.
- [31] Y. Kato, N. Fusetani, S. Matsunaga, K. Hashimoto, K. Koseki, *J. Org. Chem.* **1988**, *53*, 3930–3932.
- [32] S. Matsunaga, H. Fujiki, D. Sukata, N. Fusetani, *Tetrahedron* **1991**, *47*, 2999–3006.

- [33] S. Matsunaga, N. Fusetani, *Tetrahedron Lett.* **1991**, 32, 5605–5606.
- [34] A. Okada, K. Watanabe, K. Umeda, M. Miyakado, *Agr. Biol. Chem.* **1991**, 55, 2765–2771.
- [35] S. P. Gunasekera, M. Gunasekera, P. McCarthy, *J. Org. Chem.* **1991**, 56, 4830.
- [36] S. Sakemi, T. Ichiba, S. Kohmoto, G. Saucy, T. Higa, *J. Am. Chem. Soc.* **1988**, 110, 4851–4853.
- [37] A. Furusaki, T. Watanabe, T. Matsumoto, M. Yanagiya, *Tetrahedron Lett.* **1968**, 6301–6304.
- [38] C. Y. Hong, Y. Kishi, *J. Am. Chem. Soc.* **1991**, 113, 9693–9694.
- [39] S. Matsunaga, N. Fusetani, Y. Nakao, *Tetrahedron* **1992**, 48, 8369–8376.
- [40] J. Kobayashi, F. Itagaki, H. Shigemori, T. Sasaki, *J. Nat. Prod.* **1993**, 56, 976–981.
- [41] N. Fusetani, T. Sugawara, S. Matsunaga, *J. Org. Chem.* **1992**, 57, 3828–3832.
- [42] J. Kobayashi, K. Kondo, M. Ishibashi, M. R. Walchli, T. Nakamura, *J. Am. Chem. Soc.* **1993**, 115, 6661–6665.
- [43] K. Kondo, M. Ishibashi, J. Kobayashi, *Tetrahedron* **1994**, 50, 8355–8362.
- [44] M. V. D'Auria, C. Debitus, L. G. Paloma, L. Minale, A. Zampella, *J. Am. Chem. Soc.* **1994**, 116, 6658–6663.
- [45] M. V. D'Auria, L. G. Paloma, L. Minale, A. Zampella, C. Debitus, *J. Nat. Prod.* **1994**, 57, 1595–1597.
- [46] M. V. D'Auria, L. G. Paloma, L. Minale, A. Zampella, J.-F. Verbist, C. Roussakis, C. Debitus, *Tetrahedron* **1993**, 49, 8657–8664; **1993**, 49, 10439 (corrigendum).
- [47] G. Guella, I. Mancini, G. Chiasera, F. Pietra, *Helv. Chim. Acta* **1989**, 72, 237–246.
- [48] M. V. D'Auria, L. G. Paloma, L. Minale, A. Zampella, J.-F. Verbist, C. Roussakis, C. Debitus, J. Patisou *Tetrahedron* **1994**, 50, 4829–4834.
- [49] S. Matsunaga, N. Fusetani, Y. Kato, H. Hirota, *J. Am. Chem. Soc.* **1991**, 113, 9690–9692.
- [50] A. Zampella, M. V. D'Auria, L. Minale, C. Debitus, C. Roussakis, *J. Am. Chem. Soc.* **1996**, 118, 11085–11088.
- [51] A. Zampella, M. V. D'Auria, L. Minale, C. Debitus, *Tetrahedron* **1997**, 53, 3243–3248.
- [52] Isolation: H. Nakamura, J. Kobayashi, Y. Ohizumi, *Tetrahedron Lett.* **1984**, 25, 5401–5404; Synthesis: Y. Ichikawa, *Synlett* **1991**, 715–716; Y. Ichikawa, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2135–2139.
- [53] I. Kitagawa, N. Yoshioka, C. Kamba, M. Yoshikawa, Y. Hamamoto, *Chem. Pharm. Bull.* **1987**, 35, 928–931.
- [54] Isolation: J. Kobayashi, T. Murayama, Y. Ohizumi, T. Sasaki, T. Ohta, S. Nozoe, *Tetrahedron Lett.* **1989**, 30, 4833–4836; Synthesis: A. V. R. Rao, G. R. Reddy, B. V. Rao, *J. Org. Chem.* **1991**, 56, 4545–4547.
- [55] J. Kobayashi, K. Kondo, H. Shigemori, H. Ishibashi, T. Sasaki, Y. Mikami, *J. Org. Chem.* **1992**, 57, 6680–6682.
- [56] G. Guella, I. Mancini, D. Duhet, B. Richer de Forges, F. Pietra, *Z. Naturforsch. C Biosci.* **1989**, 44, 914–916.
- [57] H. H. Sun, S. Sakemi, *J. Org. Chem.* **1991**, 56, 4307–4308.
- [58] M. D'Ambrosio, A. Guerriero, C. Debitus, O. Ribes, B. Richer de Forges, F. Pietra, *Helv. Chim. Acta* **1989**, 72, 1451–1454.
- [59] M. D'Ambrosio, A. Guerriero, C. Debitus, O. Ribes, F. Pietra, *Helv. Chim. Acta* **1993**, 76, 1489–1496.
- [60] A. Guerriero, M. D'Ambrosio, F. Pietra, C. Debitus, O. Ribes, *J. Nat. Prod.* **1993**, 56, 1962–1970.
- [61] C. Debitus, M. Cesario, J. Guilhem, C. Pascard, M. Païs, *Tetrahedron Lett.* **1989**, 30, 1535–1538.
- [62] T. Ichiba, Y. Nakao, P. J. Scheuer, N. U. Sata, M. Kelly-Borges, *Tetrahedron Lett.* **1995**, 36, 3977–3980.
- [63] N. Fusetani, S. Matsunaga, *Chem. Rev.* **1993**, 93, 1793–1806.
- [64] Isolation: N. Fusetani, Y. Nakao, S. Matsunaga, *Tetrahedron Lett.* **1991**, 32, 7073–7074; Synthesis: K. Hayashi, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1992**, 33, 5075–5076.
- [65] T. Hamada, T. Sugawara, S. Matsunaga, N. Fusetani, *Tetrahedron Lett.* **1994**, 35, 609–612.
- [66] N. Fusetani, S. Matsunaga, H. Matsumoto, Y. Takebayashi, *J. Am. Chem. Soc.* **1990**, 112, 7053–7074.
- [67] M. Hagihara, S. L. Schreiber, *J. Am. Chem. Soc.* **1992**, 114, 6570–6571.
- [68] A. Y. Lee, M. Hagihara, R. Karmacharya, M. W. Albers, S. L. Schreiber, J. Clardy, *J. Am. Chem. Soc.* **1993**, 115, 12619–12620; B. E. Maryanoff, X. Qiu, K. P. Padmanabhan, A. Tulinsky, H. R. Almond, P. A. Gordon, M. N. Greco, J. A. Kauffman, K. C. Nicolau, A. Liu, P. H. Brungs, N. Fusetani, *Proc. Natl. Acad. Sci. USA* **1993**, 90, 8048–8052.
- [69] P. Wipf, H. Kim, *J. Org. Chem.* **1993**, 58, 5592–5594; J. G. Deng, Y. Hamada, T. Shioiri, S. Matsunaga, N. Fusetani, *Angew. Chem.* **1994**, 106, 1811–1813; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1729–1731; B. E. Maryanoff, M. N. Greco, H.-C. Zhang, P. Andrade-Gordon, J. A. Kauffman, K. C. Nicolau, A. Liu, P. H. Brungs, *J. Am. Chem. Soc.* **1995**, 117, 1225–1239; H. M. M. Bastiaans, J. L. van der Baan, H. C. J. Ottenheijm, *Tetrahedron Lett.* **1995**, 36, 5963–5966; J. Deng, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1996**, 37, 2261–2264.
- [70] Y. Nakao, S. Matsunaga, N. Fusetani, *Bioorg. Med. Chem.* **1995**, 3, 1115–1122.
- [71] E. D. de Silva, D. E. Williams, R. J. Andersen, H. Klix, C. F. B. Holmes, T. M. Allen, *Tetrahedron Lett.* **1992**, 33, 1561–1564.
- [72] K. L. Rinehart, K. Harada, M. Namikoshi, C. Chen, C. A. Harvis, M. H. G. Munro, J. W. Blunt, P. E. Mulligan, V. R. Beasley, A. M. Dahlem, W. W. Carmichael, *J. Am. Chem. Soc.* **1988**, 110, 8557–8558.
- [73] N. K. Gulavita, S. A. Pomponi, A. E. Wright, D. Yarwood, M. A. Sills, *Tetrahedron Lett.* **1994**, 35, 6815–6818.
- [74] C. A. Bewley, C. Debitus, D. J. Faulkner, *J. Am. Chem. Soc.* **1994**, 116, 7631–7636.
- [75] J. Kobayashi, M. Sato, M. Ishibashi, H. Shigemori, T. Nakamura, Y. Ohizumi, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2609–2611.
- [76] J. Kobayashi, M. Sato, T. Murayama, M. Ishibashi, M. R. Walchi, M. Kanai, J. Shoji, Y. Ohizumi, *J. Chem. Soc. Chem. Commun.* **1991**, 1050–1052; M. Ishibashi, Y. Li, M. Sato, J. Kobayashi, *Nat. Prod. Lett.* **1994**, 4, 293–296; see also: U. Schmidt, S. Weinbrenner, *Angew. Chem.* **1996**, 108, 1432–1433; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1336–1338.
- [77] J. Kobayashi, F. Itagaki, H. Shigemori, M. Ishibashi, K. Takehashi, M. Ogura, S. Nagasawa, T. Nakamura, *J. Am. Chem. Soc.* **1991**, 113, 7812–7813.
- [78] F. Itagaki, H. Shigemori, M. Ishibashi, T. Nakamura, T. Sasaki, J. Kobayashi, *J. Org. Chem.* **1992**, 57, 5540–5542.
- [79] J. Kobayashi, F. Itagaki, H. Shigemori, T. Takao, Y. Shimonishi, *Tetrahedron* **1995**, 51, 2525–2532.
- [80] N. Fusetani, T. Sugawara, S. Matsunaga, H. Hirota, *J. Am. Chem. Soc.* **1991**, 113, 7811–7812.
- [81] S. P. Gunasekera, S. A. Pomponi, P. J. McCarthy, *J. Nat. Prod.* **1994**, 57, 79–83.
- [82] S. Matsunaga, N. Fusetani, S. Konosu, *Tetrahedron Lett.* **1984**, 25, 5165–5168.
- [83] S. Matsunaga, N. Fusetani, S. Konosu, *Tetrahedron Lett.* **1985**, 26, 855–856.
- [84] S. Matsunaga, N. Fusetani, S. Konosu, *J. Nat. Prod.* **1985**, 48, 236–241.
- [85] G. Ryu, S. Matsunaga, N. Fusetani, *Tetrahedron Lett.* **1994**, 35, 8251–8254.
- [86] G. Ryu, S. Matsunaga, N. Fusetani, *Tetrahedron* **1994**, 50, 13409–13416.
- [87] J. Yatsunami, H. Fujiki, A. Komori, M. Suganuma, S. Nishiwaki, S. Okabe, R. Nishiwaka, T. Ohta, S. Matsunaga, N. Fusetani, T. Sugimura, *Proceedings of the 1st International Congress on Vitamins and Biofactors in Life Sciences, J. Nutritional Sci. Vitaminol.* **1992**, 333 (special issue).
- [88] N. Fusetani, *New J. Chem.* **1990**, 14, 721–728.
- [89] H. Tada, T. Tozyo, Y. Terui, F. Hayashi, *Chem. Lett.* **1992**, 431–434.
- [90] I. Kitagawa, M. Kobayashi, N. K. Lee, H. Shibuya, Y. Kawata, F. Sakiyama, *Chem. Pharm. Bull.* **1986**, 34, 2664–2667.
- [91] H. Nakamura, J. Kobayashi, Y. Nakamura, Y. Ohizumi, T. Kondo, Y. Hirata, *Tetrahedron Lett.* **1986**, 27, 4319–4322.
- [92] I. Kitagawa, N. K. Lee, M. Kobayashi, H. Shibuya, *Chem. Pharm. Bull.* **1987**, 35, 2129–2132.
- [93] I. Kitagawa, N. K. Lee, M. Kobayashi, H. Shibuya, *Tetrahedron* **1991**, 47, 2169–2180.
- [94] M. Kobayashi, N. K. Lee, H. Shibuya, T. Momose, I. Kitagawa, *Chem. Pharm. Bull.* **1991**, 39, 1177–1184.

- [95] M. Kobayashi, K. Kanzaki, S. Katayama, K. Ohashi, H. Okada, S. Ikegami, I. Kitagawa, *Chem. Pharm. Bull.* **1994**, *42*, 1410–1415.
- [96] N. K. Gulavita, S. P. Gunasekera, S. A. Pomponi, E. V. Robinson, *J. Org. Chem.* **1992**, *57*, 1767–1772.
- [97] A. Zampella, M. V. D'Auria, L. G. Paloma, A. Casapullo, L. Minale, C. Debitus, Y. Henin, *J. Am. Chem. Soc.* **1996**, *118*, 6202–6209.
- [98] M. V. D'Auria, A. Zampella, L. G. Paloma, L. Minale, C. Debitus, C. Roussakis, V. Le Bert, *Tetrahedron* **1996**, *52*, 9589–9596.
- [99] M. V. D'Auria, L. G. Paloma, L. Minale, A. Zampella, C. Debitus, J. Perez, *J. Nat. Prod.* **1995**, *58*, 121–123.
- [100] S. Matsunaga, N. Fusetani, K. Hashimoto, M. Walchli, *J. Am. Chem. Soc.* **1989**, *111*, 2585–2588.
- [101] C. A. Bewley, D. J. Faulkner, *J. Org. Chem.* **1994**, *59*, 4849–4852; **1995**, *60*, 2644 (corrigendum).
- [102] S. Matsunaga, N. Fusetani, *J. Org. Chem.* **1995**, *60*, 1177–1181.
- [103] C. A. Bewley, H. He, D. H. Williams, D. J. Faulkner, *J. Am. Chem. Soc.* **1996**, *118*, 4314–4321.
- [104] M. Ishibashi, R. E. Moore, G. M. L. Patterson, C. Xu, J. Clardy, *J. Org. Chem.* **1986**, *51*, 5300–5306.
- [105] F. Sasse, H. Steinmetz, G. Höfle, H. Reichenbach, *J. Antibiotics* **1993**, *46*, 741–748.
- [106] M. R. Kernan, T. F. Molinski, D. J. Faulkner, *J. Org. Chem.* **1988**, *53*, 5014–5020.
- [107] K. E. Kassühlke, B. C. M. Potts, D. J. Faulkner, *J. Org. Chem.* **1991**, *56*, 3747–3749.
- [108] J. Kobayashi, T. Murayama, S. Kosuge, F. Kanda, M. Ishibashi, Y. Ohizumi, T. Ohta, S. Nozoe, J. Sasa, *J. Chem. Soc. Perkin Trans. I* **1990**, 3301–3303.
- [109] K. L. Rinehart, K. Harada, M. Namikoshi, M. H. G. Munro, J. W. Blunt, P. E. Mulligan, V. R. Beasley, A. M. Dahlem, W. W. Carmichael, *J. Am. Chem. Soc.* **1988**, *110*, 8557–8558.
- [110] D. E. Williams, M. Craig, C. F. B. Holmes, R. J. Andersen, *J. Nat. Prod.* **1996**, *59*, 570–575.
- [111] R. Jansen, B. Kunze, H. Reichenbach, G. Höfle, *Liebigs Ann.* **1996**, 285–290.
- [112] W. R. Chan, W. F. Tinto, P. S. Marchand, L. J. Torado, *J. Org. Chem.* **1987**, *52*, 3091–3093.
- [113] H. Shigemori, M.-A. Bae, K. Yazawa, T. Sasaki, J. Kobayashi, *J. Org. Chem.* **1992**, *57*, 4317–4320.
- [114] S. Ito, Y. Hirata, *Bull. Chem. Soc. Jpn.* **1977**, 1813–1820.
- [115] See for example: J. Kobayashi, M. Ishibashi, *Chem. Rev.* **1993**, *93*, 1753–1769; reference [62].
- [116] G. L. Helms, R. E. Moore, W. P. Niemczura, G. M. L. Patterson, K. B. Tomer, M. L. Gross, *J. Org. Chem.* **1988**, *53*, 1298–1307.
- [117] S.-S. Moon, J. L. Chen, R. E. Moore, G. M. L. Patterson, *J. Org. Chem.* **1992**, *57*, 1097–1103.
- [118] J. E. Thompson, K. D. Barrow, D. J. Faulkner, *Acta Zoologica* **1983**, *64*, 199–210.
- [119] M. D. Unson, D. J. Faulkner, *Experientia* **1993**, *49*, 349–353.
- [120] M. D. Unson, N. D. Holland, D. J. Faulkner, *Mar. Biol.* **1994**, *119*, 1–11.
- [121] C. A. Bewley, N. D. Holland, D. J. Faulkner, *Experientia* **1996**, *52*, 716–722.
- [122] E. W. Schmidt, C. A. Bewley, D. J. Faulkner, *J. Org. Chem.* **1998**, *63*, 1254–1258.
- [123] One of the trials of field research is that you do not have access to most laboratory equipment. The fruit juicer, which was borrowed from the kitchen of Larry Sharron and later replaced, proved to be an excellent substitute for more sophisticated laboratory equipment.
- [124] H. Reichenbach, G. Höfle, *Biotech. Adv.* **1993**, *11*, 219–277.
- [125] A fashionable definition of natural products might be: “A remnant of a vast combinatorial library of compounds produced in a stepwise manner from primary metabolites and screened by evolutionary pressures on the producing organisms”.

Alkane oxidation by late transition metals



Homogeneous Oxidation of Alkanes by Electrophilic Late Transition Metals

Shannon S. Stahl,* Jay A. Labinger, and John E. Bercaw

Despite being the most abundant and least expensive hydrocarbon feedstocks available, alkanes find limited use as a starting material for the chemical industry. Unfortunately, few methods exist for the selective conversion of alkanes into more valuable products. Although alkanes are relatively unreactive (e.g., high ionization energies and pK_a values, low electron affinity), the main challenge facing alkane transformations is selectivity, not reactivity. Surface-catalyzed methods as well as many radical reactions often lead to overoxidation of the

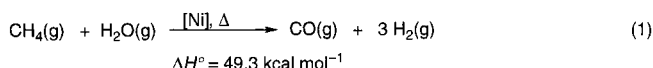
alkane to CO_2 and H_2O . In contrast, many organometallic complexes in homogeneous solutions undergo reaction with alkanes with unprecedented selectivity. Unfortunately, most of these systems are not amenable to catalytic transformations, since the reactive organometallic species is typically extremely sensitive to stoichiometric oxidants which might be used in the reaction. Recently, considerable attention has been directed toward the catalytic oxidation of alkanes in homogeneous solutions using electrophilic late transition metal ions (e.g.,

Pt^{II} , Pd^{II} , and Hg^{II}). Such systems are remarkably robust (the reactions are often carried out in aqueous or strong acid solvents in the presence of O_2) and exhibit the unusual selectivity patterns characteristic of organometallic reagents. Such reactions offer a potentially practical approach for the selective transformation of alkanes. This review will survey recent discoveries of new catalytic systems as well as advances in the mechanistic understanding of such reactions.

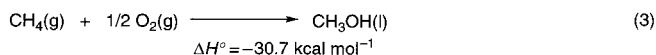
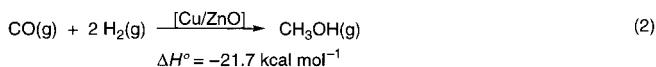
Keywords: homogeneous catalysis •

1. Introduction

Economic factors and technological innovations often induce changes in the chemical feedstocks used to produce commodity organic chemicals. These reasons caused olefins to replace acetylene in many commercial processes several decades ago. Alkanes, however, are the least expensive and most abundant hydrocarbon resource and thus represent an important potential feedstock for the chemical industry. Unfortunately, very few selective methods are available for converting alkanes into more valuable products. Furthermore, several desirable reactions utilizing alkanes are not thermodynamically favorable at reasonable temperatures. Even where alkanes are used, their transformations are often inefficient. For example, alkanes are used in the generation of synthesis gas [$\text{CO} + \text{H}_2$, “syngas”; Eq. (1)] by the “steam reforming” of methane, the primary component of natural



gas. Syngas may then be used directly in industrial reactions (e.g., hydroformylation of olefins), but it is often converted into methanol for use as a fuel or as a chemical feedstock [Eq. (2)]. The direct oxidation of methane represents a much more efficient pathway for methanol synthesis [Eq. (3)].



Attempts to selectively oxidize alkanes encounter two important problems. First, with respect to chemoselectivity, the initial product of alkane oxidation is often more reactive toward the oxidant than the alkane itself. For example, the C–H bond in methanol is 11 kcal mol^{-1} weaker than that in methane (93 and $104 \text{ kcal mol}^{-1}$, respectively). Consequently, if methane oxidation involves the abstraction of a hydrogen atom, the rate of which is usually governed by C–H bond strength, overoxidation of methanol (ultimately leading to CO_2) will dramatically reduce the desired product yield.^[1] The

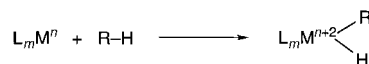
[*] Dr. S. S. Stahl
Massachusetts Institute of Technology, 18-545
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-2112
E-mail: sstahl@methane.lms.mit.edu
Dr. J. A. Labinger, Prof. J. E. Bercaw
California Institute of Technology
Pasadena, CA 91125 (USA)

regioselectivity of alkane oxidation is also problematic. In reactions with alkanes, both radical and electrophilic (i.e., superacid) reagents preferentially attack tertiary over primary and secondary C–H bonds ($3^\circ > 2^\circ > 1^\circ$).^[2, 3] However, the selectivity is often not high, and the desired preference is usually in the opposite direction.

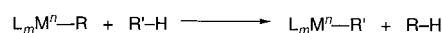
Recent work suggests that homogeneous organometallic systems can overcome some of these selectivity problems.^[4–10] Indeed, the many examples of “organometallic”^[11] alkane activations suggest that a reversed regioselectivity pattern can be attained (i.e., $1^\circ > 2^\circ > 3^\circ$). Further, strong C–H bonds can be activated selectively in the presence of weaker C–H bonds (e.g., aromatic C–H bonds are activated before benzylic C–H bonds in toluene).^[12] Several approaches to organometallic activation reactions are shown in Figure 1.^[4–9] Despite the success in this area, few systems are capable of subsequent substrate functionalization and regeneration of the metal fragment as required for catalytic turnover. In most cases the reactive metal species responsible for alkane activation is incompatible with oxidants (e.g., O_2 , H_2O_2) required for catalysis.

An important exception to this limitation is the reaction of alkanes with chloroplatinum salts in aqueous solution. Ironically, this system is one of the earliest examples of C–H activation. In 1969 Shilov and co-workers observed the incorporation of deuterium into alkanes in solutions of $K_2[PtCl_4]$ in $D_2O/[D_1]$ acetic acid.^[13] Three years later the same group reported that addition of $H_2[PtCl_6]$ to the reaction mixture generated oxidized alkane products [RCl and ROH;

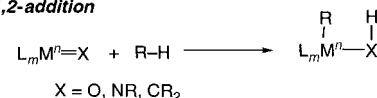
oxidative addition



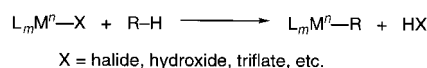
σ -bond metathesis



1,2-addition



electrophilic activation



metalloradical activation

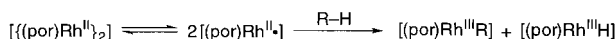
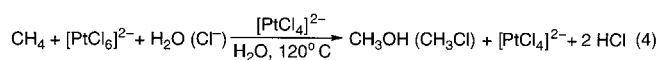


Figure 1. Various pathways discovered for the activation of alkane C–H bonds. In the reactions the stoichiometry, but not necessarily the mechanism, is specified. por = porphyrin.

Eq. (4)].^[14] This system is remarkably robust; unlike the organometallic reagents shown in Figure 1, which are ex-



tremely air- and moisture-sensitive, the platinum complexes are soluble in water, and the reactions are unaffected by the

Shannon Stahl, born in 1970, studied chemistry at the University of Illinois, Champaign-Urbana between 1988 and 1992. He received his Ph.D. in chemistry in 1997 from the California Institute of Technology for research on the mechanisms of hydroxylation of hydrocarbons by platinum salts in aqueous solutions in the research group headed by J. E. Bercaw. Since July 1997 he has been an National Science Foundation postdoctoral fellow at the Massachusetts Institute of Technology under the direction of S. Lippard.



S. S. Stahl



J. A. Labinger



J. E. Bercaw

Jay A. Labinger, born in 1947, studied at Harvey Mudd College, received his Ph.D. at Harvard University in 1974 under the direction of J. A. Osborn, and carried out postdoctoral research at Princeton University with J. Schwartz. He subsequently held a faculty position at the University of Notre Dame from 1975–1981 and conducted research for two years at Occidental Research Corporation and for three years at Atlantic Richfield Company, Los Angeles. Since 1986 he has been a Member of the Professional Staff as well as Administrator for the Beckman Institute at the California Institute of Technology.

John E. Bercaw, born in 1944, studied at North Carolina State University, received his Ph.D. in 1971 at the University of Michigan under the direction of H. Brintzinger, and carried out postdoctoral research at the University of Chicago with J. Halpern. In 1972 he moved to the California Institute of Technology as the A. A. Noyes Research Fellow in Chemistry and is now the Centennial Professor of Chemistry.

presence of O_2 . The doubly solvated complex $[PtCl_2(H_2O)_2]$ has been proposed as the active catalytic species, and the observed selectivity patterns reflect those of other organometallic activation systems, namely, $1^\circ > 2^\circ > 3^\circ$.^[8]

In recent years, several new alkane oxidations have been discovered that utilize electrophilic late transition metals in strongly acidic media (e.g., CF_3CO_2H , H_2SO_4).^[15–33] These systems exhibit significant similarities to the platinum chemistry discussed above, and together they represent an extremely promising approach to alkane functionalization. They not only offer new insights into factors necessary for selective conversion of alkanes, but also have potentially practical utility. This review will survey recent studies exploring the scope, selectivity, and mechanism for platinum(II)-catalyzed alkane oxidations in aqueous solvents,^[34] and will summarize related homogeneous oxidation reactions involving other late transition metals in strong acid solvents.

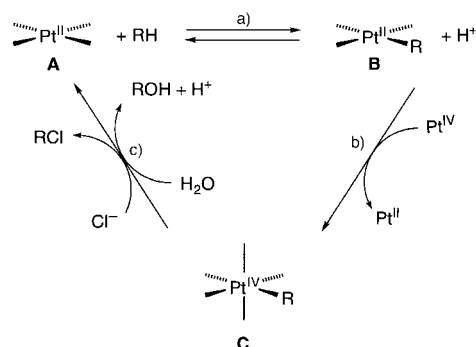
Biological and related biomimetic systems (e.g., methane monooxygenase, Gif) represent important complementary approaches to alkane oxidation. These often involve the metal-catalyzed activation of O_2 to generate an intermediate that reacts directly with alkanes. While these topics are beyond the scope of the present article, several recent reviews and monographs are recommended.^[35–41]

2. Alkane Oxidation by Platinum Complexes in Aqueous Solution

2.1. Mechanistic Studies

2.1.1. Proposed Mechanism

In 1983 Shilov et al. proposed a mechanism for platinum-catalyzed alkane oxidation consisting of three basic transformations (Scheme 1):^[42] a) activation of the alkane by Pt^{II} to generate an alkylplatinum(II) intermediate, b) two-electron oxidation of the alkylplatinum(II) intermediate to generate an alkylplatinum(IV) species, and c) reductive elimination of RX ($X = Cl$ or OH) to liberate the oxidized alkane and the Pt^{II} catalyst. This proposal has received considerable attention from several research groups. While the general catalytic cycle shown in Scheme 1 was quickly accepted, many features of the individual steps have only recently been identified. Each of



Scheme 1. Proposed catalytic cycle for the platinum-catalyzed oxidation of alkanes in aqueous solution.

the three steps in Scheme 1 can potentially proceed by (at least) two different pathways. These possibilities and the experiments used to distinguish between them are discussed in the following section. The steps of the catalytic cycle will be discussed in reverse order, according to the chronology of their elucidation.

2.1.2. Reductive Elimination of ROH/RCl from Platinum(IV)

Alkane functionalization is completed by reductive elimination of RX from a platinum(IV) complex (step (c) in Scheme 1). Two different mechanisms have been postulated for this reaction: a nucleophilic (S_N2) pathway (**D**, Figure 2)

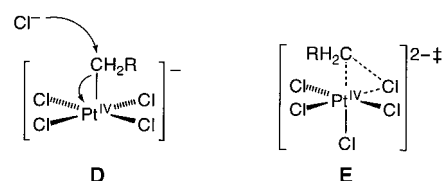
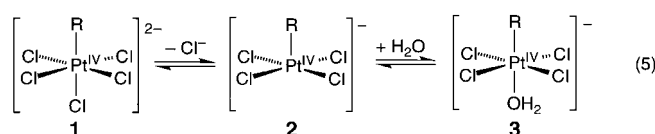


Figure 2. Two possible pathways for reductive elimination of RCH_2Cl from a platinum(IV) complex: S_N2 (**D**) and a concerted mechanism via a three-center transition state (**E**).

and a concerted reaction via a three-center transition state (**E**). Zamashchikov and co-workers were the first to examine this step directly. They prepared the alkylplatinum(IV) intermediate $[Pt(R)Cl_5]^{2-}$ (**1**) ($R = CH_3$, CH_2CH_3 , CH_2COCH_3 , etc.) independently and monitored the kinetics of its decomposition in aqueous solutions to form RCl and ROH .^[43–50] As described below, these and additional studies by Luinstra et al.^[51, 52] definitively establish that $R-X$ bond formation proceeds by an S_N2 mechanism.

Various alkylplatinum(IV) complexes are most readily prepared by oxidative addition of RI to $[PtCl_4]^{2-}$, although they also have been reported to form under certain conditions by oxidation of RH in aqueous solutions of $[PtCl_4]^{2-}/[PtCl_6]^{2-}$ (i. e., generated by steps (a) and (b) in Scheme 1).^[42, 53] These complexes exist in equilibrium with their monoquo derivatives (**3**) in aqueous solution [Eq. (5)]. Complex **2** is presumed



to be an intermediate in this equilibrium. The equilibrium constant K for $1 \rightleftharpoons 3$ when $R = \text{methyl}$ is about 0.8 M [Eq. (6)].^[44, 51, 52] The rate expression for the formation of RCl shown in Equation (7) was obtained by monitoring the

$$K = \frac{[3][Cl^-]}{[1]} \quad (6)$$

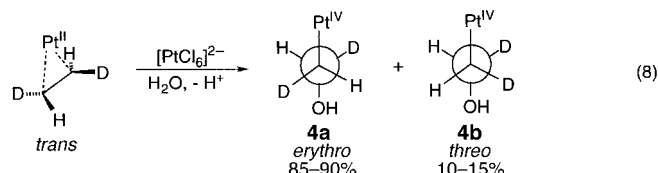
$$-\frac{d[1+3]}{dt} = k_{\text{obs}}[1+3]; \quad k_{\text{obs}} = \frac{k_1[Cl^-] + k_2[H_2O]}{1 + K^{-1}[Cl^-]} \quad (7)$$

decay of the alkylplatinum(IV) complexes **1** and **3**. The kinetics cannot distinguish between nucleophilic attack on the aquo complex **3** or the proposed five-coordinate intermediate **2**;

however, the latter is favored since it represents the microscopic reverse of oxidative addition of methyl halide to square-planar d^8 complexes.

Evidence against a three-center, concerted pathway was obtained when monitoring the decomposition of **1** and **3** in the presence of other anions such as bromide and iodide. Under reaction conditions where these halides are not incorporated into the platinum coordination sphere *cis* to the alkyl group, formation of RX ($X = Br, I$) is observed in large preference to that of RCl .^[47, 48] This result strongly supports $R-X$ bond formation by external nucleophilic attack.

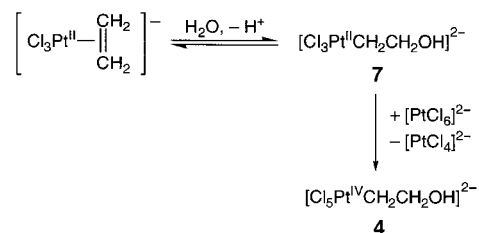
Perhaps the most definitive evidence favoring the S_N2 pathway for $R-X$ bond formation is inversion of stereochemistry at the platinum-bound carbon center upon reductive elimination.^[51, 52] (Concerted reductive elimination through a three-center transition state is expected to result in retention of configuration.) Formation of a platinum(IV) complex bearing a diastereomerically enriched alkyl group is obtained by oxidation of isotopically labeled Zeise's salt by $[PtCl_6]^{2-}$ (see Scheme 3 for the mechanism). Specifically, oxidation of Zeise's salt containing *trans*-dideuteroethylene yields predominantly ($\approx 85-90\%$) the *erythro* β -hydroxyethyl product $[Pt(CHDCHDOH)Cl_3]^{2-}$ (**4a**). The *threo* isomer (**4b**) is also formed in 10–15% [Eq. (8)]. Decomposition of **4**



Scheme 2. Two possible pathways for the oxidation of the alkylplatinum(II) intermediate by $[PtCl_6]^{2-}$.

expensive oxidants. Importantly, recent studies support the second pathway, suggesting that practical alternatives to Pt^{IV} may be possible.^[52, 54, 55]

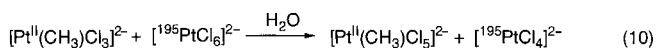
Direct study of the oxidation step was delayed for many years because the alkylplatinum(II) intermediate (**B**, Scheme 1) could not be prepared. In protic solvents the methyl derivative rapidly undergoes protonolysis to liberate methane,^[43, 52, 56] and in nonprotic media it disproportionates to $[Pt(CH_3)_2Cl_2]^{2-}$ and $[PtCl_4]^{2-}$.^[55] Luinstra et al. circumvented this problem by examining the oxidation of Zeise's salt by $[PtCl_6]^{2-}$.^[52, 54] Kinetic studies reveal that this reaction proceeds through a transient alkylplatinum(II) intermediate (**7**, Scheme 3). When isotopically labeled $Na_2[^{195}PtCl_6]$ was



Scheme 3. Oxidation of Zeise's salt by Pt^{IV} .

used, the ^1H NMR spectrum of the product **4** revealed ^{195}Pt satellites for the $Pt-CH_2CH_2OH$ peak of normal intensity, that is, 33% of the total peak area (natural abundance of $^{195}Pt \approx 33\%$). Thus, no alkyl transfer occurs in this reaction.

Recently, the methylplatinum(II) complex $[Pt(CH_3)Cl_3]^{2-}$ was prepared by reduction of $[Pt(CH_3)Cl_5]^{2-}$ by cobaltocene in THF.^[55] Rapid precipitation of the product prevents the disproportionation reaction discussed above. Subsequent dissolution of $[Pt(CH_3)Cl_3]^{2-}$ in an aqueous solution containing $[^{195}PtCl_6]^{2-}$ [Eq. (10)] confirms the result obtained for the

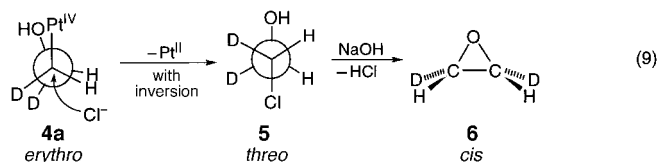


oxidation of Zeise's salt: The reaction proceeds by electron transfer, not alkyl transfer.

2.1.4. Electrophilic Activation of Alkanes by Platinum(II)

The C–H activation (step (a) in Scheme 1) appears to determine both the rate and selectivity of the alkane oxidation, thus providing significant motivation to understand

in the presence of chloride and subsequent conversion of the resulting 2-chloroethanol (**5**) into ethylene oxide (**6**) provides the *cis* isomer in isotopic purity identical to the initial alkylplatinum(IV) complex **4** [Eq. (9)]. This sequence clearly

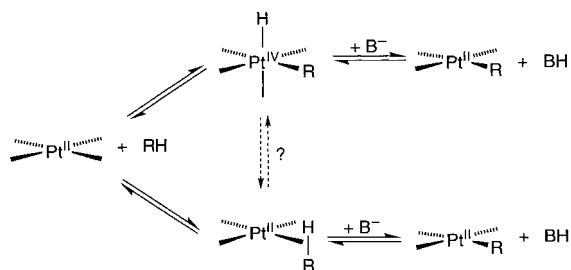


reflects inversion of stereochemistry in the reductive elimination reaction, which is consistent with an S_N2 mechanism.

2.1.3. Oxidation of RPt^{II} to RPt^{IV}

Development of a practical method for alkane oxidation requires that the reaction be coupled to consumption of an inexpensive stoichiometric oxidant (preferably O_2). Platinum(IV) is clearly impractical as a stoichiometric oxidant! Two possible mechanisms have been considered for oxidation of the alkylplatinum(II) intermediate to platinum(IV) (step (b) in Scheme 1): 1) alkyl transfer from RPt^{II} to Pt^{IV} or 2) inner-sphere, two-electron transfer from RPt^{II} to Pt^{IV} (i.e., chloronium ion transfer; Scheme 2). Whereas the former demands the presence of platinum(IV) to produce the alkylplatinum(IV) intermediate, the latter is compatible with the use of less

the details of its mechanism. Unfortunately, this step has proven to be the most difficult to study. As indicated in Scheme 1, the reaction stoichiometry involves electrophilic displacement of a proton on the alkane by Pt^{II} . Once again two different mechanisms have been considered for this reaction (Scheme 4):^[1, 8, 57–59] 1) oxidative addition of the C–H bond at Pt^{II} yielding an alkyl(hydrido)platinum(IV) complex

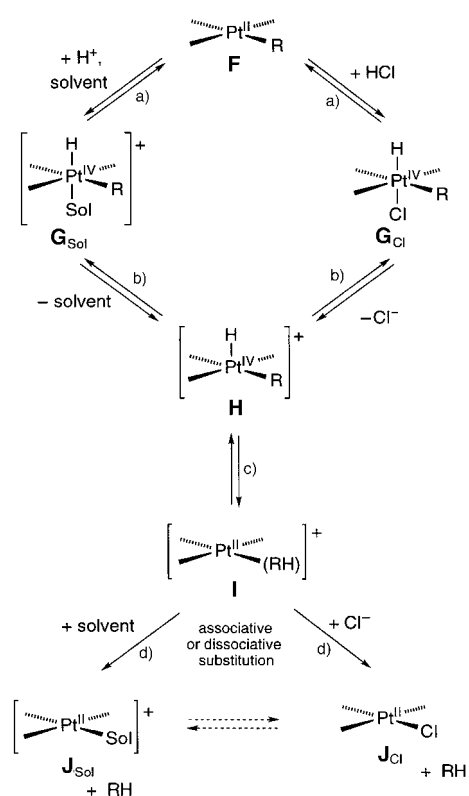


Scheme 4. Two possible pathways for alkane C–H activation by Pt^{II} : oxidative C–H addition and subsequent deprotonation of the Pt^{IV} hydride, or formation and subsequent deprotonation of an alkane σ adduct

which is subsequently deprotonated, or 2) deprotonation of an intermediate Pt^{II} –alkane σ adduct. In fact, considerable evidence has been obtained recently supporting the intermediacy of both species.^[56, 60]

Early studies of C–H activation focused on deuterium incorporation into protio alkanes in solutions of $[\text{PtCl}_4]^{2-}$ in D_2O .^[8] While substantial evidence supports the homogeneity of these reactions, deposition of platinum metal often complicates detailed studies. Furthermore, the reaction conditions ($>100^\circ\text{C}$) for C–H activation are not expected to allow detection of reactive intermediates. Consequently, most of the mechanistic information for this reaction has been obtained by studying the microscopic reverse of this reaction, namely, protonolysis of alkylplatinum(II) complexes.

Characterization of the first alkyl(hydrido)platinum(IV) complexes has recently been reported for a series of model complexes with stabilizing nitrogen, phosphane, or tris(pyr-azolylborate) ligands.^[56, 60–68] Very recently, Wick and Goldberg reported that three-coordinate (see below) $[(\eta^2\text{-Tp}')\text{Pt}^{\text{II}}(\text{CH}_3)]$ ($\text{Tp}' = \text{hydridotris}(3,5\text{-dimethylpyrazolyl})\text{borate}$), generated in situ by treatment of $[(\eta^2\text{-Tp}')\text{Pt}^{\text{II}}(\text{CH}_3)_2]^-$ with $\text{B}(\text{C}_6\text{F}_5)_3$, reacts with a solvent molecule with cleavage of C–H bonds to afford stable dialkyl(hydrido)platinum(IV) complexes $[(\eta^3\text{-Tp}')\text{Pt}^{\text{IV}}(\text{CH}_3)(\text{R})(\text{H})]$ ($\text{R} = n\text{-pentyl, cyclohexyl}$).^[69] Most alkyl(hydrido)platinum(IV) complexes are generated by addition of HX ($\text{X} = \text{halide, triflate, etc.}$) to the corresponding alkylplatinum(II) complexes at low temperatures. Furthermore, in deuterated acidic media, multiple H/D exchange into the alkyl positions is observed prior to elimination of the alkane for certain classes of these alkyl hydride complexes.^[56, 60, 61, 66] The results from these studies support the mechanism shown in Scheme 5 for the protonolysis of alkylplatinum(II) complexes: a) chloride- or solvent-mediated protonation of Pt^{II} (**F**) to generate an alkyl(hydrido)platinum(IV) intermediate (**G**); b) dissociation of the solvent molecule or chloride to generate a cationic, five-coordinate platinum(IV) species (**H**); c) reductive C–H

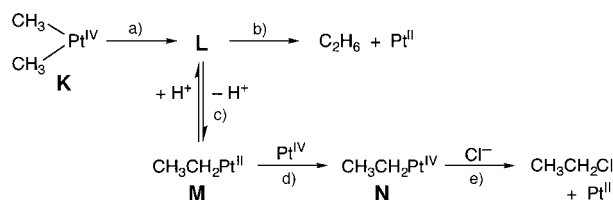


Scheme 5. Proposed mechanism for the protonolysis of alkylplatinum(II) complexes, the microscopic reverse of C–H activation by Pt^{II} .

formation producing an alkane σ complex (**I**); and d) irreversible loss of alkane, either through an associative or dissociative substitution pathway. In the presence of D^+ , deuterium incorporation into the alkyl group can be explained by the reversibility of steps (a)–(c). Extrapolation of these results to the Shilov system suggests that $[\text{Pt}^{\text{IV}}(\text{R})(\text{H})]$ and alkane σ adducts are intermediates in the C–H activation of alkanes by platinum(II). Importantly, however, formation of the alkylplatinum(II) intermediate (**B**, Scheme 1) arises from deprotonation of the $[\text{Pt}^{\text{IV}}(\text{R})(\text{H})]$ species **H**, not the σ adduct **I**.

The relevance of Scheme 5 to the Shilov system is supported by related chemistry observed for alkylplatinum(II/IV) chloride complexes. Using conditions closely resembling those of alkane oxidation (95°C , aqueous chloride solutions), Zamashchikov et al. recently examined the elimination of ethane from the dimethylplatinum(IV) complex $\text{Cs}_2[\text{Pt}(\text{CH}_3)_2\text{Cl}_4]$.^[70–73] When this reaction is carried out in D_2O , multiple deuteration is observed in the ethane produced. The range of ethane isotopomers observed in this reaction ($\text{C}_2\text{H}_{6-i}\text{D}_i$: 1:0.85:2.0:2.2:0.2:0.3:0.3 for $i = 0\text{--}6$, respectively) indicates that H/D exchange is largely localized on one of the carbon centers. Furthermore, if $[\text{PtCl}_6]^{2-}$ is present in the reaction mixture, ethyl chloride is generated. The results of the H/D exchange resemble that obtained for an isolable ethyl(hydrido)rhodium(III) complex proposed to undergo isotopic exchange through an ethane σ adduct.^[74]

The proposed mechanism shown in Scheme 6 accounts for these observations. Formation of intermediate **L** (step (a)) can either result in elimination of ethane (step (b)) or loss of a proton to generate the ethylplatinum(II) complex **M**. This



Scheme 6. Proposed decomposition pathway for $[\text{Pt}(\text{CH}_3)_2\text{Cl}_4]$ in aqueous solution at 95°C .

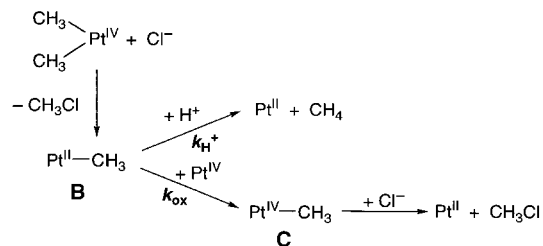
compound can then undergo a reversible protonation reaction which leads to multiple deuteration of the ethyl group in the presence of D^+ , or reaction with Pt^{IV} to produce the ethylplatinum(IV) species **N**, which decomposes into ethyl chloride and Pt^{II} . Intermediate **L** may be either a Pt^{II} –ethane σ adduct or an ethyl(hydrido)platinum(IV) species. Zamashchikov et al. have argued for the intermediacy of the latter on the basis of isotope effects;^[71] however, their analysis assumes that σ -adduct formation from free Pt^{II} and alkane exhibits no isotope effect. Recent evidence indicates that this is not a valid assumption.^[75–77] In a related study, two-electron reduction of $[\text{Pt}(\text{CH}_3)\text{Cl}_5]^{2-}$ in D_2O yields no H/D exchange, whereas multiple deuterium incorporation is observed in CD_3OD .^[56] While the data from the such studies cannot directly distinguish between the mechanistic alternatives, the results are completely consistent with the sequence shown in Scheme 5.

A recent theoretical study by Siegbahn and Crabtree examined the mechanism of C–H activation by platinum(II).^[59] The data indicate that the energy barrier for a reaction proceeding through $[\text{Pt}^{\text{IV}}(\text{R})(\text{H})]$ is somewhat lower than for a single-step, non-redox mechanism. Nevertheless, the authors argued in favor of the single-step mechanism for Pt^{II} based on analogy to Pd^{II} , which can effect similar chemistry. The +4 oxidation level is prohibitively high in energy for palladium. In summary, all of the results to date are consistent with the presence of both Pt^{II} σ adduct and $[\text{Pt}^{\text{IV}}(\text{R})(\text{H})]$ intermediates; formation of RPt^{II} (**B**, Scheme 1) arises from deprotonation of $[\text{Pt}^{\text{IV}}(\text{R})(\text{H})]$ (Scheme 5).

2.1.5. Other Mechanistic Studies: The Fate of RPt^{II} under Catalytic Conditions

As suggested in Scheme 1, the alkylplatinum(II) intermediate **B** can undergo protonolysis to regenerate the alkane or two-electron oxidation to produce the alkylplatinum(IV) intermediate **C**. Because step (b) in Scheme 1 appears irreversible under catalytic conditions, the relative ratio of these reaction rates can have important implications on the reaction selectivity. Two groups have examined this competition directly by the in situ generation of **B** in solutions containing varied concentration of H^+ and platinum(IV).^[49, 55, 70] Nucleophilic attack by chloride on $[\text{Pt}^{\text{IV}}(\text{CH}_3)_2\text{Cl}_4]^{2-}$ at 95°C in aqueous solutions liberates CH_3Cl and $[\text{Pt}^{\text{II}}(\text{CH}_3)\text{Cl}_3]^{2-}$ (see structure **D**, Figure 2). Zamashchikov and co-workers identified a branching ratio of the secondary rate constants $k_{\text{ox}}/k_{\text{H}^+}$ of about 18 (Scheme 7).^[70]

In related experiments, a ratio $k_{\text{ox}}/k_{\text{H}^+}$ of about 1 was obtained at room temperature when **B** was prepared by



Scheme 7. Determination of the relative rate constants for the protonation and oxidation of **B**.

reduction of $[\text{Pt}^{\text{IV}}(\text{CH}_3)\text{Cl}_5]^{2-}$ with cobaltocene,^[55] and a value for $k_{\text{ox}}/k_{\text{H}^+}$ of 70 was found for an ethylplatinum(II) complex at 80°C .^[49] Although the origin of these differences is not entirely clear, it appears that the ratio is larger at higher temperatures. Under catalytic conditions (typically 120°C), the oxidation of **B** by Pt^{IV} is likely much faster than the protonolysis reaction. These results explain why no deuterium incorporation was observed in hydrocarbon substrates when the catalytic reaction was carried out in D_2O .^[58, 78] This confirmation that C–H activation is the rate-determining step emphasizes the importance of understanding the detailed mechanism of this reaction.

2.2. Recent Advances in Platinum-Catalyzed Alkane Oxidation

2.2.1. Studies on the Selectivity of C–H Activation

The alkane oxidation system discovered by Shilov is especially attractive because of the unique selectivity patterns observed.^[8] The reactivity contrasts with that effected by radical reagents both from the standpoint of regio- and chemoselectivity. With respect to regioselectivity, reactions with linear alkanes often lead to selective chlorination/hydroxylation at the methyl positions rather than at the weaker, secondary C–H bonds. The chemoselectivity of the reaction is reflected by the initial oxidation products being relatively stable to overoxidation. Several recent studies have examined the scope of this reaction selectivity to identify its potentially practical utility.^[53, 58, 79–84]

Methane is perhaps the most attractive substrate for direct oxidation to its alcohol product, since it is by far the most abundant alkane and represents an enormous natural resource for use as a fuel and as a chemical feedstock.^[1] Results published by Sen et al.^[83] and Labinger, Bercaw et al.^[80] indicate that methane and methanol exhibit similar reactivity with respect to the platinum salts under standard oxidation conditions. Unfortunately, the similarity in rates combined with the greater solubility of methanol in water will limit the practicality of this system. Nevertheless, this selectivity stands in sharp contrast to that for reactions involving hydrogen-atom abstraction, where methanol can be expected to react up to six orders of magnitude faster than methane.

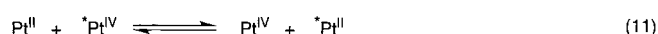
Further support for the unique selectivity patterns was obtained by oxidation of the C_2 substrates ethane and ethanol.^[53, 58, 79, 83] Here the relative rate of C–H bond activation follows the order $\text{H}-\text{CH}_2\text{CH}_3 > \text{H}-\text{CH}_2\text{CH}_2\text{OH} >$

H–CH(OH)CH₃, which is opposite to that expected on the basis of bond dissociation energies. Recent mechanistic studies by Sen and co-workers indicate that Zeise's salt, [PtCl₃(C₂H₄)][–], is an intermediate in the oxidation of both ethane and ethanol.^[83] These results support the viability of direct oxidation of ethane to ethylene glycol! An industrial process based on such technology would be a very attractive alternative to the oxidation of ethylene.

The water-soluble substrate *p*-toluenesulfonic acid is oxidized at the methyl group 1.5 times faster than the corresponding hydroxymethyl group of the product.^[58] No oxidation of the aldehyde product was observed. Furthermore, use of *p*-ethylbenzenesulfonic acid reveals comparable rates of functionalization at both the methyl and benzylic positions. Sen and co-workers have also noted the importance of the “chelate effect” in the oxidation of functionalized organic substrates such as aliphatic alcohols, carboxylic acids, sulfonic acids, and phosphonic acids.^[81, 82, 84] In their studies, they observe the following order of reactivity: $\alpha\text{-CH} \ll \beta\text{-CH} < \gamma\text{-CH} < \delta\text{-CH}$ for alcohols and $\alpha\text{-CH} \ll \beta\text{-CH} < \gamma\text{-CH} \geq \delta\text{-CH}$ for acid substrates. The trends support a reaction pathway involving initial substrate coordination to the platinum center followed by substrate activation. Thus, in addition to the inherently unusual selectivity patterns observed in Shilov chemistry, the “chelate effect” can also be employed to enhance selectivity and direct the oxidation chemistry to typically unreactive C–H bonds.

2.2.2. Substitution of Pt^{IV} with Less Expensive Oxidants

One of the most formidable challenges facing the use of the Shilov system is replacing Pt^{IV} with an economically viable oxidant. Although numerous high-potential oxidants will convert the alkylplatinum(II) intermediate **B** into the alkylplatinum(IV) species **C**, the challenge lies in identifying a reagent which will not irreversibly oxidize the Pt^{II} catalyst as well. Platinum(IV) does not encounter this dilemma since the reduced product of catalyst oxidation is the catalyst itself [Eq. (11)].



Despite several attempts to address this issue, success has been quite limited.^[78, 80, 85–87] Shortly after their initial discovery of platinum-mediated alkane oxidation, Gol'dshleger et al. reported that addition of quinones or Cu^{II} to a reaction mixture of H₂[PtCl₆]/[PtCl₄]^{2–} under air led to oxidation of acetic acid to chloroacetic acid which was catalytic in both Pt^{IV} and Pt^{II}.^[85] However, only five turnovers were achieved.

Heteropolyacids (also known as polyoxometalates) have also been employed to alleviate the need for stoichiometric amounts of Pt^{IV}.^[86, 87] Na₈HPMo₆V₆O₄₀ (HPA-6) was added to the standard reaction mixture in order to couple alkane oxidation to O₂; the reduced form of HPA-6 can be reoxidized by O₂. Although up to two turnovers were observed, the methanol generated in the reaction was typically overoxidized.^[86] Another heteropolyacid, H₃PMo₁₂O₄₀ (phosphomolybdic acid), was successfully employed as a redox mediator for the electrocatalytic oxidation of *p*-toluenesulfonic acid

under bulk-electrolysis conditions (+0.7 V vs. Ag/AgCl at 120 °C).^[87] In this case, no Pt^{IV} was added to the initial reaction mixture. Nevertheless, after about six turnovers (with respect to Pt^{II}) overoxidation of the alcohol product was observed, likely due to deposition of Pt⁰ which was observed at longer reaction times.

Recently, Horvath and co-workers reported the oxidation of methane by Cl₂ mediated by platinum salts in aqueous solution.^[78] While no deposition of metallic platinum is observed in this reaction, overoxidation products are still obtained after several hours at 125 °C. Thus, despite several attempts to circumvent the requirement for Pt^{IV} with a variety of stoichiometric oxidants and/or redox mediators, success remains elusive. (A recent exception is discussed in Section 3.2).

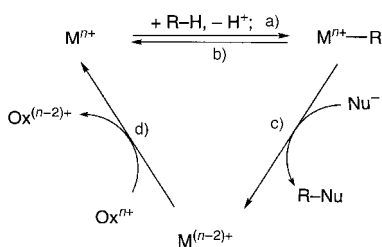
2.3. Future Challenges

The platinum-mediated chemistry described above has been fruitful for exploring a range of mechanistic and selectivity issues related to alkane oxidation by homogeneous transition metal complexes. Unfortunately, several features render it impractical in large-scale reactions. The previous section outlined some of the difficulties involved in replacing Pt^{IV} as the stoichiometric oxidant. Practical applications will clearly require the use of a less expensive reagent, preferably O₂. The selectivity of these reactions also does not appear sufficiently high for large-scale implementation. Deposition of platinum metal further erodes the characteristic selectivities of the homogeneous reaction, and unlike palladium(0), which is often reoxidized in catalytic reactions, reduction to platinum(0) appears much less reversible. These issues must be addressed in order to develop a useful system for platinum-mediated alkane oxidation. The next section will demonstrate that many of these problems can be circumvented by using different transition and main group metals and alternative solvents.

3. Alkane Oxidation by Electrophilic Metal Ions in Strong Acid Media

3.1. Overview

Considerable attention has recently been directed toward the oxidation of alkanes by electrophilic metal ions in strong acid media. At first glance, these systems seem quite similar to the platinum complexes used in aqueous media discussed above. For example, the overall reaction appears consistent with an electrophilic C–H activation followed by subsequent oxidation/functionalization. However, many of the metals are in their highest stable oxidation state (e.g., Hg²⁺, Co³⁺), suggesting that an alternative mechanism may be operating. One possibility, shown in Scheme 8, has the functionalization step preceding the oxidation step, thereby avoiding the unstable M⁽ⁿ⁺²⁾⁺ oxidation level. This mechanism suggests the organometallic intermediate RMⁿ⁺ is susceptible to both electrophilic (step (b)) and nucleophilic attack (step (c)).

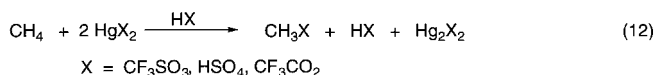


Scheme 8. Proposed catalytic cycle for the oxidation of alkanes by various metal ions (e.g., Hg^{II} and Pd^{II}) in strong acid solvents.

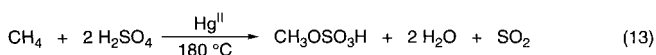
Other mechanisms (e.g., outer-sphere electron transfer) have also been proposed, and these studies remain the subject of current research efforts. Importantly, several of these systems demonstrate the viability of using O₂ as the terminal oxidant for alkane oxidation.

3.2. Metal-Catalyzed Oxidation of Methane by Sulfuric Acid

The mercury(II)-mediated system discovered by Periana and co-workers at Catalytica represents a major advance for the direct, selective oxidation of methane.^[22, 23] This reaction, shown in Equation (12), can be carried out in a variety of



strong acid solvents; it is unsuccessful in weaker acids such as acetic acid. Most importantly, in 100% sulfuric acid the reaction becomes catalytic in Hg^{II} [Eq. (13)], generating



methyl bisulfate (CH₃OSO₃H) in 43% yield (85% selectivity at 50% conversion). The high selectivity suggests that CH₄ is about 100-fold more reactive than CH₃OSO₃H. Similar reactivity was observed in trifluoromethanesulfonic and sulfuric acids in the presence of thallium(III), gold(I), palladium(II), and platinum(II)/(IV); however, no efficient catalysis was observed. A potentially viable approach for the direct conversion of methane into methanol using O₂ as the stoichiometric oxidant is shown in Figure 3

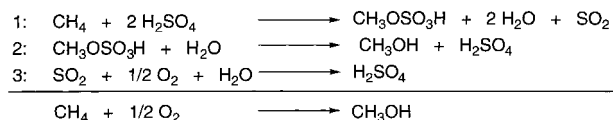
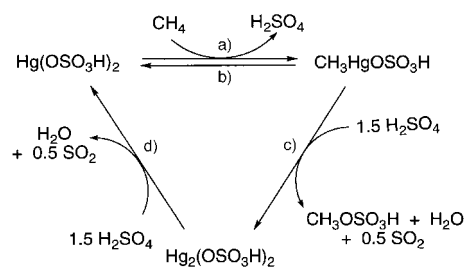


Figure 3. Possible reaction sequence allowing the direct oxidation of methane to methanol by O₂.

Based on a series of observations, the Catalytica group proposed the catalytic cycle shown in Scheme 9: 1) electrophilic activation of methane to generate a methylmercury(II) intermediate (step (a)), 2) reductive elimination of methyl bisulfate (step (c)), and 3) subsequent oxidation of mercurous

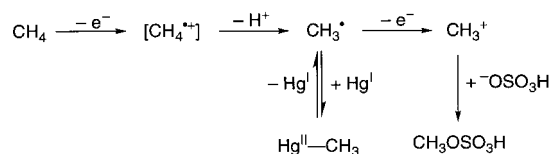


Scheme 9. Catalytic cycle for the mercury(II)-catalyzed oxidation of methane in sulfuric acid.

bisulfate to regenerate the catalyst (step (d)). As discussed above, the functionalization and oxidation steps have reversed their order relative to the Shilov system (Scheme 1) due to the inaccessibility of mercury(IV).

In support of this mechanism, low steady-state concentrations of the methylmercury(II) intermediate are observed under the reaction conditions. When this species is independently prepared, it undergoes competitive reductive elimination of methyl bisulfate (step (c)) and protonolysis (step (b)) in H₂SO₄ at 180 °C with approximately equal rates.^[23] When the catalytic reaction is carried out in D₂SO₄, deuterium incorporation into the methane is observed, reflecting the reversibility of the C–H activation step.

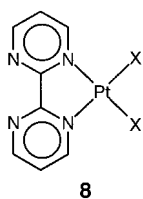
The precise mechanism of C–H activation by Hg^{II} remains the subject of some debate. While many of the features of this reaction are consistent with a simple electrophilic substitution mechanism (i.e., deprotonation of a transient Hg^{II} methane σ adduct), Sen and co-workers have recently suggested that an outer-sphere electron transfer pathway may also account for many of the observations.^[83, 88] For example, comparison of the reaction between methane and a series of one- and two-electron oxidants (including Hg^{II}) in sulfuric acid led the authors to propose that Hg^{II} was acting as a one-electron outer-sphere oxidant.^[83, 88] Formation of methylmercury(II) in the catalytic oxidation reaction can arise by combination of methyl radicals with mercury(I) in solution (Scheme 10).



Scheme 10. Possible electron transfer pathway for the activation of methane by mercury(II) in sulfuric acid.

The stability of CH₃OSO₃H under the reaction conditions is consistent with both mechanistic proposals: The electron-withdrawing OSO₃H group will not only deactivate CH₃O–SO₃H toward electrophilic attack but also toward hydrogen-atom abstraction. Moreover, increasing the solvent acidity is expected to increase the reaction rate for both electrophilic and electron transfer pathways. Strong acids enhance the electrophilicity of the metal center because their conjugate bases are weaker ligands. A similar explanation accounts for the higher redox potential of metal ions in strong acids: Less strongly donating ligands are available to stabilize the higher

oxidation state. Furthermore, the redox properties of alkanes are dramatically affected by strong acid solvents.^[2, 89, 90] Thus, while the outer-sphere oxidation of alkanes by Hg^{II} does not initially appear plausible, the reaction conditions may, in fact, promote such a pathway.

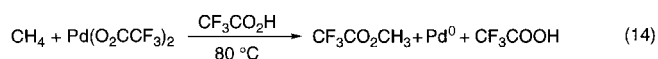


8

In a more recent development,^[91] the reaction in Equation (13) is catalyzed even more efficiently by a bipyrimidine complex of Pt^{II} (**8**): At 200 °C in fuming sulfuric acid, methyl bisulfate can be obtained in over 70 % yield based on methane (90 % conversion, 81 % selectivity). Remarkably, the organic ligand is stable to hot sulfuric acid, probably because the noncoordinated nitrogen atoms are protonated, thus reducing the susceptibility to oxidative degradation. Deposition of platinum metal is not a problem, because the Pt^{II} complex is thermodynamically stable under these conditions; indeed Pt metal can be redissolved by heating under these conditions in the presence of bipyrimidine. The mechanism appears to be closely related to Scheme 1, with step (b)—oxidation of RPt^{II} to RPt^{IV}—being rate-limiting.

3.3. Oxidation of Alkanes with Alternative Late Transition Metals or Solvents

The systems of the researchers at Catalytica were preceded by closely related chemistry involving other late transition metals. Metal ion catalyzed oxidation of hydrocarbons in strong acids has been known for more than two decades,^[92, 93] with much of the early work summarized in previous reviews.^[26, 94] In 1987, Sen and co-workers extended this chemistry to methane when they reported its palladium(II) acetate mediated oxidation to CF₃CO₂CH₃ in trifluoroacetic acid [Eq. (14)].^[15–17] Subsequently, a catalytic version of this



reaction was accomplished in trifluoroacetic anhydride with H₂O₂ as the stoichiometric oxidant.^[18] The authors suggested that the mechanism may involve electrophilic cleavage of the C–H bond by palladium (step (b) in Scheme 8), or alternatively Pd^{II} activation of peroxyacid generated in situ, leading to methane oxidation through a cyclic transition state (**9**). Unfortunately, several attempts to expand the scope of this chemistry have been complicated by difficulties in reproducing these results.^[20, 22, 25, 95]

The selective oxidation of methane and other lower alkanes by O₂ was observed by Sen and co-workers, who employed 5 % Pd/C and soluble copper(II) salts in a mixture of trifluoroacetic acid and water.^[96, 97] Methanol is the primary product of methane oxidation. Carbon monoxide must also be present in the reaction mixture in order to maintain selectivity in the reaction. The necessity of a coreductant bears striking resemblance to reactions of monooxygenase enzymes (e.g., cyto-

chrome P450), which require a reducing agent such as NADH to activate O₂ and effect substrate oxidation. The authors suggest that carbon monoxide reduces O₂ to H₂O₂, which then oxidizes alkanes in the presence of the transition metals. Future mechanistic insights should permit a more detailed comparison with the corresponding biological reactions.

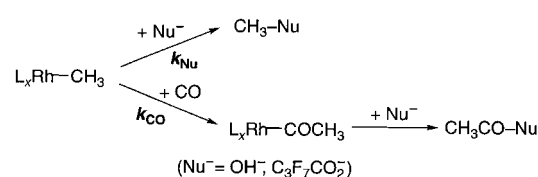
In another system cobalt(III) ions in trifluoroacetic acid were utilized to oxidize methane to CF₃CO₂CH₃ (90 % yield based on Co, at 180 °C).^[20] Importantly, the methyl ester product is stable to further oxidation under the reaction conditions. Addition of O₂ to the reaction results in a 400 % yield of CF₃CO₂CH₃ based on the cobalt(III) oxidizing equivalents available, presumably reflecting reoxidation of Co^{II} by O₂. Examination of the oxidation of ethane and propane by Co^{III} reveals that products of C–C bond cleavage form in addition to the expected alkyl trifluoroacetates.^[21] The authors proposed a mechanism involving outer-sphere electron transfer to produce an alkyl radical cation in the first step. This intermediate subsequently undergoes competitive C–H or C–C bond cleavage leading to the observed products. Similarly, rhodium(III) salts also catalyze the oxidation of higher alkanes in trifluoroacetic acid to the corresponding alkyl trifluoroacetates with H₂O₂ as the stoichiometric oxidant.^[98]

3.4. Direct Carboxylation of Alkanes Mediated by Late Transition Metals

In a series of recent papers, Sen^[24, 99] and Fujiwara^[33] have demonstrated the direct carboxylation of alkanes (including methane) catalyzed by rhodium and palladium complexes [Eq. (15)]. These systems not only effect the catalytic functionalization of C–H bonds, but also utilize O₂ as the stoichiometric oxidant.



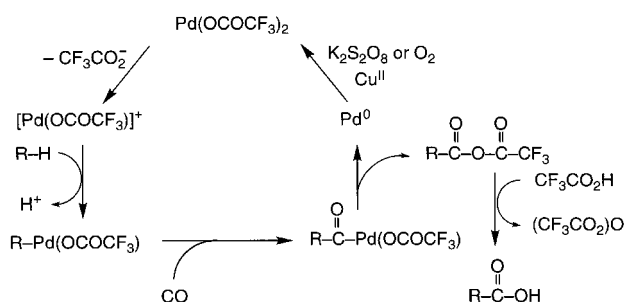
The rhodium-catalyzed reaction, which is carried out in a mixture of perfluorobutyric acid and water, generates both methanol and acetic acid from CH₄, CO, and O₂ at 80 °C.^[24, 99] Addition of several equivalents of Cl[–] and I[–] to the reaction mixture dramatically improves the reaction yields; however, the reason for this effect is currently not fully understood. While the detailed mechanism of this reaction has not yet been determined, the origin of both methanol and acetic acid can be explained by nucleophilic attack (*k*_{Nu}) competing with CO insertion (*k*_{CO}) into a rhodium–methyl bond, possibly generated by electrophilic C–H activation of methane (Scheme 11). The ratio of methanol to acetic acid can be



Scheme 11. Possible origin of both methanol and acetic acid in the rhodium-catalyzed carboxylation of methane.

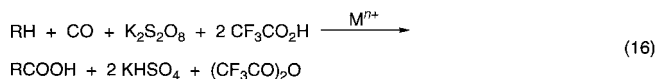
altered by changing the solvent composition. Studies of higher alkanes revealed that C–C bond cleavage is competitive with (and in many cases more favorable than) C–H cleavage. This reaction is effectively a “one-pot” catalytic system capable of both cracking and selectively oxidizing simple alkanes. The authors argue against a radical-cation mechanism that might account for cleavage of the weaker C–C bonds.

The catalytic carboxylation of alkanes such as methane, ethane, propane, and cyclohexane has also been observed with palladium and/or copper salts in trifluoroacetic acid.^[27–33] A possible catalytic cycle is shown in Scheme 12. $K_2S_2O_8$ is the



Scheme 12. Proposed catalytic cycle for the palladium-catalyzed carboxylation of alkanes.

oxidant in most of these reactions [Eq. (16)]. A recent report^[32] suggests that O_2 can also be used. Mixtures of



palladium(II) and copper(II) salts are more effective than either of the metals alone, except for the oxidation of methane where Cu^{II} alone is most efficient. Again, the detailed mechanism of these reactions is not entirely known. Kinetic deuterium isotope effects (3.0–3.2) in the reaction of cyclohexane with Pd^{II}/Cu^{II} or Pd^{II} alone suggest that C–H bond cleavage is involved in the rate-determining step.^[29] In contrast, the reactions with Cu^{II} alone do not exhibit a kinetic deuterium isotope effect, which led the authors to propose a radical mechanism.^[29]

Unfortunately, the complexity of the above systems has hindered elucidation of the detailed mechanisms. While direct electrophilic alkane activation is an attractive proposal, other possibilities such as radical and/or electron transfer pathways are difficult to rule out.

4. Summary and Outlook

The above reactions involving electrophilic late transition metals offer a promising and potentially practical approach to alkane oxidation. Importantly, the selectivities commonly associated with organometallic C–H activations (e.g., $1^\circ > 2^\circ > 3^\circ$) appear attainable in catalytic oxidation reactions as well. The recent examples from Catalytica^[22, 91] are especially encouraging since catalytic alkane oxidation in yields of 40–70% are unprecedented!

Meanwhile, a rather clear mechanistic picture has emerged for the catalytic steps of the Shilov system, although open questions remain for the mechanism of C–H activation in Shilov and other systems. Because this step often dictates both the rate and selectivity of the overall reactions, further mechanistic studies appear crucial to the advancement of this chemistry. While oxidative addition of the C–H bond may be possible in the Pt^{II} -mediated reaction, this is not a viable pathway for many of the other systems (e.g., with Hg^{II} or Co^{III}). It is possible, perhaps likely, that a single universal mechanism does not operate for all of the systems.

The solvent appears to play a crucial role in these catalytic systems. In all the examples discussed, the solvent is highly polar and in many cases a strong acid such as sulfuric or trifluoroacetic acid. Do such solvents merely provide a polar, weakly coordinating medium to enhance an electrophilic C–H activation pathway (e.g., involving deprotonation of an alkane σ adduct), or are such solvents necessary to alter the metal and alkane redox potentials to facilitate an electron transfer pathway?

Strong acid solvents also appear to play another role in these reactions, namely esterification of the alcohols produced in the reaction. By doing so, the acids deactivate the products toward further oxidation. For instance, the strong electron-withdrawing groups in $CH_3O_2CCF_3$ and CH_3OSO_3H render them much less reactive toward both electrophilic and radical reagents. Thus, even in cases where one-electron redox/radical chemistry is operating, the selectivity of the reaction can still be quite high, especially in reactions with methane.^[88] Clearly, the role of solvent cannot be ignored in these reactions.

The recent advances in this field hold great promise for the future discovery of new, practical approaches to selective, high-yield alkane functionalizations. Such developments will undoubtedly incorporate many of the features described above: product deactivation to prevent overoxidation, oxidatively robust catalysts, and use of inexpensive terminal oxidants (especially O_2). In addition, application of biphasic solvent systems may prove advantageous.^[100] For example, a system in which the substrate is more soluble than the product in the catalyst-containing phase should enhance reaction selectivity. Such ideas have been incompletely explored. Furthermore, the interactions between inexpensive terminal oxidants and late transition metal complexes are poorly understood; in many cases such interactions are mediated by other species (e.g., Cu salts or H_2SO_4). Gaining a better mechanistic understanding of this chemistry and exploiting such insight constitute important research challenges for the coming years.

Received: October 1, 1997 [A 255 IE]

German version: *Angew. Chem.* **1998**, *110*, 2298–2311

- [1] R. H. Crabtree, *Chem. Rev.* **1995**, *95*, 987–1007.
- [2] G. A. Olah, O. Farooq, G. K. S. Prakash in reference [6], pp. 27–78.
- [3] L. D. Field in reference [7], pp. 241–264.
- [4] R. H. Crabtree, *Chem. Rev.* **1985**, *85*, 245–269.
- [5] B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, *28*, 154–162.

- [6] *Activation and Functionalization of Alkanes* (Ed.: C. L. Hill), Wiley, New York, **1989**.
- [7] *Selective Hydrocarbon Activation* (Eds.: J. A. Davies, P. L. Watson, J. F. Liebman, A. Greenberg), VCH, New York, **1990**.
- [8] A. E. Shilov, *Activation of Saturated Hydrocarbons by Transition Metal Complexes*, Reidel, Dordrecht, **1984**.
- [9] J. A. Labinger, *Fuel Process. Technol.* **1995**, *42*, 325–338.
- [10] A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932.
- [11] The term “organometallic alkane activation” refers to the formation of a metal–carbon bond in the C–H activation step. The reactive metal fragment is not necessarily an organometallic complex (e.g., [(por)Rh]₂]; see Figure 1)
- [12] J. M. Buchanan, J. M. Stryker, R. G. Bergman, *J. Am. Chem. Soc.* **1986**, *108*, 1537–1550.
- [13] N. F. Gol'dshleger, M. B. Tyabin, A. E. Shilov, A. A. Shteinman, *Zh. Fiz. Khim. (Engl. Transl.)* **1969**, *43*, 1222–1223.
- [14] N. F. Gol'dshleger, V. V. Es'kova, A. E. Shilov, A. A. Shteinman, *Zh. Fiz. Khim. (Engl. Transl.)* **1972**, *46*, 785–786.
- [15] E. Gretz, T. F. Oliver, A. Sen, *J. Am. Chem. Soc.* **1987**, *109*, 8109–8111.
- [16] A. Sen, *Acc. Chem. Res.* **1988**, *21*, 421–428.
- [17] A. Sen, E. Gretz, T. F. Oliver, Z. Jiang, *New J. Chem.* **1989**, *13*, 755–760.
- [18] L.-C. Kao, A. C. Hutson, A. Sen, *J. Am. Chem. Soc.* **1991**, *113*, 700–701.
- [19] A. Sen, *Platinum Metals Rev.* **1991**, *35*, 126–132.
- [20] M. N. Vargaftik, I. P. Stolarov, I. I. Moiseev, *J. Chem. Soc. Chem. Commun.* **1990**, 1049–1050.
- [21] I. P. Stolarov, M. N. Vargaftik, D. I. Shishkin, I. I. Moiseev, *J. Chem. Soc. Chem. Commun.* **1991**, 938–939.
- [22] R. A. Periana, D. J. Taube, E. R. Evitt, D. G. Löffler, P. R. Wentrcck, G. Voss, T. Masuda, *Science* **1993**, *259*, 340–343.
- [23] a) *Natural Gas Conversion II* (Eds.: H. E. Curry-Hyde, R. F. Howe), Elsevier, New York, **1994**; b) R. A. Periana, D. J. Taube, E. R. Evitt, D. G. Löffler, P. R. Wentrcck, G. Voss, T. Masuda in reference [23 a], pp. 533–544.
- [24] M. Lin, T. E. Hogan, A. Sen, *J. Am. Chem. Soc.* **1996**, *118*, 4574–4580.
- [25] N. F. Gol'dshleger, E. I. Kresova, A. P. Moravskii, *Kinet. Katal.* **1991**, *32*, 1023.
- [26] N. F. Gol'dshleger, A. P. Moravskii, *Usp. Khim.* **1994**, *63*, 130–143.
- [27] Y. Fujiwara, T. Jintoku, Y. Uchida, *New J. Chem.* **1989**, *13*, 649–650.
- [28] Y. Fujiwara, K. Takaki, J. Watanabe, Y. Uchida, H. Taniguchi, *Chem. Lett.* **1989**, 1687–1688.
- [29] K. Nakata, T. Miyata, T. Jintoku, A. Kitani, Y. Taniguchi, K. Takaki, Y. Fujiwara, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3755–3759.
- [30] K. Nakata, Y. Yamaoka, T. Miyata, Y. Taniguchi, K. Takaki, Y. Fujiwara, *J. Organomet. Chem.* **1994**, *473*, 329–334.
- [31] K. Nakata, T. Miyata, Y. Yamaoka, Y. Taniguchi, K. Takaki, Y. Fujiwara in reference [23 a], pp. 521–526.
- [32] M. Kurioka, K. Nakata, T. Jintoku, Y. Taniguchi, K. Takaki, Y. Fujiwara, *Chem. Lett.* **1995**, 244.
- [33] Y. Fujiwara, K. Takaki, Y. Taniguchi, *Synlett* **1996**, 591–599.
- [34] Much of the early work in this area has been reviewed in a monograph by Shilov.^[8]
- [35] A. L. Feig, S. J. Lippard, *Chem. Rev.* **1994**, *94*, 759–805.
- [36] B. J. Wallar, J. D. Lipscomb, *Chem. Rev.* **1996**, *96*, 2625–2657.
- [37] *Cytochrome P450 : Structure, Mechanism, and Biochemistry* (Ed.: P. R. Ortiz de Montellano), 2nd ed., Plenum, New York, **1995**.
- [38] S.-I. Murahashi, *Angew. Chem.* **1995**, *107*, 2670–2693; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2443–2465.
- [39] A. Stassinopoulos, S. Mukerjee, J. P. Caradonna in *Mechanistic Bioinorganic Chemistry* (Eds.: H. H. Thorp, V. L. Pecoraro), American Chemical Society, Washington, DC, **1995**, pp. 83–120.
- [40] D. H. R. Barton, D. Doller, *Acc. Chem. Res.* **1992**, *25*, 504–512.
- [41] *Oxygenases and Model Systems* (Ed.: T. Funabiki), Kluwer, Boston, **1997**.
- [42] L. A. Kushch, V. V. Lavrushko, Y. S. Misharin, A. P. Moravsky, A. E. Shilov, *Nouv. J. Chim.* **1983**, *7*, 729–733.
- [43] V. V. Zamashchikov, E. S. Rudakov, S. A. Mitchenko, S. L. Litvinenko, *Teor. Eksper. Khim.* **1982**, *18*, 510–512.
- [44] V. V. Zamashchikov, S. A. Mitchenko, *Kinet. Katal.* **1983**, *24*, 254–255.
- [45] V. V. Zamashchikov, A. N. Kitaigorodskii, S. L. Litvinenko, E. S. Rudakov, O. N. Uzhik, A. E. Shilov, *Izv. Akad. Nauk. SSSR Ser. Khim.* **1985**, 1730–1733.
- [46] V. V. Zamashchikov, E. S. Rudakov, V. S. Garkusha-Bozhko, S. A. Mitchenko, S. L. Litvinenko, V. S. Chuprina, *Koord. Khim.* **1986**, *12*, 822–826.
- [47] V. V. Zamashchikov, S. L. Litvinenko, O. N. Uzhik, V. F. Galat, *Zh. Obs. Khim.* **1986**, *56*, 2417–2418.
- [48] V. V. Zamashchikov, S. L. Litvinenko, V. I. Shologon, *Kinet. Katal.* **1987**, *28*, 1059–1063.
- [49] S. A. Mitchenko, V. V. Zamashchikov, *Kinet. Katal.* **1989**, *30*, 297–302.
- [50] V. V. Zamashchikov, S. A. Mitchenko, A. A. Shubin, E. L. Kostenko, *Kinet. Katal.* **1992**, *33*, 498–502.
- [51] G. A. Luinstra, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **1993**, *115*, 3004–3005.
- [52] G. A. Luinstra, L. Wang, S. S. Stahl, J. A. Labinger, J. E. Bercaw, *J. Organomet. Chem.* **1995**, *504*, 75–91.
- [53] A. C. Hutson, M. Lin, N. Basicckes, A. Sen, *J. Organomet. Chem.* **1995**, *504*, 69–74.
- [54] G. A. Luinstra, L. Wang, S. S. Stahl, J. A. Labinger, J. E. Bercaw, *Organometallics* **1994**, *13*, 755–756.
- [55] L. Wang, S. S. Stahl, J. A. Labinger, J. E. Bercaw, *J. Mol. Catal. A* **1997**, *116*, 269–275.
- [56] S. S. Stahl, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **1996**, *118*, 5961–5976.
- [57] A. E. Shilov in reference [6], pp. 1–26.
- [58] J. A. Labinger, A. M. Herring, D. K. Lyon, G. A. Luinstra, J. E. Bercaw, I. T. Horváth, K. Eller, *Organometallics* **1993**, *12*, 895–905.
- [59] P. E. M. Siegbahn, R. H. Crabtree, *J. Am. Chem. Soc.* **1996**, *118*, 4442–4450.
- [60] M. W. Holtcamp, J. A. Labinger, J. E. Bercaw, *Inorg. Chim. Acta* **1997**, *265*, 117–125.
- [61] S. S. Stahl, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **1995**, *117*, 9371–9372.
- [62] V. De Felice, A. De Renzi, A. Panunzi, D. Tesaro, *J. Organomet. Chem.* **1995**, *488*, C13–C14.
- [63] G. S. Hill, L. M. Rendina, R. J. Puddephatt, *Organometallics* **1995**, *14*, 4966–4968.
- [64] G. S. Hill, R. J. Puddephatt, *J. Am. Chem. Soc.* **1996**, *118*, 8745–8746.
- [65] G. S. Hill, J. J. Vittal, R. J. Puddephatt, *Organometallics* **1997**, *16*, 1209–1217.
- [66] J. A. Jenkins, G. P. A. Yap, R. J. Puddephatt, *Organometallics* **1997**, *16*, 1946–1955.
- [67] S. A. O'Reilly, P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **1996**, *118*, 5684–5689.
- [68] A. J. Canty, A. Dedieu, H. Jin, A. Milet, M. K. Richmond, *Organometallics* **1996**, *15*, 2845–2847.
- [69] D. D. Wick, K. I. Goldberg, *J. Am. Chem. Soc.* **1997**, *119*, 10235–10236.
- [70] V. V. Zamashchikov, V. G. Popov, S. L. Litvinenko, *Izv. Akad. Nauk. Ser. Khim.* **1993**, *42*, 389–395.
- [71] V. V. Zamashchikov, V. G. Popov, E. S. Rudakov, S. A. Mitchenko, *Dokl. Akad. Nauk SSSR* **1993**, *333*, 34–36.
- [72] V. V. Zamashchikov, V. G. Popov, E. S. Rudakov, S. A. Mitchenko, *Izv. Akad. Nauk. Ser. Khim.* **1993**, *42*, 2142–2143.
- [73] V. V. Zamashchikov, V. G. Popov, E. S. Rudakov, *Kinet. Katal.* **1994**, *35*, 436–442.
- [74] R. A. Periana, R. G. Bergman, *J. Am. Chem. Soc.* **1986**, *108*, 7332–7346.
- [75] A. A. Bengali, R. H. Schultz, C. B. Moore, R. G. Bergman, *J. Am. Chem. Soc.* **1994**, *116*, 9585–9589.
- [76] A. A. Bengali, B. A. Arndtsen, P. M. Burger, R. H. Schultz, B. H. Weiller, K. R. Kyle, C. B. Moore, R. G. Bergman, *Pure Appl. Chem.* **1995**, *67*, 281–288.
- [77] R. H. Schultz, A. A. Bengali, M. J. Tauber, B. H. Weiller, E. P. Wasserman, K. R. Kyle, C. B. Moore, R. G. Bergman, *J. Am. Chem. Soc.* **1994**, *116*, 7369–7377.
- [78] I. T. Horváth, R. A. Cook, J. M. Millar, G. Kiss, *Organometallics* **1993**, *12*, 8–10.

- [79] J. A. Labinger, A. M. Herring, J. E. Bercaw, *J. Am. Chem. Soc.* **1990**, *112*, 5628–5629.
- [80] J. A. Labinger, J. E. Bercaw, G. A. L. Luinstra, D. K. Lyon, A. M. Herring in reference [23 a], pp. 515–520.
- [81] L.-C. Kao, A. Sen, *J. Chem. Soc. Chem. Commun.* **1991**, 1242–1243.
- [82] A. Sen, M. Lin, L.-C. Kao, A. C. Hutson, *J. Am. Chem. Soc.* **1992**, *114*, 6385–6392.
- [83] A. Sen, M. A. Benvenuto, M. Lin, A. C. Hutson, N. Basicckes, *J. Am. Chem. Soc.* **1994**, *116*, 998–1003.
- [84] N. Basicckes, A. Sen, *Polyhedron* **1995**, *14*, 197–202.
- [85] N. F. Gol'dshleger, V. V. Lavrushko, A. P. Khrushch, A. A. Shteinman, *Izv. Akad. Nauk SSSR Ser. Khim.* **1976**, 2174–2178.
- [86] Y. V. Geletii, A. E. Shilov, *Kinet. Katal.* **1983**, *24*, 486–489.
- [87] M. S. Freund, J. A. Labinger, N. S. Lewis, J. E. Bercaw, *J. Mol. Catal.* **1994**, *87*, L11–L15.
- [88] N. Basicckes, T. E. Hogan, A. Sen, *J. Am. Chem. Soc.* **1996**, *118*, 13111–13112.
- [89] J. Devynck, P.-L. Fabre, A. Ben Hadid, B. Tremillon, *J. Chem. Res. Synop.* **1979**, 200–201.
- [90] P.-L. Fabre, J. Devynck, B. Tremillon, *Chem. Rev.* **1982**, *82*, 591–614.
- [91] R. A. Periana, D. J. Taube, S. Gamble, H. Taube, T. Satoh, H. Fujii, *Science* **1998**, *280*, 560–564.
- [92] E. S. Rudakov, V. V. Zamashchikov, N. P. Belyaeva, R. I. Rudakova, *Zh. Fiz. Khim. (Engl. Transl.)* **1973**, *47*, 1542–1543.
- [93] N. F. Gol'dshleger, M. L. Khidkekel', A. E. Shilov, A. A. Shteinman, *Kinet. Katal.* **1974**, *15*, 261.
- [94] Reference [8], pp. 67–73.
- [95] K. T. Nelson, K. Foger in reference [23 a], pp. 545–550.
- [96] M. Lin, A. Sen, *J. Am. Chem. Soc.* **1992**, *114*, 7307–7308.
- [97] M. Lin, T. Hogan, A. Sen, *J. Am. Chem. Soc.* **1997**, *119*, 6048–6053.
- [98] S. Nomura, S. Uemura, *J. Chem. Soc. Chem. Commun.* **1994**, 129–130.
- [99] M. Lin, A. Sen, *Nature* **1994**, *368*, 613–615.
- [100] I. T. Horváth, J. Rábai, *Science* **1994**, *266*, 72–75.

EVENTS

Arfvedson-Schlenk-Prize

The Gesellschaft Deutscher Chemiker / GDCh (The German Chemical Society) announces that the Arfvedson-Schlenk-Award donated to the GDCh by Chemetall GmbH will be awarded for the first time in autumn 1999. The award is named after the discoverer of the element lithium, Gustav Arfvedson, and the pioneer of lithium organic chemistry, Wilhelm Schlenk.

The Arfvedson-Schlenk-Award intends to honour outstanding scientific and scientific technical achievements in the field of lithium chemistry.

Nominations for the award are to be addressed until the end of the year 1998 to the Geschäftsstelle of the GDCh, Postbox 90 04 40, D-60444 Frankfurt/Main, Germany. Proposals should include the CV of the nominee together with his/her list of publications. Self-nominations are excluded.

The prize-winner will receive the award on the occasion of a ceremonial GDCh session on September 28, 1999 in Goslar on the eve of Chemetall's VI. Hydrid Symposium.

Prof. Dr. J. Heitbaum
Chairman of the Commission

From Random Coil to Extended Nanocylinder: Dendrimer Fragments Shape Polymer Chains

Holger Frey*

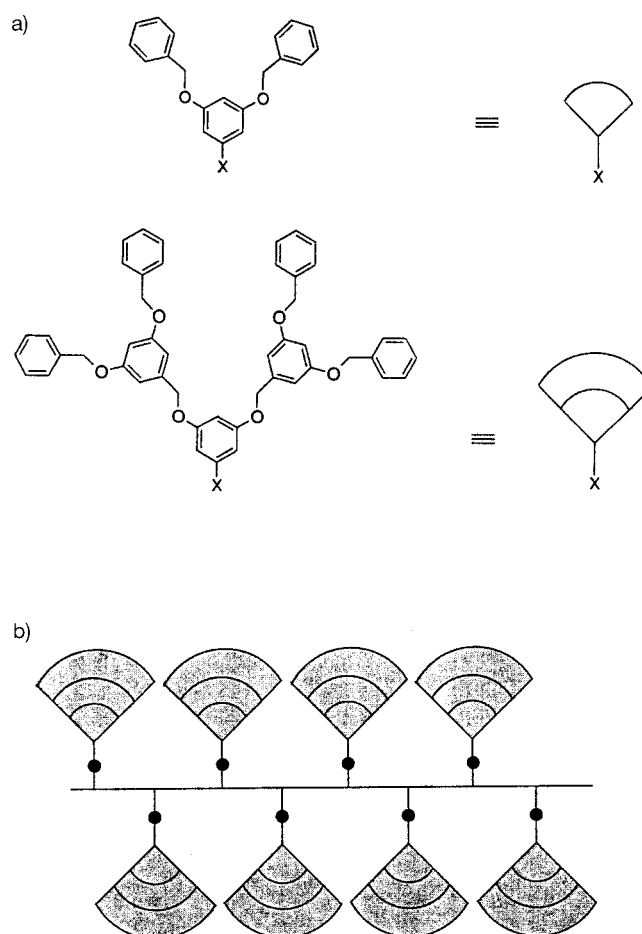
Introduction

Dendrimers—perfectly branched, highly symmetrical, tree-like macromolecules—have evolved from a curiosity into an important trend in current chemistry, attracting rapidly increasing attention from an unusually broad community of scientists.^[1] Various dendrimer construction strategies have been developed on the basis of classical organic and inorganic chemistry,^[2] as well as on transition metal complexation.^[3, 4] Based on these now well-established synthetic “algorithms”, increasing research efforts are currently directed at constructing supramolecular structures and dendrimers by self-assembly processes as well as elucidating structure–property relationships.^[5] For instance, flexible dendrimers with mesogenic branching points^[6] or end groups^[7] have been constructed that are able to induce anisotropic liquid crystalline order despite the isotropic dendrimer topology. Furthermore, self-assembly of dendrimers on surfaces to give ultrathin films with a thickness of a few nanometers has been investigated by a number of groups,^[8] with the aim of developing films for application in catalysis, sensors, or chromatographic separation.^[9]

For polymer chemists it is an interesting question as to how well-known linear polymers can be linked to dendritic architectures and what the supramolecular consequences of this approach might be. The combination of dendrimers and linear polymers in hybrid linear dendritic block copolymers has been employed to achieve particular self-assembly effects. Block copolymers with a linear polyethylene oxide block and a dendritic polybenzyl ether block form large micellar structures in solution, which depend on the size (that is, the generation) of the dendritic block.^[10] Amphiphilic block copolymers have been prepared by the combination of a linear, apolar polystyrene chain with a polar, hydrophylic poly(propylene imine) dendrimer^[11] as well as from polyethylene oxide with Boc-substituted poly- α,ϵ -L-lysine dendrimers (Boc = *tert*-butoxycarbonyl).^[12] Such block copolymers form large spherical and cylindrical micelles in solution

and have been described as “superamphiphiles” and “hydraamphiphiles”, respectively.

In contrast to these successful efforts to link dendrimers and linear polymer chains in the manner of block copolymers, only very recently a breakthrough has been achieved in the synthesis of linear polymers with dendritic side groups (Scheme 1). This will be highlighted in this contribution. Considerable synthetic effort is required to prepare suitable dendritic monomers; however, the amazing kinetic and structural features observed for such monomers and their



Scheme 1. a) Fréchet-type^[13] dendritic wedges used as conical or fanlike building units; b) schematic representation of a polymer chain with dendritic side groups.^[27]

[*] Dr. H. Frey
Freiburger Materialforschungszentrum und
Institut für Makromolekulare Chemie der Universität
Stefan-Meier-Strasse 21/31, D-79104 Freiburg (Germany)
Fax: (+49) 761-203-4709
E-mail: holfrey@fmf.uni-freiburg.de

corresponding polymers are nevertheless highly rewarding and opens up the prospect of building defined nanostructures.

Synthesis and Self-Organization of Dendrons

The term “dendron” designates a dendrimer segment possessing an AB_w -type structure, which in contrast to a perfect dendrimer is not attached to a central B_n -core unit (A and B represent the functionalities that are linked to build up the dendrimer structure). Thus, a dendron is structurally characterized by exactly one focal unit A and $w = m^g$ end groups B (m is the branching multiplicity, usually 2 or 3, and g represents the generation number). The size and number of end groups of a dendron can, of course, be varied with each generation, which gives access to a large variety of nanosize building blocks for supramolecular chemistry. The conical dendron structure may be compared to a molecular “piece of cake” (Scheme 1). In most examples where dendrons are used as supramolecular building blocks, dendritic polybenzyl ethers constructed by reactions developed by Hawker and Fréchet^[13] have been employed (Scheme 1 a). Some examples of polymerizable dendrons are shown in Figure 1.

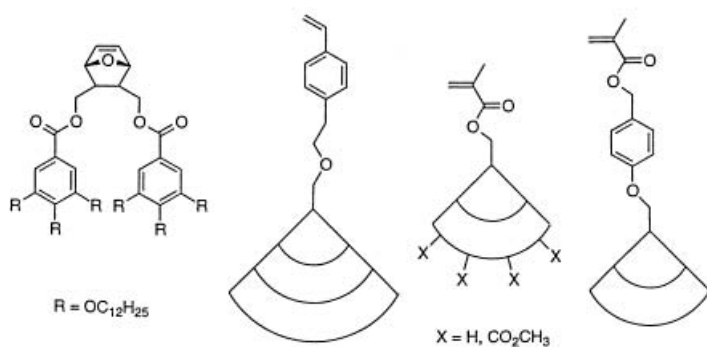
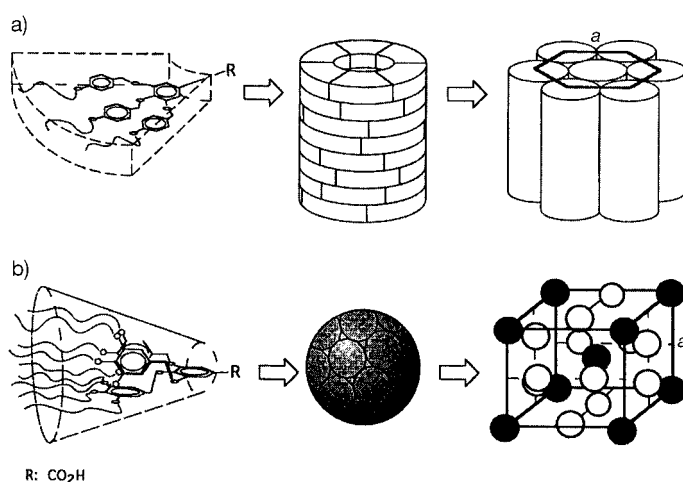


Figure 1. Examples of dendron monomers described by Percec et al., Schlüter et al., and Xi et al.

Supramolecular organization of dendrons can lead to columnar or spherical superstructures, which structure forms depends on directional and attractive interactions between such wedge-shaped molecules as well as on the size and shape of the dendrons. For instance, hydrogen-bonding interactions between diisophthalic acid moieties attached to the focal point were used by Zimmerman et al.^[14] to obtain discrete self-assembled hexamers of polybenzyl ether dendrimers. Remarkably, the self-assembled structures were stable to purification by gel chromatography and the self-assembly process was solvent dependent. When small dendrons were used less stable chainlike aggregates were obtained, thus illustrating the correlation between specific recognition processes and the shape of the dendrimer wedge.

Self-organization of tapered and dendritic—that is, fan- and cone-shaped—molecules in the solid state was reported in a series of papers by Percec et al.^[15] Detailed diffraction experiments evidenced that spherical or cylindrical (columnar) superstructures are formed, which are further packed into cubic or hexagonal columnar phases (Scheme 2).



R: CO_2H

Scheme 2. Shape-directed self-assembly of wedgelike dendrons to hexagonal-columnar and cubic superstructures according to Percec et al.^[15a]

Preparation of Polymers with Dendron Side-Chains

There are three approaches that can be used to prepare polymers with dendron side groups: A) divergent construction, analogous to divergent dendrimer synthesis, with a multifunctional linear polymer as a B_n -type core instead of a small “point like” core; B) attachment of prefabricated dendron building blocks onto a reactive polymer chain by a polymer-analogous reaction, similar to the final coupling step to the core in convergent dendrimer synthesis;^[13] and C) polymerization of dendron monomers. The basic idea behind the first strategy was mentioned as early as 1987 by Tomalia and Kirchhoff^[16a] in a patent (“comb-burst” polymers). In a recent paper, the results of this work have been published in more detail: A polyethylene imine prepared by living cationic polymerization of 2-ethyl-2-oxazoline and subsequent deprotection was used as the core for the synthesis of rod-shaped poly(amidoamine) structures.^[16b] Unfortunately, little information is given by the authors concerning control of molecular weights and polydispersities of the dendronized polyethylenimine that would permit direct comparison of this concept (A) with the other strategies (B and C) discussed below.

The second strategy (B) has been investigated intensively in the last few years by Schlüter et al. with Fréchet-type polybenzyl ether wedges and hydroxy-functional poly(*p*-phenylene) (PPP).^[17a] The key problem encountered in this case lies in the limited conversion that can be achieved in polymer-analogous reactions, particularly if higher generation dendritic wedges (G3 and higher) are employed.^[17b, c] In these cases incompletely covered polymer chains are obtained; for example, only 90% of the reactive groups at the PPP backbone are linked with dendrimer fragments of a G3 dendron. This drawback of the polymer-analogous approach has motivated intense efforts along the lines of concept C, which is based on polymerizable dendrons. If a polymerizable functionality is attached to a dendron at the focal point, “dendron monomers” are obtained (Figure 1). Large polymerizable building blocks of variable size with conical topology may be prepared depending on the dendrimer

generation employed. The fascinating questions for the polymer chemist are: Can such dendron monomers actually be polymerized, and if so, what are the properties of the resulting polymer chains with unusually large substituents?

A styrene-based copolymer with approximately 40 weight % (2 mol %) of repeating units carrying dendrons was reported by Hawker and Fréchet in 1992.^[18] However, only in the last four years have dendrimer synthesis and related characterization methods matured sufficiently that it is now possible to study dendron (macro)monomers and to exploit their potential for the synthesis of dendron-bearing polymers. One would intuitively expect polymerization of such monomers to be troublesome, as a consequence of the sterical requirements of the large dendrimer fragments as well as the increasing shielding effect on the polymerizable moiety as the number of generations increases. These problematic aspects are well known in macromonomer chemistry^[19] and are expected to be even more severe for dendron monomers. This assumption has been confirmed in the last few years by a number of authors^[20] who studied the polymerization of methacrylates with various attached dendritic fragments. Indeed, a high degree of polymerization of monodendrons to macromolecules was only possible when a spacer was inserted between the polymerizable unit and the bulky dendron group, and with very long reaction times.

In contrast, recent kinetic investigations of the polymerization of spacerless G2-dendron-substituted styrene and methyl methacrylate in solution led to the unexpected conclusion that above a certain critical monomer concentration a strong increase of the rate of the free radical polymerization is observed.^[21] The results can be explained by self-organization of the growing polymer chain to a spherical or columnar superstructure in solution, depending on the degree of polymerization (Figure 2). The rate constants and low

been prepared by Suzuki cross-coupling of dendron-substituted dibromobenzenes with alkyl-chain-substituted diboronic acids in a polycondensation type of reaction.^[17c] In this case, dendronized PPP of high molecular weight with a degree of polymerization exceeding 100 was obtained.

Properties and Visualization of Dendronized Polymers

When dendrimer fragments are attached to polymer chains, the conformation of the polymer chain is strongly affected by the large dendrimer wedges attached. "Dendronized" polymers can be considered as a subclass of comb polymers; that is, they are linear polymer chains densely substituted with polymeric side chains. These polymers are known to be extremely rigid in solution and exhibit Kuhn lengths of 100–200 nm, as compared to 1–2 nm for polystyrene or polymethyl methacrylate.^[22] For that reason, such comb polymers are sometimes designated "cylindrical brushes".

Consequently, a cylindrical shape is also expected for polymers with large dendron side chains. Of course, biomolecules such as DNA or RNA with rigid cylindrical or wormlike shapes are well known, but in these cases the supermolecular structure (the secondary and tertiary structure) is the result of well-controlled secondary (hydrogen) bonds.

For flexible synthetic polymers the chain conformation is commonly controlled by the degree of polymerization (DP); polymers with low DP have a rather extended chain conformation, and those with high DP adopt random coil conformations in solution. Recently, Percec, Möller et al. reported extensive studies concerning the chain conformation and supramolecular structure of dendron-substituted polystyrene and polymethacrylate.^[23] Remarkably, at low DP (that is, with short chains) the conical monodendrons assemble to produce a spherical superstructure with a random-coil backbone conformation (Figure 3a). On increasing the DP the self-assembly pattern of the dendrons changes, and leads to cylindrical polymers with rather extended backbones (Figure 3b). It is remarkable that this correlation between polymer conformation and the DP is opposite to that seen usually in most synthetic and natural macromolecules.

It is a fascinating consequence of the stiffness and densely covered surface of such cylindrical macromolecules that single polymer chains can be visualized. Möller et al. recently demonstrated impressively that the imaging of dendron-substituted polystyrene and polymethacrylate can be employed for an analysis of the molecular size distribution and conformation.^[24] The image shown in Figure 4 was obtained by scanning force microscopy (SFM) and shows single chains of dendronized polystyrene deposited on a pyrolytic graphite substrate. The molecules exhibit short, straight segments with bends of a characteristic angle of 60° and 120° corresponding to the threefold symmetry of the graphite. In addition, the molecules in close proximity tend to align parallel, forming hairpin bends. The height of the chains is in the range of 1.6 nm and the lateral diameter of the chains is 5.3 nm (SFM, tapping mode), which illustrates that the macromolecules are collapsed on the surface. The length of each macromolecule can be approximated from the SFM images by dividing the

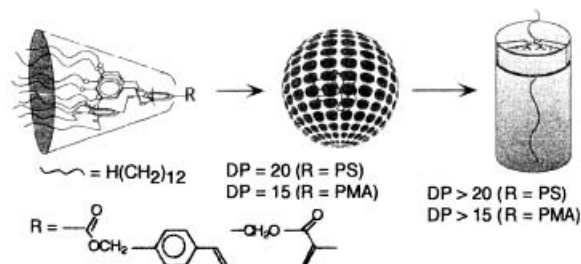


Figure 2. Dependence of the self-assembly of dendronized polymer chains on the degree of polymerization: monomers and short polymer chains assemble in spheres, whereas longer chains assemble in cylinders. This effect leads to rapid polymerization of such dendron monomers as a result of the "self-encapsulation".^[21]

initiator efficiency demonstrate that the self-assembled structure acts like a supramolecular nanoreactor that leads to a strongly enhanced local concentration of polymerizable groups. Thus, the kinetics of the polymerization is determined by self-assembly and can be viewed as "self-encapsulated" and "self-accelerated".

Polycondensation of suitable monomers represents an alternative route to dendronized polymers of high molecular weight; for example, PPP with attached dendron segments has

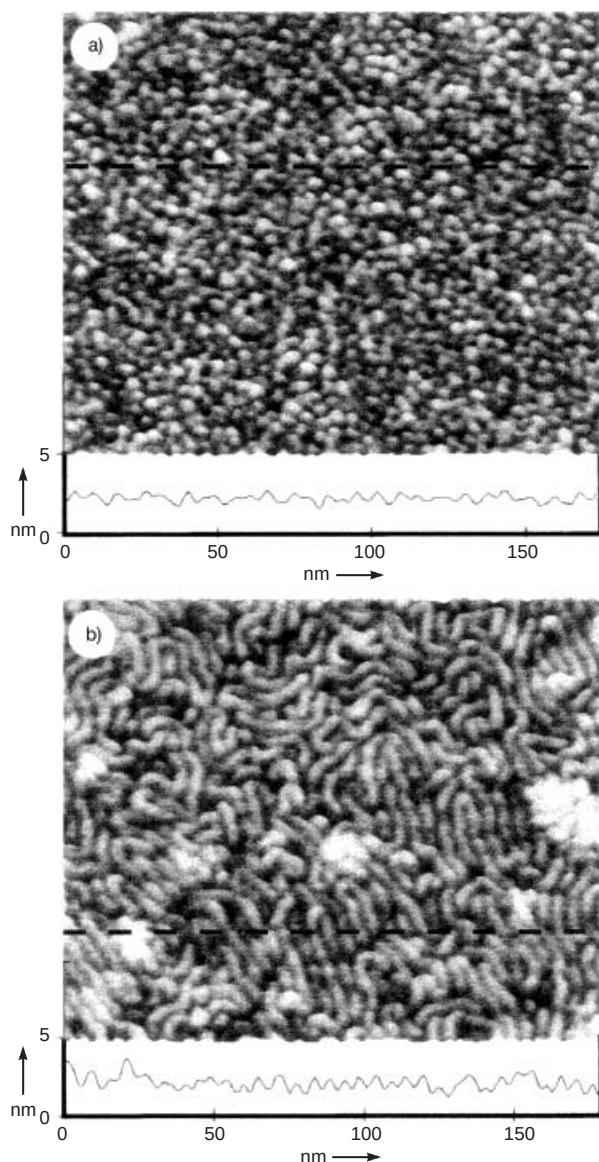


Figure 3. Topographic SFM images (tapping mode) of monomolecular films of dendron-bearing polystyrene; a) $M_n = 10800$; b) $M_n = 186500$. Spherical and cylindrical (wormlike) features are observed; cylindrical features arise from single dendronized macromolecules.^[23]

wormlike contours into segments of 10–20 nm, and then the distribution of the contour lengths may be calculated.

It is an intriguing question as to whether the molecular weight distribution can be determined in the solid state. Comparison of the apparent length of the macromolecules determined from the images shows that for large dendron side groups this is in good agreement with that expected, whereas when lower generation dendrons are attached, the contour length determined from the images is considerably lower than the calculated length of the extended chains. This demonstrates that the degree of extension (uncoiling) of the chains is determined by the size of the dendrons attached.

As interaction between the surface and the substrate may affect the images, it is an interesting question as to whether the polymers actually possess cylindrical shape in solution. Small angle neutron scattering (SANS) experiments have

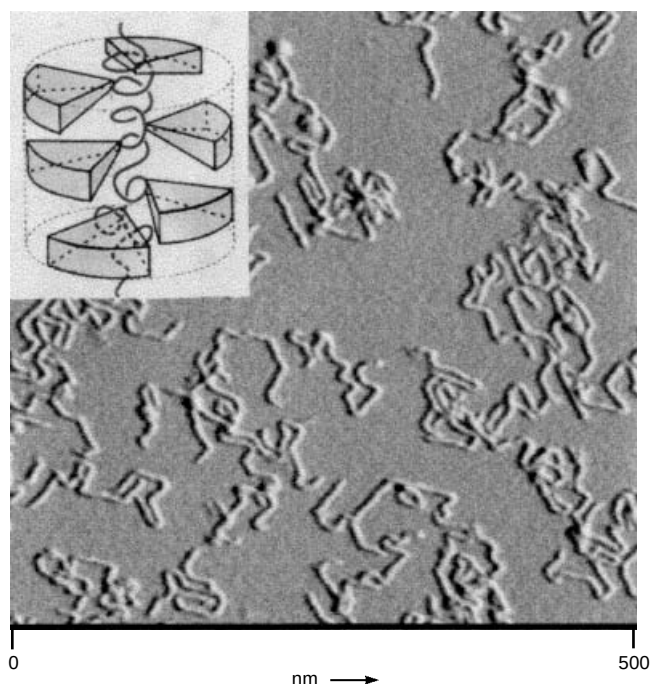


Figure 4. Single "wormlike" polymer chains of dendronized polystyrene deposited on pyrolytic graphite, imaged by topographic SFM.^[24]

been employed to answer this question. Figure 5 shows the scattering curve of a dendron-substituted polystyrene (G3 dendrons).^[25] It is possible to describe the scattering curve by assuming that the dendron-substituted polystyrene exhibits a

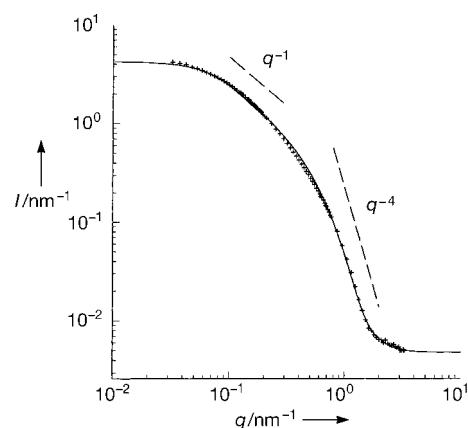


Figure 5. SANS scattering curve ($I(q)$ versus q) q = scattering vector of a G3-dendronized polystyrene, obtained by Förster, Schlüter et al.^[25] The scattering curve at larger q follows the Porod q^{-4} law, and arises from the scattering at the surface of a cylinder. This observation confirms the stiff, wormlike character of the macromolecules.

rod like structure. Thus, the persistence length of the molecule is of the order of the contour length, supporting the presence of stiff, cylindrical macromolecules in solution.

Conclusion and Outlook

In summary, the attachment of dendron building blocks to common monomers leads to dramatic kinetic and structural consequences. Once more, it should be kept in mind that it is only the shape of the side groups attached that governs conformation and structure of the resulting polymer chains, not hydrogen-bonding interactions, which are ubiquitous in the self-assembly of biological macromolecules.

Based on the breakthrough achieved in the synthesis and visualization of “dendronized” polymers, it is a safe bet that this novel class of extremely stiff macromolecules will stimulate further interdisciplinary efforts to understand their physical behavior in bulk and in solution, as well as to assess their usefulness for a future nanotechnology based on “molecular objects”. On the other hand, these developments may lead to libraries of shapes that can be combined to create any nanometer-sized cylindrical object with programmed length and diameter.^[26] Block copolymers with one “dendronized” cylindrical block and one coiled block can also be envisaged.^[27] In addition, dendrons bearing protected functionalities developed by Schlüter et al. offer further possibilities for the functionalization of such nanocylinders.^[20c] Let's wait for the shape of other exciting molecular objects based on dendrimer wedges to come!

German version: *Angew. Chem.* **1998**, *110*, 2313–2318

Keywords: dendrimers • force microscopy • nanostructures • polymers

- [1] a) D. A. Tomalia, A. M. Naylor, W. A. Goddard III, *Angew. Chem.* **1990**, *102*, 119–157; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138–175; b) D. A. Tomalia, H. D. Durst, *Top. Curr. Chem.* **1993**, *165*, 193–313; c) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Macromolecules: Concepts, Syntheses, Perspectives*, 1st ed, VCH, Weinheim, **1996**; d) J. M. J. Fréchet, C. J. Hawker, *React. Funct. Polym.* **1995**, *26*, 127–150; e) B. I. Voit, *Acta Polymer.* **1995**, *46*, 87–99; f) H. Frey, K. Lorenz, L. Lach, *Chem. Unserer Zeit* **1996**, *75*–85; g) O. A. Matthias, A. N. Shipway, J. F. Stoddart, *Prog. Polym. Sci.* **1998**, *23*, 1–56.
- [2] H. Frey, C. Lach, K. Lorenz, *Adv. Mater.* **1998**, *10*, 279–293.
- [3] C. Gorman, *Adv. Mater.* **1998**, *10*, 295–309.
- [4] W. T. S. Huck, F. C. J. M. van Veggel, D. N. Reinhoudt, *Angew. Chem.* **1996**, *108*, 1304–1306; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1213–1215.
- [5] a) F. Zeng, S. C. Zimmerman, *Chem. Rev.* **1997**, *97*, 1681–1712; b) S. C. Zimmerman, *Curr. Opin. Coll. Interf. Sci.* **1997**, *2*, 89–99; c) J. S. Moore, *Acc. Chem. Res.* **1997**, *30*, 402–413.
- [6] a) V. Percec, P. W. Chu, G. Ungar, J. P. Zhou, *J. Am. Chem. Soc.* **1995**, *117*, 11441–11454; b) J. F. Li, K. A. Crandall, P. W. Chu, V. Percec, R. G. Petschek, C. Rosenblatt, *Macromolecules* **1996**, *29*, 7813–7819.
- [7] a) K. Lorenz, D. Hölter, B. Stühn, R. Mülhaupt, H. Frey, *Adv. Mater.* **1996**, *8*, 414–416; b) S. A. Ponomarenko, E. A. Rebrov, A. Y. Bobrovsky, N. I. Boiko, A. M. Muzafarov, *Liq. Cryst.* **1996**, *21*, 1–12; c) K. Lorenz, H. Frey, R. Mülhaupt, *Macromolecules* **1997**, *30*, 6860–6868.
- [8] a) S. Watanabe, S. L. Regen, *J. Am. Chem. Soc.* **1994**, *116*, 8855–8856; b) M. Wells, R. M. Crooks, *J. Am. Chem. Soc.* **1996**, *118*, 3988–3989; c) S. S. Sheiko, G. Eckert, G. Ignat'eva, A. M. Muzafarov, J. Spickermann, H. J. Räder, M. Möller, *Macromol. Rapid Commun.* **1996**, *17*, 283–297; d) M. Collaud Coen, K. Lorenz, J. Kressler, H. Frey, R. Mülhaupt, *Macromolecules* **1996**, *29*, 8069–8076.
- [9] a) S. A. Kuzdzal, C. A. Monnig, G. R. Newkome, C. N. Moorefield, *J. Chem. Soc. Chem. Commun.* **1994**, 2139–2140; b) P. G. H. M. Muijselaar, H. A. Claessens, C. A. Cramers, J. F. G. A. Jansen, E. W. Meijer, E. M. de Brabender-Van den Berg, S. Vanderwal, *J. High Res. Chromat.* **1995**, *18*, 121–123.
- [10] a) I. Gitsov, K. L. Wooley, C. J. Hawker, P. T. Ivanova, J. M. J. Fréchet, *Macromolecules* **1993**, *26*, 5621–5627; b) I. Gitsov, J. M. J. Fréchet, *Macromolecules* **1993**, *26*, 6536–6546; c) J. M. J. Fréchet, I. Gitsov, *Macromol. Symp.* **1995**, *98*, 441–465.
- [11] a) J. C. M. van Hest, D. A. P. Delnoye, M. W. P. L. Baars, M. H. P. van Genderen, E. W. Meijer, *Science* **1995**, *268*, 1592–1595; b) J. C. M. van Hest, M. W. P. L. Baars, R. C. Elissenroman, M. H. P. van Genderen, E. W. Meijer, *Macromolecules* **1995**, *28*, 6689–6691.
- [12] T. M. Chapman, G. L. Hillyer, E. J. Mahan, K. A. Shaffer, *J. Am. Chem. Soc.* **1994**, *116*, 11195–11196.
- [13] C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.
- [14] S. C. Zimmerman, F. W. Zeng, D. E. C. Reichert, S. V. Kolotuchin, *Science* **1996**, *271*, 1095–1098.
- [15] a) V. S. K. Balagurusamy, G. Ungar, V. Percec, G. Johansson, *J. Am. Chem. Soc.* **1997**, *119*, 1539–1555; b) S. D. Hudson, H.-T. Jung, V. Percec, W. D. Cho, G. Johansson, G. Ungar, V. S. K. Balagurusamy, *Science* **1997**, *278*, 449–452.
- [16] a) D. A. Tomalia, P. M. Kirchhoff, Dow Chemical Co., US-Patent 834993, **1987** [*Chem. Abstr.* **1998**, *108*, 56832]; b) R. Yin, Y. Zhu, D. A. Tomalia, H. Ibuki, *J. Am. Chem. Soc.* **1998**, *120*, 2678–2679.
- [17] a) R. Freudenberger, W. Claussen, A. D. Schlüter, H. Wallmeier, *Polymer* **1994**, *35*, 4496–4501; b) B. Karakaya, W. Claussen, A. Schäfer, A. Lehmann, A. D. Schlüter, *Acta Polym.* **1996**, *47*, 79–84; c) B. Karakaya, W. Claussen, K. Gessler, W. Saenger, A. D. Schlüter, *J. Am. Chem. Soc.* **1997**, *119*, 3296–3301.
- [18] C. J. Hawker, J. M. J. Fréchet, *Polymer* **1992**, *33*, 1507–1513.
- [19] *Chemistry and Industry of Macromonomers* (Ed.: Y. Yamashita), Hüthig & Wepf, Basel, **1993**.
- [20] a) G. Draheim, H. Ritter, *Macromol. Chem. Phys.* **1995**, *196*, 2211–2222; b) Y. M. Chen, C.-F. Chen, Y.-F. Liu, Y. F. Li, F. Xi, *Macromol. Rapid Commun.* **1996**, *17*, 401–407; c) I. Neubert, R. Klopsch, W. Claussen, A. D. Schlüter, *Acta Polym.* **1996**, *47*, 455–459.
- [21] V. Percec, C.-H. Ahn, B. Barboiu, *J. Am. Chem. Soc.* **1997**, *119*, 12978–12979.
- [22] a) Y. Tsukahara, Y. Tsutsumi, Y. Yamashita, S. Shimada, *Macromolecules* **1990**, *23*, 5201–5208; b) M. Wintermantel, M. Gerle, K. Fischer, M. Schmidt, I. Wataoka, H. Urakawa, K. Kajiwarra, Y. Tsukahara, *Macromolecules* **1996**, *29*, 978–983; c) S. S. Sheiko, M. Gerle, K. Fischer, M. Schmidt, M. Möller, *Langmuir* **1997**, *13*, 5368–5372; d) P. Dziezok, S. S. Sheiko, K. Fischer, M. Schmidt, M. Möller, *Angew. Chem.* **1997**, *109*, 2894–2897; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2812–2815.
- [23] V. Percec, C.-H. Ahn, G. Ungar, D. J. P. Yearley, M. Möller, S. S. Sheiko, *Nature* **1998**, *391*, 161–164.
- [24] S. A. Prokhorava, S. S. Sheiko, M. Möller, C.-H. Ahn, V. Percec, *Macromol. Rapid Commun.* **1998**, in press.
- [25] W. Stocker, B. L. Schürmann, J. P. Rabe, S. Förster, P. Lindner, I. Neubert, A. D. Schlüter, *Adv. Mater.* **1998**, in press.
- [26] V. Percec, Makromolekulares Kolloquium Freiburg, **1998**.
- [27] A. D. Schlüter, *Top. Curr. Chem.* **1998**, in press.

Stretching, Tearing, and Dissecting Single Molecules of DNA**

Bruno Samorì*

Chemists usually sample Avogadro numbers of molecules for their experiments. The properties they measure are averaged on the entire ensemble of those molecules and over all conformations accessible to them. A new exciting dimension has now been opened: A single molecule can be simultaneously touched and observed, and then also dissected and mechanically manipulated to drive its structure towards new conformations and states that otherwise can be very hard to reach.

Bulk studies have shown that DNA can undergo transitions from the native B form to the A and Z forms, but the repertoire of structural changes open to the double helix is much wider than that. For instance, during recombination the RecA protein stretches DNA beyond its natural contour length. DNA strands are locally unzipped and pulled apart by RNA polymerase during transcription. Topoisomerases underwind DNA, thus forcing its chain to supercoil around itself like a telephone cord does when we twist the receiver. A remarkable series of experiments, carried out in the last few years in several laboratories, was able to reproduce and study all these DNA structural modifications in single molecules. These investigations started from the pioneering work of Bustamante and co-workers, who made force versus extension measurements on a single DNA molecule that had been anchored on one side to a glass slide and on the other to a magnetic bead.^[1] They determined that forces of 5 pN were required to stretch an individual λ -DNA (bacteriophage) dimer (97 kb) to nearly its full contour length. This experiment provided the strictest test of entropic polymer elasticity to date, and it also demonstrated the limitation of the freely jointed chain (FJC) model with respect to the wormlike chain (WLC) model for a polymer such as DNA. While the former model represents the DNA as a chain of rigid rods connected by revolving pivots, the latter treats DNA as a uniform elastic rod and describes its path as a continuum curve.^[2]

Optical tweezers (OT) and bendable microneedles (BM), obtained by pulling optical fibers under heat to microscopic dimensions, were introduced as force sensors in subsequent experiments where the DNA could be pulled beyond 10 pN. Unlike the low force or entropic elasticity regime, this intermediate force or "intrinsic elasticity" regime has an enthalpic origin, which corresponds to the stretching of the molecule through the straining of the chemical bonds and the gradual deformation of the double helix. The research groups

of Bustamante and Caron independently found that by applying forces in the range of 20–50 pN they could stretch the DNA beyond its natural length and, surprisingly, when they increased the force to about 70 pN the DNA yielded abruptly and extended to almost twice its contour length: It underwent a sharp and reversible transition to a new distinct form of extended DNA.^[3, 4]

At the end of their paper on the entropic elasticity of DNA,^[1] Smith et al. suggested the possibility of introducing the capability to simultaneously twist and pull a DNA molecule by rotating the magnetic field in their magnetic-bead manipulation tool. The twisting of the bead over- or underwinds the molecule, thus forcing it to supercoil. This experiment, carried out a few years later by Strick et al.,^[5] showed that a little tension (about 5 pN) can prevent the writhing of the chain by converting the deficit in the linking number into a deficit in the number of twists in the Watson–Crick helix. This process originates melted regions in the helix and is a very important result for our understanding of transcription. RNA polymerase (RNAP) overwinds DNA ahead and underwinds it behind itself during its tracking of the double helix.^[6] Guptasarma proposed recently that the underwound DNA behind a RNAP assembly can melt and form new transcription bubbles.^[7] The experiment by Strick et al.,^[5] if considered together with the recent demonstration by Yin et al.^[8] that RNAP can exert a force as large as 14 pN on the DNA molecule, shows how these bubbles could be produced.

The most recent force versus extension measurements in the two regimes of intrinsic elasticity and overstretching of the DNA were carried out by Shivashankar and Libchaber with a scanning force microscopy (SFM) apparatus.^[9] One end of a linear λ -DNA molecule was grafted onto a glass coverslip with a biotin–streptavidin linker and the other end to a 3.2- μ m latex bead, again with the same linker. This DNA-tethered bead was brought into contact and attached to a SFM cantilever by means of an optical tweezer. The DNA molecule was extended by moving the bead away from the coverslip. The forces, measured from the deflection of the cantilever, were basically the same as those obtained by the other groups with optical tools.^[3, 4] This coincidence could raise doubts about the reliability of those measurements, because, as we will see in a while, different manipulation tools are expected to drive the experiments along different energy pathways. But the doubts disappear if we analyze these data in terms of force loading rates (see below and reference [17]).

DNA was more recently subjected to a much worse "torture". Essevez-Roulet et al. opened a single λ -DNA molecule by pulling apart its complementary strands, like the two sides of a zipper.^[10] At one end of the double-stranded DNA molecule one strand was linked to the microscope slide and the other strand to the bead. The other end of the molecule was capped with an oligonucleotide forming a

[*] Prof. B. Samorì

Dipartimento di Biochimica, Università di Bologna
via Irnerio 48, 40126 Bologna (Italy)
Fax: (+390) 51-354-387
E-mail: samori@alma.unibo.it

[**] I thank C. Bustamante, S. Smith, E. Evans, G. V. Shivashankar, G. Lee, K. Schultzen, and my students I. Jacoboni and G. Zuccheri for enlightening discussions and comments on the manuscript. I acknowledge MURST (Programma Biologica Strutturale 1997) and CNR (5% Comitato Biotec. e Biol. Mol.) for their financial support.

hairpin (Figure 1 a) to prevent separation of the two strands when reaching the end of the opening process and so allow unzipping–zipping cycles to occur. The mechanical forces that were required to separate the strands were in the range of 10 to 15 pN per base pair. Figure 1 b reports the fluctuations in the force required to directionally melt the double helix and

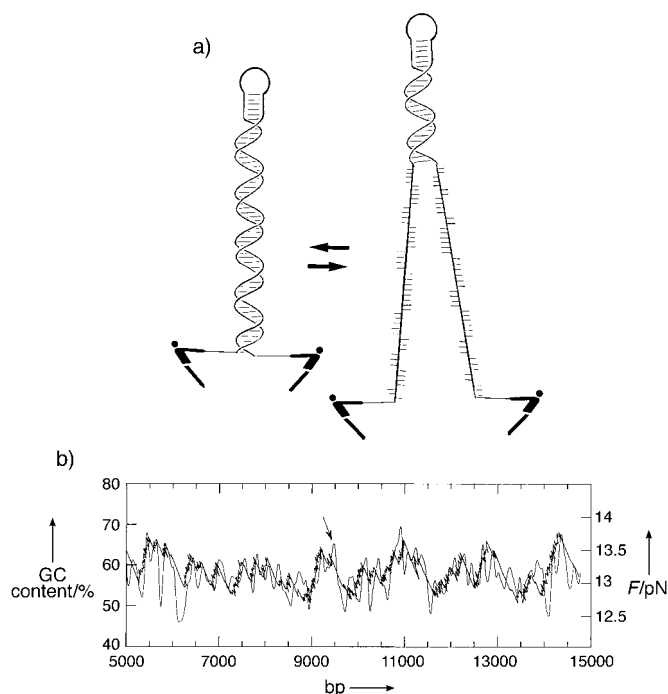


Figure 1. a) Cartoon representation of the unzipping experiment carried out by Essevaz-Roulet et al.^[10] on a single λ -DNA molecule (48.5 kb). b) Comparison between the average GC content [%] along a segment from 5000 to 15000 bp of the sequence of λ -DNA (smooth curve) and the fluctuations of the force F required to directionally melt the same segment (less smooth curve). The GC content was averaged over 100 bases. (Reproduced with permission from reference [10], copyright (1997) National Academy of Sciences, U.S.A.)

shows that the forces are related to the GC and AT content of the DNA sequence. The peaks in the graph correspond to a higher GC content, which transiently blocks the opening of the double helix until the force reaches a level where the opening occurs quickly in the chain segment that follows. In the complete opening of the DNA sequence, the number of these events was one every 500 bases. This kind of resolution is probably still too low for these mechanical measurements to become a source of intermediate-scale information on long pieces of DNA that could complement and support enzymatic sequencing methods, as suggested by the authors.

Much higher sequence resolution was achieved in a similar experiment carried out by Lee et al. with an SFM apparatus.^[11] They covalently linked one end of a single-stranded oligonucleotide that was 20 base-long to a spherical probe attached to a SFM cantilever. The probe was brought into contact with a surface where the complementary single-stranded oligonucleotide had been tethered, so that annealing could be attained. By pulling away the probe they sheared the 20 base strands at once: The forces they used were of the

order of 1000 pN, about 50 pN per base pair. This is a much larger value than that measured by Essevaz-Roulet for breaking base pairs.^[10] The difference in values could be the result of different geometries of pulling, but also other explanations can be proposed. As once suggested to me by Steve Smith, in Lee's experiment the molecule should go into the extended form at 70 pN^[3, 4] and then fray (melt) from its ends. That process may take too long, hence a higher force is required (see below). Alternatively, it may be that the force they measured was that of breaking double-stranded DNA instead. Bensimon et al. estimated this force to be about 470 pN.^[12]

The rupture forces between base pairs were measured in another SFM experiment by Boland et al.^[13] Self-assembled monolayers of purines and pyrimidines were deposited onto gold-coated surfaces and onto gold-coated SFM tips. The directional hydrogen-bonding interaction was measured between complementary and noncomplementary individual bases. A separation force of 54 pN was reported for a single AT base pair: This value obtained by SFM was much larger than that found with BM.^[10] One further reason for these larger values can be envisaged. The SFM methods were developed to map surfaces with a very high vertical resolution. Their precision in measuring the extension in manipulation experiments is, therefore, very high and makes it possible to investigate much shorter DNA molecules than with OT or BM. This is a great advantage but, at the same time, the working distance could become so small that nonspecific interactions between the tip and the surface holding the other end of the molecule could be included. These interactions can contribute to increase the force in the SFM experiments.

The general approach of all the experiments described above is to induce ruptures of noncovalent interactions by applying an external force to lower the activation barrier as much as necessary to trigger, on the time scale of the experiment, an otherwise unlikely event.^[14–16] In these experiments the surmounting of the potential barrier is expected to be still thermally activated. This can take place provided that: 1) the applied force is not large enough to eliminate the activation barrier and 2) the pulling velocity is slow enough to leave the molecule thermally fluctuating at the barrier for a time compatible with a thermally activated process. The width of the thermal fluctuations within the potential well is determined by the “stiffness” of the tool which loads the external force. The force loading rate, as defined by Evans and Ritchies,^[14] is thus the most useful dynamic parameter that can be utilized in the analysis of force data.^[17]

These force-directed processes are accompanied by irreversible work (viscous friction force), which is spent in addition to the work required by the thermodynamic potentials. As shown by Schultzen and colleagues, the thermodynamic potentials of the processes under investigation cannot be reconstructed because of these irreversible components of the work and because of the superposition of an external potential.^[15] This is a limitation of this type of experiments if we are interested in equilibrium processes. On the other hand they open very attractive prospects of tailoring the manipulations of single molecules for studying nonequilibrium

reactions. Features of nonequilibrium “energy landscapes”^[15] can be explored along the different pathways we can select by changing the stiffness of the tool and the pulling rate.

The SFM method offers one further opportunity for micromanipulating single molecules. Its probe, after having imaged a single molecule, can be stopped at a given position and used there as a dissecting scalpel. The first experiments of this type were carried out in air by James Vesenka et al.^[18] and Eric Henderson.^[19]

Figure 2 shows a circular DNA molecule transformed into a linear molecule in solution by a double-strand cut that is induced by the local pressure of the SFM tip. This experiment

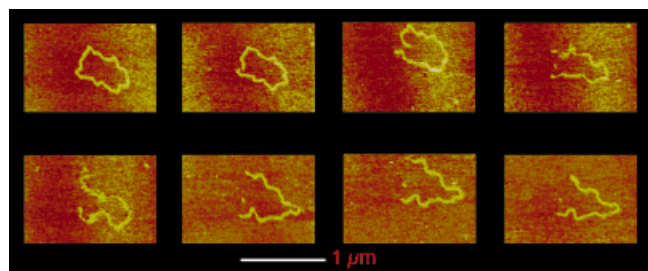


Figure 2. SFM images (tapping mode, deionized water) of pBR322 plasmids deposited on mica from a buffer solution (4 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES), 1 mM MgCl_2 , pH 7.4). The relaxed plasmid displayed in the first picture was cut in situ, while imaging, by the SFM tip. The linearized molecule started searching amongst conformations with a higher end-to-end distance than its initial zero value. In the fourth frame the molecule already bore very little resemblance to its original shape. We can modulate the adhesion of the molecule on the surface of mica by changing the ionic strength of the solution.^[20] An injection of water, after the sixth frame, improved the resolution owing to the reduction in the molecular mobility. This experiment was carried out by G. Zuccheri.^[21]

was performed in our laboratory, and a linear DNA molecule was thus created in situ. Also this single molecule manipulation creates a structure which is expected to be very poorly populated: The distance between the two newly created ends of the linear molecule was almost zero. As this experiment was carried out in liquid, we could switch the SFM back to the imaging mode after the cut, and see the two ends move apart. We could observe, in real time, the conformational rearrangement that led this molecule to an end-to-end distance of the order of magnitude theoretically expected to be the most populated for a polymer of its length.

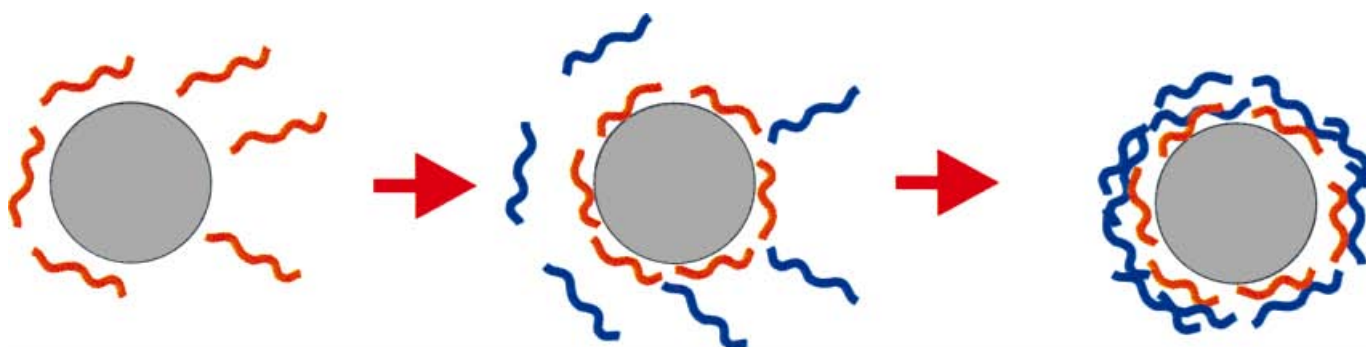
Topics of polymer chemistry and biology can now be transferred to the single-molecule level. Our understanding of many issues has been limited so far because the traditional bulk measurements are averaged over unknown molecular distributions and not necessarily homogeneous. Experiments carried out on individual molecules can cast a new light on these issues. Further advances in the theory are still necessary for both the tailoring of the experiments and the interpretation of the data. The methodologies are being developed very

rapidly, and future advances will depend on technical improvements in the time resolution of the measurements and the mechanical and thermal stability of the manipulation tools. The measurement of the spring constants is still very cumbersome and poorly reliable. A Dutch proverb says that “everything has its science, with the exception of catching fleas: that is an art”. Also “catching” individual molecules is still quite an art, but no fundamental limitations appear to prevent it from becoming an established tool offered to the ingenuity of chemists and biologists.

German version: *Angew. Chem.* **1998**, *110*, 2318–2321

Keywords: DNA cleavage • DNA structures • nanostructures • scanning force microscopy • single-molecule chemistry

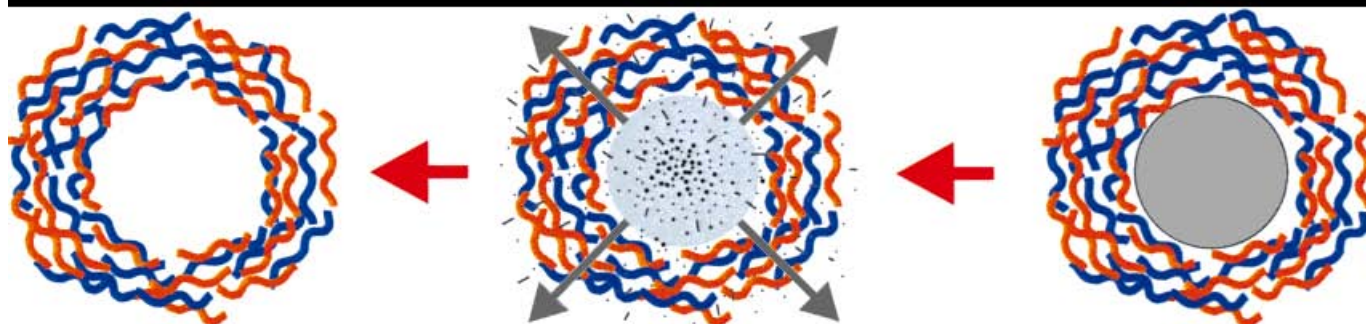
- [1] S. B. Smith, L. Finzi, C. Bustamante, *Science* **1992**, *258*, 1122–1126.
- [2] C. Bustamante, J. F. Marko, E. D. Siggia, S. B. Smith, *Science* **1994**, *265*, 1599–1600.
- [3] S. B. Smith, Y. Cui, C. Bustamante, *Science* **1996**, *271*, 795–798.
- [4] P. Cluzel, A. Lebrun, C. Heller, R. Lavery, J. Viovy, D. Chatenay, F. Caron, *Science* **1996**, *271*, 792–794.
- [5] T. R. Strick, J.-F. Allemand, D. Bensimon, A. Bensimon, V. Croquette, *Science* **1996**, *271*, 1835–1837.
- [6] L. F. Liu, J. C. Wang, *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 7024–7027.
- [7] P. Guptasarma, *BioEssays* **1996**, *18*, 325–332.
- [8] H. Yin, M. D. Wang, K. Svoboda, R. Landick, S. M. Block, J. Gelles, *Science* **1995**, *270*, 1653–1657.
- [9] G. V. Shivashankar, A. Libchaber, *Appl. Phys. Lett.* **1997**, *25*, 3727–3729.
- [10] B. Essevaz-Roulet, U. Bockelmann, F. Heslot, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 11935–11940.
- [11] G. U. Lee, L. A. Chrisey, R. J. Colton, *Science* **1994**, *266*, 771–773.
- [12] D. Bensimon, A. J. Simon, V. Croquette, A. Bensimon, *Phys. Rev. Lett.* **1995**, *74*, 4754–4757.
- [13] T. Boland, B. D. Ratner, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 5297–5301.
- [14] E. Evans, K. Ritchie, *Biophys. J.* **1997**, *72*, 1541–1555.
- [15] S. Israilev, S. Stepaniants, M. Balsera, Y. Oono, K. Schultzen, *Biophys. J.* **1997**, *72*, 1568–1581.
- [16] M. Balsera, S. Stepaniants, S. Israilev, Y. Oono, K. Schultzen, *Biophys. J.* **1997**, *73*, 1281–1287.
- [17] The force loading rate $R_f = (\text{spring constant}) \times (\text{speed of retraction})$ used in reference [10] was $(0.0017 \text{ pN nm}^{-1}) \times (40 \text{ nm s}^{-1}) = 0.068 \text{ pN s}^{-1}$. We can infer that the R_f values used in the SFM experiment by Lee et al.^[11] were in the range 4.8–1200 pN s^{-1} . This suggests that a number of strands larger than they expected could have been involved in the latter experiment. When the experiments carried out in references [9] and [4] are compared on this same basis we discover that, in spite of having used different tools, the R_f values were of the same order of magnitude. The pulling velocity used by Shivashankar and Libchaber was $10 \mu\text{m min}^{-1}$ (personal communication): the resulting R_f of 1600 pN s^{-1} is within the range of the values that were used in reference [4].
- [18] J. Vesenka, M. Guthold, C. L. Tang, D. Keller, C. Delain, C. Bustamante, *Ultramicroscopy* **1992**, *42*, 1243–1249.
- [19] E. Henderson, *Nucleic Acids Res.* **1992**, *20*, 445–447.
- [20] G. Zuccheri, R. T. Dame, M. Aquila, I. Muzzalupo, B. Samorì, *Appl. Phys. A* **1998**, *66*, S585–S589.
- [21] G. Zuccheri, S. Gramentieri, B. Samorì, unpublished results.



Polyelectrolyte shells with controlled thickness and composition are fabricated by stepwise adsorption of oppositely charged polyelectrolytes onto melamin resin templates which are subsequently solubilized.



The confocal micrograph of a shell that is 8 μm in diameter and made up of nine layers demonstrates both the integrity and deformability of the shell walls. See the following pages.



Novel Hollow Polymer Shells by Colloid-Templated Assembly of Polyelectrolytes**

Edwin Donath,* Gleb B. Sukhorukov, Frank Caruso, Sean A. Davis, and Helmuth Möhwald

The fabrication of micro- and nano-sized capsules (or shells) which enable the encapsulation of various materials are of both scientific and technological interest.^[1] Particles embedded in a solid shell (core-shell particles) have been extensively used as microcapsules for the controlled release and targeting of drugs as well as for the protection of sensitive agents such as enzymes and proteins.^[1, 2] Such particles can be prepared by interfacial polymerization or by phase separation from a polymer-solvent mixture.^[3] There are, however, a number of common problems associated with their fabrication including polydispersity, uneven shell coverage, and core solidification. Lipid liposomes are another well-known example of systems which have been used to encapsulate a variety of inorganic and organic materials.^[4] Although liposomes are employed as delivery systems for various species in the pharmaceutical and cosmetic industries, their limited stability and low permeability for polar molecules presents serious limitations for general use.

A method for preparing multilayer ultrathin organic films by the consecutive deposition of oppositely charged polyelectrolytes from dilute aqueous solution onto charged solid substrates was recently introduced by Decher et al.^[5] This technique utilizes the electrostatic attraction and complex formation between polyanions and polycations to form supramolecular multilayer assemblies of polyelectrolytes. The majority of studies have thus far focused on film formation on macroscopically flat substrates (e.g. silicon, glass, gold wafers). Techniques such as X-ray reflectivity, UV/Vis and IR spectroscopy, ellipsometry, neutron scattering, and

quartz crystal microbalance gravimetry have been employed to follow polyelectrolyte multilayer film growth as well as their structures and properties.^[5, 6] As an extension of this technique, a variety of materials (e.g. biological macromolecules, surfactants, phospholipids, nanoparticles, inorganic crystals, and multivalent dyes) have been successfully incorporated into polyelectrolyte films by replacing one of the polyelectrolytes with another species of the same charge to fabricate composite polyelectrolyte multilayer films.^[7]

Recently, we demonstrated that the step-wise adsorption of polyelectrolytes can also be performed onto charged colloidal polystyrene latex particles in solution to produce multilayer films.^[8] Whilst the complex formation of polyelectrolytes in bulk solution has been intensively studied,^[9] the template-based polyelectrolyte step-wise adsorption technique has not been applied to produce hollow polyelectrolyte shells of given size and topology. Such shells represent an interesting class of stable structures in the nano- to micrometer size range.

Here we describe a method for constructing hollow polyelectrolyte shells by colloid-templated consecutive polyelectrolyte adsorption followed by decomposition of the templating core (Figure 1). Micron-size polyelectrolyte shells

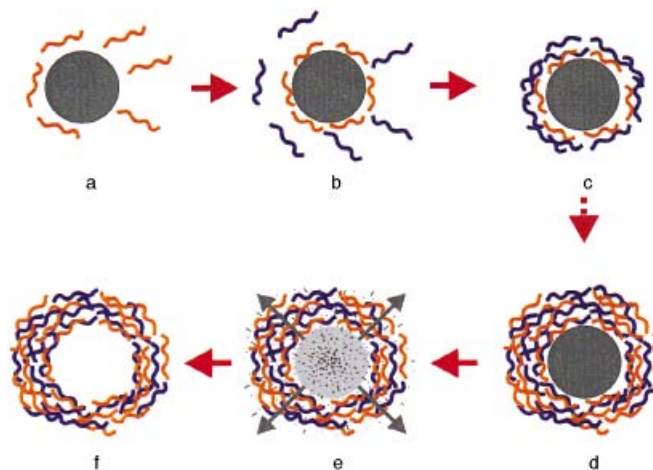


Figure 1. Schematic illustration of the polyelectrolyte deposition process and of subsequent core decomposition. The initial steps (a–d) involve step-wise film formation by repeated exposure of the colloids to polyelectrolytes of alternating charge. The excess polyelectrolyte is removed by cycles of centrifugation and washing before the next layer is deposited. After the desired number of polyelectrolyte layers are deposited, the coated particles are exposed to 100 mm HCl (e). The core immediately decomposes, as evidenced by the fact that the initially turbid solution becomes essentially transparent within a few seconds. Three additional washings with 100 mm HCl ensure removal of the dissolved MF oligomers. Finally, a suspension of free polyelectrolyte hollow shells is obtained (f).

of poly(sodium styrenesulfonate) (PSS) and poly(allylamine hydrochloride) (PAH), with thicknesses ranging from a few to tens of nanometers, have been produced. The stability, selectivity, and permeability of these polyelectrolyte shells make them rather distinct from hollow core-shell particles or liposomes currently available.

The first stage of shell fabrication involves step-wise deposition of polyelectrolytes from dilute aqueous solutions onto monodisperse weakly cross-linked melamine formaldehyde (MF) colloidal particles.^[10] These particles decompose in

[*] Dr. E. Donath, Dr. G. B. Sukhorukov,^[+] Dr. F. Caruso, Dr. S. A. Davis,^[++] Prof. Dr. H. Möhwald
Max-Planck-Institute of Colloids and Interfaces
Rudower Chaussee 5, D-12489 Berlin (Germany)
Fax: (+49) 30-6392-3102
E-mail: donath@mpikg.fka-berlin.de

[+]Permanent address:
Institute of Crystallography, Russian Academy of Sciences
Leninsky pr. 59, Moscow 117333 (Russia)

[++]New address:
Department of Chemistry, University of Bath
Bath BA2 7AY (UK)

[**] F.C. acknowledges the Alexander von Humboldt Foundation for a Research Fellowship, S.A.D. the Max Planck Society for a Schlossmann Scholarship, and G.B.S. the German Research Foundation for financial support. We thank K.-H. Lerche from Microparticles GmbH for producing and donating the MF particles; M. Breulmann for conducting the time-of-flight mass spectrometry experiments; V. I. Popov from the Institute of Cell Biophysics, Pushchino, Russia, for the TEM measurements; H. Zastrow for assistance with the electrophoretic mobility measurements; D. Walther from the University of California, San Francisco, for conducting MD simulations of MF oligomers; H. Lichtenfeld for measurements of polyelectrolyte layer thicknesses; and A. Voigt for establishing the pH sensitivity of the MF particles. The confocal micrograph in the frontispiece was taken in cooperation with P. Klein, Humboldt-Universität, Lehrstuhl für Membranphysiologie.

aqueous media at pH values below 1.6. The polyelectrolyte multilayer film is formed by the alternate adsorption of oppositely charged polyions, beginning with adsorption of the negatively charged polyanion (PSS) onto the positively charged MF particles. After each adsorption step the non-adsorbed polyelectrolyte in solution is removed by repeated centrifugation and washing. In this way, the desired number of polyelectrolyte layers can be deposited, allowing control of the multilayer film thickness.^[8]

As illustrated in Figure 1, subjecting the polyelectrolyte-coated MF particles to low pH results in decomposition of the core. Time-of-flight mass spectrometry experiments reveal that MF oligomers consisting mostly of 5–10 monomers of tetramethylol-melamine are produced.^[11] The MF oligomers, which have a characteristic cross-sectional extension of about 1 nm,^[12] are expelled from the core and permeate through the polyelectrolyte layers forming the shells. This observation is consistent with the finding that polyelectrolyte-coated MF particles are readily permeable to molecules of a few nanometers in size.^[13] The MF oligomers are finally separated from the hollow shells by centrifugation.

The polyelectrolyte shells fabricated were characterized with scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM). A SEM image of nine-layer [(PSS/PAH)₄/PSS] polyelectrolyte shells is shown in Figure 2. The numerous folds and creases observed are attributed to drying of the shells. The shells are also flattened and some spreading is noticed; the diameters (both short- and long-axis) of the shells

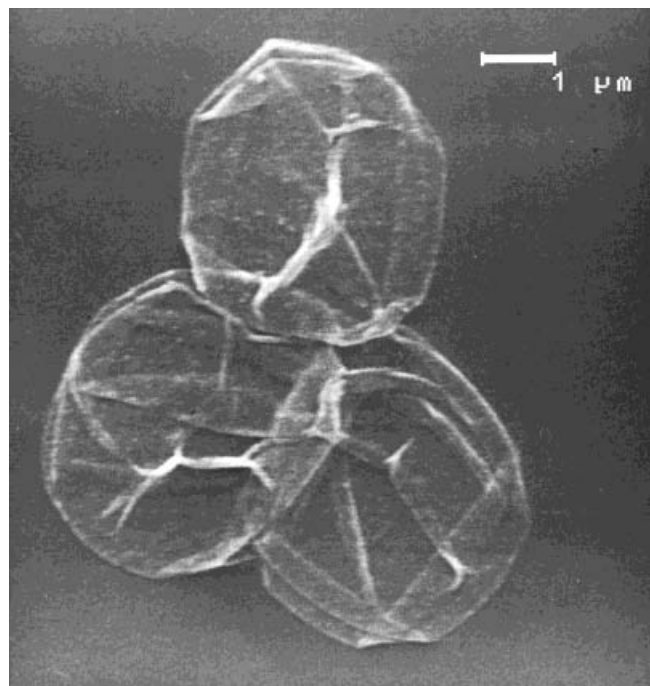


Figure 2. SEM image of nine-layer [(PSS/PAH)₄/PSS] polyelectrolyte shells after solubilization of the MF core. The outer layer is PSS. The strong electrostatic attraction of the shells to the positively charged PEI-coated glass surface leads to some spreading of the polyelectrolyte shell. The drying process induces a number of folds and creases. Drying, together with the topological constraints of the closed surface, results in a completely folded upper hemisphere.

lie within the value $4.0 \pm 0.5 \mu\text{m}$, which is larger than that of the MF particle ($3.3 \mu\text{m}$). This increase in diameter is ascribed to a combination of drying and the forces exerted on the shells upon their electrostatic immobilization onto the PEI-coated glass substrates [PEI = poly(ethyleneimine)]. The shells also exhibit a somewhat rough surface texture. This may be characteristic of the polyelectrolyte film, although some residual MF is present in the shells. Within the limit of resolution of the SEM technique, no holes or traces of rupture are identified in the shells.

The TEM images of hollow nine-layer [(PSS/PAH)₄/PSS] polyelectrolyte shells are displayed in Figure 3. The homogeneous curvature of the shells proves that, provided the interior

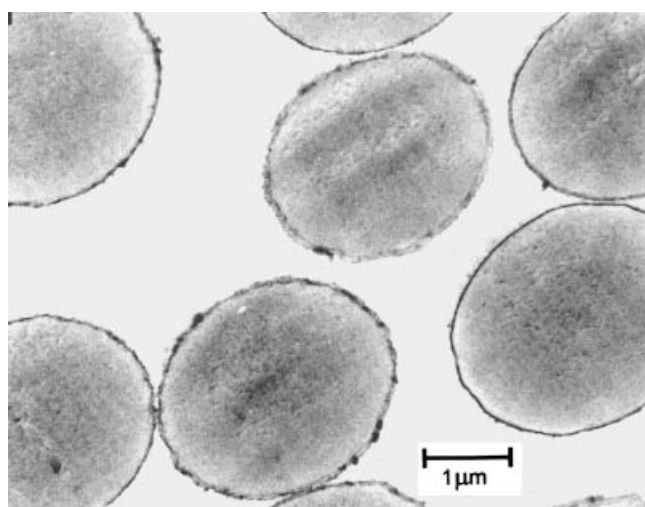


Figure 3. TEM image of nine-layer [(PSS/PAH)₄/PSS] polyelectrolyte shells. The template MF particles used have a diameter of $2 \mu\text{m}$. The stained polyelectrolyte layer surrounding the less stained shell interior can be clearly identified. The polyelectrolyte layer thickness is of the order of 20 nm. Some surface roughness of the outer layer is observed. Apart from some longitudinal deformation, an artefact of thin sectioning the shell, the shells are close to spherical.

aqueous solution has not been removed, the fabricated shells preserve both the diameter and the spherical shape of the template particles. This is further evidence that the creases and folds seen in the SEM pictures are due to bending and tension forces exerted on the polyelectrolyte shell upon drying. Additional support for this comes from the real-time monitoring of decomposition of the MF core of a three-layer [PSS/PAH/PSS] or seven-layer [(PSS/PAH)₃/PSS] polyelectrolyte-coated MF particle in solution with high-resolution video microscopy, which confirms that the shells retain their integrity upon dissolution of the core.^[14] From the TEM image it can also be deduced that the thickness of the polyelectrolyte film is of the order of 20 nm for the nine-layer polyelectrolyte film. This value is consistent with the layer thickness obtained for polyelectrolyte-coated polystyrene latex particles from single-particle light-scattering data.^[8] This suggests that the nature of the colloid in these cases, does not significantly affect the thickness of the polyelectrolyte layers. In agreement with the SEM data, the outer surface of the polyelectrolyte

film is also seen to be rough, and there is no evidence of a distinct layered structure to the film. In addition, the TEM image does not provide any evidence of existing holes larger than a few nanometers in the polyelectrolyte shells.

Atomic force microscopy in the tapping mode (TM) was employed to investigate the topography of the fabricated polyelectrolyte shells in more detail. All AFM images in Figure 4 indicate that the three-dimensional polyelectrolyte shells are continuous films which, in accordance with the SEM observations (Figure 2), exhibit creases and folds resulting from evaporation of the aqueous content. Figure 4A shows an AFM image of polyelectrolyte shells consisting of three

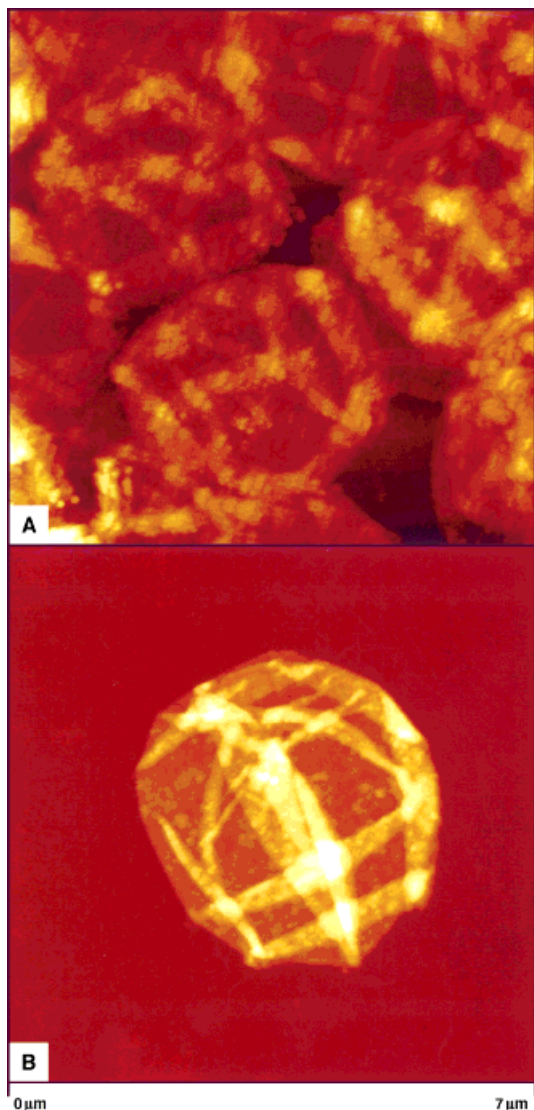


Figure 4. AFM images (tapping mode) of three-layer [PSS/PAH/PSS; A] and nine-layer [(PSS/PAH)₄/PSS; B] polyelectrolyte shells prepared on MF particle templates of 3.3 μm in diameter. The maximum height of the shell in image A is of the order of 50 nm, and 100 nm for the shell in image B.

layers [PSS/PAH/PSS]. This image is an example of the exceptionally strong electrostatic forces involved in the formation of these ultrathin polyelectrolyte layers. The diameter of the shell in Figure 4A is approximately 3 μm . In this image it appears that some of the shells are overlaying

others beneath them. The average thickness of the shells (obtained from height measurements), is about 50 nm, suggesting that even when dried the shells are not completely flattened. Although some remaining MF material is seen in the shells, some lower regions (darker spots in the images) have a minimum height comparable to about two superimposed shell walls (ca. 10 nm). Figure 4B presents an AFM image of a shell consisting of nine polyelectrolyte layers [(PSS/PAH)₄/PSS]. An increase in both the diameter (ca. 4 μm) and in the height (maximum value ca. 120 nm) of the shell, compared to that of the three-layer shell, is observed. Some residual MF is also clearly seen in the shell.

It has been shown that the use of soluble cores as templates for the step-wise deposition of polyelectrolytes is a successful pathway to fabricate novel three-dimensional hollow polymer shells. These films combine the advantages of thin organic films of polyelectrolytes with the easy handling and applications of colloids. The most important novel features of the fabricated polyelectrolyte shells are that 1) the composition and thickness of the shells can be controlled, 2) they can be fabricated with controlled physical and chemical properties, and 3) they offer novel structures for micro- and nano-compartmentalization of materials. In addition, unlike liposome structures,^[4] the fabricated shells are readily permeable by small (ca. 1–2 nm in diameter) polar molecules^[13] and are extremely stable against chemical and physical influences. It is envisaged that different species can be incorporated into the shell structure giving them unique tailored properties, and making them attractive for a wide range of applications. For example, the incorporation of catalytic materials inside or onto the inner surface of the shells, together with the easy diffusion of reaction products and substrates, is a promising way to both control and increase the efficiency of catalytic processes. The hollow polyelectrolyte shells may also have potential as micro- and nanocarriers for molecules and nanoparticles, as well as biological species for the controlled release and targeting of drugs. They can also serve as cages for chemical reactions in restricted volumes. The control of the chemical composition of the inner surface (or likewise the outer surface) can be used to produce nucleation centers for subsequent crystal growth in constrained environments, which is also a novel way to produce nanocomposites. Preliminary experiments have shown that monodisperse crystals can be successfully grown inside these novel capsules.

Experimental Section

PEI ($M_w = 50\,000$), PSS ($M_w = 70\,000$), and PAH ($M_w = 8\,000 - 11\,000$) were obtained from Aldrich. PEI and PAH were used as received, whereas PSS was dialyzed against Milli-Q water (cut-off 14000) and lyophilized before use. The water used in all experiments was prepared in a three-stage Millipore Milli-Q Plus 185 purification system and had a resistivity higher than 18.2 M $\Omega\text{ cm}$.

Typical adsorption conditions used to form the polyelectrolyte layers on the MF particles were 1 mgmL⁻¹ of polyelectrolyte in 0.5 M NaCl, and a particle concentration of 0.5% (v/v). The adsorption time was 20 min. The MF particles have a density of 1.5 gcm⁻³. Centrifugation speeds of 2000 min⁻¹ (Eppendorf rotor) were more than sufficient to settle the polyelectrolyte-coated particles. Three washings in Millipore water were

carried out prior to addition of the next polyelectrolyte to ensure removal of the nonadsorbed polyelectrolyte.

SEM measurements were conducted with a Zeiss DSM 40 instrument operated at an accelerated voltage of 15 kV. After the required number of polyelectrolyte layers were deposited, the MF core was removed by exposure to an aqueous solution of low pH. Samples were prepared by applying a drop of the shell solution to PEI-coated glass. After allowing the shells to settle the slides were extensively rinsed in Millipore water and then dried under a gentle stream of nitrogen.

The TEM specimens were fixed with glutaraldehyde, OsO_4 , and $\text{K}_2\text{Cr}_2\text{O}_7$, and dehydrated in ethanol/acetone. The samples were embedded in Epon 812/Araldite M resin and polymerized in an oven for two days.^[15] Thin sections (80–100 nm) were cut with a Reichert ultratome, and stained with uranyl acetate and lead citrate. Measurements were performed on a JEOL 100 B electron microscope.

The AFM images were obtained with a Digital Instruments Nanoscope IIIa in the tapping mode. Samples were prepared by applying a drop of the shell solution to PEI-coated glass. After allowing the shells to settle the slides were extensively rinsed in Millipore water and then dried under a gentle stream of nitrogen.

Received: February 13, 1998 [Z114791E]

German version: *Angew. Chem.* **1998**, *110*, 2324–2327

Keywords: colloids • layered compounds • nanostructures • polyelectrolytes • polymers

- [1] D. D. Lewis in *Biodegradable Polymers and Drug Delivery Systems* (Eds.: M. Chasin, R. Langer), Marcel Dekker, New York, **1990**.
- [2] J. P. McGee, S. S. Davis, D. T. O'Hagan, *J. Control. Release* **1995**, *34*, 77.
- [3] a) B. Miksa, S. Slomkowski, *Colloid Polym. Sci.* **1995**, *273*, 47; b) G. Crotts, T. G. Park, *J. Control. Release* **1995**, *35*, 91; c) S. L. Regen, J.-S. Shin, *J. Am. Chem. Soc.* **1984**, *106*, 5756; d) J. Hotz, W. Meier, *Langmuir* **1998**, *14*, 1031; e) K. B. Thurmond, T. Kowalewski, K. L. Wooley, *J. Am. Chem. Soc.* **1997**, *119*, 6656.
- [4] D. D. Lasic, *Liposomes: From Physics to Applications*, Elsevier, Amsterdam, **1993**.
- [5] a) G. Decher, *Science* **1997**, *277*, 1232, and references therein; b) G. Decher, J.-D. Hong, *Macromol. Chem. Macromol. Symp.* **1991**, *46*, 321; c) G. Decher in *Templating, Self Assembly and Self-Organisation*, Vol. 9 (Eds.: J.-P. Sauvage, M. W. Hosseini), Pergamon, Oxford, **1996**, pp. 507–528.
- [6] a) F. Caruso, K. Niikura, D. N. Furlong, Y. Okahata, *Langmuir* **1997**, *13*, 3422; b) G. J. Kellogg, A. M. Mayes, W. B. Stockton, M. Ferreira, M. F. Rubner, S. K. Satija, *Langmuir* **1996**, *12*, 5109; c) G. Decher, J. D. Hong, J. Schmitt, *Thin Solid Films* **1992**, *210/211*, 831.
- [7] a) F. Caruso, K. Niikura, D. N. Furlong, Y. Okahata, *Langmuir* **1997**, *13*, 3427; b) G. B. Sukhorukov, H. Möhwald, G. Decher, Y. M. Lvov, *Thin Solid Films* **1996**, *285*, 220; c) Y. Lvov, K. Ariga, T. Kunitake, *J. Am. Chem. Soc.* **1995**, *117*, 6117; d) S. W. Keller, S. A. Johnson, E. S. Brigham, E. H. Yonemoto, T. E. Mallouk, *J. Am. Chem. Soc.* **1995**, *117*, 12879; e) G. Decher, B. Lehr, K. Lowack, Y. Lvov, J. Schmitt, *Biosens. Bioelectron.* **1994**, *9*, 677; f) G. B. Sukhorukov, M. M. Montrel, A. I. Petrov, L. I. Shabarchina, B. I. Sukhorukov, *Biosens. Bioelectron.* **1996**, *11*, 913; g) G. B. Sukhorukov, J. Schmitt, G. Decher, *Ber. Bunsen-Ges. Phys. Chem.* **1996**, *100*, 948; h) Y. L. Liu, M. Q. Zao, D. E. Bergbreiter, R. M. Crooks, *Angew. Chem.* **1997**, *109*, 2204; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2114.
- [8] G. B. Sukhorukov, E. Donath, H. Lichtenfeld, E. Knippel, M. Knippel, H. Möhwald, *Colloids Surfaces A: Physicochem. Eng. Aspects*, **1998**, *137*, 253.
- [9] a) B. Philipp, H. Dautzenberg, K.-J. Linow, J. Kötzt, W. Dawydoff, *Prog. Polym. Sci.* **1989**, *14*, 91; b) V. A. Kabanov, A. B. Zevin, *Pure Appl. Chem.* **1984**, *56*, 343; c) V. A. Kabanov, A. B. Zevin, V. A. Izumrudov, T. K. Bronich, K. N. Bakeev, *Macromol. Chem. Suppl.* **1985**, *18*, 137.
- [10] The MF particles employed in this work were either 2.0 or 3.3 μm in diameter.

- [11] E. Donath, M. Breulmann, unpublished results.
- [12] The cross-sectional extension of the MF oligomers was determined by molecular dynamics simulations using the program DISCOVERY.
- [13] a) F. Caruso, E. Donath, H. Möhwald, *J. Phys. Chem. B*, **1998**, *102*, 2011; b) R. V. Klitzing, H. Möhwald, *Macromolecules* **1996**, *29*, 6901; c) R. V. Klitzing, H. Möhwald, *Langmuir* **1995**, *11*, 3554.
- [14] E. Donath, unpublished results.
- [15] V. I. Popov, A. A. Moiseeva, H. P. Zippel, *J. Hirnforsch.* **1994**, *35*, 415.

Cation-Induced Macroscopic Ordering of Non-Mesomorphic Modules—A New Application for Metallohelicates**

Abdelkrim El-ghayoury, Laurent Douce,* Antoine Skoulios, and Raymond Ziessel*

A major goal in the emerging field of supramolecular chemistry is to relate local molecular architecture to the macroscopic ordering of the system. Such large-scale organization is probably essential for the construction of practical devices from molecular units.^[1–3] Despite this realization, little genuine progress has been made with regard to the integration of local order into large-scale multidimensional arrays.^[4] In marked contrast, tremendous advances have been made in the construction of exotic supermolecules by stepwise accretion of simple building blocks.^[5, 6]

We now present a strategy that exploits a metallohelicate, assembled from non-mesomorphic but lipid-like organic strands, to promote formation of a liquid crystalline state at ambient temperature. The key element of this approach lies with the helix that provides rigidity and polarizability to counterbalance the flexibility and nonpolarizability of the paraffinic chains (amphiphilic character). This subtle balance between organized and chaotic domains controls the fate of the mesomorphic material. This system, the first liquid crystalline metallohelicate, illustrates the tremendous organ-

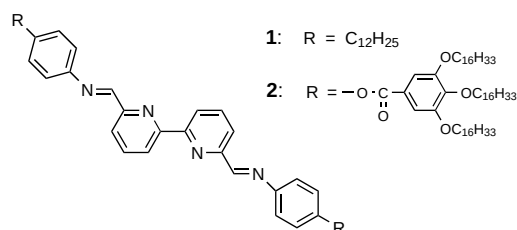
[*] Dr. L. Douce, Dr. R. Ziessel, A. El-ghayoury
Laboratoire de Chimie, d'Electronique
et de Photonique Moléculaires
Ecole Chimie, Polymères, Matériaux (ECPM)
UPRES-A 7008 au CNRS
1 rue Blaise Pascal, F-67008 Strasbourg Cedex (France)
Fax: (+33)388416825
E-mail: ziessel@chimie.u-strasbg.fr

Dr. A. Skoulios
Groupe des Matériaux Organiques
Institut de Physique et Chimie des Matériaux, UMR 7504 au CNRS
23 rue du Loess, F-67037 Strasbourg Cedex (France)

[**] We thank Sebastien Ottogalli, Engineer CNRS (UMR 7504) for his help with the art work, and Professor Anthony Harriman for helpful and fruitful discussions during this work and for his comments on the manuscript. This work was partially supported by the Centre National de la Recherche Scientifique (CNRS) and by the Engineering School of Chemistry (ECPM).

izational ability of copper(i) cations. It is, in fact, remarkable that the cation is able to induce order at both molecular and supramolecular levels, considering the large volume and structural disorder inherent in the nondiscoidal ligand. This point is well illustrated by comparison of the molar volumes calculated for the ligand ($V_m = 1356 \text{ cm}^3 \text{ mol}^{-1}$) and the cation ($V_m = 2.2 \text{ cm}^3 \text{ mol}^{-1}$).^[7]

Our recent discovery^[8] that a stable copper(i) helicate with bridging diiminobipyridine subunits is formed selectively and quantitatively by a cooperative process has prompted exploration of other polycatenar iminobipyridine ligands as building blocks. These nondiscoidal units are the key element by which the local molecular architecture (double helix) is incorporated into an organized macroscopic ensemble. Ligands **1** and **2** were synthesized in 90 and 99% yield, respectively, by reaction of 6,6'-diformyl-2,2'-bipyridine^[9] with



the corresponding aniline derivative^[10] in the presence of trace amounts of acid. As expected, both ligands self-associate in the presence of [Cu(CH₃CN)₄](BF₄)^[11] to afford deep-green, air-stable materials in excellent yield. These products were identified as the corresponding dinuclear copper(i) complexes with the formulae [Cu₂(**1**)₂](BF₄)₂ (**3**) and [Cu₂(**2**)₂](BF₄)₂ (**4**).

On the basis of mass spectrometry and elemental analysis, it was concluded that these dinuclear copper(i) complexes were not contaminated with mononuclear or slipped polymeric structures (**3**: positive ion FAB-MS: m/z 1611.8 [$M^+ - \text{BF}_4$], 1524.8 [$M^+ - 2\text{BF}_4$]; **4**: MALDI TOF-MS: 4388 [M], 4301 [$M - \text{BF}_4$], 4214 [$M - 2\text{BF}_4$]). The well-defined ¹H and ¹³C NMR spectra of both complexes (Figure 1) reveal that the ligands are equivalent and symmetric about the center. In both complexes, the imine H signal is shifted upfield by $\Delta\delta = 0.3$ due to direct involvement of the nitrogen atom in the coordination sphere of the copper ion. This situation was confirmed by solid-state and solution-phase FT-IR studies which showed a shift of the imino stretching vibration by about 40 cm⁻¹ versus the free ligand.

The most striking effect of complexation is found for the signals of atoms H3 and H3' (*ortho* to the exocyclic bipyridine C–C bond), which are shifted downfield by $\delta = 1.9$ in **3** and 1.3 in **4**. This shift arises because each ligand wraps around the two copper(i) cations, with the iminopyridine fragment chelated in a *cis* fashion and the two pyridine units twisted about the central exocyclic C–C bond (i.e., 40° in complex **3**^[12]). This process forces H3 and H3' to reside within the shielding region exerted by the iminophenyl ring of the complementary ligand. Less significant shifts are observed for other H atoms of the bipyridine and phenyl fragments attached to the imine. The unique mode of coordination of this α,α' -imino-substituted bipyridine is confirmed by the

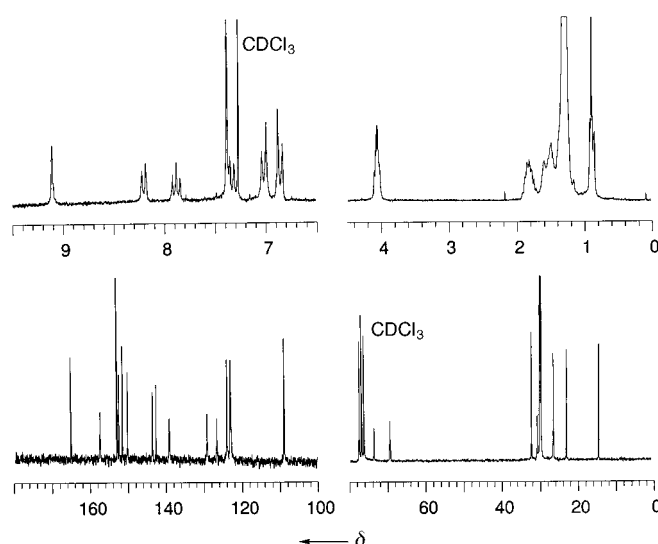


Figure 1. NMR spectra of complex **4** in CDCl₃. Top: ¹H NMR (200 MHz); bottom: ¹³C{¹H} NMR (50.3 MHz). The aromatic regions of the spectra (left) have been multiplied by four versus the aliphatic regions (right).

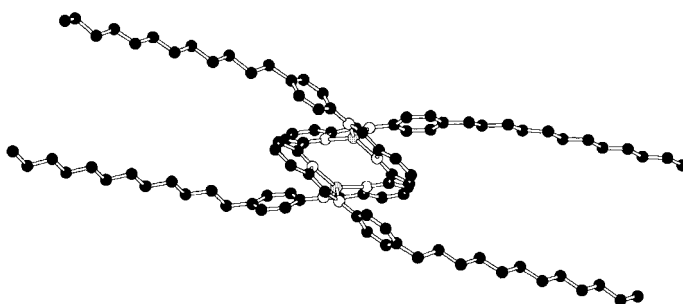
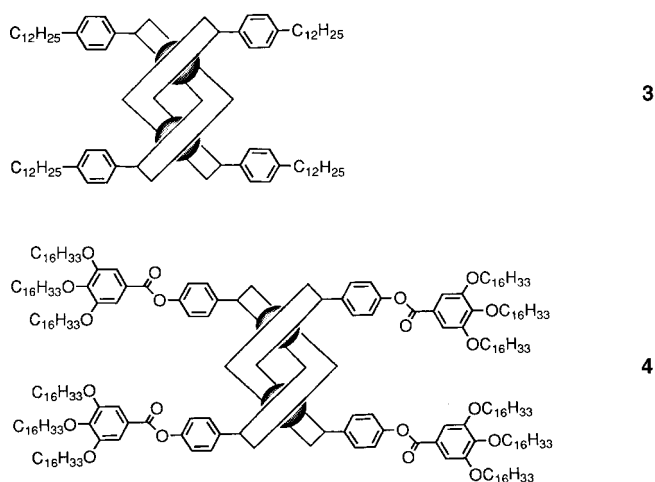


Figure 2. The structure of the cation in **3** in the crystal.

crystallographic structure of **3**^[12] (Figure 2), where the central unit is not chelating but adopts a bridging coordination mode (see structure formulae of **3** and **4**).



When observed under a polarizing optical microscope and analyzed by differential scanning calorimetry (DSC), ligands **1** and **2** and complex **3** appear non-mesomorphic with well-defined melting points. In **3** we assume that the balance between the aromatic core and the paraffinic chains is not

favorable for the formation of mesophases. The polymorphic behavior of complex **4** was investigated as a function of temperature by DSC and polarizing optical microscopy. The DSC thermograms were measured by heating and subsequent cooling over the range 0 to 200 °C and revealed the presence of two sharp peaks indicative of reversible first-order phase transitions. The peak at 25 °C ($\Delta H \approx 132 \text{ kJ mol}^{-1}$) is related to the appearance of a liquid crystalline phase, while the peak at 181 °C ($\Delta H \approx 3.1 \text{ kJ mol}^{-1}$) is due to melting into an isotropic liquid. The optical textures observed upon slow cooling of the isotropic melt (Figure 3, top) clearly show the existence of a

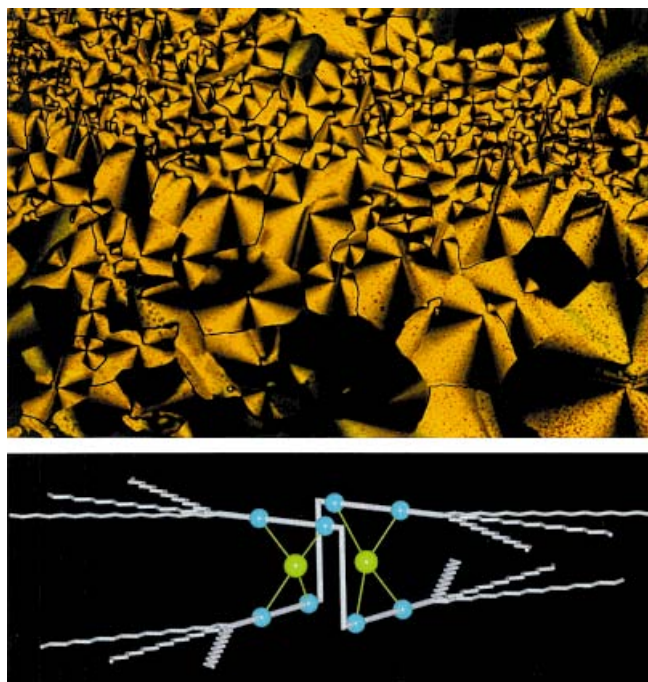
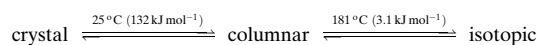


Figure 3. Top: Optical textures of complex **4** observed with a polarizing microscope on slow cooling from the isotropic melt: pseudo-focal-conic texture at 100 °C. Bottom: Schematic view of an isolated molecule of **4**. Nitrogen: blue, copper: green.

viscous columnar phase (appearance of a pseudo-focal-conic texture which turns into a classical texture). These observations may be summarized as follows:



The columnar nature of the liquid crystalline phase was confirmed by X-ray diffraction. The presence of a diffuse band at 4.6 Å (Figure 4) indicates that the alkyl chains adopt a liquidlike conformation. The diffuse band at 10 Å corresponds to the height of the rigid organometallic cores, as estimated by molecular modeling of the crystal packing and subsequently confirmed by crystallographic study of single crystals of complex **3** (Figure 2).^[12]

A schematic representation of the cation in **4** is given in the lower part of Figure 3. The cores are stacked on top of each other in a disordered fashion to form columns. However, the presence of two sharp reflections at 39.2 and 21.8 Å shows that, although disordered within the columns, the molecules are nevertheless arranged periodically at the macroscopic

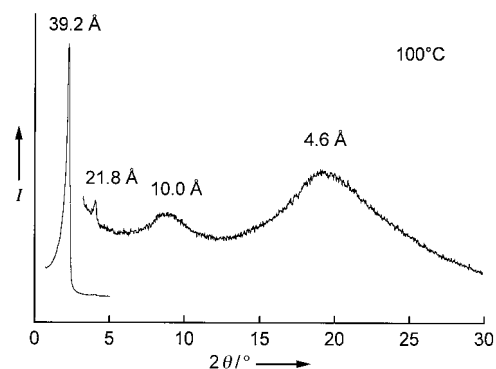
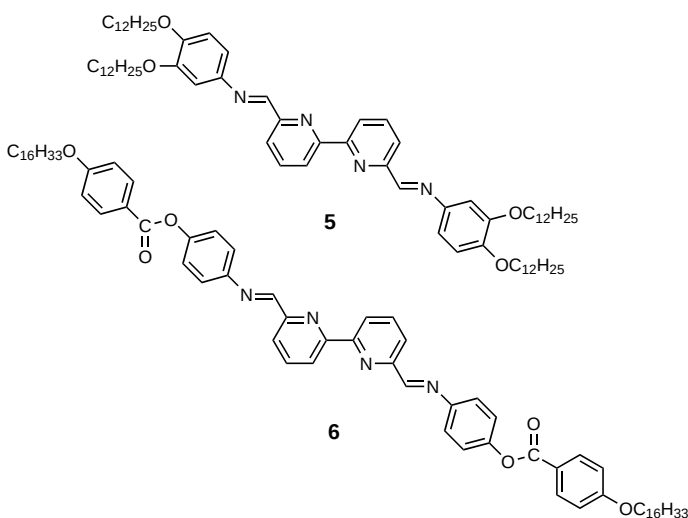


Figure 4. Typical X-ray diffraction patterns of **4** in the columnar phase at 100 °C. Intensity *I* in arbitrary units.

level. It is important to note that the measured Bragg spacings are in a noncrystallographic ratio ($\sqrt{3.2}$) which indicates the existence of a two-dimensional crystal lattice. The structure of the liquid crystalline phase appears, therefore, to consist of columns of rigid cores surrounded by molten alkyl chains and laterally packed in a two-dimensional lattice of rectangular or oblique symmetry. From the dimensions of the rigid organometallic cores ($8 \times 8 \times 10 \text{ Å}$; Figure 3, bottom), it is possible to calculate the area around the aromatic cores covered by the twelve alkyl chains of each complex molecule: $4 \times (8 \times 10) = 320 \text{ Å}^2$, which corresponds to a molecular area of $320/12 \approx 27 \text{ Å}^2$ per alkyl chain.

The realization that α, α' -diimino-substituted 2,2'-bipyridine nondiscoidal ligands form stable copper(I) helicates that display liquid crystalline behavior opens the door to several broad and fruitful areas of supramolecular chemistry. While numerous examples of copper(I) helicates are known, it has proved extremely difficult to assemble such structures into organized assemblies. It is necessary to select the number, length, and nature of the lipid-like chains with great care. In most cases non-mesomorphic metallohelicates are formed, and it is clear that there is a high barrier to arranging the metallohelicate into ordered columns (ligands **1**, **5**, and **6** were greatly inferior to **2**). Thermotropic liquid crystalline bipyridine ligands are known,^[13] but despite considerable effort expended on the development of bipyridine-based metal-



lomesogens only a few examples have been reported so far.^[14] In this respect, the onset of liquid crystalline behavior can be seen as a result of a fine balance between order (helix) and chaos (alkyl chains). Optimization of this balance will produce a low-temperature metallomesogen. As shown here and previously observed in many cases,^[2] the use of a discoidal ligand is not mandatory for the generation of columnar mesophases.

The initial step in the overall process is the formation of a stable metallohelicate, and is itself a challenge in view of the bulky alkyl chains that complicate the gathering of the ligands around the cations. The helix provides essential rigidity that favors subsequent stacking of the aromatic cores. While it is unclear if a helicate is a prerequisite for liquid crystalline behavior, it is clear that some kind of ordered central structure is essential for macroscopic ordering. The pivotal role of the central metal cation cannot be overstated in such systems. The combination of properties (color, polarizability, and magnetism) within the self-assembled supermolecule is quite unique and provides new opportunities for the future application of liquid crystals that are addressable by weak magnetic or optical fields. We are currently exploring the properties of other fascinating multinuclear complexes constructed with terpyridines, naphthyridines, pyridine-substituted diazines, pyrazines, and anthyridines to gain further insights into the chemistry and material science properties of these challenging systems.

Experimental Section

Ligand 2: A Schlenk tube was successively charged with 6,6'-diformyl-2,2'-bipyridine (0.015 g, 0.07 mmol), 4-(3,4,5-tri(hexadecyloxy)benzoyloxy)aniline (0.137 g, 0.14 mmol), EtOH (15 mL), and acetic acid (1 drop). During heating for 6 h at 80 °C, the ligand precipitated. After the reaction mixture was cooled to room temperature, the white solid was filtered off and washed with EtOH (3 × 15 mL). Yield: 0.143 g of **2** (99%). M.p. 102–104 °C; UV/Vis (CH₂Cl₂): λ_{max} (ϵ) = 228 (72400), 280 (54400), 301 nm (55200 M⁻¹ cm⁻¹); ¹H NMR (200.1 MHz, CDCl₃, 25 °C): δ = 8.76 (s, 2H; imine H), 8.62 (dd, ³J = 7.8 Hz, ⁴J = 1.1 Hz, 2H; H₃, H_{3'}), 8.31 (d, ³J = 6.7 Hz, 2H; H₅, H_{5'}), 8.00 (t, ³J = 7.7 Hz, 2H; H₄, H_{4'}), 7.43 (s, 4H), 7.34 (AB system, J_{AB} = 8.7 Hz, $\Delta\nu$ = 27.1 Hz, 8H), 4.07 (m, 12H; OCH₂), 1.81 (m, 12H; CH₂), 1.48 (m, 12H; CH₂), 1.27 (s, 144H; CH₃), 0.88 (t, ³J = 6.3 Hz, 18H; CH₃); IR (CaF₂ cell, CH₂Cl₂): $\tilde{\nu}$ = 2919 (s), 2849 (m), 1725 (m), 1629 (w), 1587 (w), 1498 (w), 1465 (w), 1432 (w), 1384 (w), 1334 (m), 1289 (w), 1196 (s), 1120 cm⁻¹ (s); positive ion FAB-MS (thioglycerol matrix): m/z (%): 2043(20) [M^+], 1801(7) [M^+ – OC₁₆H₃₃], 1560(27) [M^+ – 2OC₁₆H₃₃], 1202(15) [M^+ – OCOC₆H₂(sOC₁₆H₃₃)₃], 360(23) [M^+ – 2(OCOC₆H₂(OC₁₆H₃₃)₃); elemental analysis calcd for C₁₃₄H₂₁₈N₄O₁₀: C 78.69, H 10.74, N 2.74; found: C 78.51, H 10.46, N 2.64.

Helicate 4: A solution of [Cu(CH₃CN)₄]BF₄ (0.016 g, 0.051 mmol) in CH₃CN (10 mL) was transferred through a cannula to a stirred solution of **2** (0.100 g, 0.049 mmol) in CH₂Cl₂ (15 mL) at room temperature and under argon. During the addition, the color of the solution turned deep green, indicating fast Cu^I complexation. The mixture was heated at about 60 °C for 5 min and then stirred for 2 h at room temperature. The solution was filtered over celite and evaporated to dryness. The residue was recrystallized in CH₂Cl₂/Et₂O to give 0.087 g of **4** (81% yield). UV/Vis (CH₂Cl₂): λ_{max} (ϵ) = 227 (140800), 280 (96600), 314 (113300), 452 (sh, 5700), 600 nm (sh, 2200 M⁻¹ cm⁻¹); ¹H NMR (200.1 MHz, CDCl₃, 25 °C): δ = 9.11 (s, 4H; imine H), 8.20 (d, ³J = 7.5 Hz, 4H; H₅, H_{5'}), 7.88 (t, ³J = 7.8 Hz, 4H; H₄, H_{4'}), 7.38 (s, 8H), 7.33 (d, ³J = 7.8 Hz, 4H; H₃, H_{3'}), 6.93 (AB system, J_{AB} = 8.6 Hz, $\Delta\nu$ = 30.8 Hz, 16H), 4.07 (m, 24H; OCH₂), 1.81 (m, 24H; CH₂), 1.49 (m, 24H; CH₂), 1.26 (s, 288H; CH₂), 0.88 (m, 36H; CH₃); ¹³C{¹H} NMR (50.3 MHz, CDCl₃, 25 °C): δ = 165.3 (C=O), 157.6 (C=N), 153.1, 152.6, 151.7, 150.3, 143.7, 142.7, 139.2, 129.2, 124.0, 123.1, 122.9, 108.8, 77.0 (OCH₂),

69.5 (OCH₂), 31.9 (OCH₂CH₂), 30.4 (OCH₂CH₂), 29.7 (CH₂), 29.4 (CH₂), 26.1 (CH₂), 22.6 (CH₂), 14.0 (CH₃); IR (CaF₂ cell, CH₂Cl₂): $\tilde{\nu}$ = 3046 (w), 2926 (s), 2854 (m), 1729 (m), 1589 (w), 1499 (w), 1463 (w), 1429 (w), 1384 (w), 1336 (m), 1189 (s), 1062 cm⁻¹ (m); elemental analysis calcd for C₂₆₈H₄₃₆Bu₂Cu₂F₈N₈O₂₀: C 73.31, H 10.01, N 2.55; found: C 73.00, H 9.74, N 2.19.

Differential scanning calorimetry: Perkin-Elmer DSC 7, heating/cooling rate of 10 °C min⁻¹. Polarizing optical microscope: Leitz Orthoplan, Mettler FP 82 hot stage. X-ray diffraction: Guinier camera, Cu_{K α} radiation, powder samples in Lindemann capillaries, INSTEC hot stage, INEL CPS-120 detector.

Received: February 16, 1998 [Z11483IE]
German version: *Angew. Chem.* **1998**, *110*, 2327–2331

Keywords: copper • helical structures • metallomesogens • N ligands • supramolecular chemistry

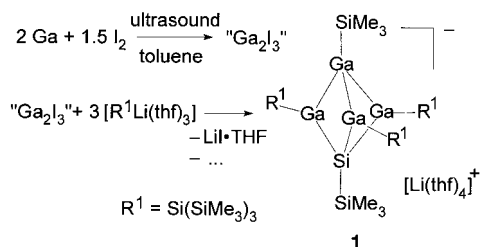
- [1] S. I. Stupp, V. LeBonheur, K. Walker, L. S. Li, K. E. Huggins, M. Keser, A. Amstutz, *Science* **1997**, *276*, 384.
- [2] R. Kleppinger, C. P. Lillya, C. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 4097, and references therein.
- [3] J. N. H. Reek, A. H. Priem, H. Engelkamp, A. E. Rowan, J. A. A. W. Elemans, R. J. M. Nolte, *J. Am. Chem. Soc.* **1997**, *119*, 9956.
- [4] J. L. Serrano, *Metallomesogens*, VCH, Weinheim, **1996**.
- [5] C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005.
- [6] J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, **1995**.
- [7] A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441.
- [8] R. Ziessel, A. Harriman, J. Suffert, M.-T. Youinou, A. De Cian, J. Fischer, *Angew. Chem.* **1997**, *109*, 2621; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2509.
- [9] J. E. Parks, B. E. Wagner, R. H. Holm, *J. Organomet. Chem.* **1973**, *56*, 53.
- [10] H.-T. Nguyen, C. Destrade, J. Malthête, *Adv. Mater.* **1997**, *9*, 375, and references therein.
- [11] B. J. Hathaway, D. G. Holah, J. D. Poslethwaite, *J. Chem. Soc.* **1961**, 3215.
- [12] Crystal data for **3**: C₉₆H₁₃₄N₈Cu₂ · 2BF₄ · H₂O (M_w = 1718.90), triclinic, space group $P\bar{1}$, a = 13.056(1), b = 15.378(1), c = 24.045(1) Å, α = 79.17(1), β = 84.83(1), γ = 88.42(1)°, V = 4725.5(6) Å³, Z = 2, M_{Ox} , number of measured data 17026, number of data with $I > 3\sigma(I)$ 9056, R = 0.059, R_w = 0.084; N. Kyritsakas, A. De Cian, J. Fischer, A. El-ghayoury, L. Douce, R. Ziessel, unpublished results.
- [13] K. Hanabusa, J.-I. Higashi, T. Koyama, H. Shirai, N. Hojo, A. Kurose, *Makromol. Chem.* **1989**, *190*, 1; T. Kuboki, K. Araki, M. Yamada, S. Shiraishi, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 948; L. Douce, R. Ziessel, R. Seghrouchni, A. Skoulios, E. Campillos, R. Deschenaux, *Liq. Cryst.* **1995**, *18*, 157; L. Douce, R. Ziessel, R. Seghrouchni, A. Skoulios, E. Campillos, R. Deschenaux, *Liq. Cryst.* **1996**, *20*, 235; A. El-ghayoury, L. Douce, R. Ziessel, R. Seghrouchni, A. Skoulios, *Liq. Cryst.* **1996**, *21*, 143; K. E. Rowe and D. W. Bruce, *Liq. Cryst.* **1996**, *20*, 183; A. R. A. Palmans, J. A. J. M. Vekemans, E. E. Havinga, E. W. Meijer, *Angew. Chem.* **1997**, *109*, 2763; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2648.
- [14] K. E. Rowe, D. W. Bruce, *J. Chem. Soc. Dalton Trans.* **1996**, 3913; A. El-ghayoury, L. Douce, A. Skoulios, R. Ziessel, *Angew. Chem.* **1998**, *37*, 1303; *Angew. Chem. Int. Ed.* **1998**, *37*, 1255.

A Silatetragallane—Classical Heterobicyclopentane or *closo*-Polyhedron?

Gerald Linti,* Wolfgang Köstler, Holger Piotrowski, and Alexander Rodig

The cluster chemistry of gallium has received increasing attention during the last few years. Bulky silyl groups have proved particularly favorable for stabilizing cluster compounds, and their application has enabled the synthesis of electron-precise oligogallanes such as R_4Ga_2 ^[1] and gallium clusters such as $(R^1GaCl)_4$ ^[2] ($R^1 = Si(SiMe_3)_3$) and $\{R^1Ga[R^1Ga(I)]_3\}^-$ ^[3] as well as the electron-deficient clusters $(R_4Ga)_4$ ($R = C(SiMe_3)_3$,^[4a] $Si(SiMe_3)_3$,^[4b] and $SiBu_3$)^[4c] and $[R_6Ga_9]^-$.^[3] Among other known oligogallanes are $[(tBu_3Si)_2GaGaSi(tBu_3)]^+$,^[5] $M_2Ga_3Ar_3$ ($M = Na, K$; $Ar = 2,6$ -dimesitylphenyl),^[6] $Ga_3I_5(PEt_3)_3$,^[7] $[Cl_2Ga(OEt_2)]_3[ClGa(OEt_2)_2]^-$,^[8a] and $Ga_8I_8(PEt_3)_6$.^[8b] Cp^*Ga , though monomeric in solution, also forms hexameric aggregates in the crystal.^[9] In comparison with the rich chemistry of borane clusters this seems to be very limited, but also shows distinct differences. In spite of the wealth of heteroboranes, silaboranes have only recently been discovered and are confined to a few icosahedral clusters.^[10] Herein, we describe the first example of a silagallane, that is a cluster with a III/IV framework.

The ultrasonication of gallium with 1.5 equivalents of iodine in toluene^[3, 11] yields insoluble gallium subhalides together with toluene-soluble $Ga[GaI_4]$. This is also achieved with a Ga/I mixture in a 1:1 ratio, if the sonication is interrupted before the reaction is complete. Addition of tris(trimethylsilyl)silyllithium $\cdot 3$ THF to these gallium halide mixtures affords in a complex reaction the anionic gallium cluster **1** (Scheme 1), which is isolated as black-violet crystals.



Scheme 1.

The X-ray structure analysis of **1**^[12] shows a C_3 -symmetric clusteranion (Figure 1) with a trigonal-bipyramidal Ga_4Si backbone. The counterion is $[Li(thf)_4]^+$. The gallium atoms in

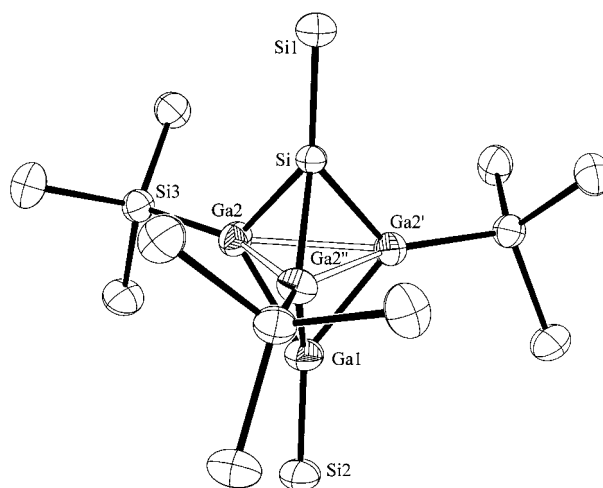


Figure 1. Structure of **1** in the crystal. Methyl groups are omitted in the drawing for clarity. Selected distances [pm] and bond angles $^\circ$: $Ga1-Ga2$ 244.0(1), $Ga2-Ga2'$ 279.0(1), $Ga2-Si$ 240.2(2), $Si-Si1$ 227.1(4), $Ga1-Si2$ 233.8(3), $Ga2-Si3$ 237.6(2); $Ga2-Ga1-Ga2'$ 69.74(4), $Ga1-Ga2-Si$ 96.58(4), $Ga2-Si-Ga2'$ 71.00(6), $Si2-Ga1-Ga2$ 138.69(2), $Si3-Ga2-Si$ 128.73(6), $Si3-Ga2-Ga1$ 134.64(5), $Si3-Ga2-Ga2'$ 151.58(6), $Si3-Ga2-Ga2''$ 148.08(6).

the equatorial plane bear hypersilyl groups, the gallium atom and the silicon atom in axial positions trimethylsilyl groups. The $Ga-SiMe_3$ bond ($d_{Ga-Si} = 233.8(3)$ pm) is 4 pm shorter than the bond between gallium and the hypersilyl group. A similar difference is also observed in the only other structurally characterized compound with a $Ga-SiMe_3$ unit, that is the four-membered ring heterocyclic anion $[Ga_3SiR_3^-(SiMe_3)_3]^-$ ($R^1 = Si(SiMe_3)_3$).^[13] The $Ga-Si$ distances of the silicon atom in the cluster (240.2(2) pm) are comparable to those of the ring-silicon atoms in $[R_2GaSi(SiMe_3)_2]_2$.^[13] The $Ga-Ga$ distances to the apical gallium atom are 244.0 pm, and thus 14 pm shorter than in R_4Ga_4 (258.2 pm)^[4b] and also markedly shorter than in $R_4Ga_4Cl_4$ (250.5 pm)^[2] or in $R^1Ga[R^1Ga(I)]_3$ (253.3 pm).^[3] The $Ga-Ga$ distances of 279.0 pm in the equatorial plane are distinctly longer, but are still in a range, where $Ga-Ga$ interactions are likely. In $[(CO)_3Fe(GaR^1)_3Fe(CO)_3]$, which also has a trigonal-bipyramidal framework, but is described without $Ga-Ga$ interactions, the gallium atoms are 328.9 pm apart;^[14] that is 50 pm more than in **1**. A consequence of the smaller equatorial $Ga-Ga$ distances are very acute bond angles at the axial, distorted tetrahedrally coordinated cluster atoms ($Ga2-Si-Ga2'$ 71.00(6)°, and $Ga2-Ga1-Ga2a$: 69.74(4)°). The $Si-Ga2-Ga1$ angle (96.58(4)°) is 22° wider than the $Fe-Ga-Fe$ angle in the above-mentioned $GaFe$ cluster. Six cluster bonding electron pairs are available for the Ga_4Si core of **1**, thus this cluster may be described as electron-precise with six 2e2c bonds (see **A** in Figure 2). The short equatorial $Ga-Ga$ distances are indicative of the *closo* cluster **B** with three 2e2c and three 2e3c bonds (Figure 2).

Density functional calculations^[15] were performed on $R'Ga(R_3Ga_3)SiR'$ (Table 1) to gain a better insight. All structures were optimized in point group C_3 . The substituents evidently have a negligible influence on the Ga_4Si core. Shared electron numbers (SEN) obtained from Ahlrichs-Heinzmann population analysis^[16] reveal only weak two-

[*] Dr. G. Linti, Dipl.-Chem. W. Köstler, Dipl.-Chem. H. Piotrowski, Dipl.-Chem. A. Rodig
Institut für Anorganische Chemie der Universität
Engesserstrasse, Geb. 30.45, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4854
E-mail: linti@achpc9.chemie.uni-karlsruhe.de

[**] On the chemistry of gallium, Part 15: This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. Dr. P. Klüfers for diffractometer time. Part 14: Ref. [13].

Table 1. Results of RI-DFT calculations (BP86-functional, def-SV(P)-base; distances in pm, q = shared electron number).

	Ga–Si _{ap}	Ga _{eq} –Ga _{ap}	Ga _{eq} –Ga _{eq}	$q_{\text{Ga-Si}}$	$q_{\text{Ga-Ga}_{\text{eq}}}$	$q_{\text{Ga}_{\text{eq}}-\text{Ga}_{\text{eq}}}$	$q_{\text{Ga-Ga-Ga}}$	$q_{\text{Ga-Ga-Si}}$
[R'Ga(RGa) ₃ SiR'] [–] in C ₃								
R	R'							
H	H	236.1	241.0	286.7	1.52	1.65	0.70	0.35
SiMe ₃	SiMe ₃	236.9	242.1	280.3	1.46	1.63	0.76	0.35
Si(SiMe ₃) ₃	SiMe ₃	238.7	244.0	284.2	–	–	–	–
NH ₂	H	238.3	242.6	294.1	1.47	1.60	0.63	0.36
HGa(H ₂ Ge) ₃ SiH		235.7 ^{GeSi}	245.7 ^{GeGa}	325.8 ^{GeGe}	1.30 ^{GeSi}	1.28 ^{GaGe}	0.06 ^{GeGe}	0.01 ^{GaGe2}
[(CO) ₃ Fe] ₂ (GaH) ₃		236.2 ^{GaFe}	–	323.3	–	–	0.40	–
<i>tbp</i> [H ₅ Ga ₃] ^{2–}	–	–	243.8	281.5	–	1.67	0.84	0.37
<i>okt</i> [H ₆ Ga ₆] ^{2–}	–	–	250.4	250.4	–	1.45	1.45	0.45
1,5-(HSi) ₂ (GaH) ₃	239.5	–	–	254.1	1.29	–	1.15	–
T _d -Ga ₄ H ₄	–	249.0	–	–	–	1.40	–	0.36

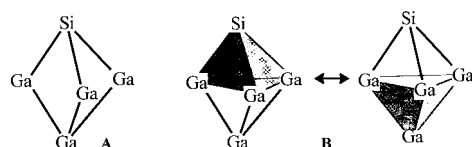


Figure 2. Classical (A) and *closo*-cluster representation (B) for a Ga₄Si cluster.

center interactions in the equatorial plane compared to Ga–Ga single bonds. But, those and the three-center interactions for the Ga₂Si and Ga₃ facets are markedly larger than that calculated for comparable electron-precise compounds. Similar three-center SEN (0.36) are calculated for borane clusters like H₃B₃C₂. Very recent theoretical^[17] and experimental studies^[18] on related trigonal-bipyramidal boron, aluminum, and indium compounds support the description as *closo* cluster compounds, although this is discussed controversially. As in **1**, these compounds have long distances between the equatorial atoms and short ones to the axial atoms. For example, in [(Me₃Si)₃CIn]₂S the axial In–In distances are 55 pm shorter than the equatorial ones.^[18c]

With the characterization of **1** we present a *closo*-silagallane that promises a rich chemistry. The cleavage of the Ga–Ga bonds with iodine, for example, affords (Me₃Si)Si(GaR^I)₃. This trifunctional building block, which is isoelectronic to {R^IGa[GaR^I(I)]₃}[–], might provide access to novel cage molecules.

Experimental Section

1: Gallium (0.38 g, 5.3 mmol) and iodine (1.01 g, 8.0 mmol) in toluene (20 mL) were treated in a ultrasonic bath until the mixture had reached a pale yellow to yellow-greenish color. A solution of LiSi(SiMe₃)₃·3 THF^[19] (3.78 g, 8.0 mmol) in toluene (40 mL) was added dropwise to this solution at –78 °C. After the mixture had been allowed to warm up slowly to ambient temperature, it was stirred for an additional 12 h. After concentration of the reaction solution to dryness, the residue was extracted with pentane (50 mL). After separation of colorless to yellow crystallizing by-products (LiI·THF, I₃GaSi(SiMe₃)₃·Li(THF)_{2,3} and further not yet characterized compounds) from the violet-red solution, **1** (0.36 g, 19% with respect to Ga) precipitated as black hexagonal prismatic crystals (deep violet in thin layers). Once crystallized, **1** was no longer soluble in pentane; with THF stable, intense violet solutions of **1** were obtained. ¹H NMR (300 MHz, [D₈]THF, 300 K): δ = 0.51, 0.39 (9H each, SiMe₃), 0.17 (81H, Si(SiMe₃)₃); ¹³C NMR ([D₈]THF, 300 K): δ = 6.9, 6.2 (SiMe₃), 3.8 (Si(SiMe₃)₃); ²⁹Si NMR ([D₈]THF, 300 K): δ = –1.8 (SiSiMe₃), –5.5 (GaSiMe₃), –9.1 (Si(SiMe₃)₃), –60.2 (SiSiMe₃), –127.1 (Si(SiMe₃)₃); MS (70 eV, EI, ⁶⁹Ga): m/z (%): 1191 (15) [Ga₄Si[Si(SiMe₃)₃]₃(SiMe₃)₂]⁺ = [A]⁺,

1118 (77) [A–SiMe₃]⁺, 1045 (35) [A–2SiMe₃]⁺, 944 (82) [A–Si(SiMe₃)₃]⁺, 871 (81) [A–Si(SiMe₃)₄]⁺, 729 (80) [Ga₃Si[Si(SiMe₃)₃]₂]⁺, 389 (100) [Ga[Si(SiMe₃)₃](SiMe₃)]⁺. IR (KBr): $\tilde{\nu}$ [cm^{–1}] = 2925, 2855, 1592, 1461, 1378, 1240, 1091, 1042, 833, 735, 682, 623; correct elemental analysis.

Received: March 2, 1998 [Z11535IE]
German version: *Angew. Chem.* **1998**, *110*, 2331–2333

Keywords: clusters • density functional calculations • gallium • silicon • structure elucidation

- a) W. Uhl, *Angew. Chem.* **1993**, *105*, 1449–1461; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1386–1397; b) C. Dohmeier, D. Loos, H. Schnöckel, *ibid.* **1996**, *108*, 141–161 and **1996**, *35*, 129–149.
- G. Linti, W. Köstler, *Angew. Chem.* **1996**, *108*, 593–595; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 550–552.
- G. Linti, W. Köstler, *Angew. Chem.* **1997**, *109*, 2758–2760; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2644–2646.
- a) W. Uhl, W. Hiller, M. Layh, W. Schwarz, *Angew. Chem.* **1992**, *104*, 1378–1380; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1364–1367; b) G. Linti, *J. Organomet. Chem.* **1996**, *520*, 107–113; c) N. Wiberg, *Coord. Chem. Rev.* **1997**, *163*, 217–252.
- N. Wiberg, K. Amelunxen, H. Nöth, H. Schwenk, W. Kaim, A. Klein, T. Scheiring, *Angew. Chem.* **1997**, *109*, 1258–1261; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1213–1215.
- a) X.-W. Li, W. T. Pennington, G. H. Robinson, *J. Am. Chem. Soc.* **1995**, *117*, 7578–7580; b) X.-W. Li, Y. Xie, P. R. Schreiner, K. D. Gripper, R. C. Crittendon, C. F. Campana, H. F. Schaefer, G. H. Robinson, *Organometallics* **1996**, *15*, 3798–3803.
- A. Schnepf, C. Doriat, E. Möllhausen, H. Schnöckel, *Chem. Commun.* **1997**, 2111–2112.
- a) D. Loos, H. Schnöckel, D. Fenske, *Angew. Chem.* **1993**, *105*, 1124–1125; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1059–1060; b) C. U. Doriat, E. Baum, A. Ecker, H. Schnöckel, *ibid.* **1997**, *109*, 2057–2059 and **1997**, *36*, 1969–1971.
- D. Loos, E. Baum, A. Ecker, H. Schnöckel, A. J. Downs, *Angew. Chem.* **1997**, *109*, 894–896; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 860–862.
- z. B. a) D. Seyferth, K. Büchner, W. S. Rees, Jr., W. M. Davis, *Angew. Chem.* **1990**, *102*, 911–913; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 918–920; b) L. Wesemann, U. Englert, *ibid.* **1996**, *108*, 586–587 and **1996**, *35*, 527.
- Analogous to the preparation of GaI: M. L. H. Green, P. Mountford, G. J. Smout, S. R. Speel, *Polyhedron* **1990**, *9*, 2763–2765.
- Crystal structure analysis of **1**: STOE IPDS, MoK α radiation, structure solved by direct methods, and full-matrix least-squares refinement against F², hydrogen atoms were included as riding model with Siemens SHELXTL 5.0 (PC) and SHELXL97. Crystal dimensions: 0.15 × 0.15 × 0.10 mm, trigonal, space group P31c (no. 159), a , b = 1568.0(2), c = 1956.0(2) pm, V = 4.1650(8) nm³, Z = 2, ρ_{calcd} = 1.189 g cm^{–3}, μ = 1.528 mm^{–1}, $F(000)$ = 1588, 19740 measured reflections in 2θ = 5–52°, 5381 [with $F > 4\sigma(F)$: 3915] independent

reflections, numerical absorption correction (min./max. transmission: 0.546/0.664), 256 parameters. $R_1 = 0.042$, $wR_2 = 0.122$ (all data), max. residual electron density 0.64 e Å⁻³. In the refinement a merohedral twinning from 6/*m* into 6/*mmm* with volume fractions of 91:9 was considered. One THF molecule of the [Li(thf)₄]⁺ ion is disordered over a C₃ axis. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101051. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [13] G. Linti, W. Köstler, A. Rodig, *Eur. J. Inorg. Chem.* **1998**, 745, 749.
 [14] G. Linti, W. Köstler, *Chem. Eur. J.* **1998**, 4, 942–949.
 [15] RI-DFT calculations with program package TURBOMOLE. All distances were multiplied by 0.97 to fit with experimental data of **1**: R. Ahlrichs, Universität Karlsruhe; K. Eichkorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chem. Phys. Lett.* **1995**, 240, 283.
 [16] a) E. R. Davidson, *J. Chem. Phys.* **1967**, 46, 3320; b) K. R. Roby, *Molec. Phys.* **1974**, 27, 81; c) R. Heinzmann, R. Ahlrichs, *Theoret. Chim. Acta* **1976**, 42, 33.
 [17] P. von R. Schleyer, G. Subramanian, A. Dransfeld, *J. Am. Chem. Soc.* **1996**, 118, 9988–9989.
 [18] a) [As₂(AlCp*)₃]: C. K. F. von Hänisch, C. Üffing, M. A. Junker, A. Ecker, B. O. Kneisel, H. Schnöckel, *Angew. Chem.* **1996**, 108, 3003–3005; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2875–2877; b) Et₃B₃C₂: M. Antipin, R. Boese, D. Bläser, A. Maulitz, *J. Am. Chem. Soc.* **1997**, 119, 326–333; c) [(Me₃Si)₃CIn]₄S: W. Uhl, R. Graupner, W. Hiller, M. Neumayer, *Angew. Chem.* **1997**, 109, 62–64; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 62–64.
 [19] a) H. Gilman, C. L. Smith, *J. Organomet. Chem.* **1968**, 14, 91; b) G. Gutekunst, A. G. Brook, *ibid.* **1982**, 225, 1; c) A. Heine, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, *Inorg. Chem.* **1993**, 32, 2694–2698.

Olefin Epoxidation by Methyltrioxorhenium: A Density Functional Study on Energetics and Mechanisms**

Philip Gisdakis, Serge Antonczak, Sibylle Köstlmeier,
Wolfgang A. Herrmann, and Notker Rösch*

Oxygen transfer reactions mediated by transition metals, such as olefin epoxidation^[1] and dihydroxylation,^[2] are currently attracting much interest from both experimentalists and theoreticians. Many investigations, several of them of computational thrust, have unraveled details of olefin dihydroxylation as catalyzed by oxo complexes of the type MO₄ (M = Os, Ru).^[3] Extensive experimental work has been

devoted to the structurally similar compound methyltrioxorhenium (MTO) which has proven to be a highly efficient olefin epoxidation catalyst in the presence of hydrogen peroxide.^[4] MTO reacts with H₂O₂ resulting in mono- and bisperoxo compounds; an additional aquo ligand has been found to stabilize the latter complex.^[5] Recent experimental work shows the possibility for olefin epoxidation also by inorganic compounds like ReO₄⁻, even without explicit use of H₂O₂.^[6] Herrmann et al.^[5] and Espenson et al.^[7] have proposed reaction mechanisms for epoxidation by MTO-related complexes that involve differently oxygenated and hydrated forms of these catalysts. Also conceivable are processes in which hydroperoxo species participate.^[8] However, in contrast to dihydroxylation by oxo complexes,^[3] quite a few details of the reaction mechanism involving peroxo complexes remain to be clarified. Previous computational studies focused on structural aspects of MTO-related oxo complexes.^[9] Here, we use density functional (DF) calculations^[10, 11] to analyze structural and energetic properties of various mono-, bis-, and hydroperoxo derivatives of MTO and to estimate the activation barriers of the corresponding oxygen-transfer reactions.

We start by considering various rhenium–oxo and -peroxo complexes: MTO (**1**) as well as the corresponding monoperoxo (**2**) and bisperoxo (**3**) complexes, each of them in free (**A**) and monohydrated (**B**) form (Figure 1). The water ligand of

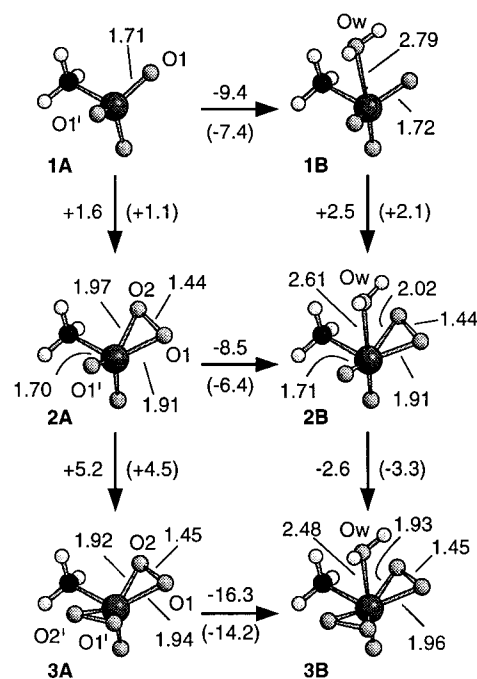


Figure 1. Optimized structures of **1A** and the corresponding monoperoxo (**2A**) and bisperoxo complexes (**3A**) as well as the mono-hydrated complexes **1B**, **2B**, and **3B**. Bond lengths in Å, energy and enthalpy (in parentheses) changes of peroxidation (columns) and hydration (rows) in kcal mol⁻¹. Experimental bond lengths for **3B**:^[5] Re–O1 1.91, Re–O2 1.90, O1–O2 1.47, Re–Ow 2.25.

complexes **B** was added in *cis* position to the methyl group, as suggested by an X-ray structure analysis for the bisperoxo complex.^[5] A second water molecule in *trans* position is

[*] Prof. Dr. N. Rösch, Dipl.-Chem. P. Gisdakis, Dr. S. Antonczak, Dr. S. Köstlmeier
 Lehrstuhl für Theoretische Chemie
 der Technischen Universität München
 D-85747 Garching (Germany)
 Fax: (+49) 89-289-13622
 E-mail: roesch@theochem.tu-muenchen.de
 Prof. Dr. W. A. Herrmann
 Anorganisch-chemisches Institut der Technischen Universität München (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, Bayerischer Forschungsverbund Katalyse (FORKAT), the German Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (no. 03D0050B), and the Fonds der Chemischen Industrie.

reflections, numerical absorption correction (min./max. transmission: 0.546/0.664), 256 parameters. $R_1 = 0.042$, $wR_2 = 0.122$ (all data), max. residual electron density 0.64 e Å⁻³. In the refinement a merohedral twinning from 6/*m* into 6/*mmm* with volume fractions of 91:9 was considered. One THF molecule of the [Li(thf)₄]⁺ ion is disordered over a C₃ axis. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101051. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [13] G. Linti, W. Köstler, A. Rodig, *Eur. J. Inorg. Chem.* **1998**, 745, 749.
 [14] G. Linti, W. Köstler, *Chem. Eur. J.* **1998**, 4, 942–949.
 [15] RI-DFT calculations with program package TURBOMOLE. All distances were multiplied by 0.97 to fit with experimental data of **1**: R. Ahlrichs, Universität Karlsruhe; K. Eichkorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chem. Phys. Lett.* **1995**, 240, 283.
 [16] a) E. R. Davidson, *J. Chem. Phys.* **1967**, 46, 3320; b) K. R. Roby, *Molec. Phys.* **1974**, 27, 81; c) R. Heinzmann, R. Ahlrichs, *Theoret. Chim. Acta* **1976**, 42, 33.
 [17] P. von R. Schleyer, G. Subramanian, A. Dransfeld, *J. Am. Chem. Soc.* **1996**, 118, 9988–9989.
 [18] a) [As₂(AlCp*)₂]: C. K. F. von Hänisch, C. Üffing, M. A. Junker, A. Ecker, B. O. Kneisel, H. Schnöckel, *Angew. Chem.* **1996**, 108, 3003–3005; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2875–2877; b) Et₃B₃C₂: M. Antipin, R. Boese, D. Bläser, A. Maulitz, *J. Am. Chem. Soc.* **1997**, 119, 326–333; c) [(Me₃Si)₃CIn]₄S: W. Uhl, R. Graupner, W. Hiller, M. Neumayer, *Angew. Chem.* **1997**, 109, 62–64; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 62–64.
 [19] a) H. Gilman, C. L. Smith, *J. Organomet. Chem.* **1968**, 14, 91; b) G. Gutekunst, A. G. Brook, *ibid.* **1982**, 225, 1; c) A. Heine, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, *Inorg. Chem.* **1993**, 32, 2694–2698.

Olefin Epoxidation by Methyltrioxorhenium: A Density Functional Study on Energetics and Mechanisms**

Philip Gisdakis, Serge Antonczak, Sibylle Köstlmeier,
Wolfgang A. Herrmann, and Notker Rösch*

Oxygen transfer reactions mediated by transition metals, such as olefin epoxidation^[1] and dihydroxylation,^[2] are currently attracting much interest from both experimentalists and theoreticians. Many investigations, several of them of computational thrust, have unraveled details of olefin dihydroxylation as catalyzed by oxo complexes of the type MO₄ (M = Os, Ru).^[3] Extensive experimental work has been

devoted to the structurally similar compound methyltrioxorhenium (MTO) which has proven to be a highly efficient olefin epoxidation catalyst in the presence of hydrogen peroxide.^[4] MTO reacts with H₂O₂ resulting in mono- and bisperoxo compounds; an additional aquo ligand has been found to stabilize the latter complex.^[5] Recent experimental work shows the possibility for olefin epoxidation also by inorganic compounds like ReO₄⁻, even without explicit use of H₂O₂.^[6] Herrmann et al.^[5] and Espenson et al.^[7] have proposed reaction mechanisms for epoxidation by MTO-related complexes that involve differently oxygenated and hydrated forms of these catalysts. Also conceivable are processes in which hydroperoxo species participate.^[8] However, in contrast to dihydroxylation by oxo complexes,^[3] quite a few details of the reaction mechanism involving peroxo complexes remain to be clarified. Previous computational studies focused on structural aspects of MTO-related oxo complexes.^[9] Here, we use density functional (DF) calculations^[10, 11] to analyze structural and energetic properties of various mono-, bis-, and hydroperoxo derivatives of MTO and to estimate the activation barriers of the corresponding oxygen-transfer reactions.

We start by considering various rhenium–oxo and -peroxo complexes: MTO (**1**) as well as the corresponding monoperoxo (**2**) and bisperoxo (**3**) complexes, each of them in free (**A**) and monohydrated (**B**) form (Figure 1). The water ligand of

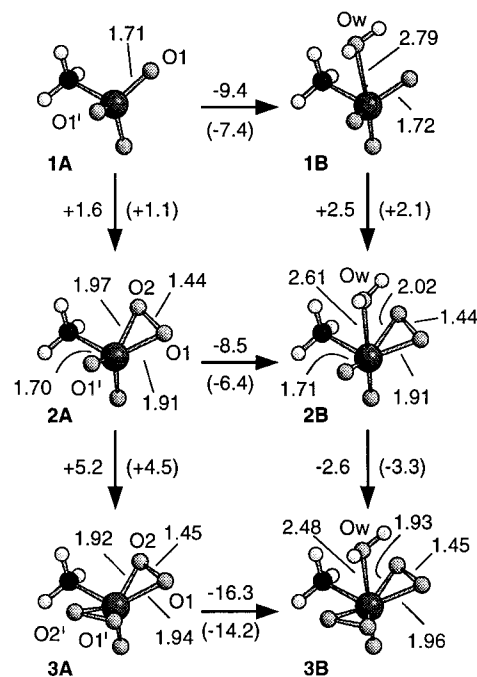


Figure 1. Optimized structures of **1A** and the corresponding monoperoxo (**2A**) and bisperoxo complexes (**3A**) as well as the mono-hydrated complexes **1B**, **2B**, and **3B**. Bond lengths in Å, energy and enthalpy (in parentheses) changes of peroxidation (columns) and hydration (rows) in kcal mol⁻¹. Experimental bond lengths for **3B**:^[5] Re–O1 1.91, Re–O2 1.90, O1–O2 1.47, Re–Ow 2.25.

complexes **B** was added in *cis* position to the methyl group, as suggested by an X-ray structure analysis for the bisperoxo complex.^[5] A second water molecule in *trans* position is

[*] Prof. Dr. N. Rösch, Dipl.-Chem. P. Gisdakis, Dr. S. Antonczak, Dr. S. Köstlmeier
 Lehrstuhl für Theoretische Chemie
 der Technischen Universität München
 D-85747 Garching (Germany)
 Fax: (+49) 89-289-13622
 E-mail: roesch@theochem.tu-muenchen.de
 Prof. Dr. W. A. Herrmann
 Anorganisch-chemisches Institut der Technischen Universität München (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, Bayerischer Forschungsverbund Katalyse (FORKAT), the German Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (no. 03D0050B), and the Fonds der Chemischen Industrie.

calculated to be weaker bound in the pertinent complexes of **2** and **3** (not shown in Figure 1). Furthermore, a water ligand in **1** in *trans* position has a slightly shorter bond length to the metal center, but essentially the same binding energy as one in *cis* position. To facilitate comparison, we discuss in the following only model structures with the aquo ligand in *cis* position. As expected for a Re center with strong Lewis acidity,^[16] hydration leads to significant stabilization, yielding an important contribution to the energy of MTO peroxidation (Figure 1). The hydration energies for MTO **1A** and the monoperoxo complex **2A** are similar and much closer to each other than that of the bisperoxo complex **3A**, which is especially large (-16.3 kcal mol⁻¹). This latter finding underlines the particular stability of complex **3B** for which an X-ray structure is available.^[5] Agreement between calculated and experimental^[5] geometries of **3B** is very satisfactory; the bond length deviations are, in general, at most 0.04 Å. The Re–Ow bond length is an exception (exp. 2.25 Å,^[5] calc. 2.48 Å); this deviation can be rationalized by a co-crystallized ether molecule.^[5] If this crystal environment effect is modeled by two dimethyl ether molecules that form hydrogen bonds with the coordinated water, the calculated value of the Re–Ow bond length reduces to 2.34 Å (exp. 2.25 Å^[5]). The peroxy groups are asymmetrically bound to the rhenium center; the tilting of the peroxy ligands relative to the “front” and “back” side (that is, the side that is furthest from and nearest to the methyl ligand, respectively) is different in complexes **2** and **3** (cf. bond lengths Re–O1 and Re–O2, Figure 1).

MTO is catalytically active in the presence of H₂O₂.^[5, 7] Therefore, we studied olefin epoxidation by the unsolvated (**2A**, **3A**) and monosolvated peroxy complexes (**2B** and **3B**), and characterized transition states^[17] for various mechanisms (Figure 2). Direct oxygen transfer to the olefin, in spiro fashion,^[18] as all located transition states showed (see below), may occur when the olefin double bond directly attacks the peroxy group O1–O2 either from the front (O1, “spiro”, **S**) or back (O2, “back-spiro”, **BS**). Insertion (**I**) via a [2+2]-like arrangement^[19] leads to a five-membered ring intermediate involving the metal center and a peroxy ligand (Figure 2); the epoxide is extruded from the complex via a second transition state (not discussed subsequently because the corresponding first step is energetically unfavorable compared to the spiro processes). In the calculations no precoordination^[19] of the olefin to the Re center was found for this reaction. Furthermore, we located five transition states^[17] with spiro structures for attacks on the hydroperoxo derivative **4** (Scheme 1), which can be formally derived from **3B** by proton transfer from the aquo ligand to a peroxy group. With the OOH and OH groups stabilized by an interligand hydrogen bond, **4** is about 10 kcal mol⁻¹ higher in energy than **3B**. An olefin attack at the β-O atom of the hydroperoxo group may be followed by proton transfer to three different groups (oxo, hydroxo, or peroxy, Scheme 1 c). Attack at the α-O center may occur from either front or back (Scheme 1 a, b), accompanied by the back transfer of the OH group to the Re center. Since the activation barriers of hydroperoxo processes are calculated to be rather high ($\Delta E^\ddagger = 29.8$ kcal mol⁻¹ and higher, oxygen transfer to the olefin, Scheme 1 a), we refrain from further discussing these transition states.

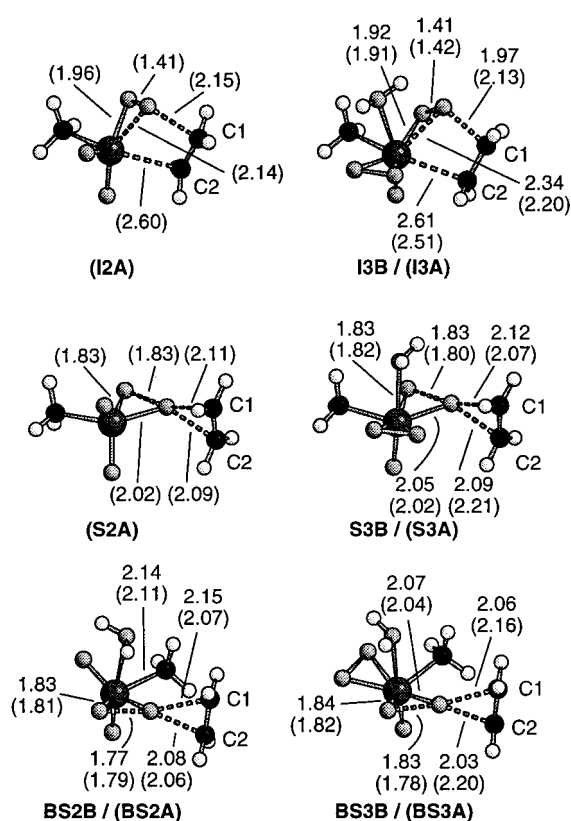
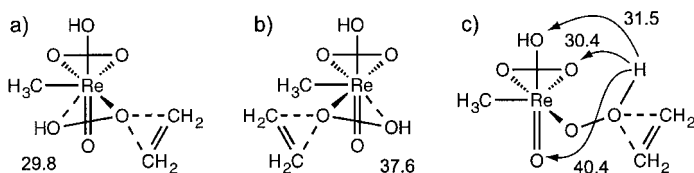


Figure 2. Various transition state structures for ethylene epoxidation by MTO-derived peroxy complexes (bond lengths in Å): spiro (**S**), back-spiro (**BS**), and insertion (**I**) processes involving complexes **2B** and **3B** (non-hydrated transition states **2A** and **3A** in parentheses).



Scheme 1. Transition states for the ethylene epoxidation by the hydroperoxo complex **4** (in various conformations): attack of the α-O center from the “front” (a) and the “back” (b) as well as β-O approach (c) with subsequent H transfer to oxo, peroxy, or hydroxo ligands. Activation barriers (in kcal mol⁻¹) are given relative to complex **3B**.

In the following we will focus on oxygen transfer processes starting from the peroxy derivatives **2** and **3**; the calculated activation barriers $\Delta E^\ddagger$ and corresponding enthalpies $\Delta H_{298}^\ddagger$ for ethylene epoxidation are compared in Table 1. We shall identify these processes by their reaction type **S**, **BS**, or **I**

Table 1. Activation barriers $\Delta E^\ddagger$ and enthalpies $\Delta H_{298}^\ddagger$ (in parentheses) for the spiro (**S**), back-spiro (**BS**), and insertion (**I**) processes starting from complexes **2A**, **2B**, **3A**, and **3B** (see Figure 1). Energies given in kcal mol⁻¹.

	S	BS	I
2A	18.8 (18.5)	18.9 (18.8)	30.9 (31.7)
2B	— ^[a]	16.2 (16.6)	— ^[a]
3A	12.4 (13.0)	19.2 (19.6)	25.8 (26.6)
3B	16.2 (16.7)	23.3 (23.8)	38.7 (39.5)

[a] No transition state was localized since the water ligand is expelled during the search.

combined with the metal complex involved, for example epoxidation via the spiro transition state with complex **3B** as catalyst is denoted as **S3B**. For complex **2B**, we were able to locate only transition state **BS2B** since the aquo ligand was expelled during the search for processes **S2B** and **I2B**.

In the transition states (Figure 2) the C–C olefin double bond is lengthened by 0.04 (**S**) to 0.07 Å (**I**). Compared to calculated transition states of organic epoxidation reactions,^[20] the **S** and **BS** transition states feature an almost concerted approach of the olefin double bond to the active oxygen center where the attacked peroxo bond O1–O2 is significantly lengthened by about 0.4 Å, while the Re–O bond of the oxygen center to be transferred (**S**: O1, **BS**: O2) is elongated by about 0.1 Å only. The other Re–O bond of the attacked peroxo ligand shortens by the same amount on the way to a Re–O double bond. For process **S3B** (the one with the lowest activation barrier with respect to reactant **2A**), we verified that the reaction products are reached directly by following the transition vector.^[21] During insertion the attacked Re–O bond is more elongated than in the mechanisms which proceed via spiro structures, while the corresponding O–O bond is somewhat contracted (Figure 2).

A comparison of the activation energies (Table 1) shows that for each complex insertion exhibits a noticeably higher barrier than either spiro approach. Comparing the two spiro approaches for each starting complex we note that for **3** a spiro attack from the front is clearly favored over a back-spiro process (by about 7 kcal mol^{−1}), while the opposite holds for **2**, even to the extent of aquo ligand extrusion in **S2B**. The water ligand in **2B** and **3B** enhances the barriers for all three types of mechanisms, with the exception of **BS2B** (cf. **BS2A/B**). This statement may be taken to include **S2B** and **I2B** where the transition states are essentially the same as in **S2A** and **I2A**, but the reactants are more stable due to water ligation. Apparently, two effects of hydration counteract each other to different degrees. While electron-donating and steric effects seem to dominate in **3** (although all metal–ligand bonds increase somewhat, compare **3A** and **3B**, Figure 1), the low barrier for **BS2B** correlates with a significant elongation of the attacked bond Re–O2 (by 0.05 Å, compare **2A** and **2B**). The transition state **S3A** has the lowest calculated barrier, but complex **3A** is significantly less stable than **3B** (by 16.3 kcal mol^{−1}, Figure 1). Thus, we conclude that epoxidation starting from **3** will proceed via transition state **S3B**. Compared to the measured activation enthalpy,^[7] 10.2 ± 0.4 kcal mol^{−1}, for epoxidation of 4-methoxystyrene with a bisperoxo complex, the calculated energy barriers are of the same magnitude. The back-spiro process **BS2B** has essentially the same activation energy as **S3B**. Since the monoperoxo complex **2B** is only slightly less stable (by 2.6 kcal mol^{−1}) than the bisperoxo complex **3B**, processes **S3B** and **BS2B** are quite competitive.

Taking into account energies of hydration and peroxidation (Figure 1) as well as energies of activation (Table 1), one concludes that olefin epoxidation catalyzed by MTO/H₂O₂ occurs as direct oxygen transfer via transition states of spiro structure, likely involving both mono- and bisperoxo complexes depending on reaction conditions.^[5, 7] Given the rather small differences among various lower lying transition states,

entropy effects (not included in the present study) may influence the selection among possible catalytically active complexes. Interaction of olefin substituents with the methyl ligand of the Re center along back-spiro pathways may further differentiate among the two spatial variants of attack (from front or back sides), and may thus influence the competition between mono- and bisperoxo starting complexes.

Received: January 23, 1998

Revised version: March 18, 1998 [Z11395 IE]

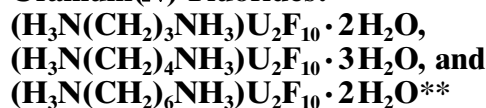
German version: *Angew. Chem.* **1998**, *110*, 2333–2336

Keywords: density functional calculations • epoxidations • peroxo complexes • rhenium • transition states

- [1] a) E. N. Jacobsen in *Catalytic Asymmetric Synthesis*, (Ed.: I. Ojima), VCH, New York, **1993**, p. 159; b) R. A. Sheldon, *Catalytic Oxidations with Hydrogen Peroxides as Oxidant*, Kluwer, Rotterdam, **1992**; c) K. A. Jorgensen, *Chem. Rev.* **1989**, *89*, 431.
- [2] a) H. C. Kolb, M. S. VanNieuwenzhe, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; b) R. A. Johnson, K. B. Sharpless, *Catalytic Asymmetry Synthesis*, VCH, Weinheim, **1993**.
- [3] a) S. Dapprich, G. Ujaque, F. Maseras, A. Lledos, D. G. Musaev, K. Morokuma, *J. Am. Chem. Soc.* **1996**, *118*, 11660; b) U. Pidun, C. Boehme, G. Frenking, *Angew. Chem.* **1996**, *108*, 3008; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2817; c) D. W. Nelson, A. Gypser, P. T. Ho, H. C. Kolb, T. Kondo, H. Kwong, D. V. McGrath, A. E. Rubin, P. Norrby, K. P. Gable, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 1840; d) M. Torrent, L. Deng, M. Duran, M. Sola, T. Ziegler, *Organometallics* **1997**, *16*, 13; e) E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1996**, *118*, 319.
- [4] a) W. A. Herrmann, *J. Organomet. Chem.* **1995**, *500*, 149; b) W. A. Herrmann, F. E. Kühn, *Acc. Chem. Res.* **1997**, *30*, 169; c) C. C. Romão, F. E. Kühn, W. A. Herrmann, *Chem. Rev.* **1997**, *97*, 3197.
- [5] W. A. Herrmann, R. W. Fischer, W. Scherer, M. U. Rauch, *Angew. Chem.* **1993**, *105*, 1209; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1157.
- [6] A. K. Yudin, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 11537.
- [7] A. M. Al-Ajlouni, J. H. Espenson, *J. Am. Chem. Soc.* **1995**, *117*, 9243; A. M. Al-Ajlouni, J. H. Espenson, *J. Org. Chem.* **1996**, *61*, 3969.
- [8] a) Y. Wu, D. K. W. Lai, *J. Org. Chem.* **1995**, *60*, 673; b) W. R. Thiel, *Chem. Ber.* **1996**, *129*, 575.
- [9] a) T. Szyperki, P. Schwerdtfeger, *Angew. Chem.* **1989**, *101*, 1271; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1228; b) S. Köstlmeier, G. Pacchioni, W. A. Herrmann, N. Rösch, *J. Organomet. Chem.* **1996**, *514*, 111; c) S. Köstlmeier, O. D. Häberlen, N. Rösch, W. A. Herrmann, B. Solouki, H. Bock, *Organometallics* **1996**, *15*, 1872.
- [10] Gaussian 94, Revision D.4, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1995**.
- [11] The geometries of the complexes were optimized by using the B3LYP exchange correlation functional^[12] with effective core potentials and double- ζ basis sets, LanL2DZ^[13] on Re and 6–311G(d,p)^[14] on H, C, and O, followed by single-point energy calculations, with a (441/2111/21/11) decontracted LanL2DZ basis set on Re^[15] where two f-type exponents (0.5895 and 0.2683) were added on Re. For **3A**, **3B**, **S3B**, and **BS2A**, geometries were checked at the decontracted (441/2111/21) LanL2DZ level, yielding changes of bond lengths of less than 0.01 Å and of activation barriers of less than 0.2 kcal mol^{−1}. The enthalpy values ($T=298.15$ K) were calculated by using unscaled vibrational frequencies obtained at the LanL2DZ level; the effect of

- this smaller basis set on the enthalpy correction terms was checked, and found to be less than 0.3 kcal mol⁻¹.
- [12] a) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, 37, 785.
- [13] a) T. H. Dunning, P. J. Hay in *Modern Theoretical Chemistry*, Vol. 3 (Ed.: H. F. Schaefer III), New York, **1976**, p. 1; b) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, 82, 299.
- [14] a) R. Krishnan, J. Binkley, R. Seeger, J. Pople, *J. Chem. Phys.* **1980**, 72, 650; b) A. McLean, G. Chandler, *J. Chem. Phys.* **1980**, 72, 5639.
- [15] G. Frenking, I. Antes, M. Böhme, S. Dapprich, A. W. Ehlers, V. Jonas, A. Neuhaus, M. Otto, R. Stegmann, A. Veldkamp, S. F. Vyboishchikov in *Reviews in Computational Chemistry*, Vol. 8 (Eds.: K. B. Lipkowitz, D. B. Boyd), VCH, New York, **1996**, p. 63.
- [16] S. Köstlmeier, V. A. Nasluzov, W. A. Herrmann, N. Rösch, *Organometallics* **1997**, 16, 1786.
- [17] All transition states were checked by a vibrational analysis at the LanL2DZ level.
- [18] K. B. Sharpless, J. M. Townsend, D. R. Williams, *J. Am. Chem. Soc.* **1972**, 94, 195.
- [19] H. Mimoun, I. S. d. Roch, L. Sajus, *Tetrahedron* **1970**, 26, 37.
- [20] a) D. A. Singleton, S. R. Merrigan, J. Liu, K. N. Houk, *J. Am. Chem. Soc.* **1997**, 119, 3385; b) R. D. Bach, C. M. Estévez, J. E. Winter, M. N. Glukhovtsev, *J. Am. Chem. Soc.* **1998**, 120, 680.
- [21] Internal reaction coordinate analysis carried out at the LanL2DZ level; see C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1990**, 94, 5523.

The First Organically Templated Layered Uranium(IV) Fluorides:



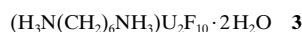
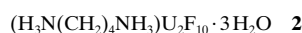
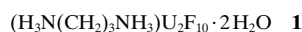
Robin J. Francis, P. Shiv Halasyamani, and Dermot O'Hare*

Hydrothermal chemistry in the presence of organic structure-directing agents has been demonstrated to be a highly versatile technique for the synthesis of new layered and three-dimensional framework materials.^[1, 2] The versatility of the technique derives from the exquisite control over the detailed topology of the inorganic framework that can be achieved by the systematic variation of the synthesis conditions and the template employed, and over recent years a vast range of novel open-framework and layered materials have been reported. All these materials contain the common structural feature of an inorganic anionic framework within which the cationic organic structure-directing agent is occluded. The continued interest in the synthesis of new materials in this class stems from their suitability for a range of materials chemistry applications including heterogeneous catalysis,^[3]

molecular sieving, ion-exchange,^[4] and as host materials for nanochemical applications.^[5] Although to date the vast majority of compounds have been derived from main group elements such as silicon and aluminum,^[2] over recent years there has been increasing interest in incorporating transition metals within three-dimensional and layered framework structures.^[6] Such materials have the potential of combining the shape selectivity demonstrated by framework materials with the catalytic, magnetic, optical, and redox properties associated with d-block elements.

However, with the exception of two organically templated uranium(VI) phosphate phases which we recently reported,^[7] we are not aware of any syntheses of organically templated materials in which actinide elements such as uranium are incorporated into a layered or microporous framework. We have been interested in the synthesis of these materials for a number of reasons. First, the high coordination numbers and variety of coordination geometries adopted by actinide elements could be expected to result in the formation of new, complex framework architectures when the syntheses are performed in the presence of bulky organic templates. Clearfield and co-workers have demonstrated that in the synthesis of uranyl phosphonates the presence of sterically demanding organic groups on the phosphonate ligands leads to the formation of novel structure types, including porous structures.^[8–10] Second, these materials can also be envisioned to exhibit useful catalytic, ion-exchange, and intercalation properties. For example, hydrogen uranyl phosphate (HUP) is a fast hydrogen ion conductor and a versatile ion-exchange reagent,^[11–13] and uranium oxide based materials have recently been shown to be effective halocarbon oxidation catalysts.^[14] Finally, the existence of a number of stable oxidation states of actinides offers the possibility of synthesizing materials with useful optical and magnetic properties.

The addition of fluoride ions in hydrothermal syntheses has been shown to be a particularly effective method for the synthesis of novel structure types.^[15] The fluoride appears to play a role both in aiding the crystallization of the product, and in stabilizing the increased coordination of the metal atoms thus leading to new and more complex framework architectures. We have been exploring the hydrothermal synthesis of new uranium based materials in the presence of both organic templates and fluoride ions, and we report here the synthesis and structural characterization of the first organically templated layered uranium(IV) fluorides to be isolated, namely **1–3**.



The fluorides **1–3** are synthesized in a one-step process by the reaction of UO₂ under autogenous hydrothermal conditions at 180 °C in the presence of aqueous orthophosphoric acid, aqueous hydrofluoric acid, and the organic structure-directing agent. The materials are isolated as phase pure rhomboid-shaped single crystals in high yield (ca. 70 % based

[*] Dr. D. O'Hare, Dr. R. J. Francis, Dr. P. S. Halasyamani
Inorganic Chemistry Laboratory
University of Oxford
South Parks Road, Oxford, OX1 3QR (UK)
Fax: (+44) 1865-272690
E-mail: dermot.ohare@icl.ox.ac.uk

[**] This work was supported by British Nuclear Fuels Limited, the Leverhulme Fund (R.J.F.), and EPSRC. P.S.H. would like to thank Christ Church, Oxford, for a Junior Research Fellowship.

on uranium). Compounds **1–3** form a structurally related series of layered materials, which contain negatively charged uranium fluoride sheets separated by charge balancing organic cations and occluded water molecules.^[16] Figure 1 shows the structure of a single uranium fluoride layer of **1**

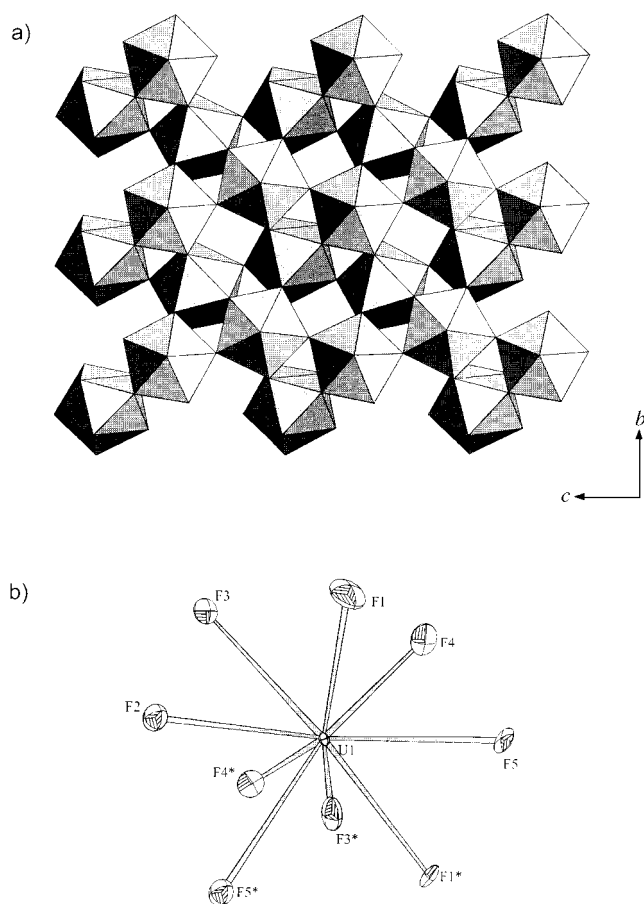


Figure 1. a) The structure of a single uranium fluoride layer in **1** viewed perpendicular to the layers (along the [100] direction), showing how the layers are constructed from corner-sharing $[UF_9]$ tricapped trigonal prisms. Compounds **2** and **3** contain essentially identical layers. b) A view of the local coordination around each uranium atom.

viewed perpendicular to the layer (along the [100] direction). The local geometry around each uranium atom is shown in Figure 1b. Each uranium atom is bonded to nine fluorine atoms in a tricapped trigonal-prismatic coordination. A similar uranium coordination geometry has been previously observed in condensed uranium fluorides such as β - NH_4UF_5 ,^[17] $LiUF_5$,^[18] and KU_2F_9 .^[19] Equivalent UF_9 polyhedra share three edges with three adjacent polyhedra and share two corners with two additional polyhedra to form uranium fluoride sheets. The ninth fluorine atom of each polyhedra is terminal and projects out of the layers and towards adjacent sheets, but does not connect them. Thus the connectivity within the layers can be described as $[UF_{8/2}F_{1/1}]^-$. The U–F bond involving the terminal fluorine atom is significantly shorter than the bridging U–F bonds; the U–F distance for the terminal fluorine is 2.17(1) Å, whereas for the bridging fluorine atoms the average U–F distance is 2.35 Å (with a range of 2.32(1) to 2.39(1) Å). The uranium fluoride sheets

stack along the [100] direction and are separated by charge balancing $[H_3N(CH_2)_3NH_3]^{2+}$ ions and occluded water molecules. Figure 2 shows the structure of **1** viewed along the [010] direction and shows the location of the occluded template.

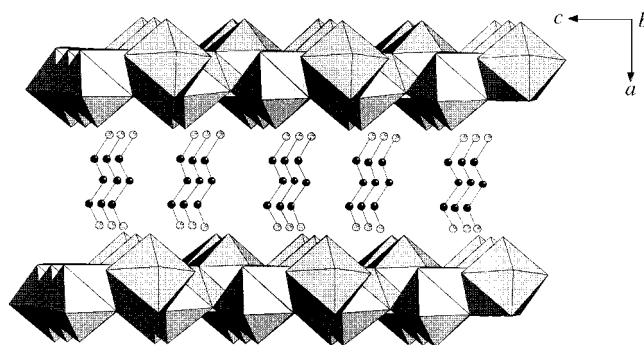


Figure 2. The structure of **1** viewed perpendicular to the uranium fluoride layers (along the [010] direction), showing the location of the organic template. The $[H_3N(CH_2)_3NH_3]^{2+}$ ion lies on an inversion center and the end carbon atom is disordered around this position. For clarity this disorder is not represented in the figure and only one orientation of the template is shown.

The structure of the uranium fluoride layers in compounds **2** and **3** is essentially identical to that seen in compound **1**, which is reflected in two of the lattice parameters, b and c , being almost identical for each compound. In all three materials the $[H_3N(CH_2)_nNH_3]^{2+}$ ions lie almost perpendicular to the uranium fluoride layers, at angles of about 90, 85, and 75° for $n = 3, 4$, and 6, respectively. Hence, as the size of the organic cation increases the separation between uranium fluoride layers also steadily increases. The layers in each compound are bound together through a complex network of strong hydrogen bonds between the substituted ammonium groups and the fluorine atoms of the layers, the oxygen atoms of the water molecules and the fluorine atoms, and the ammonium groups and the water molecules.

Thermal analysis of each material revealed similar behavior. When heated in air all three undergo a weight loss of 5–8% between room temperature and 200°C due to the loss of occluded water. Between about 220°C and 350°C the materials undergo a more substantial weight loss which can be attributed to the combustion of the template and its loss from the materials. Immediately following this, a further substantial weight loss corresponding to decomposition of the uranium fluoride layers occurs, a weight loss which is associated with a loss in crystallinity of the materials. The initial loss of occluded water is fully reversible; that is, if the materials are heated to 165°C, then cooled back down to room temperature, complete rehydration occurs within an hour. When heated in flowing N_2 , the materials showed thermal behavior similar to that in air.

The magnetic behavior of phases **1–3** was also investigated. As shown in Figure 3, over the range 20–300 K all three materials displayed magnetic susceptibilities that could be fitted well to the simple Curie–Weiss equation. Below 20 K there is slight levelling off of the magnetic susceptibility, a feature most marked for **3**. This is indicative of either very

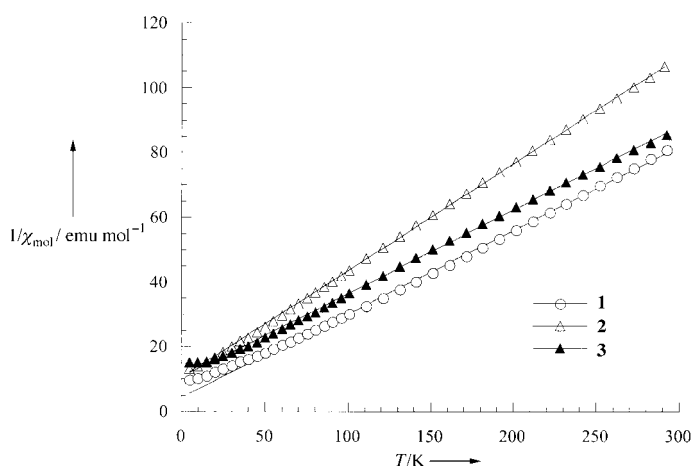


Figure 3. Plot of the variation of inverse molar magnetic susceptibility with temperature for **1–3** at a magnetic field of 0.5 T.

weak local antiferromagnetic ordering between U^{4+} ions, or temperature-dependent paramagnetism due to changing populations of atomic energy levels of individual U^{4+} ions. Fitting of the high-temperature (above 20 K) data to the Curie–Weiss equation yielded negative values for the Weiss constant in each case, which is consistent with weak antiferromagnetism. Values of μ_{eff} of 5.66, 4.91, and $5.57 \mu_{\text{B}}$ were obtained for **1**, **2**, and **3**, respectively. These values are somewhat higher than would be expected for U^{IV} ions. However, interpreting effective magnetic moments of uranium compounds is complex because spin–spin, orbit–orbit, spin–orbit, and ligand–field interactions are of a comparable importance and must all be considered in a full treatment.

The negatively charged frameworks and large interlayer separations present in these materials suggested that they may act as good host materials for cationic ion-exchange applications. The ion-exchange properties of these materials were therefore investigated. These experiments revealed that compounds **1–3** are extremely robust in their ion-exchange behavior. We were able to fully exchange the organic templates for Na^+ , K^+ , or Co^{2+} by stirring suspensions of the compounds in solutions of the appropriate metal salt at room temperature for 48 h. In all cases the exchange was accompanied by a large decrease in the interlayer spacing, and complete exchange was confirmed by the absence of the host 001 reflection and any carbon or nitrogen in the exchanged materials. The ion-exchanged materials were highly crystalline, and powder X-ray diffraction revealed that the exchange of **1–3** with any particular cation produced identical products. The diffraction pattern of the potassium exchanged materials matched that of a reported material “ $\text{K}_7\text{U}_6\text{F}_{31}$ ”.^[20] However, given the synthetic route to the ion-exchanged material we believe the empirical formula is likely to be $\text{KUF}_5 \cdot x\text{H}_2\text{O}$ (“ $\text{K}_6\text{U}_6\text{F}_{30}$ ”). The powder X-ray patterns of the Na^+ and Co^{2+} -exchanged materials did not match any known phases. Initial powder X-ray diffraction measurements indicate that the materials are pure and have unit cells that are related to the starting materials. We are currently in the process of determining the structure of these new exchanged phases. Thus, compounds **1–3** provide a facile route for the low-

temperature synthesis of new alkali and transition metal uranium(IV) fluorides.

In summary, a simple, high-yield, single-step route for the exclusive synthesis of the first compounds of a new class of organically templated uranium(IV) fluorides has been outlined. The materials have been shown to reversibly dehydrate when heated, display weak antiferromagnetic properties, and undergo facile ion-exchange reactions with a variety of other cations leading to the low-temperature formation of new condensed uranium(IV) phases. The isolation of compounds **1–3** is another demonstration of how hydrothermal synthesis can be exploited to synthesize novel hybrid organic–inorganic materials. Of particular interest is the contrasting stoichiometry, coordination, and structure of the uranium(IV) materials reported here, synthesized in the presence of fluoride, and the uranium(VI) materials reported previously. Given the huge variety of possible templates that could be used, and the number of possible reaction variables that could be altered, the scope for the synthesis of new materials displaying interesting structural, catalytic, ion-exchange, magnetic, and redox properties is very large.

Experimental Section

All of the syntheses were performed in 23-mL Teflon stainless steel vessels filled to about 25% volume. The UO_2 was supplied by British Nuclear Fuels Limited and used as received. The H_3PO_4 (85% solution, BDH 99%), HF (40% solution, Fisons 98%), and $\text{H}_2\text{N}(\text{CH}_2)_n\text{NH}_2$ ($n = 3$ and 4, Aldrich 99%; $n = 6$, Lancaster 98%) were also used as received.

Compounds **1–3** were synthesized by combining UO_2 (0.243 g), H_3PO_4 (1.11 g), HF (0.485 g), H_2O (3.21 g), and either $\text{H}_2\text{N}(\text{CH}_2)_3\text{NH}_2$ (0.181 g), $\text{H}_2\text{N}(\text{CH}_2)_4\text{NH}_2$ (0.214 g), or $\text{H}_2\text{N}(\text{CH}_2)_6\text{NH}_2$ (0.283 g) at room temperature. The respective mixtures were heated to 180°C for 1 day and cooled at 6°C per hour over an additional day. In all three instances, pure monophasic crystals were recovered in about 70% yields based on UO_2 . Elemental analyses: **1**: found (calcd): C 4.44 (4.63), H 2.05 (2.07), N 3.43 (3.60), U 62.19 (61.17), F 24.20 (24.41); **2**: found (calcd): C 5.86 (5.93), H 2.19 (2.59), N 3.29 (3.46), U 56.73 (58.75), F 23.56 (23.50); **3**: found (calcd): C 7.94 (8.79), H 2.56 (2.70), N 3.10 (3.42), U 56.35 (58.04), F 22.92 (23.17).

Received: February 16, 1998 [Z11484 IE]
German version: *Angew. Chem.* **1998**, *110*, 2336–2339

Keywords: crystal growth • ion-exchange • layered compounds • template synthesis • uranium

- [1] R. Szoostak, *Molecular Sieves: Principles of Synthesis and Identification*, Van Nostrand Reinhold, New York, **1989**.
- [2] M. E. Davis, R. F. Lobo, *Chem. Mater.* **1992**, *4*, 756.
- [3] P. B. Venuto, *Microporous Mater.* **1994**, *2*, 297.
- [4] A. Clearfield, *Chem. Rev.* **1988**, *88*, 125.
- [5] G. A. Ozin, *Adv. Mater.* **1992**, *4*, 612.
- [6] R. C. Haushalter, L. A. Mundi, *Chem. Mater.* **1992**, *4*, 31, and references therein.
- [7] R. J. Francis, M. J. Drewitt, P. S. Halasyamani, C. Ranganathachar, D. O'Hare, W. Clegg, S. J. Teat, *Chem. Commun.* **1998**, 279.
- [8] D. Grohol, M. A. Subramanian, D. M. Poojary, A. Clearfield, *Inorg. Chem.* **1996**, *35*, 5264.
- [9] D. M. Poojary, D. Grohol, A. Clearfield, *Angew. Chem.* **1995**, *107*, 1650; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1508.
- [10] D. M. Poojary, A. Cabeza, M. A. G. Aranda, S. Bruque, A. Clearfield, *Inorg. Chem.* **1996**, *35*, 1468.
- [11] C. H. Johnson, M. G. Shilton, A. T. Howe, *J. Solid State Chem.* **1981**, *37*, 37.

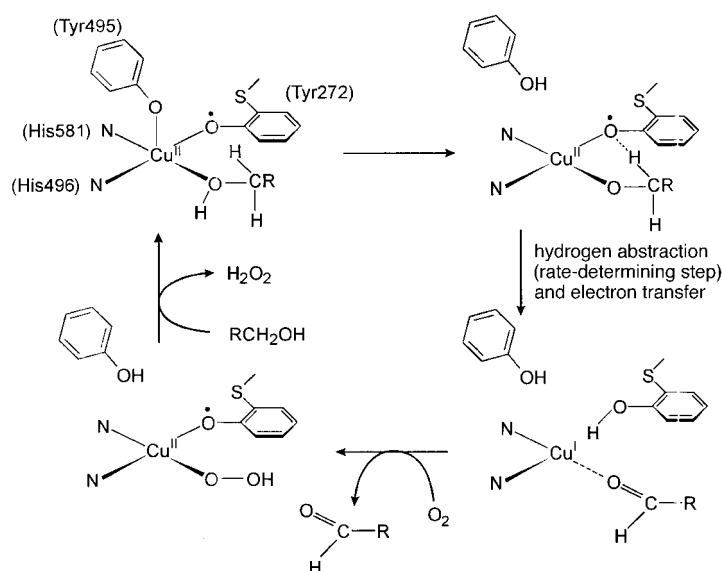
- [12] L. Moreno-Real, R. Pozas-Tormo, M. Martinez-Lara, S. Bruque-Gamez, *Mater. Res. Bull.* **1987**, 22, 19.
- [13] D. Grohol, E. L. Blinn, *Inorg. Chem.* **1997**, 36, 3422.
- [14] G. J. Hutchings, C. S. Heneghan, I. D. Hudson, S. H. Taylor, *Nature* **1996**, 384, 341.
- [15] J. L. Guth, H. Kessler, R. Wey, *Stud. Surf. Sci. Catal.* **1986**, 28, 121.
- [16] Crystal data for **1–3**: For all three materials the data were collected on an Enraf-Nonius DIP 2000 Image Plate diffractometer using MoK α radiation. For **1**: monoclinic $P2_1/c$, $a = 10.715(1)$, $b = 7.097(1)$, $c = 8.767(1)$ Å, $\alpha = 93.804(6)^\circ$, $V = 665.21(3)$ Å ^{3} , $Z = 2$, $T = 200$ K. For 1097 observed reflections with $I > 5\sigma(I)$ and 97 variables, $R(R_w) = 0.052(0.060)$. For **2**: triclinic, $P\bar{1}$, $a = 12.024(2)$, $b = 7.149(3)$, $c = 8.765(2)$ Å, $\alpha = 90.063(4)$, $\beta = 107.133(5)$, $\gamma = 92.098(3)^\circ$, $V = 719.46(3)$ Å ^{3} , $Z = 1$, $T = 200$ K. For 1218 observed reflections with $I > 5\sigma(I)$ and 190 variables $R(R_w) = 0.079(0.091)$. For **3**: monoclinic, $P2_1/c$, $a = 13.800(2)$, $b = 7.056(2)$, $c = 8.720(3)$ Å, $\alpha = 108.338(3)^\circ$, $V = 805.97(2)$ Å ^{3} , $Z = 2$, $T = 200$ K. For 892 reflections with $I > 5\sigma(I)$ and 100 variables $R(R_w) = 0.034(0.039)$. Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crystdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-408217, CSD-408218, and CSD-408219.
- [17] R. A. Penneman, R. R. Ryan, *Acta Crystallogr. Sect. B* **1974**, 30, 1966.
- [18] G. Brunton, *Acta Crystallogr.* **1966**, 21, 814.
- [19] G. Brunton, *Acta Crystallogr. Sect. B* **1969**, 25, 1919.
- [20] JC-PDF Catalogue No. 10-0150. (Insky, McVay, Thomas, White; Oak Ridge National Lab, USA).

From Structural Models of Galactose Oxidase to Homogeneous Catalysis: Efficient Aerobic Oxidation of Alcohols**

Phalguni Chaudhuri,* Martina Hess, Ulrich Flörke, and Karl Wieghardt*

Dedicated to Professor Achim Müller on the occasion of his 60th birthday

The fungal enzyme galactose oxidase (GO) catalyzes the aerobic oxidation of primary alcohols to aldehydes and H $_2$ O $_2$.^[1] The structure^[2] of this biomolecule and its reaction mechanism^[3] are well established (Scheme 1): In its catalytically active form there is an *ortho*-S-modified tyrosyl radical (Tyr 272) coordinated to a single copper(II) ion and a unique radical cofactor. The rate-determining step of this catalysis (k_H/k_D 6–8)^[4] upon binding of the alcohol substrate to the Cu^{II} ion is the hydrogen abstraction from the α -carbon atom of the



Scheme 1. Proposed mechanism of catalysis by galactose oxidase (according to Whittaker).^[3c]

alcohol with formation of a coordinated ketyl radical anion. Rapid intramolecular electron transfer with reduction of Cu^{II} to Cu^I then leads to the formation of the unbound aldehyde. The reduced enzyme reacts with dioxygen with formation of H $_2$ O $_2$ and regeneration of the active radical cofactor.

While structural models for the active form of the enzyme containing Cu^{II}–phenoxyl moieties have been synthesized and characterized spectroscopically,^[5] it appears to be much more demanding to model the reactivity of GO.^[5a, 6] Stack et al.^[7] have reported recently mononuclear functional Cu^{II} model complexes which catalyze the aerobic oxidation of activated benzyl and allyl alcohols with concomitant formation of H $_2$ O $_2$. We describe here a novel *dinuclear* Cu^{II}–phenoxyl radical species that catalytically oxidizes primary and secondary alcohols with dioxygen (air) to the corresponding aldehyde, ketone, and/or to 1,2-glycol derivatives; the reduction product is in all cases H $_2$ O $_2$.

The reaction of Cu^{II}Cl with 2,2'-thiobis(2,4-di-*tert*-butylphenol) (LH $_2$) and triethylamine (1:1:2) in dry methanol under argon produces a yellow solution that becomes deep blue upon controlled exposure to air. From this solution microcrystalline blue [Cu^{II}L(NEt $_3$)] (**1**) is precipitated. Figure 1 displays the structure of the mononuclear neutral complex **1**: The tridentate dianion L $^{2-}$ is coordinated to a Cu^{II} ion and a fourth coordination site is occupied by an NEt $_3$ ligand; the resulting coordination polyhedron is intermediate between square planar and tetrahedral. Complex **1** is paramagnetic (1.79 μ_B ; 3–300 K). The cyclic voltammogram (CV) of **1** in CH $_2$ Cl $_2$ (0.10 M [(*n*Bu) $_4$ N]⁺PF $_6^-$; glassy carbon working electrode) at 20°C displays two quasireversible one-electron oxidation processes at $E_{1/2} = 0.52$ and 0.89 V versus ferrocene/ferrocene (Fc⁺/Fc) which are ascribed to two successive oxidations of the coordinated ligand L to generate two phenoxyl radicals.

Passing a stream of dry O $_2$ through the above yellow solution in tetrahydrofuran (THF) for 1 h induces a color change from deep blue to green and, finally, microcrystalline

[*] Priv. Doz. Dr. P. Chaudhuri, Prof. Dr. K. Wieghardt, M. Hess
Max-Planck-Institut für Strahlenchemie
Stiftstrasse 34–36, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-3952
E-mail: chaudh@mpi-muelheim.mpg.de
wieghardt@mpi-muelheim.mpg.de

Dr. U. Flörke
Anorganische und Analytische Chemie
Universität-Gesamthochschule Paderborn (Germany)

[**] We thank Prof. Dr. C. von Sonntag for helpful discussions, Mrs. U. Westhoff for many GC analyses, and the Fonds der Chemischen Industrie for financial support

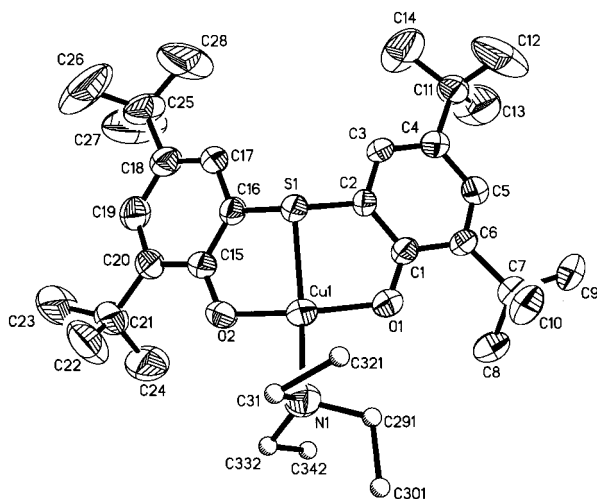
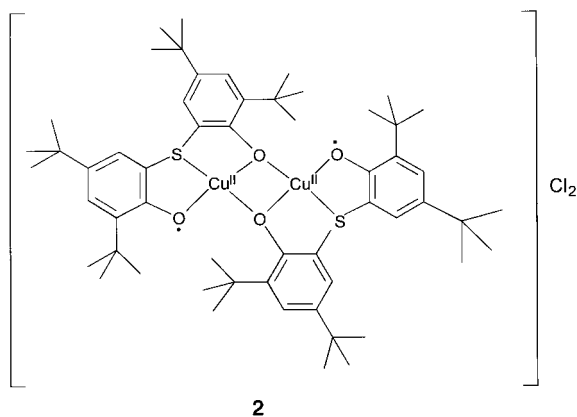


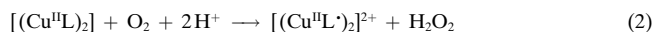
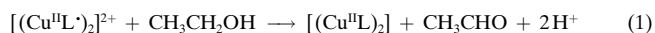
Figure 1. Crystal structure of the neutral complex $[\text{Cu}^{\text{II}}(\text{L}(\text{NEt}_3))]$ **1**. Selected bond lengths [Å] and angles [°]: Cu–O1 1.889(3), Cu–O2 1.895(3), Cu–N1 2.050(4), Cu–S1 2.290(2); O1–Cu–O2 152.2(2), O1–Cu–N1 97.9(2), O2–Cu–N1 98.0(2), O1–Cu–S1 87.6(1), O2–Cu–S1 88.0(1), N1–Cu–S1 154.0(1).

green $[(\text{Cu}^{\text{II}}\text{L}^{\cdot})_2]\text{Cl}_2$ (**2**) precipitates. Complex **2** is diamagnetic. The presence of a coordinated phenoxyl group in **2** is



evident from both the electronic spectrum in THF ($\lambda_{\text{max}} \approx 404 \text{ nm}$ ($\epsilon = 8.0 \times 10^3 \text{ L mol}^{-1} \text{ cm}^{-1}$) and the resonance Raman spectrum ($\lambda_{\text{exc}} = 458 \text{ nm}$, $\tilde{\nu}(\text{C}=\text{O}^{\cdot}) = 1451 \text{ cm}^{-1}$, $\tilde{\nu}(\text{C}=\text{C}) = 1579, 1594, 1606 \text{ cm}^{-1}$).^[5b] We propose that the structure of dinuclear **2**^[5c, d] has two bridging phenolate groups and two phenoxyl ligands. Whether the chloride anions are coordinated or not is unknown. This proposal readily explains the observed diamagnetism of **2** by an intramolecular antiferromagnetic exchange coupling between the phenoxyl groups ($S = 1/2$) and the Cu^{II} ions (d^9 ; $S = 1/2$).

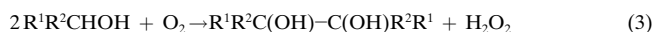
The addition of excess ethanol (10:1) to a deoxygenated green solution of **2** in THF under argon at 20°C induces a color change to blue. The formation of one equivalent of acetaldehyde [Eq. (1)] has been established photometrically (see Table 1). Subsequent exposure of this blue solution to air affords the above green solution within minutes; the electronic spectrum of this solution is nearly identical to that of a solution of **2** in THF without substrate. In this instance the formation of H_2O_2 (approximately one equivalent) has been established [Eq. (2)].



The CV of **2** in CH_2Cl_2 (otherwise the conditions are the same as above) displays two reversible one-electron reduction waves at $E_{1/2} = -1.26$ and -0.29 V versus Fc^+/Fc , which are assigned to the successive reduction of the phenoxyl radicals. These negative potentials readily account for the oxidizability of **2** by O_2 (**1** cannot be oxidized by O_2).

The combination of Equations (1) and (2) gives, in principle, the homogeneously catalyzed oxidation of ethanol with dioxygen to afford acetaldehyde and H_2O_2 . This is indeed the case, as summarized in Table 1. Remarkably, GC analysis of the products of aerobic oxidation of ethanol and benzyl alcohol reveals that in addition to the aldehydes small amounts of the corresponding 1,2-glycols, their α -hydroxyketones, and their α -diketones are formed. Mixtures of **2** in THF in the presence of H_2O_2 and a large excess of acetaldehyde or benzaldehyde are stable in air: No disproportionation of H_2O_2 , oxidation of the aldehydes to carboxylic acids, or formation of C–C coupling products is observed. Therefore, we conclude that the formation of 1,2-glycols upon oxidation of alcohols by air proceeds by a second reaction pathway which differs mechanistically from that of the aldehyde formation. This implies that secondary alcohols—in contrast to GO—can be catalytically oxidized by air with **2** as the catalyst.

Indeed, both 2-propanol and diphenylcarbinol can be employed as substrates in the above catalysis, and in both cases the corresponding 1,2-glycol derivative is the only detectable organic product (formed through oxidative C–C coupling). The simple ketones acetone and benzophenone were identified in only trace amounts^[9] or not at all. The stoichiometry of this reaction was established as that in Equation (3). On the other hand, oxidation of 2-butanol with O_2 yields the ketone 2-butanone exclusively (Table 1) and one equivalent of H_2O_2 .



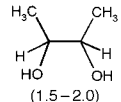
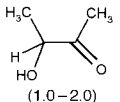
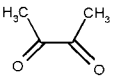
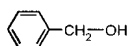
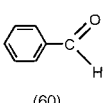
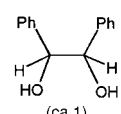
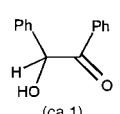
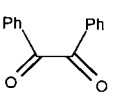
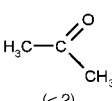
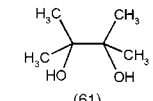
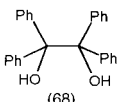
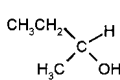
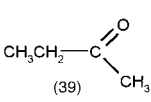
The kinetics of these catalysis reactions have been measured by variation of the total concentrations of $[\text{Cu}^{\text{II}}\text{L}]$, and the alcohol. The time-dependent product formation (H_2O_2 and aldehyde, ketone, or 1,2-glycol) and the O_2 consumption (manometrically) have been measured and the two rate laws Equations (4) and (5) have been established.



Thus, there are two independent pathways where aldehyde and ketone formation obey Equation (4), whereas the generation of 1,2-glycol follows Equation (5). The effect of the steric requirements of the Cu^{II} -coordinated starting materials and the electronic requirements of the putative coordinated ketyl radical anions on product formation are at present unknown.

With the selectively deuterated substrates $\text{CH}_3\text{CD}_2\text{OH}$ and $(\text{CH}_3)_2\text{CDOH}$ kinetic isotope effects $k_{\text{H}}/k_{\text{D}}$ of 8 and 10,

Table 1. Aerobic oxidation of primary and secondary alcohols.^[a]

Substrate	Products (yield [%]) ^[b]					Rate law
CH ₃ CH ₂ OH	 (63)	 (1.5–2.0)	 (1.0–2.0)	 (3–5)	H ₂ O ₂ (70)	Eq. (4)
	 (60)	 (ca.1)	 (ca.1)	 (3–4)	H ₂ O ₂ (65)	Eq. (4)
	 (< 2)	 (61)			H ₂ O ₂ (32)	Eq. (5)
	 (68)				H ₂ O ₂ (33)	Eq. (5)
	 (39)				H ₂ O ₂ (40)	Eq. (4)

[a] Experimental conditions: Cu^{II}Cl₂, LH₂ (1.25×10^{-5} mol each, NEt₃ (2.5×10^{-5} mol) in dry THF (50 mL) were heated at 50 °C under argon. After addition of the respective alcohol (6.25×10^{-3} mol) the solution was stirred at 20 °C in the presence of air for 12 h. Product analysis: the overall yield of the organic products was determined by gas chromatography; H₂O₂ was determined spectrophotometrically after complexation of the peroxide with titanium sulfate in aqueous H₂SO₄: G. M. Eisenberg, *Anal. Chem.* **1943**, *15*, 327; acetaldehyde was also determined spectrophotometrically: E. Sawicki, T. R. Hauser, T. W. Stanley, W. Elbert, *Anal. Chem.* **1961**, *33*, 93. [b] Yield of organic products: moles of C_n moieties in the product per mole of starting C_n alcohol (in percent); H₂O₂: moles of H₂O₂ per mole of starting alcohol (in percent).

respectively, have been found. This indicates that hydrogen abstraction from the α -carbon atom of the alcohols is the rate-determining step in both reaction pathways. Furthermore, it implies that the form of the catalyst prior to this step has the highest stationary concentration during catalysis. The electronic spectrum of a reaction mixture measured under turnover conditions is, therefore, very similar to that of a solution of **2** in THF (without substrate); the Cu^{II}–phenoxyl species is the dominant chromophore in both cases.

Since both rate laws display a second-order dependence on [Cu^{II}L]₂, the dinuclear form **2** constitutes the active catalyst, which is in equilibrium with its—catalytically inactive—monomeric form as shown in Equation (6). A strong donor solvent such as acetonitrile is, therefore, a very efficient inhibitor of the catalysis.



(S = solvent molecule or alcohol)

Scheme 2 exhibits two mechanistic proposals for the aerobic oxidation of primary and secondary alcohols with O₂ which is in agreement with all of the experimental results described above.

We would like to emphasize an important difference between our system and the enzymatic reaction of GO or Stack's model system.^[7] Catalyst **2** uses only the oxidation equivalents stored in the two phenoxyl radical ligands; the Cu^I oxidation state is not involved. Since two oxidation equiv-

alents are needed only the dinuclear form containing two phenoxyl ligands is catalytically relevant.

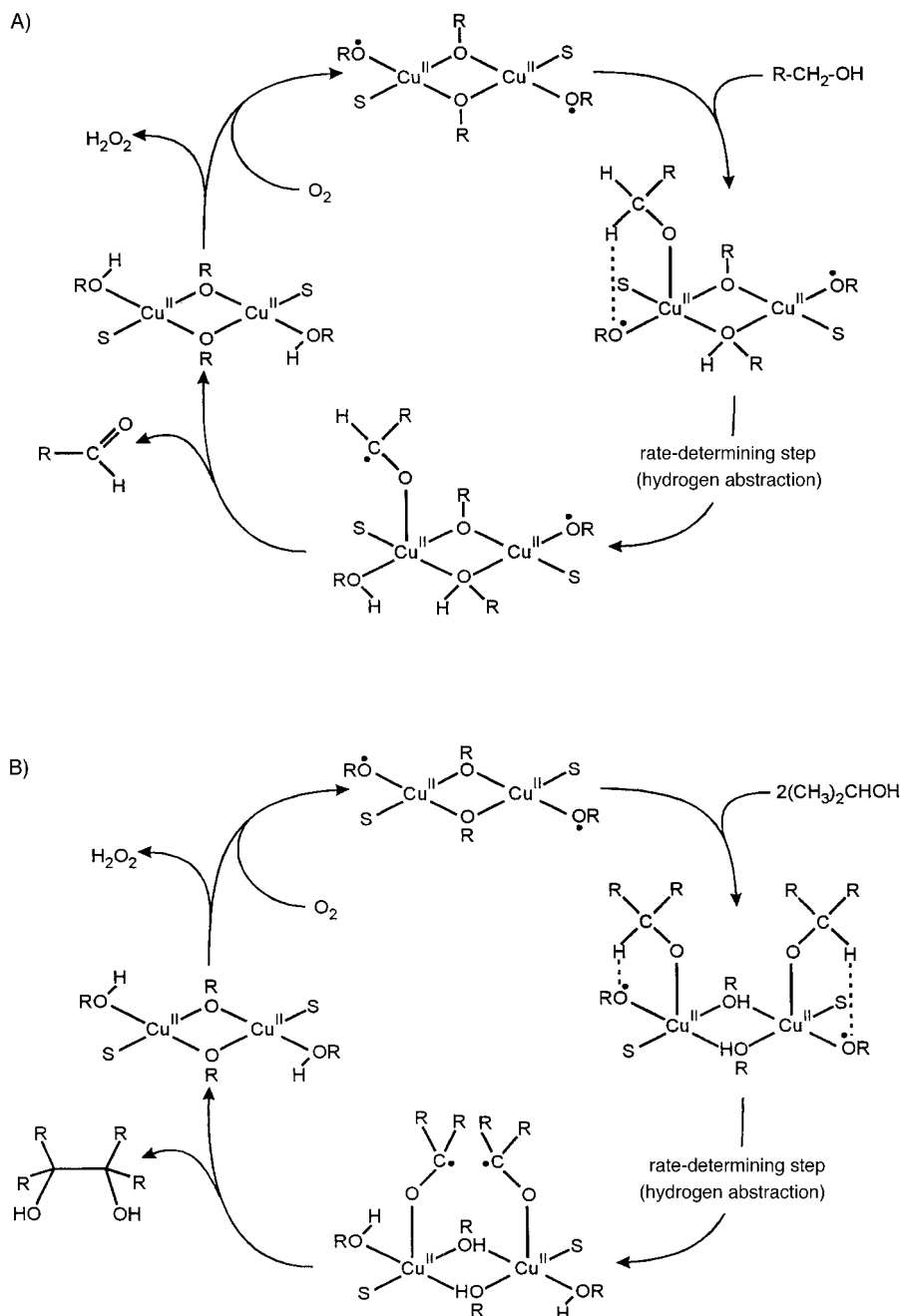
Two factors are decisive for the catalytic activity of **2**: the C–H abstraction from the coordinated alcoholate anion must be thermodynamically favorable—that is, the C–H bond should be relatively weak (therefore, methanol is *not* a substrate)—and the Cu^{II}–phenolate form must be reactive towards O₂.

Finally, the present system is not only capable of oxidizing alcohols under mild conditions, but at the same time highly concentrated H₂O₂ is formed at room temperature from air. The products are readily separated by extraction of the organic products with, for example, THF. Efficient Cu-catalyzed aerobic oxidation of alcohols has recently been described by Marko et al., but in their system water is the reduction product^[10] and oxidative C–C coupling is not observed.

Experimental Section

The ligand LH₂ has been prepared according to published procedures.^[11]

1: A suspension of CuCl (0.10 g, 1.0 mmol), LH₂ (0.44 g, 1.0 mmol), and NEt₃ (0.5 mL) in dry, deoxygenated CH₃OH (50 mL) was heated to reflux for 1 h under Ar. Careful exposure of the clear yellow solution to air at 20 °C initiated a color change to deep blue. After approximately 2 d in an open vessel at ambient temperature blue microcrystals of **1** precipitated. Recrystallization from CH₃OH:n-pentane (2:1) afforded blue rhombic crystals suitable for X-ray structure analysis. Yield: 0.48 g, 80%. Elemental analysis calcd for C₃₄H₅₅NO₂SCu: C 63.62, H 8.97, S 5.00, N 2.18, Cu 9.90;



Scheme 2. Proposed mechanisms for the catalytic oxidation of primary and secondary alcohols with **2** according to Equation (4) (A) and Equation (5) (B).

found: C 64.01, H 9.04, N 2.20, S 4.83, Cu 9.74; UV/Vis (THF): λ_{max} [nm] (ϵ [L mol⁻¹ cm⁻¹]): 400sh (ca. 370), 600sh (300), 700 (370).

2: A suspension of CuCl, LH₂, and NEt₃ (same amounts as for **1**) in dry(!) THF was heated to reflux Ar for 30 min. A stream of dry dioxygen was passed through the clear yellow solution at 20°C for 1 h (the absence of H₂O is important). The solution changed from blue to green and a green precipitate of **2** slowly formed, which was recrystallized from dry THF. Yield: 0.12 g, 11 %. Elemental analysis calcd for C₅₆H₈₀O₄S₂Cl₂Cu₂: C 62.32, H 7.47, S 5.94, Cl 6.57, Cu 11.77; found: C 61.95, H 7.48, S 5.88, Cl 6.47, Cu 11.75; UV/Vis (THF): λ_{max} , [nm] (ϵ [L mol⁻¹ cm⁻¹]): 400sh, 408 (8.0 × 10³), 424sh, 650(660).

Received: February 19, 1998 [Z11497IE]
German version: *Angew. Chem.* **1998**, *110*, 2340–2343

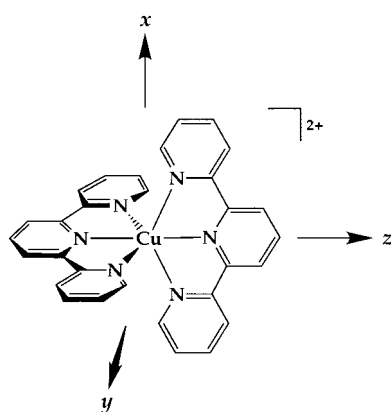
Keywords: alcohols • copper • galactose oxidase • homogeneous catalysis • metalloenzymes

- [1] a) J. W. Whittaker in *Metal Ions in Biological Systems*, Vol. 30 (Eds.: H. Sigel, A. Sigel), Marcel Dekker, New York, **1994**, pp. 315–360; b) P. F. Knowles, N. Ito in *Perspectives in Bio-inorganic Chemistry*, Vol. 2 (Eds.: R. W. Hay, J. R. Dilworth, K. B. Nolan), Jai, London, **1994**, pp. 207–244.
- [2] a) N. Ito, S. E. V. Phillips, C. Stevens, Z. B. Ogel, M. J. McPherson, J. N. Keen, K. D. S. Yadav, P. F. Knowles, *Nature* **1991**, *350*, 87; b) N. Ito, S. E. V. Phillips, K. D. S. Yadav, P. F. Knowles, *J. Mol. Biol.* **1994**, *238*, 794.
- [3] a) R. M. Wachter, M. P. Montague-Smith, B. P. Branchaud, *J. Am. Chem. Soc.* **1997**, *119*, 7743; b) B. P. Branchaud, M. P. Montague-Smith, D. J. Kosman, F. R. McLaren, *J. Am. Chem. Soc.* **1993**, *115*, 798; c) M. M. Whittaker, J. W. Whittaker, *Biophys. J.* **1993**, *64*, 762; d) R. M. Wachter, B. P. Branchaud, *J. Am. Chem. Soc.* **1996**, *118*, 2782.
- [4] A. Maradufu, G. M. Cree, A. S. Perlin, *Can. J. Chem.* **1971**, *49*, 3429.
- [5] a) J. A. Halfen, B. Jazdzewski, S. Mahapatra, L. M. Berreau, E. C. Wilkinson, L. Que, Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1997**, *119*, 8217; b) A. Sokolowski, H. Leutbecher, T. Weyhermüller, R. Schnepf, E. Bothe, E. Bill, P. Hildebrandt, K. Wieghardt, *J. Biol. Inorg. Chem.* **1997**, *2*, 444; c) D. Zurita, I. Gautier-Luneau, S. Menage, J.-L. Pierre, E. Saint-Aman, *J. Biol. Inorg. Chem.* **1997**, *2*, 46; d) S. Itoh, S. Takayama, R. Arakawa, A. Furuta, M. Komatsu, A. Ishida, S. Takamuku, S. Fukuzumi, *Inorg. Chem.* **1997**, *36*, 1407; d) D. Zurita, S. Menage, J.-L. Pierre, E. Saint-Aman, *New J. Chem.* **1997**, *21*, 1001; e) J. Müller, T. Weyhermüller, E. Bill, P. Hildebrandt, L. Ould-Moussa, T. Glaser, K. Wieghardt, *Angew. Chem.* **1998**, *110*, 637; *Angew. Chem. Int. Ed.* **1998**, *37*, 616.
- [6] Y. Wang, T. D. P. Stack, *J. Am. Chem. Soc.* **1996**, *118*, 13097.
- [7] Y. Wang, J. L. DuBois, B. Hedman, K. O. Hodgson, T. D. P. Stack, *Science*, **1998**, *279*, 537.
- [8] Crystal structure determination of **1**: blue crystal (0.65 × 0.45 × 0.12 mm³); C₃₄H₃₅CuNO₂S, *M*_r = 605.4; monoclinic, space group *P*₂₁/*n*, *a* = 15.659(3), *b* = 13.107(3), *c* = 18.321(4) (Å), β = 105.55(3)°, *V* = 3623(1) (Å³), *Z* = 4, *T* = 293(2) K; ρ_{calcd} = 1.11 g cm⁻³; μ_{Mo} = 0.687 mm⁻¹; semiempirical absorption correction, full-matrix, least-squares refinement on *F*² with 6917 reflections [*I* > 2σ(*I*)] and 348 variables, final *R* values: *R*(*F*) = 0.068 and *wR*2 = 0.135. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101165. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] Small amounts of acetone are formed from isopropyl alcohol in THF in the presence of Cu^{II} ions with air (autoxidation?).
- [10] I. E. Marko, P. R. Giles, M. Tsukazaki, S. M. Brown, C. J. Urch, *Science* **1996**, *274*, 2044.
- [11] S. D. Pastor, J. D. Spivack, L. P. Steinhuebel, *J. Heterocycl. Chem.* **1984**, *21*, 1285.

Steric Control of the Electronic Ground State in Six-Coordinate Copper(II) Complexes**

Nayan K. Solanki, Eric J. L. McInnes, Frank E. Mabbs, Sanja Radojevic, Mary McPartlin, Neil Feeder, John E. Davies, and Malcolm A. Halcrow*

Although the six-coordinate Cu^{II} ion is a paradigm for the Jahn–Teller effect in d-block chemistry, the number of Cu^{II} complexes that exhibit an axially compressed octahedral or rhombic geometry, as characterized by a {d_z}¹ electronic ground state, is extremely small.^[1, 2] The salts [Cu(terpy)₂]₂X₂ (terpy = 2,2':6',2''-terpyridyl; X = NO₃[−],^[3] PF₆[−],^[4] Br[−]^[5]) were long believed to exhibit this property in the solid state,^[1] since this complex has a compressed rhombic geometry along the molecular z axis according to room-temperature crystallography (Scheme 1), whereas its room-temperature powder

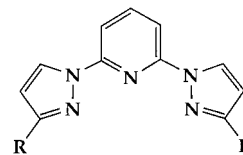


Scheme 1. Molecular axes of [Cu(terpy)₂]²⁺.

EPR spectra exhibit an “inverse” $g_{\perp} > g_{\parallel} > g_e$ pattern.^[5] However, detailed EPR studies have shown that these observations in fact reflect a dynamically disordered axis of elongation about the molecular x and y vectors. Thus, at low temperatures in the solid the Jahn–Teller axis of [Cu(terpy)₂]₂X₂ becomes static in the molecular xy plane (an example of “Jahn–Teller cooperativity”^[2]), and the low-temperature

EPR spectra of this complex exhibit the more usual $g_{\parallel} > g_{\perp} > g_e$ pattern consistent with a {d_{x²−y²}}¹ ground state.^[5, 6]

The Jahn–Teller distortion of [Cu(terpy)₂]²⁺ depends on the ability of the Cu–N distances along the molecular x and y axes to vary between 2.0 and 2.3 Å.^[5] We reasoned that addition of bulky substituents in the position α to the “outer” N atoms in terpy or related tris-imine ligands might prevent close approach of these donors to the metal ion, and thus enforce an axial compression at the Cu^{II} center along the molecular z axis. Rather than 6,6''-disubstituted terpy derivatives, we chose 3,3''-disubstituted 2,6-di(pyrazol-1-yl)pyridines (L^R; Scheme 2) because of their straightforward synthesis.^[7] While [M(L^R)₂]²⁺ (M = Ru, R = H) has been prepared,^[8] no other complexes of this stoichiometry with other metal ions or L^R ligands have been reported.



Scheme 2. L^R; R = H, Mes.

Ligand L^H was prepared by the literature procedure,^[7] while L^{Mes} was synthesized from 3{5}-mesitylpyrazole^[9] and 2,6-dibromopyridine by the same methodology. Complexation of various Cu^{II} salts by two equivalents of L^R in MeNO₂ followed by crystallization from Et₂O afforded green solids of composition [Cu(L^R)₂]₂X₂ (L^R = L^H, L^{Mes}; X[−] = BF₄[−], ClO₄[−]). The UV/Vis spectra of both complexes are typical of six-coordinate Cu^{II}^[10] showing one absorption with $\epsilon_{\max} \approx 50 \text{ M}^{-1} \text{ cm}^{-1}$ and no long-wavelength shoulder. In each case the energy of this peak is identical for solutions in MeCN and MeNO₂, which suggests that ligand dissociation in these solvents is minimal.

Single-crystal X-ray structures of [Cu(L^H)₂](BF₄)₂ and [Cu(L^{Mes})₂](ClO₄)₂·2CH₃NO₂ were determined at 223 and 180 K, respectively. Both complexes exhibit the expected compressed-rhombic stereochemistry (Figures 1 and 2). The Cu–N bond lengths can be grouped into crystallographically distinct short z [N(1)–Cu–N(4)], medium y [N(2)–Cu–N(3)], and long x [N(5)–Cu–N(6)] axes at the copper center. In

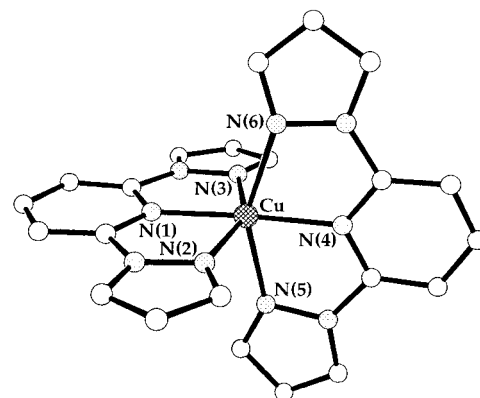


Figure 1. Perspective view of the dication of [Cu(L^H)₂](BF₄)₂. For clarity, all hydrogen atoms have been omitted. Selected bond lengths [Å] and angles [°]: Cu–N(1) 1.980(5), Cu–N(2) 2.153(7), Cu–N(3) 2.142(7), Cu–N(4) 2.001(6), Cu–N(5) 2.196(8), Cu–N(6) 2.213(8); N(1)–Cu–N(2) 76.8(2), N(1)–Cu–N(3) 76.7(2), N(1)–Cu–N(4) 176.8(4), N(1)–Cu–N(5) 100.0(3), N(1)–Cu–N(6) 107.3(3), N(2)–Cu–N(3) 153.5(2), N(2)–Cu–N(4) 102.7(2), N(2)–Cu–N(5) 93.6(3), N(2)–Cu–N(6) 95.3(3), N(3)–Cu–N(4) 103.7(2), N(3)–Cu–N(5) 90.2(3), N(3)–Cu–N(6) 93.3(3), N(4)–Cu–N(5) 76.8(3), N(4)–Cu–N(6) 75.9(3), N(5)–Cu–N(6) 152.6(2).

[*] Dr. M. A. Halcrow,^[+] N. K. Solanki, Dr. N. Feeder, Dr. J. E. Davies
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge CB21EW (UK)
Fax: (+44) 1223-336362
E-mail: malcolm.halcrow@ch.cam.ac.uk

Dr. E. J. L. McInnes, Dr. F. E. Mabbs
EPSRC CW EPR Service
Department of Chemistry, University of Manchester
Oxford Road, Manchester M139PL (UK)

S. Radojevic, Prof. M. McPartlin
School of Applied Chemistry, University of North London
166–220 Holloway Road, London N78DB (UK)

[+] Current address:
School of Chemistry, University of Leeds
Leeds LS29JT (UK)

[**] The authors gratefully acknowledge funding by The Royal Society (M.A.H.), the EPSRC (N.K.S., S.R.), ICI Group (N.K.S.), the University of Cambridge, and St. Catherine's College.

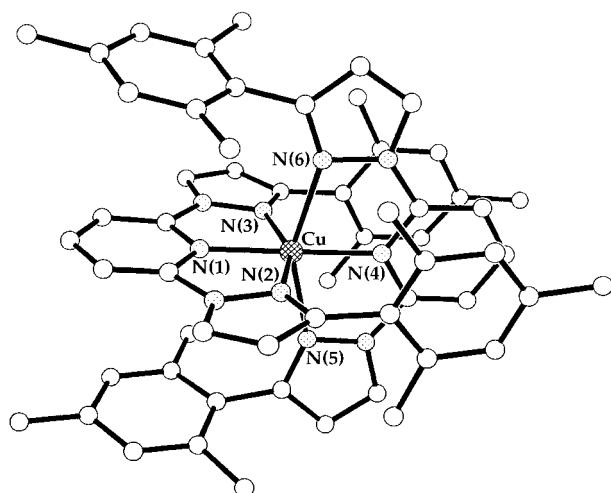


Figure 2. Perspective view of the dication of $[\text{Cu}(\text{L}^{\text{Mes}})_2](\text{ClO}_4)_2 \cdot 2\text{CH}_3\text{NO}_2$. For clarity, all hydrogen atoms have been omitted. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Cu–N(1) 1.948(6), Cu–N(2) 2.136(6), Cu–N(3) 2.142(6), Cu–N(4) 1.972(6), Cu–N(5) 2.227(6), Cu–N(6) 2.256(6); N(1)–Cu–N(2) 78.3(2), N(1)–Cu–N(3) 78.8(2), N(1)–Cu–N(4) 179.5(2), N(1)–Cu–N(5) 103.9(2), N(1)–Cu–N(6) 102.1(2), N(2)–Cu–N(3) 157.0(2), N(2)–Cu–N(4) 102.0(2), N(2)–Cu–N(5) 92.2(2), N(2)–Cu–N(6) 92.3(2), N(3)–Cu–N(4) 100.9(2), N(3)–Cu–N(5) 95.2(2), N(3)–Cu–N(6) 90.6(2), N(4)–Cu–N(5) 76.5(2), N(4)–Cu–N(6) 77.5(2), N(5)–Cu–N(6) 154.0(2).

comparison with the structure of $[\text{Cu}(\text{L}^{\text{H}})_2]^{2+}$, $[\text{Cu}(\text{L}^{\text{Mes}})_2]^{2+}$ has a slightly shorter z and longer x axis, as well as a slightly larger ligand bite angle.

All EPR spectra in this study were recorded at the Q band; simulation data are listed in Table 1. As a powder at 293 K, $[\text{Cu}(\text{L}^{\text{H}})_2](\text{BF}_4)_2$ shows an axial $g_\perp > g_\parallel > g_e$ pattern, which gains rhombic character as the temperature is lowered. In MeCN at 115 K, the same compound shows a typical $\{d_{x^2-y^2}\}^1$ spectrum.^[11] The EPR behavior of this complex in solid and solution phases thus closely resembles that of $[\text{Cu}(\text{terpy})_2]^{2+}$ salts.^[2, 5, 6] The powder EPR spectra of $[\text{Cu}(\text{L}^{\text{Mes}})_2]\text{X}_2$ ($\text{X} = \text{BF}_4^-, \text{ClO}_4^-$) are barely distinguishable and exhibit the rhombic symmetry expected from the three distinct molecular axes detected crystallographically (Figure 3a); these spectra show only small variations with decreasing temperature. The spectrum of this complex in solution at 115 K is axial

Table 1. Selected Q -band EPR parameters of $[\text{Cu}(\text{L}^{\text{H}})_2](\text{BF}_4)_2$ and $[\text{Cu}(\text{L}^{\text{Mes}})_2](\text{ClO}_4)_2$.

	T [K]	g_1	g_2	g_3	A_1 [a]	A_2 [a]	A_3 [a]
$[\text{Cu}(\text{L}^{\text{H}})_2](\text{BF}_4)_2$ (powder)	290		2.190	2.042	–	–	–
$[\text{Cu}(\text{L}^{\text{H}})_2](\text{BF}_4)_2$ (powder)	115	2.223	2.162	2.042	–	–	–
$[\text{Cu}(\text{L}^{\text{H}})_2](\text{BF}_4)_2$ (in solution) ^[b]	115	2.279	2.096	2.053	156	–	–
$[\text{Cu}(\text{L}^{\text{Mes}})_2](\text{ClO}_4)_2$ (powder)	290	2.237	2.157	2.017	104	–	94
$[\text{Cu}(\text{L}^{\text{Mes}})_2](\text{ClO}_4)_2$ (powder)	115	2.248	2.145	2.015	110	–	94
$[\text{Cu}(\text{L}^{\text{Mes}})_2](\text{ClO}_4)_2$ (in solution) ^[b]	115		2.200	2.007		77	97

[a] Hyperfine coupling constants to $^{63,65}\text{Cu}$ [10^{-4}cm^{-1}]. [b] Spectrum in MeCN/toluene (10/1).

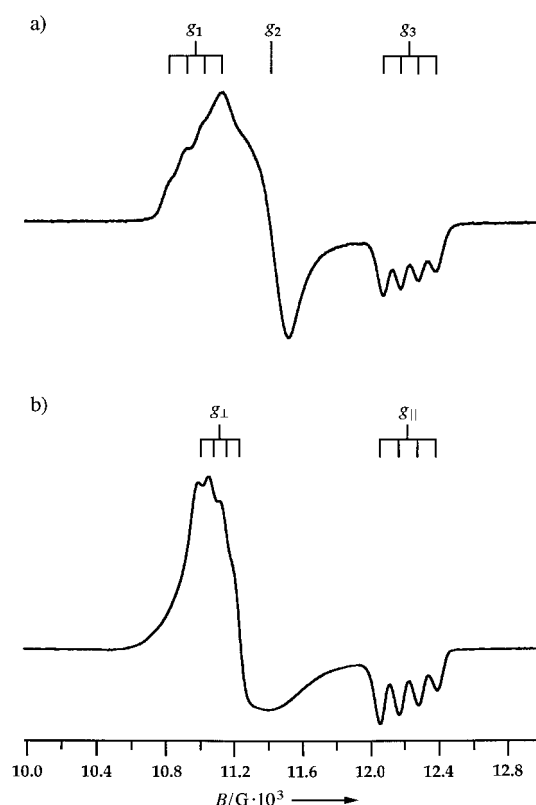


Figure 3. Q -band EPR spectra of $[\text{Cu}(\text{L}^{\text{Mes}})_2](\text{ClO}_4)_2$ as a powder at 290 K (a) and in MeCN/toluene (10/1) at 115 K (b).

(Figure 3b) and clearly shows the $g_\perp > g_\parallel \approx g_e$ pattern indicative of an approximate $\{d_{z^2}\}^1$ ground state. The nearly temperature independent g values of $[\text{Cu}(\text{L}^{\text{Mes}})_2]\text{X}_2$ as a powder and in frozen solution are consistent with an axially compressed electronic structure of $[\text{Cu}(\text{L}^{\text{Mes}})_2]^{2+}$. The spectra of both $[\text{Cu}(\text{L}^{\text{R}})_2]^{2+}$ complexes in MeCN and MeNO₂ were indistinguishable.

To conclude, we have shown that by a simple ligand substitution an unprecedented change in electronic ground state can be enforced onto a six-coordinate Cu^{II} center, from the usual $\{d_{x^2-y^2}\}^1$ structure to a $\{d_{z^2}\}^1$ form. This effect derives from steric interactions within the molecules and is thus an intrinsic molecular property rather than simply a solid-state phenomenon. In light of this result, the similarity of the solution d–d spectra of $[\text{Cu}(\text{L}^{\text{H}})_2]^{2+}$ ($\tilde{\nu}_{\text{max}} = 14.3 \times 10^3 \text{cm}^{-1}$) and $[\text{Cu}(\text{L}^{\text{Mes}})_2]^{2+}$ ($\tilde{\nu}_{\text{max}} = 14.4 \times 10^3 \text{cm}^{-1}$) is striking; this implies that, despite their different ground states, the Cu^{II} ions in these two complexes experience almost identical ligand fields. Full characterization of the electronic structures of these complexes and studies of the coordination chemistry of L^{Mes} and related ligands with other metals are in progress.

Experimental Section

L^{Mes} : To a solution of 3[5]-mesitylpyrazole^[9] (11.8 g, 0.064 mol) in diglyme (80 mL) under N_2 was added KH (2.6 g, 0.064 mol), and the mixture was stirred at room temperature for 2 h. 2,6-Dibromopyridine (7.5 g, 0.032 mol) was then added, and the mixture stirred at 130 °C for 5 d. After cooling, addition of an equal volume of water afforded a cream precipitate, which was recrystallized from THF to give white needles (7.0 g). ^1H NMR (250.1 MHz, CDCl_3): δ = 8.67 (d, J = 2.6 Hz, 2H), 7.87 (pseudo t, J = 3.4 Hz,

3H), 6.97 (s, 4H), 6.44 (d, $J = 2.6$ Hz, 2H), 2.34 (s, 12H), 2.21 (s, 6H); MS (EI): m/z : 448 $[M+H]^+$; elemental analysis calcd for $C_{29}H_{29}N_5$: C 77.8, H 6.53, N 15.6; found: C 77.3, H 6.65, N 15.4.

$[Cu(L^H)_2](BF_4)_2$: MS (FAB): m/z : 485 $[^{63}Cu(L^H)_2]^+$, 274 $[^{63}Cu(L^H)]^+$; elemental analysis calcd for $C_{22}H_{18}B_2CuF_8N_{10}$: C 40.1, H 2.75, N 21.2; found: C 39.6, H 2.74, N 20.8; UV/Vis (MeCN): $\tilde{\nu}_{max}$ $[10^3 cm^{-1}]$ (ϵ_{max} $[M^{-1} cm^{-1}]$) = 14.3 (58), 24.4 (105), 32.8 (27700), 36.7 (35100), 37.7 (31900), 40.2 (44700).

$[Cu(L^{Mes})_2](BF_4)_2$: MS (FAB): m/z : 958 $[^{63}Cu(L^{Mes})_2]^+$, 510 $[^{63}Cu(L^{Mes})]^+$; elemental analysis calcd for $C_{58}H_{58}B_2CuF_8N_{10}$: C 61.5, H 5.16, N 12.4; found: C 61.3, H 5.17, N 12.3; UV/Vis (MeCN): $\tilde{\nu}_{max}$ $[10^3 cm^{-1}]$ (ϵ_{max} $[M^{-1} cm^{-1}]$) = 14.4 (46), 24.0 (sh), 29.8 (25200), 30.6 (sh), 35.5 (sh), 36.6 (31100), 45.4 (sh).

$[Cu(L^{Mes})_2](ClO_4)_2$: elemental analysis calcd for $C_{58}H_{58}Cl_2CuN_{10}O_8$: C 60.2, H 5.05, N 12.1; found: C 59.4, H 5.03, N 11.9.

Crystal data for $[Cu(L^H)_2](BF_4)_2$: $C_{22}H_{18}B_2CuF_8N_{10}$, crystal dimensions $0.50 \times 0.50 \times 0.30$ mm, monoclinic, space group $P2_1$ (no. 4), $a = 8.4555(13)$, $b = 8.531(2)$, $c = 18.828(5)$ Å, $\beta = 96.639(13)^\circ$; $V = 1349.0(5)$ Å³, $\rho_{calcd} = 1.624$ g cm⁻³; Siemens P4 diffractometer, $4 \leq 2\theta \leq 50^\circ$, $MoK\alpha$ radiation, $\lambda = 0.71073$ Å, $\theta/2\theta$ scans, $T = 223(2)$ K; of 3515 measured reflections, 2893 were independent and 2000 were observed with $I > 2\sigma(I)$, $-10 \leq h \leq 1$, $-1 \leq k \leq 10$, $-22 \leq l \leq 22$; $R = 0.048$, $wR = 0.129$, $GOF = 0.972$ for 388 parameters, Flack parameter = $-0.02(3)$, $\Delta\rho_{max} = 0.59$ e Å⁻³. Crystal data for $[Cu(L^{Mes})_2](ClO_4)_2 \cdot 2CH_3NO_2$: $C_{60}H_{64}Cl_2CuN_{12}O_{12}$, crystal dimensions $0.30 \times 0.25 \times 0.25$ mm, monoclinic, space group $P2_1/c$ (no. 14), $a = 12.048(4)$, $b = 19.808(8)$, $c = 25.36(2)$ Å, $\beta = 99.92(4)^\circ$; $V = 5963(5)$ Å³, $\rho_{calcd} = 1.426$ g cm⁻³; Rigaku AFC7R diffractometer, $5 \leq 2\theta \leq 50^\circ$, $MoK\alpha$ radiation, $\lambda = 0.71069$ Å, $\omega/2\theta$ scans, $T = 180(2)$ K; of 12975 measured reflections, 10518 were independent and 6041 were observed with $I > 2\sigma(I)$, $0 \leq h \leq 14$, $0 \leq k \leq 23$, $-30 \leq l \leq 29$; $R = 0.083$, $wR = 0.309$, $GOF = 1.040$ for 784 parameters, $\Delta\rho_{max} = 1.10$ e Å⁻³. The structures were solved by direct methods (SHELXTL Plus^[12]) and developed by least-squares refinement against $|F^2|$ (SHELXL93^[13]). All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101277. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: March 27, 1998 [Z11650IE]

German version: *Angew. Chem.* **1998**, *110*, 2344–2346

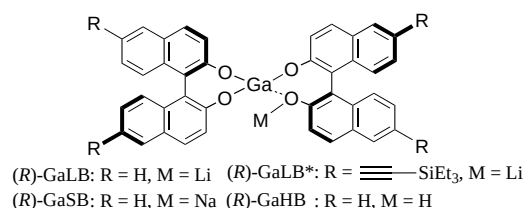
Keywords: copper • EPR spectroscopy • Jahn–Teller distortion • N ligands

- [1] B. J. Hathaway in *Comprehensive Coordination Chemistry*, Vol. 5 (Eds.: G. Wilkinson, R. D. Gillard, J. E. McCleverty), Pergamon, Oxford, **1987**, pp. 610–611.
- [2] Recent reviews: a) C. J. Simmons, *New J. Chem.* **1993**, *17*, 77–95; b) M. A. Hitchman, *Comments Inorg. Chem.* **1994**, *15*, 197–254; c) L. R. Falvello, *J. Chem. Soc. Dalton Trans.* **1997**, 4463–4475.
- [3] R. Allmann, W. Henke, D. Reinen, *Inorg. Chem.* **1978**, *27*, 378–382.
- [4] M. I. Arriortua, T. Rojo, J. M. Amigó, G. Germain, J. P. Declercq, *Acta Crystallogr. Sect. B* **1982**, *38*, 1323–1324.
- [5] J.-V. Folgado, W. Henke, R. Allmann, H. Strateimer, D. Beltrán-Porter, T. Rojo, D. Reinen, *Inorg. Chem.* **1990**, *29*, 2035–2042.
- [6] W. Henke, D. Reinen, *Z. Anorg. Chem.* **1977**, *436*, 187–200.
- [7] D. L. Jameson, K. A. Goldsby, *J. Org. Chem.* **1990**, *55*, 4992–4994.
- [8] D. L. Jameson, J. K. Blaho, K. T. Kruger, K. A. Goldsby, *Inorg. Chem.* **1989**, *28*, 4312–4314.
- [9] A. L. Rheingold, C. B. White, S. Trofimenko, *Inorg. Chem.* **1993**, *32*, 3471–3477.
- [10] A. B. P. Lever, *Inorganic Electronic Spectroscopy*, 2nd ed., Elsevier, Amsterdam, **1984**, pp. 554–572.
- [11] B. A. Goodman, J. B. Raynor, *Adv. Inorg. Chem.* **1970**, *13*, 135–362.
- [12] G. M. Sheldrick, SHELXTL Plus, PC version, Siemens Analytical Instruments Inc., Madison, WI, **1990**.
- [13] G. M. Sheldrick, SHELXL 93, Universität Göttingen, **1993**.

Enantioselective Ring Opening of Epoxides with 4-Methoxyphenol Catalyzed by Gallium Heterobimetallic Complexes: An Efficient Method for the Synthesis of Optically Active 1,2-Diol Monoethers**

Takehiko Iida, Noriyoshi Yamamoto, Shigeki Matsunaga, Hee-Gweon Woo, and Masakatsu Shibasaki*

The enantioselective ring opening of achiral epoxides by nucleophilic addition is an attractive method, which is invaluable in asymmetric synthesis.^[1] We reported recently an asymmetric ring opening reaction of epoxides with *t*BuSH that is catalyzed by a Ga–Li-bis(binaphthoxide) complex (GaLB) in the presence of 4-Å molecular sieves (Scheme 1).^[2] The high enantioselectivity of these reactions prompted us to



Scheme 1. Proposed structures of Ga–M-bis(binaphthoxide) (GaMB) and of Ga–Li-bis((6,6'-(triethylsilyl)-ethynyl)binaphthoxide) (GaLB*).

investigate the possible use of other nucleophiles. Oxygen nucleophiles are interesting candidates since their reaction with achiral epoxides provides an effective route to valuable chiral building blocks such as 1,2-diol derivatives.^[3] Quite recently Jacobsen et al. reported the enantioselective ring opening of symmetrical epoxides with carboxylic acids, and an efficient kinetic resolution of racemic terminal epoxides with water by using a (salen)Co^{II} catalyst (salen = *N,N'*-bis(salicylidene)ethylenediamine dianion).^[4] However, this type of reaction has not been realized so far with alcohols or phenols. Herein we report the development of a catalytic enantioselective ring opening of epoxides with 4-methoxyphenol by utilizing gallium heterobimetallic complexes.

Hydroxyarene derivatives, such as 4-chlorophenol, 2,4-dinitrophenol, and 4-methoxyphenol, were first examined as nucleophiles for the epoxide opening reaction [Eq. (1)]

[*] Prof. Dr. M. Shibasaki, Dr. T. Iida, N. Yamamoto, S. Matsunaga
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: mshibasa@mol.f.u-tokyo.ac.jp
Prof. Dr. H.-G. Woo
Department of Chemistry, College of Natural Science
Chonnam National University
300 Yongbong-Dong, Puk-Ku, Kwangju 500–757 (Republic of Korea)
Fax: (+82) 62-530-3389;
E-mail: hgwoo@chonnam.chonnam.ac.kr

[**] We are grateful to Prof. H. Sasai for his generous support. This study was financially supported by CREST, the Japan Science and Technology Corporation (JST), and by a Grant-in Aid for Scientific Research from the Japanese Ministry of Education, Science, and Culture.

because the corresponding aryl ether products can be converted easily into 1,2-diols.^[5] Of these hydroxyarenes, 4-methoxyphenol (**1**) showed an aptitude for the reaction with cyclohexene oxide (**3**) in the presence of (*R*)-GaLB (20 mol %) and 4-Å molecular sieves (toluene, 50 °C) (Table 1 entry 2) to give 1,2-diol monoether **10** in 48 % yield (93 % *ee*). The absolute configuration of (*1R,2R*)-**10** was determined by identifying the sense of the specific optical rotation of the corresponding 1,2-diol **17**;^[6] this was readily obtained in 76 % yield by treatment with ammonium cerium(IV) nitrate (CAN)^[7] (Scheme 2). GaLB catalysis was found to be applicable to a wide range of unfunctionalized and functionalized symmetrical epoxides (Table 1) affording: **9** (86 % *ee*), **11** (67 % *ee*), **12** (87 % *ee*), **13** (80 % *ee*), and **14** (90 % *ee*), although the yields were only modest to passable (31–75 %, entries 1 and 3–6). These reduced yields can probably be ascribed to an undesired ligand exchange of **1** for 1,1'-binaphthol, thus resulting in the formation of side products.^[8]

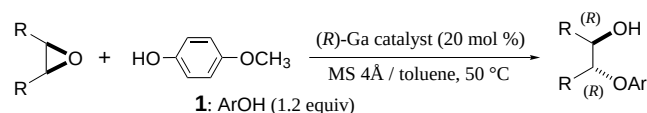
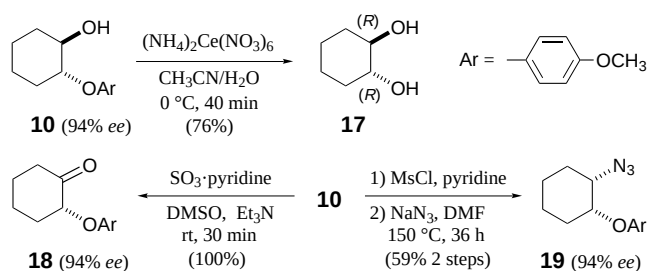


Table 1. Catalytic enantioselective epoxide ring opening with 4-methoxyphenol (**1**) promoted by gallium heterobimetallic complexes in the presence of 4-Å molecular sieves

Entry	Epoxide	Product	<i>t</i> [h]	GaLB yield [%]	<i>ee</i> [%]	<i>t</i> [h]	GaSO yield [%]	<i>ee</i> [%]
1		2 9	72 (72) ^[a]	75 (89) ^[a]	86	4	77	54
2		3 10	72 (72) ^[a]	48 (94) ^[a]	93 (4) ^[b]	4 (61) ^[b]	73 (51) ^[b]	56
3		4 11	72	31	67	4	67	58
4		5 12	72 (72) ^[a]	70 (69) ^[a]	87 (92) ^[a]	24	90	55
5 ^[c]		6 13	96	34	80	48	83	43
6 ^[d]		7 14	160	51	90	19	44	34
7		8 15	72	[e]	[e]	7	75	50
8 ^[f]		3 16	–	–	–	4	75	61

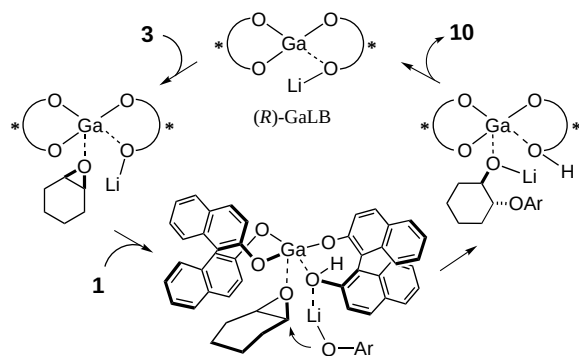
[a] Values in parentheses show the results of the GaLB* catalyzed reaction. [b] 5 mol % GaSO was used. [c] R¹ = CH₂OSiPh₂tBu. [d] R² = 2,4,6-Trimethylbenzenesulfonyl; 30 mol % GaLB was used. [e] No reaction. [f] 4-Methoxy-1-naphthol was used instead of **1**.



Scheme 2. Transformations of **10** into the optically active 1,2-diol **17**, ketone **18**, and azide **19** (yields are given in parentheses); DMSO = dimethyl sulfoxide, DMF = *N,N*-dimethylformamide, MsCl = methanesulfonyl chloride.

After several attempts,^[9] we found that the use of GaLB*, prepared from (*R*)-6,6'-bis((triethylsilyl)ethynyl)binaphthol, improved the yields of the ring opening reactions. The reason for this may be that GaLB* has a higher stability than GaLB with respect to ligand exchange.^[10] Thus **10** was obtained in 60 % yield without reduction of enantiomeric excess (Table 1, entry 2 in parentheses). In addition, **9** and **12** were obtained in good yields with 89 % *ee* and 92 % *ee*, respectively (Table 1, entries 1 and 4 in parentheses). As shown in Scheme 2, **10** could not only be converted into 1,2-diol **17** but also into α -aryloxyketone **18** and β -aryloxy azide **19** without any reduction of its optical purity.

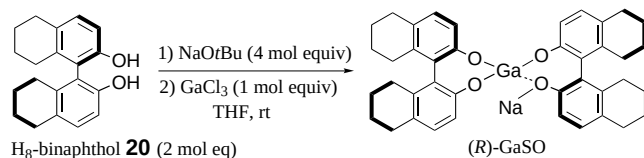
Achiral reactions of epoxides with oxygen nucleophiles are not well-known, and the epoxide opening with hydroxyarenes under common basic or acidic conditions seems to be difficult. Actually, the reaction of **3** with **1** at 50 °C did not proceed at all in the presence of catalytic and/or stoichiometric amounts of bases such as *n*BuLi, NaOtBu, KOtBu, K₂CO₃, and Cs₂CO₃. Likewise, the addition of Lewis acids such as BF₃·Et₂O and ZnCl₂ was also ineffective for the reaction. In contrast to these results, the GaLB complex showed prominent catalytic activity as mentioned above. A model for the GaLB-catalyzed epoxide-opening reaction is shown in Scheme 3. GaLB is a heterobimetallic complex^[11] composed of a lithium binaphthoxide moiety and a central gallium atom. The former appears to function as a Brønsted base by activating and controlling the orientation of **1**, and the latter seems to act as a Lewis acid by activating and controlling the orientation of **3**, thereby enabling an enantioselective ring opening of **3** with **1**.^[12] Furthermore, the addition of 4-Å molecular sieves,



Scheme 3. Model for the GaLB-catalyzed ring opening of cyclohexene oxide (**3**) with 4-methoxyphenol (**1**).

which might assist the decomplexation of **10** from the catalyst, was extremely effective in enhancing the reaction rate: The reaction of **3** in the absence of the molecular sieves (50 °C, 73 h) afforded **10** in only 5 % yield but with 95 % *ee*.

To develop even more effective catalysts, we then prepared a number of new heterobimetallic gallium complexes with various asymmetric ligands.^[13] Of these, the complexes using (*R*)-5,5',6,6',7,7',8,8'-octahydrobinaphthol (**20**: H₈-binaphthol)^[14] showed higher catalytic activities for the present reactions.^[15] The proposed structure of the Ga-Na-bis(H₈-binaphthoxide) complex (GaSO) is shown in Scheme 4.^[16]



Scheme 4. Preparation of Ga-Na-bis(H₈-binaphthoxide) (GaSO).

The reaction of **3** with **1**, catalyzed by GaSO (20 mol %), proceeded smoothly in toluene at 50 °C in only 4 h to afford **10** (73 % yield) albeit in modest enantioselectivity (56 % *ee*, Table 1, entry 2). Moreover, the catalytic amount of GaSO could be lowered to 5 mol % without serious reduction of reactivity; **10** was produced with 51 % *ee* in 61 % yield (entry 2 in parentheses). A wide range of symmetrical epoxides could be subjected to GaSO catalyzed ring opening with **1** to give good to excellent yields (except for **7**), although the enantioselectivities were only modest (43–58 % *ee*). It is noteworthy that the ring opening of the acyclic substrate **8** readily proceeded in 7 h at 50 °C in the presence of GaSO (20 mol %) to afford **15** (50 % *ee*, 75 % yield), although the GaLB catalysis had been ineffective for **8** (Table 1, entry 7). Furthermore, the use of the sterically more hindered 4-methoxy-1-naphthol gave a slightly higher enantiomeric excess (Table 1, entry 8).

In contrast to GaLB, sodium was the most suitable alkali metal to make the heterobimetallic gallium H₈-binaphthoxide complex effective.^[17] It seems likely that different Ga–O bond lengths account for the observed alkali metal ion effects. Furthermore, the GaSO and the GaLB catalysts seem to be equipped with characteristic dihedral angles of the axial biaryl groups.^[18]

We have developed the first catalytic enantioselective ring opening of epoxides with hydroxyarenes using gallium heterobimetallic complexes such as GaLB, GaLB*, and GaSO, in combination with 4-Å molecular sieves. The reaction of a wide range of epoxides with 4-methoxyphenol catalyzed by GaLB afforded synthetically versatile 1,2-diol monoethers in excellent enantiomeric excess and reasonable yields. Further applications with other nucleophiles such as ROH, RNH₂, HN₃, and/or HCN, as well as experiments for further tuning the catalysts are under study.

Experimental Section

All reactions were carried out under argon.

General procedure: A mixture of powdered 4-Å molecular sieves (400 mg), dried at 180 °C under reduced pressure for 6 h prior to use, and a 0.05 M solution of (*R*)-GaLB^[2] (4.0 mL, 0.20 mmol) prepared in THF:Et₂O:hexane (6:1:1) was evaporated in vacuo to remove the solvents. A solution of 4-methoxyphenol (**1**) (149 mg, 1.2 mmol) in toluene (2.0 mL) and cyclopentene oxide (**2**) (87.5 μL, 1.0 mmol) were added to the residue at room temperature, and the mixture was stirred at 50 °C for 72 h. The resultant mixture was diluted with Et₂O (30 mL) and filtered over a Celite pad to remove the molecular sieves. The filtrate was washed successively with 5 % aqueous citric acid (10 mL), 1 N aqueous NaOH (10 mL), saturated aqueous NH₄Cl (10 mL), and brine (10 mL), then dried over MgSO₄, and evaporated in vacuo. The residue was purified by flash chromatography (SiO₂, hexane: acetone (10:1)) to afford (*1R,2R*)-**9** (157 mg, 75 %) in 86 % *ee* as a colorless oil; $[\alpha]_D^{25} = -36.0$ (*c* = 1.08 in CHCl₃); ¹H NMR (270 MHz, CDCl₃): δ = 1.58–1.84 (m, 4H; CHHCH₂CHH), 2.01–2.16 (m, 3H; CHHCH₂CHH overlapped with OH), 3.75 (s, 3H, CH₃), 4.28 (m, 1H, CHOH), 4.43 (m, 1H; CHAr), 6.83 (m, 4H; Ar); ¹³C NMR (678 MHz, CDCl₃): δ = 21.0, 29.8, 32.5, 55.7, 77.2, 85.2, 114.6, 116.6, 151.9, 153.8; the enantiomeric excess of **9** was determined by HPLC analysis on a chiral stationary phase (Daicel Chiralpak AS, eluent: hexane:2-propanol (90:10)); flow-rate: 1.0 mL min^{−1}; retention time: 10.1 min for the *1S,2S* isomer and 25.5 min for the *1R,2R* isomer; detection at 254 nm).

Received: March 24, 1998 [Z 11633 IE]

German version: *Angew. Chem.* **1998**, *110*, 2383–2386

Keywords: asymmetric catalysis • asymmetric synthesis • epoxides • gallium • oxygen nucleophiles

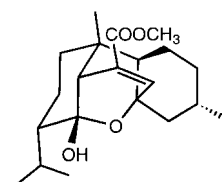
- [1] For a review, see D. M. Hodgson, A. R. Gibbs, G. P. Lee, *Tetrahedron* **1996**, *52*, 14361–14384.
- [2] T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–4784.
- [3] For an alternative approach to the synthesis of optically active 1,2-diols by the catalytic asymmetric dihydroxylations of olefins, which was realized by K. B. Sharpless et al., see H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
- [4] a) E. N. Jacobsen, F. Kakiuchi, R. G. Konsler, J. F. Larrow, M. Tokunaga, *Tetrahedron Lett.* **1997**, *38*, 773–776; b) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938.
- [5] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, New York, **1991**, pp. 46–47.
- [6] (*1R,2R*)-**17**: $[\alpha]_D^{25} = -42$ (*c* = 0.19 in H₂O); literature value of $[\alpha]_D^{25} = -46.5$ (*c* = 1.6 in H₂O); N. A. B. Wilson, J. Read, *J. Chem. Soc.* **1935**, 1269–1273.
- [7] T. Fukuyama, A. A. Laird, L. M. Hotchkiss, *Tetrahedron Lett.* **1985**, *26*, 6291–6292.
- [8] The product from the ring opening of **3** with binaphthol was obtained in 24 % yield (based on binaphthol).
- [9] The use of (*R*)-6,6'-bis(trimethylsilyl)-, dibromo-, or dimethoxybinaphthol, 3,3'-dimethyl- or difluorobinaphthol, 3-hydroxymethylbinaphthol,^[19] and 4,4'-dibromo- or dimethylbinaphthol gave less satisfactory results.

- [10] Another application of 6,6'-bis((trialkylsilyl)ethynyl)-binaphthol is in catalytic asymmetric nitroaldol reactions: a) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *23*, 7388–7389; b) E. Takaoka, N. Yoshikawa, Y. M. A. Yamada, H. Sasai, M. Shibasaki, *Heterocycles* **1997**, *46*, 157–163.
- [11] For a review on heterobimetallic catalysts, see a) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236–1256; b) H. Steinhagen, G. Helmchen, *Angew. Chem.* **1996**, *108*, 2489–2492; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2339–2342.
- [12] Ga-Na-bis(binaphthoxide)^[20] (41 % yield, 52 % *ee*), alkali metal-free Ga-bis(binaphthoxide)^[21] (22 % yield, 37 % *ee*), or Al-Li-bis(binaphthoxide)^[22] (20 % yield, 72 % *ee*) gave much less satisfactory results.
- [13] The use of 10,10'-dihydroxy-9,9'-biphenanthryl,^[23] 3,3'-dihydroxy-4,4'-biphenanthryl (BIPO),^[24] and $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-2-methyl-2-phenyl-1,3-dioxolane-4,5-dimethanol (TADDOL)^[25] gave unsatisfactory results.
- [14] D. J. Cram, R. C. Helgeson, S. C. Peacock, L. J. Kaplan, L. A. Domeier, P. Moreau, K. Koga, J. M. Mayer, Y. Chao, M. G. Siegel, D. H. Hoffman, G. D. Y. Sogah, *J. Org. Chem.* **1978**, *43*, 1930–1946.
- [15] For asymmetric alkylations catalyzed by a Ti(H₈-binaphthoxide) complex see: a) A. S. C. Chan, F.-Y. Zhang, C.-W. Yip, *J. Am. Chem. Soc.* **1997**, *119*, 4080–4081; b) F.-Y. Zhang, A. S. C. Chan, *Tetrahedron: Asymmetry*, **1997**, *8*, 3651–3655.
- [16] GaSO was prepared in a similar manner to GaLB (from a 1:2 ratio of GaCl₃ and disodium H₈-binaphthoxide). This ratio was found to give the maximum reactivity and enantiomeric excess. The influence of the ratio of GaCl₃ and disodium H₈-binaphthoxide on the reaction of **3** with **1** at 50 °C is as follows: 1:1 (10 % yield, 30 % *ee*), 1:1.5 (53 % yield, 53 % *ee*), 1:2 (73 % yield, 56 % *ee*), 1:2.5 (65 % yield, 49 % *ee*), 1:3 (trace). The structure of GaSO is supported by positive-ion laser-desorption/ionization time-of-flight mass spectrometry (LDI-TOF; reflectron mode): *m/z*: 701 ([*M*⁺+Na] for ⁷¹Ga).
- [17] Ga-Li-bis(H₈-binaphthoxide) (39 % yield, 33 % *ee*) and Ga-K-bis(H₈-binaphthoxide) (58 % yield, 52 % *ee*) gave less satisfactory results.
- [18] By comparison with Takaya's catalytic enantioselective hydrogenations with the H₈(S)-[2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl] complex (H₈-BINAP), T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki, H. Takaya, *J. Org. Chem.* **1996**, *61*, 5510–5516.
- [19] M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 2329–2330.
- [20] T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1368–1372.
- [21] This complex was prepared from GaCl₃ (1 mmol), 1,1'-(*R*)-binaphthol (2 mmol), and *n*BuLi (3 mmol) in THF at room temperature.
- [22] T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem.* **1996**, *108*, 103–105; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104–106.
- [23] F. Toda, K. Tanaka, *J. Org. Chem.* **1988**, *53*, 3607–3609.
- [24] K. Yamamoto, K. Nada, K. Okamoto, *J. Chem. Soc. Chem. Commun.* **1985**, 1065–1066.
- [25] a) D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo, A. Wonnacott, *Helv. Chim. Acta.* **1987**, *70*, 954–974; b) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, J. Sugimori, *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345.

Total Synthesis of Chatancin**

Josef Aigner, Edda Gössinger,* Hanspeter Kählig, Georg Menz, and Karin Pflugseder

Chatancin (**1**) was discovered within a large program to screen physiologically active compounds from marine invertebrates.^[1] This tetracyclic diterpene, which is isolated from a soft coral (*Sarcophyton sp.*), is an antagonist of the platelet activating factor (PAF) and thus of potential use against hypotension and respiratory, inflammatory, and cardiovascular diseases.^[2] The physiological activity as well as the fact that this oxygen-bridged dodecahydrophenanthrene derivative with its unusual



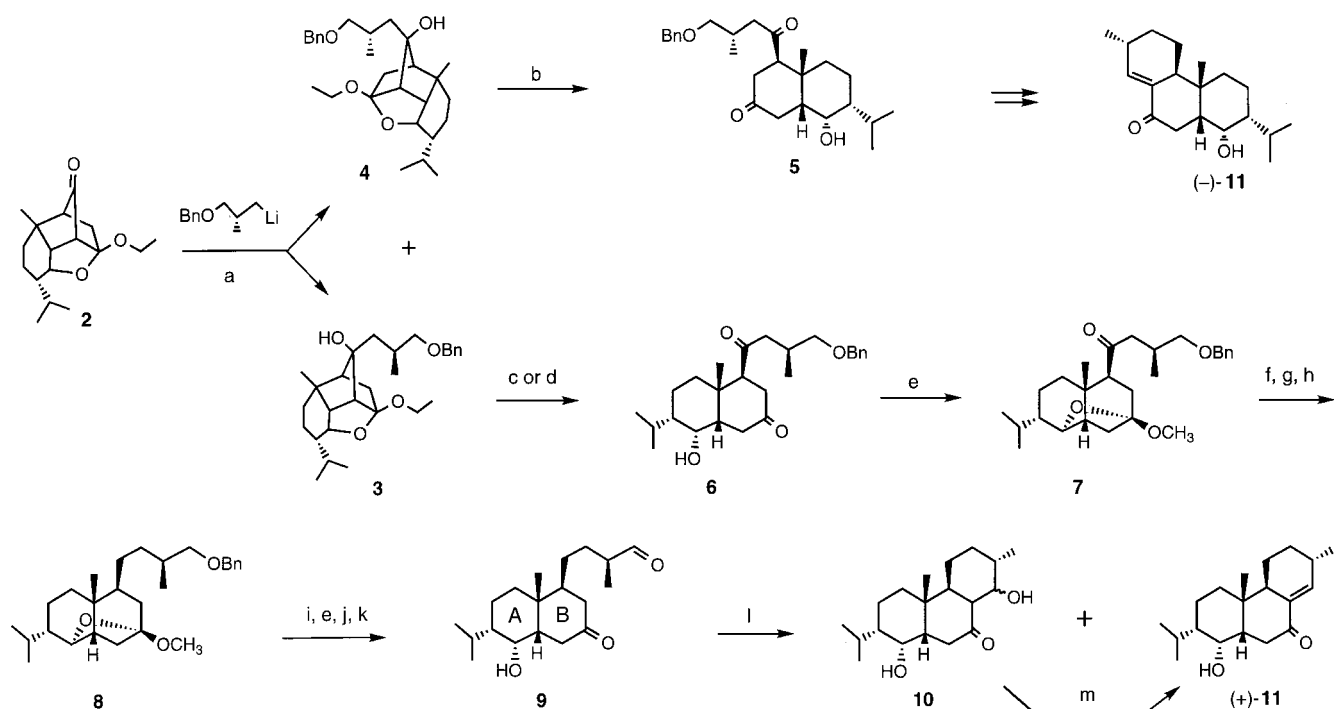
chatancin **1**

substitution pattern and the seven stereogenic centers has never been synthesized so far prompted us to look for a suitable stereoselective access to **1**.

We chose a protocol for the stereoselective preparation of substituted *cis*-decalinones developed in our laboratory^[3] to achieve the highly stereoselective generation of four of the seven stereogenic centers of **1** starting from easily available symmetrical compounds. To develop an enantiomerically pure synthesis the third carbocycle was fashioned by attaching a small chiral side chain that is readily accessible from methyl (*R*)-3-hydroxyisobutyrate.^[4] Thus five of the seven stereogenic centers of **1** could be established. This part of our synthetic efforts has been published earlier.^[5] Starting with thymoquinone and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene the tricyclic Diels–Alder adduct was formed, which was converted into the tetracyclic ketone ($\pm$ -**2** by stereo- and regioselective group transformations. Racemic ($\pm$ -**2**) was allowed to react with (*S*)-3-lithio-2-methyl-1-benzyloxypropane to yield the diastereomeric tertiary alcohols (+)-**3** and (–)-**4** (Scheme 1). However, attempts to save chiral reagent by using only half an equivalent of the alkyllithium compound failed. This is due to a significantly higher reaction rate for the formation of the undesired diastereomer (–)-**4** than for (+)-**3**. The structure of (–)-**4** was established unambiguously by X-ray crystal structure analysis. Twofold ring opening of the diastereomeric pair (+)-**3** and (–)-**4** under acidic conditions led to the diastereomeric *cis*-decalinones (+)-**6** and (–)-**5**, respectively. Owing to the large

[*] Prof. E. Gössinger, Dr. J. Aigner, Dr. H. Kählig, Dr. G. Menz, Dr. K. Pflugseder
Institut für Organische Chemie der Universität
Währingerstrasse 38, A-1090 Wien (Austria)
Fax: (+43) 131-367-2280
E-mail: edgo@felix.orc.univie.ac.at

[**] Attempts towards Enantiomerically Pure Preparation of Chatancin, part 2. This work was supported by the Austrian Science Foundation (project no. P09643). J.A. and K.P. thank the Universität Wien for a research scholarship. We are grateful to Dr. Aiya Sato, New Lead Research Laboratories, Sankyo, for a small sample of natural chatancin and for spectra of chatancin and a few derivatives, as well as for the communication of experimental data concerning the stability of chatancin. In particular, we have to thank Miss Anna Fuchs for her cooperation. Part 1: reference [5].



Scheme 1. a) Toluene/ $\text{O}(\text{C}_2\text{H}_5)_2$ (1/2), $-60^\circ\text{C} \rightarrow \text{RT}$ (room temperature); RT, 22 h, 89%; b) $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$ (10 equiv), CH_3CN , -15°C , 4 h, 85%; c) $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$ (10 equiv), CH_3CN , -15°C , 2 d, 95%; d) 5 M LiClO_4 , H^+ , $\text{O}(\text{C}_2\text{H}_5)_2$, RT, 6 h, 99%; e) $\text{HC}(\text{OCH}_3)_3$, H^+ , CH_3OH , RT, 4 h, 97%; f) LiAlH_4 , $\text{O}(\text{C}_2\text{H}_5)_2$, $0^\circ\text{C} \rightarrow \text{RT}$; RT, 4 h, 92%; g) ClCOCOOCH_3 , $\text{C}_5\text{H}_5\text{N}$, DMAP, 30°C , 3 h, 97%; h) Bu_3SnH , AIBN, toluene, reflux, 8 h, 70–75%; i) H_2 , $\text{Pd}(10\%) / \text{C}$, CH_2Cl_2 , RT, 15 h, 85%; j) Dess–Martin periodinane, CH_2Cl_2 , RT, 2 h, 93%; k) 2% aq HCl / THF (1/1), RT, 40 min, 99%; l) KOtBu , HOtBu , argon, RT, 45 min; m) H^+ , CHCl_3 , argon, RT, 60 h, 86% over two steps. Bn = benzyl, DMAP = 4-dimethylaminopyridine, AIBN = azobisisobutyronitrile.

difference in the rates of fragmentation, the two decalinones could be separated kinetically.^[5]

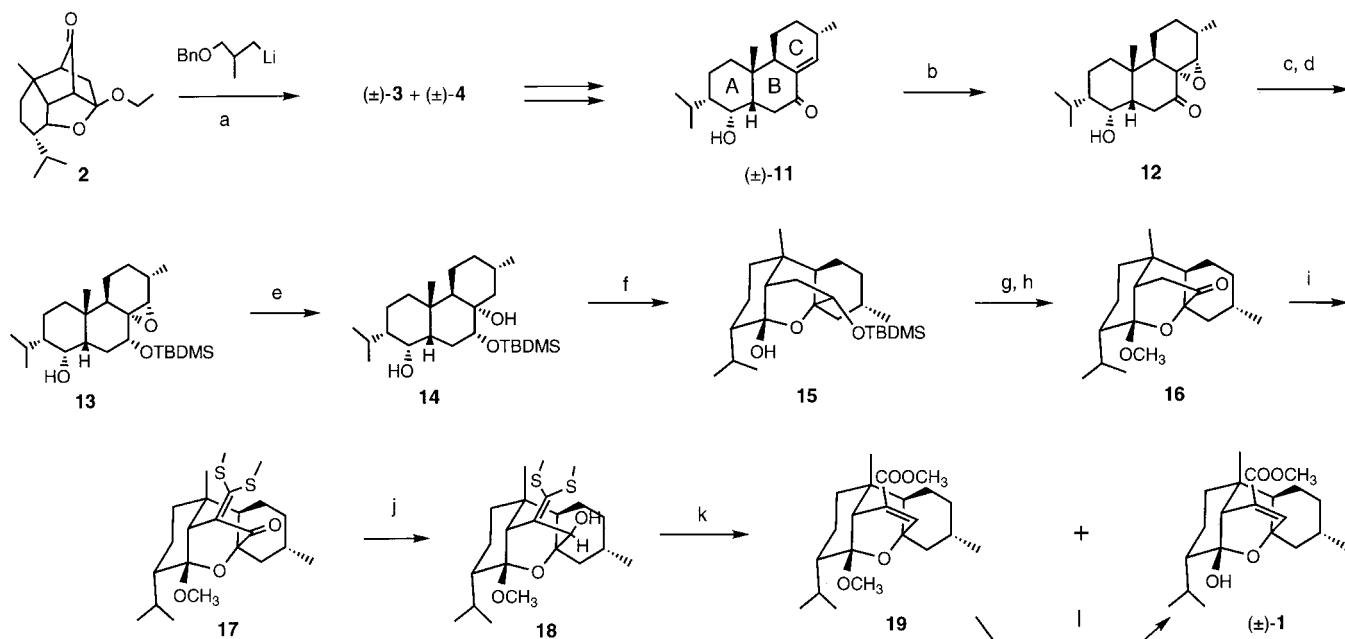
Enantiomerically pure (+)-6^[5] is then used to synthesize the dodecahydrophenanthrenone. To achieve the deoxygenation of the now superfluous keto group of the side chain, the cyclic ketone has to be protected as the tricyclic ketal (–)-7. To overcome the severe steric hindrance the following strategy is chosen: Ketone (–)-7 is reduced with lithium aluminum hydride to the epimeric alcohols, which are esterified to the mixed oxalic esters^[6] and subsequently treated with tributylstannane to yield (–)-8.^[7] Hydrogenolysis of the benzyl group is accompanied by partial ring cleavage to the hydroxy ketone. Since protection of the hydroxyl group of ring A is essential, the cyclic ketal is regenerated by treatment with methyl orthoformate in acidic methanol. Subsequently, the primary alcohol is oxidized to the aldehyde with Dess–Martin periodinane,^[8] and the cyclic ketal is hydrolyzed with aqueous acid. Treatment of ketoaldehyde 9 with base leads to the oxygen-sensitive mixture of aldol (–)-10 and enone (+)-11, which is completely dehydrated to (+)-11 with acidic chloroform.

The same reaction sequence starting with the diastereomeric decalinone derivative (–)-5 leads exclusively to enone (–)-11 by total epimerization of the stereogenic center adjacent to the aldehyde moiety under the conditions of the aldol reaction. This unexpected result is advantageous for several reasons. First, it constitutes a stereodivergent synthesis of (+)- and (–)-11 and, consequently, (+)-chatancin and unnatural (–)-chatancin in enantiopure form for further

physiological testing without loss of starting material. Second, if only one of the two enantiomers is required, chatancin can be prepared more economically due to the fact that the alcohol 4 that is preferentially formed can be used in both cases. As a consequence, to obtain natural (+)-chatancin only half an equivalent of (*R*)-3-lithio-2-methyl-1-benzyloxypropane has to be utilized to produce enone (+)-11 via (+)-4. Third, the entire starting material can be transformed into (±)-chatancin by utilizing the racemic alkyl lithium compound.

Because of the preliminary difficulties we experienced with the next steps of our synthetic plan,^[9] we decided to investigate the further route towards chatancin with the racemic enone (±)-11. Thus, 2-methyl-1,3-propanediol is converted into 3-benzyloxy-2-methylpropanol.^[10] Transformation of the primary alcohol into the iodide and subsequent halogen–metal exchange with *tert*-butyllithium yields racemic 3-lithio-2-methyl-1-benzyloxypropane,^[5] which is treated with ketone (±)-2. The diastereomeric mixture of the tertiary alcohols (±)-3 and (±)-4 obtained is converted into (±)-11 as described for (+)-11 (Scheme 2).

Enone (±)-11 is treated with *m*-chloroperbenzoic acid to yield the *endo*-epoxide 12 through the directing effect of the *endo* hydroxyl group^[11] of ring A. Thus, the sixth stereogenic center of chatancin is established. To obtain reproducible good yields it is essential to add radical scavengers, as reported by Kishi et al.^[12] The keto functionality of 12 is stereoselectively reduced with sodium borohydride. To suppress the directing effect of the newly generated hydroxyl



Scheme 2. a) Toluene/ $O(C_2H_5)_2$ (1/2), $-60^\circ\text{C} \rightarrow \text{RT}$; RT, 22 h, 89%; b) *m*-chloroperbenzoic acid, 2,6-di-*tert*-butyl-4-methylphenol, CH_2Cl_2 , 4°C , 12 h, 85%; c) NaBH_4 , CH_3OH , $0^\circ\text{C} \rightarrow \text{RT}$; RT, 4 h; d) TBDMSCl, $(C_2H_5)_3\text{N}$, DMF, RT, 2 h, 70% over two steps; e) $\text{LiB}(C_2H_5)_3\text{H}$ (8 equiv), $(C_2H_5)_2\text{O}$, reflux, 12 h, 93%; f) Jones reagent, acetone, 0°C , 20 min, 91%; g) $\text{HC}(\text{OCH}_3)_3$, H^+ ; CH_3OH , 0°C , 40 min, 96%; h) Dess–Martin periodinane, CH_2Cl_2 , RT, 2 h, 90%; i) LiHMDS , HMPTA, THF, -78°C , 2 h; CS_2 , 0°C , 2 h; LiHMDS , -78°C , 30 min; CH_3I , RT, 2 h, 77%; j) $\text{LiB}(C_2H_5)_3\text{H}$, $(C_2H_5)_2\text{O}$, reflux, 1 h, 99%; k) PIFA, CH_3OH , RT, 12 h; l) 0.2% aq HCl/THF (1/1), RT, 12 h, 30% over two steps. TBDMS = *tert*-butyldimethylsilyl, LiHMDS = lithium bis(trimethylsilyl)amide, HMPTA = hexamethyl phosphoramide phenyliodine(III) bis(trifluoroacetate).

group in ring B, this alcohol is regioselectively protected as silylether **13** prior to the reductive epoxide cleavage. However, many attempts at selective epoxide opening were necessary. Finally, prolonged heating of **13** with a large excess of lithium triethylborohydride affords high yields of the tertiary alcohol **14**. Jones oxidation of the secondary hydroxyl group in ring A leads via the hydroxy ketone to the hemiketal **15** by spontaneous cyclization. Treatment of **15** with methyl orthoformate in acidic methanol yields the mixed cyclic ketal with simultaneous loss of the silyl group. With this ketal formation the last of the seven stereogenic centers of chatancin is established.

The secondary alcohol is then oxidized to ketone **16** to permit the introduction of the carboxylic group. All efforts to use activated carbonic acid derivatives to attach the ester group of **1** by Claisen condensation failed. Due to the severe steric hindrance only enol esters are formed. The ester group is successfully introduced with the following reaction sequence: The lithium enolate of **16** is allowed to react with carbon disulfide and is subsequently treated with methyl iodide under basic conditions. The keto group of the dimethyldithioketalketene **17** thus obtained is quantitatively reduced to the *exo*-hydroxyl group in **18**. The conversion of the dithioketalketene into the methyl carboxylate is achieved by reaction with phenyliodine(III) bis(trifluoroacetate)^[13] accompanied by spontaneous dehydration to yield *O*-methylchatancin (**19**) as the main product and small amounts of chatancin (($\pm$)-**1**). Treatment with highly diluted aqueous HCl also converts **19** into racemic chatancin. Thus, chatancin is prepared in 33 steps with an overall yield of 0.7% starting from thymoquinone and 5,5-dimethoxy-1,2,3,4-tetrachlorocy-

clopentaene. The spectroscopic data of synthetic chatancin are in full agreement with those of natural chatancin.

Received: March 2, 1998 [Z11539 IE]
German version: *Angew. Chem.* **1998**, *110*, 2386–2389

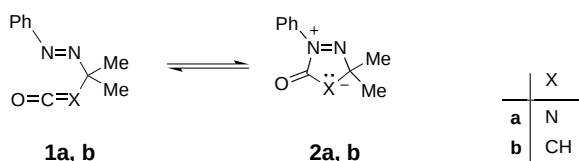
Keywords: chatancin • natural products • terpenoids • total synthesis

- [1] M. Sugano, T. Shindo, A. Sato, Y. Iijima, T. Oshima, H. Kuwano, T. Hata, *J. Org. Chem.* **1990**, *55*, 5803–5805.
- [2] P. Braquet, L. Touqui, T. Y. Shen, B. B. Vargrafitg, *Pharm. Rev.* **1987**, *39*, 97–145; K. Cooper, M. Parry, *Annu. Rep. Med. Chem.* **1989**, *24*, 81–90.
- [3] a) E. Gössinger, R. Müller, *Tetrahedron* **1989**, *45*, 1377–1390; b) K. Böhm, E. Gössinger, R. Müller, *Tetrahedron* **1989**, *45*, 1391–1408; c) E. Gössinger, R. Müller, T. Pitterna, *Tetrahedron* **1990**, *46*, 407–422.
- [4] J. D. White, M. Kawasaki, *J. Org. Chem.* **1992**, *57*, 5292–5300.
- [5] W. D. Aichberger, J. Aigner, E. Gössinger, K. Gruber, G. Menz, *Monatsh. Chem.* **1994**, *125*, 991–1010.
- [6] G. A. Flynn, D. W. Beight, *Tetrahedron Lett.* **1988**, *29*, 423–426.
- [7] a) A. Kakefuda, Y. Yoshimura, T. Sasaki, A. Matsuda, *Tetrahedron* **1993**, *49*, 8513–8528; b) Y. Yoshimura, T. Iino, A. Matsuda, *Tetrahedron Lett.* **1991**, *32*, 6003–6006.
- [8] a) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; b) R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899–2899.
- [9] Spectroscopic data and experimental details will be published together with the synthesis of enantiopure chatancin.
- [10] E. L. Eliel, L. Clawson, D. E. Knox, *J. Org. Chem.* **1985**, *50*, 2707–2710.
- [11] H. B. Henbest, R. A. L. Wilson, *J. Chem. Soc.* **1957**, 1958–1965.
- [12] Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, *J. Chem. Soc. Chem. Commun.* **1972**, 64–65.
- [13] G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 287–290.

Azomethine Imines in Four- and Five-Membered Rings: Stable Cyclic Valence Isomers of an α -(Phenyldiazenyl)ketocarbene**

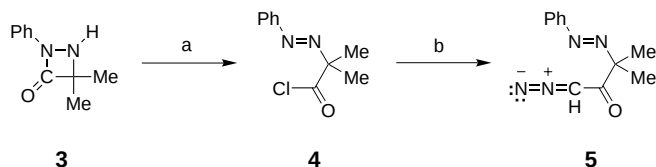
Joachim G. Schantl,* Arno S. Rettenbacher, and Klaus Wurst

The investigation of intramolecular interactions of functional groups and the resulting differences in reactivity constitutes a fascinating research area. For example, the reactivity of 1-(1-isocyanato-1-methylethyl)-2-phenyl-1-diazene (**1a**) is partly due to its cyclic valence isomer **2a**^[1] (Scheme 1). The synthesis of 3-methyl-3-(2-phenyl-1-diazenyl)-1-buten-1-one (**1b**) was attempted in order to explore the extent to which the cyclic valence isomer **2b** might contribute to this reactivity.



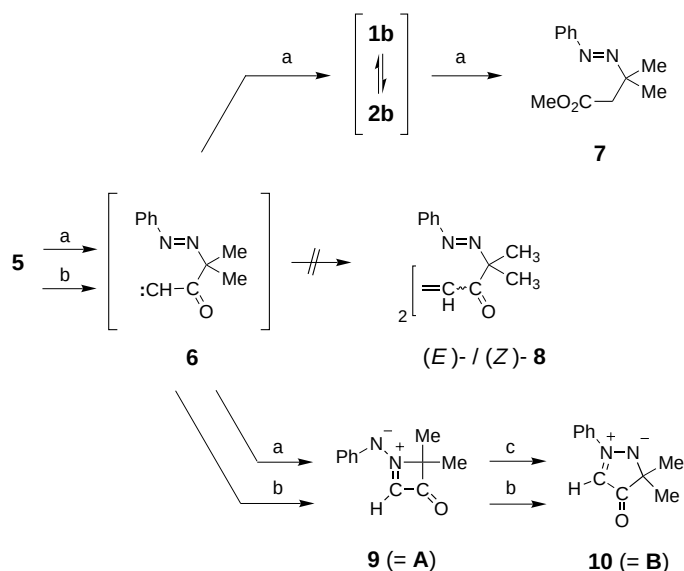
Scheme 1. Equilibrium between **1a** and its cyclic valence isomer **2a**^[1] as well as the conceivable analogous isomerism between **1b** and **2b**.

To this end, 4,4-dimethyl-2-phenyldiazetid-3-one (**3**)^[2] was transformed with *tert*-butyl hypochlorite into 2-methyl-2-(2-phenyl-1-diazenyl)propanoic chloride (**4**),^[3] which in turn was treated with diazomethane to give 1-diazo-3-methyl-3-(2-phenyl-1-diazenyl)butan-2-one (**5**, Scheme 2). In the presence



Scheme 2. Synthesis of **5**: a) *t*BuOCl, CH₂Cl₂, 0 °C; b) CH₂N₂, Et₂O.

of methanol and under conditions which promote the Wolff rearrangement^[4] diazoketone **5** extruded nitrogen to give two products: Methyl 3-methyl-3-(2-phenyl-1-diazenyl)butanoate (**7**) is the product expected from Wolff rearrangement to ketene **1b** via the ketocarbene **6** (Scheme 3). In addition, a second product **A** was isolated as light yellow crystals. The



Scheme 3. Synthesis of **7** and **9**: a) CH₃OH, C₆H₅CO₂Ag, Et₃N. Synthesis of **9** and **10**: b) CH₂Cl₂, [Rh₂(O₂CCH₃)₄], 0 °C. Isomerization of **9** to **10**: c) AcOH, N₂, 50 °C.

elemental analysis of **A** indicated the loss of dinitrogen from the starting material **5**. Transformation of **5** into **A** was faster in the presence of catalytical amounts of dimeric rhodium(II) acetate; however, under these conditions a 10:1 mixture of **A** and another yellow compound **B** was obtained. Compound **B** was also formed upon treatment of **5** with acetic acid at 70 °C as well as by acetic acid induced isomerization of **A** at 50 °C.

Heteronuclear multiple bond connectivity (HMBC) ¹³C NMR experiments with **A** and **B** revealed the same carbon connectivity as in diazoketone **5**, thus ruling out structures **1b** and **2b**. The presence of an ion at *m/z* 377 in the fast atom bombardment (FAB) mass spectrum of **A** and **B** could be indicative of ketocarbene dimers (*E*)-**8** and (*Z*)-**8**, which are typical side products of reactions involving a ketocarbene intermediate.^[4] The structure assignments of **A** and **B** were ultimately achieved by X-ray analyses.^[5,6] **A** and **B** turned out to be *N*-(2,3-dihydro-2,2-dimethyl-3-oxo-1-azetio)phenyl-imide (**9**, Figure 1) and 3,4-dihydro-3,3-dimethyl-4-oxo-1-phenyl-imide (**10**, Figure 2).

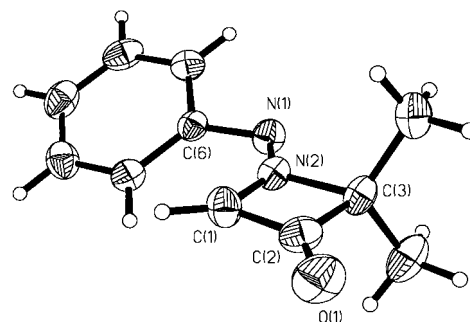


Figure 1. Molecular structure of **9** (thermal vibrational ellipsoids drawn at the 50 % probability level). Selected bond lengths [Å] and angles [°]: C(1)–C(2) 1.420(3), C(2)–C(3) 1.534(3), C(2)–O(1) 1.224(2), C(3)–N(2) 1.519(2), N(2)–C(1) 1.358(2), N(1)–N(2) 1.276(2), N(1)–C(6) 1.421(2); C(1)–C(2)–C(3) 91.2(2), C(2)–C(3)–N(2) 82.12(13), C(3)–N(2)–C(1) 94.28(14), N(2)–C(1)–C(2) 92.4(2), C(1)–C(2)–O(1) 136.8(2), O(1)–C(2)–C(3) 131.9(2), C(3)–N(2)–N(1) 123.3(2), N(1)–N(2)–C(1) 142.4(2), N(2)–N(1)–C(6) 117.6(2).

[*] Prof. Dr. J. G. Schantl, Mag. A. S. Rettenbacher
Institut für Organische Chemie der Universität
Innrain 52a, A-6020 Innsbruck (Austria)
Fax: (+ 43) 512-507-2855
E-mail: joachim.schantl@uibk.ac.at

Dr. K. Wurst
Institut für Allgemeine, Anorganische und
Theoretische Chemie der Universität
Innrain 52a, A-6020 Innsbruck (Austria)

[**] This work has been supported by the Fonds zur Förderung der Wissenschaftlichen Forschung (FWF; project no. P10462-MOB).

nyl-2*H*-pyrazol-1-ium-2-ide (**10**, Figure 2), respectively. Both products are valence isomers of ketocarbene **6** and contain an azomethine imine functionality as part of a four-membered ring in **9** and a five-membered ring in **10**.

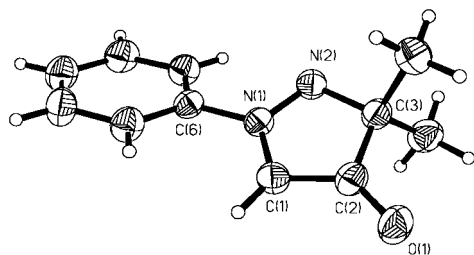


Figure 2. Molecular structure of **10** (thermal vibrational ellipsoids drawn at the 50% probability level). Selected bond lengths [Å] and angles [°]: C(1)–C(2) 1.402(3), C(2)–C(3) 1.516(3), C(2)–O(1) 1.246(2), C(3)–N(2) 1.468(3), N(2)–N(1) 1.303(2), N(1)–C(1) 1.351(3), N(1)–C(6) 1.449(3); C(1)–C(2)–C(3) 105.0(2), N(2)–C(3)–C(2) 105.9(2), C(3)–N(2)–N(1) 104.0(2), N(2)–N(1)–C(1) 118.5(2), N(1)–C(1)–C(2) 106.6(2), C(1)–C(2)–O(1) 130.0(2), O(1)–C(2)–C(3) 125.0(2), N(2)–N(1)–C(6) 118.2(2).

Crystal structure analyses of **9** and **10** revealed N–N bond lengths of 1.276(2) and 1.303(2) Å, respectively; both are greater than the length of N–N double bonds in typical diazenes (1.25 Å).^[8] The endocyclic azomethine N–C bond lengths of 1.358(2) Å in **9** and 1.351(3) Å in **10** correspond well with those of delocalized systems (e.g. 1.34 Å in pyridine^[8]). The C–O and C–C bonds (between carbonyl and azomethine carbon atoms) in the four-membered ring **9** (1.224(2) and 1.420(3) Å) are comparable to those of an α,β -unsaturated ketone (1.22 and 1.46 Å);^[8] the corresponding distances in the five-membered ring **10** (1.246(2) and 1.402(3) Å) are indicative of some enolate contribution. Both heterocycles are planar, and the C–O and C–H bonds as well as the N–N (in **9**) and N–C_{phenyl} bonds (in **10**) are in the plane of the respective heterocyclic rings; only the tetrahedral carbon atom of **10** is situated slightly above the plane defined by the four other ring members (dihedral angle 2.17(25)°). This deviation from planarity may be due to crystal packing, because the ¹H and ¹³C NMR spectra show only one methyl signal. The significant difference of the ¹³C NMR shift ($\Delta\delta \approx 20$) of the carbonyl groups of **9** and **10** is remarkable. The IR carbonyl frequencies of both compounds are distinctly different ($\tilde{\nu} = 1764$ and 1661 cm^{−1}, respectively, in CHCl₃), reflecting not only the different ring sizes but also some enolate contribution in **10**. The most intensive IR absorption of **9** at $\tilde{\nu} = 1514$ cm^{−1} (in CHCl₃) may be due to the vibration of the polar exocyclic N–N bond;^[9] compound **10** is lacking a similar absorption of the endocyclic N–N bond.

The terminal carbonyl atom of the azomethine imine functionality of **9** and **10** is attached to a carbonyl group. Numerous examples of azomethine imines (open-chain, or partly or completely incorporated into a ring system) can be found in the literature.^[10] However, the only known azomethine imines found within a four-membered ring are 1-methylen-3-oxo-1,2-diazetid-1-ium-2-ides which have an exocyclic ylide carbon atom.^[11] Thus, **9** represents a novel class of four-membered-ring azomethine imines with an exocyclic imide nitrogen atom. On the other hand, in **10** the

azomethine imine functionality is completely embedded in the five-membered ring. The known analogues of this type of compound are sydnones;^[12] thus, **10** represents the first example of a carba-sydnone in which the ring oxygen atom of a sydnone is replaced by a tetrahedral carbon atom. Although the mesoionic aromatic nature of sydnones is absent in **10**, this does apparently not alter the remarkable thermodynamic stability of azomethine imine **10**.

The isoelectronic character of diazene and carbonyl groups prompts a comparison between the α -(phenyldiazenyl)ketocarbene **6** (derived from diazoketone **5**) and β -carbonylketocarbenes which can be similarly generated in situ from β -carbonyl diazoketones. The formal analogy is perpetuated in the azomethine imine functionalities of **9** and **10** (the two stable valence isomers of ketocarbene intermediate **6**) and in carbonyl ylides, which are transient cyclic valence isomers of carbonyl ketocarbenes.^[13] In the latter species, the oxygen atom of the carbonyl group is capable of interacting intramolecularly with the carbene center to form a carbonyl ylide with a five-membered ring as an interceptable dipolar intermediate. By contrast, both diazene nitrogen atoms of α -(phenyldiazenyl)ketocarbene **6** interact with the carbene center to afford both four- and five-membered azomethine imines. Apparently, valence isomer **9** is the kinetically controlled product; treatment with acid at 50–70 °C induces its conversion into the thermodynamically more stable isomer **10**. Both novel azomethine imines **9** and **10** provide promising possibilities for further syntheses that are currently under investigation.

Experimental Section

4: To a stirred and ice-cooled solution of **3**^[2] (2.0 g, 11.4 mmol) in absolute dichloromethane (30 mL) was added *tert*-butyl hypochlorite (1.9 g, 17 mmol). After 10 min the reaction mixture was evaporated in vacuo (0.005 mbar). Because of its tendency to decompose, the residual lachrymatory yellow oil **4** (2.4 g, 100%) was directly employed for the following reaction. *R_F* = 0.75 (silica gel; petroleum ether/diethyl ether 1/1). IR (film) $\tilde{\nu} = 3065, 2990, 2937, 1793$ (C=O) cm^{−1}; ¹H NMR (200 MHz, CDCl₃): $\delta = 1.70$ (s, 6H; 2CH₃), 7.46–7.54 (m, 3H; 2,4,6-H (C₆H₃)), 7.70–7.79 (m, 2H; 3,5-H (C₆H₃)); ¹³C NMR (50 MHz, CDCl₃):^[14] $\delta = 23.4$ (CH₃), 82.1 (C–CH₃), 122.6, 129.1, 131.5, 151.5, (3,5-, 2,6-, 4-, 1-C (C₆H₃)), 176.4 (C=O).

5: Dropwise addition of a solution of **4** (2.4 g, 11.4 mmol) in absolute diethyl ether (100 mL) to a stirred solution of diazomethane in diethyl ether (140 mL, ca 0.26 M) induced gas evolution. Excess of diazomethane and the solvent were removed in vacuo. The residual red oil was brought to crystallization by scratching at −100 °C: orange crystals **5** (2.17 g, 88%), m.p. 43–45 °C (pentane fraction), *R_F* = 0.72 (petroleum ether/diethyl ether 1/1). IR (KBr): $\tilde{\nu} = 3139, 3065, 2986, 2935, 2154, 2103$ (C=N=N), 1617 (C=O), 1460, 1374, 1354, 766, 695 cm^{−1}; ¹H NMR (200 MHz, CDCl₃): $\delta = 1.47$ (s, 6H; 2CH₃), 5.72 (s, 1H; HC–N),^[15] 7.45–7.50 (m, 3H; 2,4,6-H (C₆H₃)), 7.68–7.74 (m, 2H; 3,5-H (C₆H₃)); ¹³C NMR (50 MHz, CDCl₃):^[14] $\delta = 22.9$ (CH₃), 53.6 (HC–N), 78.5 (C–CH₃), 122.3, 129.1, 131.0, 151.9 (3,5-, 2,6-, 4-, 1-C (C₆H₃)), 196.5 (C=O).

7 and 9: To a stirred solution of **5** (0.5 g, 2.31 mmol) in absolute methanol (50 mL) were added ten drops of a solution of silver benzoate (1.0 g) in triethylamine (9.1 g) (Newman's reagent^[16]). Gas evolution ceased after about 15 min, and a few more drops of the reagent were added, whereupon silver metal began gradually to deposit. Monitoring by thin-layer chromatography (TLC) indicated completion of the reaction after 2 h. The precipitate was filtered off, and the solvent was removed in vacuo from the

filtrate. The residue was subjected to flash chromatography (silica gel (10 g), petroleum ether/diethyl ether 1/1) to afford two products:

Yellow oil **7** (0.28 g, 55%), b.p. 100 °C (0.1 mbar); n_D^{20} = 1.5520; R_F = 0.65 (petroleum ether/diethyl ether 60/40). IR (film): $\tilde{\nu}$ = 3065, 2986, 2935, 1738 (C=O), 1468, 1444, 1374, 1354, 1214, 772, 695 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ = 1.45 (s, 6H; 2CH₃), 2.77 (s, 2H; CH₂), 3.65 (s, 3H; OCH₃), 7.39–7.45 (m, 3H; 2,4,6-H (C₆H₅)), 7.60–7.67 (m, 2H; 3,5-H (C₆H₅)); ^{13}C NMR (50 MHz, CDCl_3):^[14] δ = 25.1 (C–CH₃), 44.0 (CH₂), 51.3 (OCH₃), 68.8 (C–CH₃), 122.0, 128.9, 130.2, 152.0 (3,5-, 2,6-, 4-, 1-C (C₆H₅)), 171.9 (C=O).

Yellow crystals **9** (0.15 g, 35%), m.p. 85 °C (petroleum ether); R_F = 0.50 (petroleum ether/diethyl ether 1/1); R_F = 0.72 (diethyl ether). IR (KBr): $\tilde{\nu}$ = 3114, 3069, 2979, 2935, 1770 (C=O), 1751 (C=O), 1495, 1374, 1354, 772, 689 cm^{-1} ; IR (CHCl₃): $\tilde{\nu}$ = 3030, 3018, 1764 (C=O), 1514 (N=N), 804, 683 cm^{-1} ; UV/Vis (CHCl₃): λ_{max} (log ϵ) = 241 (3.79), 348 nm (4.31); ^1H NMR (200 MHz, CDCl_3): δ = 1.70 (s, 6H; 2CH₃), 6.57 (s, 1H; HC–N), 7.20–7.30 (m, 3H; 2,4,6-H (C₆H₅)), 7.38–7.50 (m, 2H; 3,5-H (C₆H₅)); ^{13}C NMR (50 MHz, CDCl_3):^[14] δ = 19.6 (C–CH₃), 94.3 (C–CH₃), 117.8 (HC–N), 121.7, 127.1, 129.4, 147.4 (3,5-, 4-, 2,6-, 1-C (C₆H₅)), 184.5 (C=O); EI-MS (70 eV) m/z (%): 188 (38) [M^+], 133 (74) [M^+ – NCHCO], 118 (68) [M^+ – Me₂C=C=O], 91 (100) [$\text{C}_6\text{H}_5\text{N}^+$], 77 (60) [C_6H_5^+], 69 (63) [$\text{HC}=\text{NCMe}_2^+$], 42 (58) [$\text{CH}_2=\text{CHCH}_3^+$]; FAB-MS (NOBA): m/z (%): 377 (23) [$2M^++H$], 189 (100) [M^++H], 188 (29) [M^+]; elemental analysis calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$: C 70.19, H 6.43, N 14.88; found: C 70.65, H 6.59, N 15.11.

10: Slow addition of **5** (1.0 g, 4.62 mmol) to a stirred solution of 98% acetic acid (10 mL) at 5 °C induced a vigorous gas evolution and a strong exothermic reaction requiring efficient external cooling. After the gas evolution has ceased the mixture was stirred at 70 °C for 30 min before the solvent was distilled off in vacuo. The residue was dissolved in ether, the solution was washed with a saturated solution of sodium bicarbonate and with water until neutral, and dried over MgSO_4 . The solid residue after removal of the solvent was recrystallized from petroleum ether/diethyl ether (1/1): dark yellow crystals **10** (0.69 g, 80%), m.p. 100 °C, R_F = 0.05 (petroleum ether/diethyl ether 1/1). IR (KBr): $\tilde{\nu}$ = 3114, 3069, 2973, 2922, 1636 (C=O), 1476, 1367, 759, 683 cm^{-1} ; IR (CHCl₃): $\tilde{\nu}$ = 1661 (C=O) cm^{-1} ; UV/Vis (CHCl₃): λ_{max} (log ϵ) = 257 (3.85), 376 nm (3.71); ^1H NMR (200 MHz, CDCl_3): δ = 1.44 (s, 6H; 2CH₃), 7.13 (s, 1H; HC–N), 7.50–7.64 (m, 3H; 2,4,6-H (C₆H₅)), 7.80–7.87 (m, 2H; 3,5-H (C₆H₅)); ^{13}C NMR (50 MHz, CDCl_3):^[14] δ = 21.5 (C–CH₃), 78.4 (C–CH₃), 113.7 (HC–N), 121.4, 129.6, 131.9, 140.9 (3,5-, 2,6-, 4-, 1-C (C₆H₅)), 204.2 (C=O); EI-MS (70 eV) m/z (%): 188 (43) [M^+], 104 (95) [$\text{C}_6\text{H}_5\text{NCH}^+$], 77 (100) [C_6H_5^+]; FAB-MS (NOBA): m/z (%): 377 (17) [$2M^++H$], 189 (100) [M^++H]; elemental analysis calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$: C 70.19, H 6.43, N 14.88; found: C 70.37, H 6.55, N 14.97.

9 and **10** from **5**: To a stirred solution of **5** (0.5 g, 2.31 mmol) in dichloromethane (10 mL) at 0 °C was added [$\text{Rh}_2(\text{O}_2\text{CCH}_3)_4$] (< 1 mg), setting off a vigorous gas evolution. After 12 h the solvent was distilled off in vacuo at room temperature, and the residual oil was separated by flash chromatography (silica gel (10 g), diethyl ether) to provide **9** (0.39 g, 90%) and **10** (0.04 g, 9%).

Received: March 19, 1998 [Z116091E]

German version: *Angew. Chem.* **1998**, *110*, 2346–2349

Keywords: azo compounds • carbenes • imines • isomerizations • rearrangements

- [1] a) J. G. Schantl, H. Gstach, *Monatsh. Chem.* **1985**, *116*, 1051–1064; b) H. Gstach, P. Seil, J. G. Schantl, A. Gieren, T. Hübner, J. Wu, *Angew. Chem.* **1986**, *98*, 1111–1112; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1132–1133.
- [2] J. G. Schantl, J. J. Daly, M. Decristoforo, *Tetrahedron Lett.* **1987**, *28*, 6577–6580.
- [3] The parent acid of **4** is unknown; attempts to prepare the acid resulted in decarboxylation indicating the similar reactivity of β -keto- and α -diazenylcarboxylic acids.
- [4] H. Meier, K.-P. Zeller, *Angew. Chem.* **1975**, *87*, 52–63; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32–43.

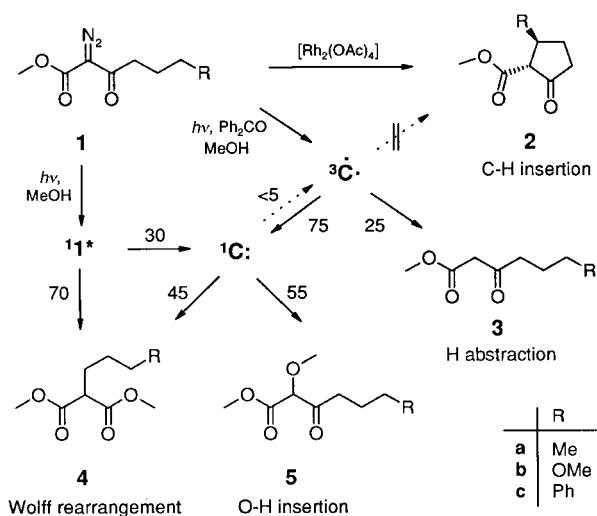
- [5] a) Crystal structure analysis of **9** ($\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$, M_r = 188.23): crystal size $0.60 \times 0.40 \times 0.11$ mm, monoclinic, space group $P21/c$ (no. 14), a = 12.337(1), b = 6.823(1), c = 12.263(1) Å, β = 99.47(1)°, V = 1018.2(2) Å³, Z = 4, $F(000)$ = 400, ρ_{calcd} = 1.228 g cm^{−3}, T = 213 K; Siemens P4 diffractometer, $\text{MoK}\alpha$ (λ = 0.71073 Å), μ = 0.081 mm^{−1}. Data were measured with ω scans and corrected for Lorentz and polarization effects; of 1081 reflections collected, 1017 were independent and 854 with $I \geq 2\sigma(I)$; structure solution by direct methods (SHELXS-86) and refinement against F^2 (SHELXL-93)^[7] of 128 parameters with GOF = 1.058. Hydrogen atoms were placed in calculated positions. $R1$ = 0.0306 (against $|F|$), $wR2$ = 0.0737 (against $|F^2|$). b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100588. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [6] Crystal structure analysis of **10** ($\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$, M_r = 188.23):^[5b] crystal size $0.60 \times 0.30 \times 0.28$ mm, triclinic, space group $P\bar{1}$ (no. 2), a = 5.352(1), b = 8.601(1), c = 11.022(1) Å, α = 77.95(1), β = 85.60(1), γ = 84.96(1), V = 493.38(12) Å³, Z = 2, $F(000)$ = 200, ρ_{calcd} = 1.267 g cm^{−3}, T = 203 K, μ = 0.083 mm^{−1}. Data were measured with ω scans and corrected for Lorentz and polarization effects; of 1549 reflections collected, 1107 were independent and 972 with $I \geq 2\sigma(I)$. Structure solution by direct methods (SHELXS-86) and refinement against F^2 (SHELXL-93)^[7] of 128 parameters with GOF = 1.044; $R1$ = 0.0396 (against $|F|$), $wR2$ = 0.1077 (against $|F^2|$); max./min. residual electron density 0.168/−0.179 e Å^{−3}.
- [7] G. M. Sheldrick, SHELXL93, Program for crystal structure refinement, Universität Göttingen, **1993**.
- [8] M. J. S. Dewar, W. Thiel, *J. Am. Chem. Soc.* **1977**, *99*, 4907–4917.
- [9] D. Lin-Vien, N. B. Colthup, W. G. Fateley, J. G. Grasselli, *The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules*, Academic Press, San Diego, **1991**, pp. 196–198.
- [10] a) R. Huisgen, *Angew. Chem.* **1963**, *75*, 604–637; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598; b) C. G. Stuckwisch, *Synthesis* **1973**, 469–483; c) R. Grashey in *1,3-Dipolar Cycloaddition Chemistry, Vol. 1* (Ed.: A. Padwa), Wiley, New York, **1984**, pp. 733–817.
- [11] a) R. B. Greenwald, E. C. Taylor, *J. Am. Chem. Soc.* **1968**, *90*, 5272–5273; b) P. C. Ip, K. Ramakrishnan, J. Warkentin, *Can. J. Chem.* **1974**, *52*, 3671–3675; c) K. Ramakrishnan, J. B. Fulton, J. Warkentin, *Tetrahedron* **1976**, *32*, 2685–2688; d) E. C. Taylor, N. F. Haley, R. J. Clemens, *J. Am. Chem. Soc.* **1981**, *103*, 7743–7752.
- [12] F. H. C. Stewart, *Chem. Rev.* **1964**, *64*, 129–147.
- [13] A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223–269.
- [14] The assignment of ^{13}C signals is based on DEPT and HSQC experiments.
- [15] The chemical shift $\delta(\text{HC–N})$ varies with the concentration of **5** from 5.72 (20 mg mL^{−1}) to 5.10 (100 mg mL^{−1}).
- [16] M. S. Newman, P. F. Beal, *J. Am. Chem. Soc.* **1950**, *72*, 5163–5165.

Intramolecular Reactivity of Triplet Carbonylcarbenes

Johannes Fien and Wolfgang Kirmse*

α -Diazocarbonyl compounds have a long history of useful applications in organic chemistry.^[1] Intramolecular insertion into C–H bonds and addition to π systems is mediated by transition metal catalysts, such as $[\text{Rh}_2\text{L}_4]$.^[2] These reactions involve metal carbenoids and provide opportunities for asymmetric syntheses with a chiral catalyst. The Wolff rearrangement is the major reaction induced by photolysis or thermolysis of α -diazo ketones.^[1, 3] The [1,2] shift that leads to ketenes proceeds in the singlet state, accompanying or following the loss of N_2 . The ground state of carbonylcarbenes is triplet, as attested by ESR spectroscopy.^[4] However, the reactivity of triplet carbonylcarbenes has received little attention, except that nonstereospecific addition reactions with alkenes and abstraction of hydrogen from the solvent were observed in sensitized photolyses of diazomalones.^[5] Our studies of functionalized arylcarbenes revealed that geometrical constraints affect the participation of singlet and triplet states.^[6] This experience prompted us to explore the intramolecular reactivity of triplet carbonylcarbenes.

The photolysis of methyl 2-diazo-3-oxoheptanoate (**1a**)^[7] in methanol afforded **4a** (86 %, Wolff rearrangement) and **5a** (14 %, O–H insertion).^[8] In the presence of benzophenone as a sensitizer **3a** was formed in addition to **4a** and **5a** (Scheme 1). Neither direct nor sensitized photolysis induced



Scheme 1. Reaction pathways for the decomposition of methyl 2-diazo-3-oxo-6-R-hexanoates (**1**) in methanol. Numbers are averages for **1a**–**1c**.

cyclization to give **2a**, although **2a** is readily obtained from **1a** under Rh^{II} catalysis.^[7] To facilitate the intramolecular abstraction of hydrogen, methoxy and phenyl groups were

introduced. However, **1b** and **1c** behaved very much like **1a**.^[9] On sensitization the amount of **3** (a triplet product) and **5** (a singlet product) increase at the expense of **4**, as illustrated for **1a** in Figure 1.^[10] These observations indicate that 1) on direct

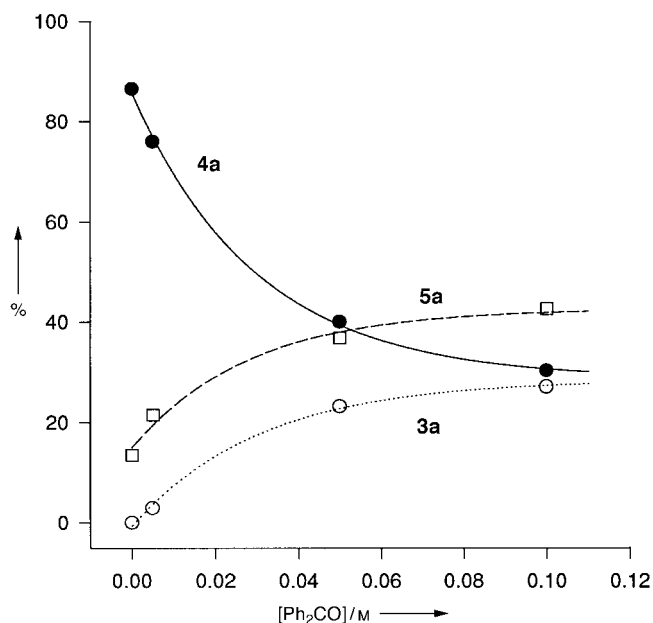


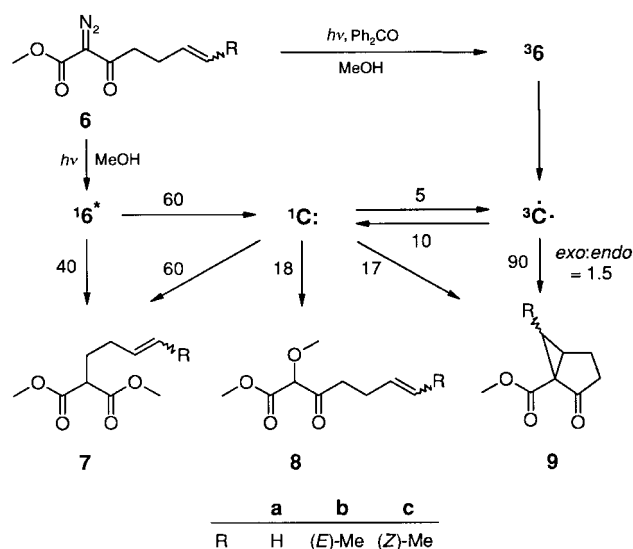
Figure 1. Photolyses of **1a** in methanol with benzophenone as sensitizer. Product distributions (%) are shown as functions of the concentration of benzophenone.^[8, 10]

photolysis a large fraction of **4** arises from the excited diazo compound **1**^{*} and 2) spin inversion of the triplet carbene is faster than hydrogen abstraction from the solvent, $k_{\text{TS}} > k_{\text{T}}$. A quantitative evaluation is shown in Scheme 1; the numbers are averages for **1a**–**c** from which the individual species differ by ± 2 . Conformational effects suggested earlier that the Wolff rearrangement can proceed in concert with the extrusion of nitrogen.^[11] This notion is fully confirmed by the present, entirely different, approach.

With unsaturated analogues of **1**, such as methyl 2-diazo-3-oxo-6-heptenoate (**6a**),^[12] the triplet carbene undergoes intramolecular addition to the double bond to give **9a** (Scheme 2). As shown in Figure 2, benzophenone sensitization minimizes the Wolff rearrangement ($\rightarrow 9\%$) and O–H insertion ($\rightarrow 3\%$), so that $k_{\text{TS}} < k_{\text{T}}$. Relative to intramolecular addition, abstraction of hydrogen from the solvent is negligible in methanol (< 0.01), competitive in ethanol (0.68), and predominant in 2-propanol (1.8). The stereochemistry of the cyclopropanation was probed with **6b**^[12] and **6c**.^[13] Incomplete retention of configuration was observed in direct photolyses, whereas complete sensitization led to nearly stereorandom addition (Table 1).^[14] The data indicate that small amounts of intersystem crossing occurs in both directions; the numbers recorded in Scheme 2 are averages for **6b** and **6c**.

If the double bond is separated from the carbene by four rather than three carbon atoms, the intramolecular addition is only slightly affected (**10a**^[15] $\rightarrow$ **11a** versus **6a** $\rightarrow$ **9a**). With five carbon atoms interposed, however, the yield of the bicyclic

[*] Prof. Dr. W. Kirmse, Dr. J. Fien
Fakultät für Chemie der Universität
Universitätsstrasse 150, D-44780 Bochum (Germany)
Fax: (+49) 234-7094-353
E-mail: kirmse@xenon.orch.ruhr-uni-bochum.de



Scheme 2. Reaction pathways for photolyses of **6** in methanol. Numbers are averages for **6b** and **6c**.

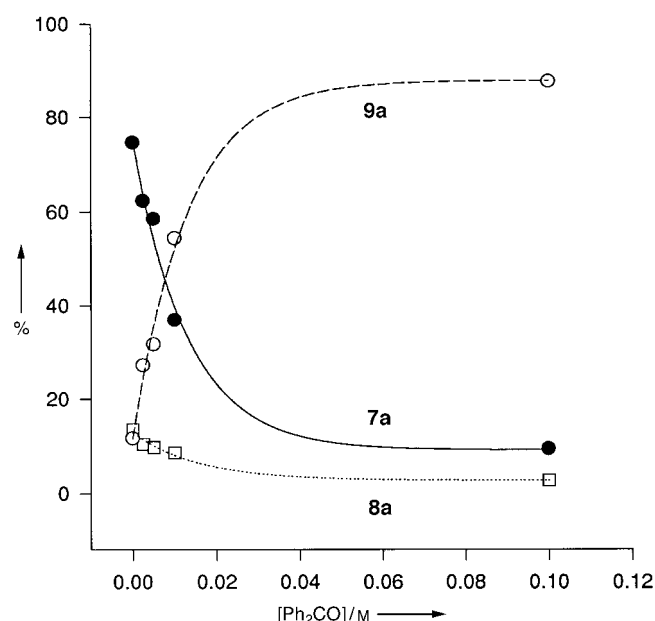


Figure 2. Photolyses of **6a** in methanol with benzophenone as sensitizer. Product distributions (%) are shown as functions of the concentration of benzophenone.^[8, 10]

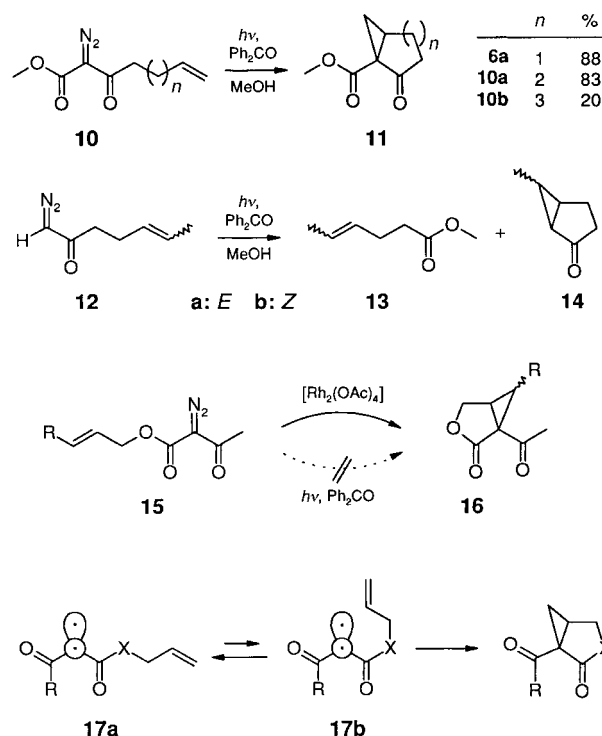
Table 1. Photochemically induced intramolecular addition reactions of carbonylcarbenes.^[a]

Precursor	Product	[Ph ₂ CO]=0		[Ph ₂ CO]→∞	
		[%]	<i>exo:endo</i>	[%]	<i>exo:endo</i>
6b	9	11.3	15	91.3	1.6
6c	9	13.8	0.14	92.8	1.4
12a	14	2.5	11	46.7	2.3
12b	14	3.0	0.30	51.4	1.7

[a] Solvent: methanol. Product distributions extrapolated to $t=0$.

adduct drops to 20 % (**10b**^[9] → **11b**). The remaining products arise by abstraction of hydrogen atoms from the solvent (11 %) and intersystem crossing, which leads eventually to O–H insertion (37 %) and Wolff rearrangement (32 %).

Scheme 3). The methoxycarbonyl group present in **6** and **10** assists the intramolecular addition but is not indispensable. Triplet carbonylcarbenes, generated by sensitized photolyses of 1-diazo-5-hepten-2-ones (**12**),^[16] cyclize less efficiently than



Scheme 3. Structural and conformational effects influencing the intramolecular reactivity of triplet carbonylcarbenes.

analogous dicarbonylcarbenes (Table 1). Approximately 50 % of Wolff rearrangement and divergent stereoselectivities of **12a** and **12b** point to substantial triplet $\rightarrow$ singlet interconversion ($k_{\text{TS}} \approx k_{\text{r}}$).

Sensitized photolyses of 2-alkenyl 2-diazo-3-oxobutanoates (**15**)^[17] by benzophenone do not give rise to the bicyclic lactones **16** (which are formed, however, under Cu^[17] or Rh^[18] catalysis). The product distributions obtained from **15** are similar to those from **1**, rather than to those from **6**. The failure of the intermediate triplet carbenes to attack the double bond is attributed to conformational effects. The X–C bond of **17** must assume the *s-E* conformation (X = O, $\angle$ O–C–O–C = 180°) or the skew conformation **17b** (X = CH₂, $\angle$ O–C–C–C = 120°) in order for the alkene to approach the half-filled σ orbital, which is the reactive site of the triplet carbene. Relative to the most stable *s-Z* conformer **17a** ($\angle$ O–C–X–C = 0°), the energy difference is much smaller for ketones (for example, $\Delta E \approx 8$ kJ mol^{–1} for 2-butanone)^[18] than for esters (for example, $\Delta E \approx 35$ kJ mol^{–1} for ethyl acetate).^[19, 20]

In summary, in contrast to 2-alkylarylcarbenes^[6] triplet carbonylcarbenes do not abstract hydrogen from δ - or ε -C-H bonds. Intramolecular addition to double bonds, leading to five- and six-membered rings, occurs with dicarbonylcarbenes $\text{RCO-C-CO-CH}_2(\text{CH}_2)_n\text{CH=CHR'}$ and (less readily) with carbonylcarbenes $\text{H-C-CO-CH}_2(\text{CH}_2)_n\text{CH=CHR'}$, but fails with (alkenyloxycarbonyl)carbenes RCO-C-CO-O-

$(\text{CH}_2)_n\text{CH}=\text{CHR}'$. Intersystem crossing to the singlet state is a major reaction of all triplet carbonylcarbenes that are not rapidly scavenged intramolecularly. Thus, with the exceptions outlined above, the lifetimes of carbonylcarbenes are controlled by the rate of spin inversion rather than by the reactivity of the triplet ground state.

Received: March 10, 1998 [Z11568IE]
German version: *Angew. Chem.* **1998**, *110*, 2352–2355

Keywords: carbenes • cyclizations • diazo compounds • rearrangements

- [1] Reviews: a) H. Zollinger, *Diazo Chemistry II*, VCH, Weinheim, **1995**; b) M. Regitz, G. Maas, *Diazo Compounds*, Academic Press, London, **1986**; c) *The chemistry of diazonium and diazo groups* (Ed. S. Patai), Wiley, Chichester, **1978**.
- [2] Reviews: a) M. P. Doyle, M. A. McKervey, *Chem. Commun.* **1997**, 983–989; b) A. Padwa, D. J. Austin, *Angew. Chem.* **1994**, *106*, 1881–1899; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1797–1814; c) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160; d) M. P. Doyle, *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305–316; e) J. Adams, D. M. Spero, *Tetrahedron* **1991**, *47*, 1765–1808; f) G. Maas, *Top. Curr. Chem.* **1987**, *137*, 75–253; g) M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919–939.
- [3] Review: H. Meier, K.-P. Zeller, *Angew. Chem.* **1975**, *87*, 52–63; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32–43.
- [4] Review: W. Sander, G. Bucher, S. Wierlacher, *Chem. Rev.* **1993**, *93*, 1583–1621.
- [5] a) M. Jones, Jr., W. Ando, M. E. Hendrick, A. Kulczycki, Jr., P. M. Howley, K. F. Hummel, D. S. Malament, *J. Am. Chem. Soc.* **1972**, *94*, 7469–7479; b) W. Ando, T. Hagiwara, T. Migita, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1951–1952; c) H. Tomioka, M. Itoh, S. Yamakawa, Y. Izawa, *J. Chem. Soc. Perkin Trans. 2* **1980**, 603–609.
- [6] a) G. Hömberger, A. E. Dorigo, W. Kirmse, K. N. Houk, *J. Am. Chem. Soc.* **1989**, *111*, 475–477; b) W. Kirmse, G. Hömberger, *ibid.* **1991**, *113*, 3925–3934; c) M. Guth, W. Kirmse, *Acta Chem. Scand.* **1992**, *46*, 606–613; d) W. Kirmse, I. S. Özkir, D. Schnitzler, *J. Am. Chem. Soc.* **1993**, *115*, 792–793; e) W. Kirmse, D. Schnitzler, *Tetrahedron Lett.* **1994**, *35*, 1699–1702; f) W. Kirmse, W. Konrad, D. Schnitzler, *J. Org. Chem.* **1994**, *59*, 3821–3829; g) M. Dorra, K. Gomann, M. Guth, W. Kirmse, *J. Phys. Org. Chem.* **1996**, *9*, 598–610; h) F. Gotzhein, W. Kirmse, *Tetrahedron Lett.* **1997**, *38*, 1373–1376, 1377–1380; i) W. Kirmse, W. Konrad, I. S. Özkir, *Tetrahedron* **1997**, *53*, 9935–9964; k) W. Kirmse, B. Krzossa, *Tetrahedron Lett.* **1998**, *39*, 799–802.
- [7] a) S. Hashimoto, N. Watanabe, S. Ikegami, *Tetrahedron Lett.* **1990**, *31*, 5173–5174; b) H. Brunner, K. Wutz, M. P. Doyle, *Monatsh. Chem.* **1990**, *121*, 755–764.
- [8] All product distributions in this paper were extrapolated to $t=0$ in order to eliminate the effects of secondary photolyses.
- [9] Alkylation of the dianion of methyl 3-oxobutanoate (S. N. Huckin, L. Weiler, *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087) was followed by transfer of the diazo group with $\text{TsN}_3/\text{Et}_3\text{N}$ (M. Regitz, A. Liedhegener, *Chem. Ber.* **1966**, *99*, 3128–3147) to obtain α -diazo- β -oxo esters.
- [10] The dependence of product distributions on the concentration of benzophenone is reasonably approximated by exponential functions, $f = a \pm b \exp(-c[\text{Ph}_2\text{CO}])$ (lines in Figures 1 and 2). Data for complete sensitization ($[\text{Ph}_2\text{CO}] \rightarrow \infty$) were obtained by extrapolation; for example 28% of **2a**, 29% of **4a**, and 43% of **5a** from **1a**.
- [11] a) F. Kaplan, M. L. Mitchell, *Tetrahedron Lett.* **1979**, 759–762; b) H. Tomioka, H. Okuno, Y. Izawa, *J. Org. Chem.* **1980**, *45*, 5278–5283; c) V. A. Nikolaev, V. V. Popik, *Tetrahedron Lett.* **1992**, *33*, 4483–4486.
- [12] D. F. Taber, J. C. Amedio, R. G. Sherill, *J. Org. Chem.* **1986**, *51*, 3382–3384.
- [13] D. F. Taber, J. C. Amedio, K. Raman, *J. Org. Chem.* **1988**, *53*, 2984–2990.
- [14] A small amount of singlet–triplet crossing was observed earlier: The carbene produced by direct photolysis of dimethyl diazomalonate led

to only about 90% retention of configuration in its addition reactions with alkenes.^[5a]

- [15] D. F. Taber, E. H. Petty, *J. Org. Chem.* **1982**, *47*, 4808–4809.
- [16] R. Malherbe, H. Dahn, *Helv. Chim. Acta* **1974**, *57*, 2492–503.
- [17] S. Julia, G. Cannic, G. Linstumelle, C. R. Hebd. Seances Acad. Sci. Ser. C **1967**, *264*, 1890–1892.
- [18] a) K. B. Wiberg, E. Martin, *J. Am. Chem. Soc.* **1985**, *107*, 5035–5041; b) J. R. Durig, F. S. Feng, A. Wang, H. V. Phan, *Can. J. Chem.* **1991**, *69*, 1827–1844; c) see also J. P. Bowen, A. Pathiaseril, S. Profeta, N. L. Allinger, *J. Org. Chem.* **1987**, *52*, 5162–5166.
- [19] a) X. Wang, K. N. Houk, *J. Am. Chem. Soc.* **1988**, *110*, 1870–1872; b) K. B. Wiberg, K. E. Laidig, *ibid.* **1988**, *110*, 1872–1874.
- [20] ΔE of methyl acetate is attenuated in polar solvents: a) K. B. Wiberg, M. W. Wong, *J. Am. Chem. Soc.* **1993**, *115*, 1078–1084; b) J. D. Evanseck, K. N. Houk, J. M. Briggs, W. L. Jorgensen, *J. Am. Chem. Soc.* **1994**, *116*, 10630–10638.

A New Heterocyclic Multicomponent Reaction For the Combinatorial Synthesis of Fused 3-Aminoimidazoles**

Hugues Bienaymé* and Kamel Bouzid

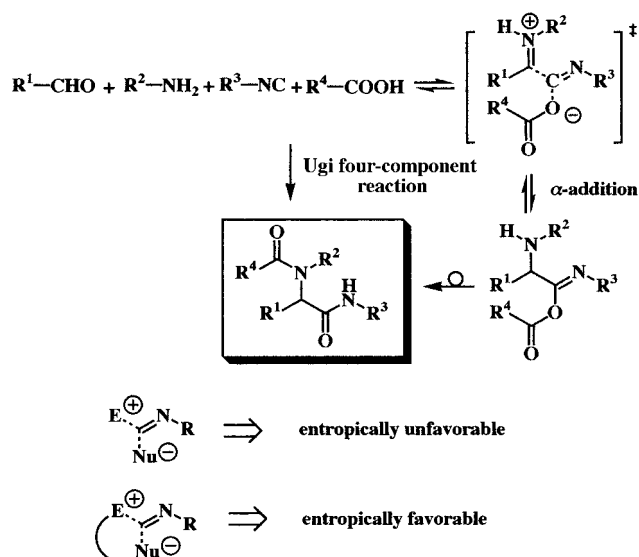
Combinatorial chemistry and high-throughput screening have changed, and are still changing, the face of modern drug discovery.^[1] From the organic chemist's point of view, these new approaches emphasize the need for highly efficient and expeditious protocols. Multicomponent reactions—which combine two major principles of organic synthesis, convergence and atom economy—were prone to be recognized and used in library syntheses.^[2] A prototypical example is the Ugi four-component reaction (Scheme 1),^[3] though several other classical heterocyclic syntheses have also been used.^[4] However, these transformations, which are of enormous potential value, remain scarce.^[5] We therefore embarked on a program aimed at finding and exploiting new and high-yielding multicomponent reactions. Here we disclose our first results in this domain.

To be of industrial relevance, a multicomponent reaction should possess the following characteristics:

- It must be general enough to create libraries with 10000 to 100000 compounds (not a trivial situation!).
- It must be reliable (i.e., give high yields within its reactivity domain).
- It must be amenable to high-throughput automated synthesis (i.e., with a simple reaction protocol; ideally one would like to simply mix reactant solutions).

[*] Dr. H. Bienaymé, K. Bouzid
Rhône-Poulenc Technologies
BP 62, F-69192 St-Fons (France)
Fax: (+33)4-72-93-67-21
E-mail: hugues.bienayme@rhone-poulenc.com

[**] We thank our colleagues from the analytical department (M. Lanson, L. Godde, J. L. Dumoulin, J. Guillaud-Saumur) for their skilled and dedicated contribution, the X-ray Structural Centre of the Russian Academy of Science for X-ray measurements, and Rhône-Poulenc for permission to publish these results.

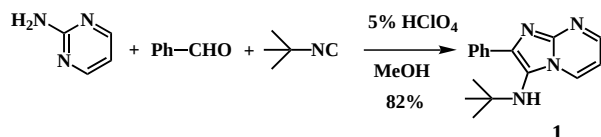


Scheme 1. The Ugi four-component reaction.

- It should give access to novel carbon frameworks, or known ones with original substitution patterns (an important feature when considering patenting libraries).^[6]

When this program was started three years ago, no described reaction fulfilled all these requirements. We assumed that reliability problems associated with some multicomponent reactions with isonitriles arose from subtle kinetic and stereoelectronic factors in the key α -addition step (no less than three distinct functional groups must join simultaneously through covalent bonds). One way to overcome such an entropically unfavorable event is to create a covalent link between two reagents (Scheme 1).^[7] Furthermore, original and patentable accesses to heterocyclic systems can be envisioned with this “bridging strategy”.

Screening various substrate combinations in which an electrophile (a protonated iminium species, as in Ugi multicomponent reactions) and a nucleophile (a heteroatom) are linked, we found (partly by chance!) that heteroaromatic amidines, such as 2-aminopyridine or pyrimidine, reacted with isonitriles and aldehydes in the presence of a catalytic amount of protic acids by a very efficient new three-component reaction (Scheme 2). The structure of adduct **1** was established by ¹H and ¹³C NMR and IR spectroscopy as well as



Scheme 2. Synthesis of 3-tert-butylamino-2-phenylimidazo[1,2-a]pyrimidine.

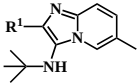
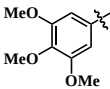
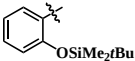
mass spectrometry, and confirmed by an X-ray diffraction study.^[8] The high yield, simple reaction protocol, and originality of the 3-aminoimidazo[1,2-a]pyri(mi)dine ring system^[9] prompted us to explore this unusual transformation more closely.

A preliminary study showed that methanol is the solvent of choice (substrate concentration $c = 0.3\text{--}0.5\text{ M}$), and that

various protic acids can be used with almost equal success in this transformation (for instance, 0.05–0.10 equiv of perchloric acid). Aldehydes (1.2–3.0 equiv) and isonitriles (1.2–1.5 equiv) are best used in slight excess to the 2-aminoazine component. In most cases, reactions are fast at room temperature (2–12 h, 25 °C) and are not sensitive to oxygen or moisture. Thus, library syntheses could be carried out within 24 hours without heating in either vials or microtiter plate-formatted reactors (96 wells).

Tables 1–3 report (part of) the structural variations which are tolerated by this new multicomponent reaction. Alde-

Table 1. Fused 3-aminoimidazoles: variation of the aldehyde (R¹).

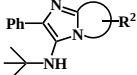
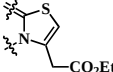
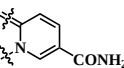
					
Entry	R ¹	Yield ^[a] [%]	Entry	R ¹	Yield ^[a] [%]
1		95	6		76 ^[b]
2		98	7		98
3		84	8		96
4		95	9		92
5		94			

[a] Yields refer to isolated, purified compounds. The identity of the new compounds was determined by ¹H and ¹³C NMR spectroscopy and elemental analysis and/or high-resolution mass spectrometry. [b] Yield of crystalline compound isolated by filtration (no recovery from mother liquor); hence, the total yield may be higher.

dehydes do not represent a major limitation to its scope (Table 1): Aromatic (electron-rich or electron-poor, entries 1–3, 9), aliphatic (even sterically encumbered, entries 4, 5), and heteroaromatic aldehydes (entries 6–8) all gave the corresponding products in excellent yields. The same is true for the different isonitriles (Table 3, entries 25–31).

As shown in Table 2, many heteroaromatic amidines can participate in this multicomponent reaction, though for most electron-poor amidines (entries 14, 16, 17, 21, 22) the reactions tend to be slow and side products accumulate. With these “borderline” cases an often encountered side product arises from the addition of methanol to the intermediate Schiff base (Scheme 3). For instance, with 2-amino-1,3,4-thiadiazole (entry 21) a nonnucleophilic solvent is used: trifluoroethanol. Very electron-poor amidines (2-amino-5-nitrothiazole or

Table 2. Fused 3-aminoimidazoles: variation of the amidine (R^2).

					
Entry	R ²	Yield ^[a] [%]	Entry	R ²	Yield ^[a] [%]
10		95	18		95
11		98	19		60 ^[b]
12		90	20		86 ^[b]
13		80 ^[b]	21		76 ^[c]
14		69	22		50
15		87	23		94 ^[b]
16		75	24		33 ^[b]
17		82			

[a], [b] See Table 1. [c] Trifluoroethanol was used as solvent.

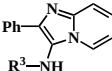
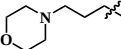
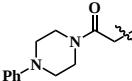
adenine, data not shown) and aliphatic amidines (benzamidine or 2-amino-2-thiazoline, data not shown) remain unchanged under these conditions.

A probable mechanism which accounts for most of the observed results involves a (nonconcerted) [4+1] cycloaddition^[10] between the protonated Schiff base (which holds both the electrophile and nucleophile) and the isonitrile (which behaves as a vinylidene carbenoid). A subsequent prototropic shift gives the final aromatic fused 3-aminoimidazole (Scheme 3).

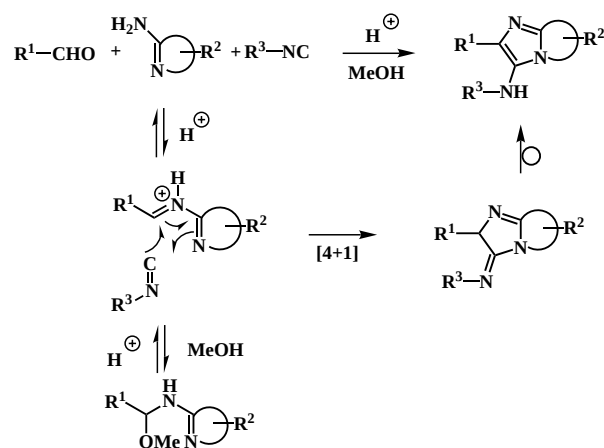
Though protonated Schiff bases of 2-aminopyridines are known to undergo [4+2] cycloadditions with electron-rich olefins,^[11] this is the first example of a [4+1] cycloaddition involving these species.

Thus, by virtue of the bridging strategy, we have discovered a highly efficient and practical approach to fused 3-aminoimidazoles of high structural diversity. With this chemistry almost 30000 different compounds have been prepared in our laboratories, either by parallel or small-mixture syntheses.^[12]

Table 3. Fused 3-aminoimidazoles: variation of the isonitrile (R^3).

					
Entry	R ³	Yield ^[a] [%]	Entry	R ³	Yield ^[a] [%]
25		90	29		93
26		95	30		53 ^[b]
27		86	31		40
28		90			

[a], [b] See Table 1.



Scheme 3. Mechanistic rationale for the synthesis of fused 3-aminoimidazoles.

Experimental Section

Typical procedure for the preparation of fused 3-aminoimidazoles: 3-*tert*-Butylamino-2-(2-pyridyl)-6-methylimidazo[1,2-*a*]pyridine: 2-Amino-5-picoline (0.415 g, 3.84 mmol) is dissolved in methanol (8 mL). Pyridine-2-carbaldehyde (0.62 g, 5.79 mmol) and *tert*-butylisonitrile (0.50 mL, 4.42 mmol) are added at room temperature (22 °C). A 1M solution of perchloric acid in methanol (0.38 mL) is added, and the formation of the strongly UV-active adduct is followed by TLC (CH₂Cl₂/MeOH, 10/1; *R*_f = 0.45). After 18 h at room temperature the crude reaction mixture is diluted with dichloromethane (50 mL) and extracted successively with water (50 mL), a saturated solution of glutamic acid (pH 10, 20 mL), and brine (50 mL). After filtration over a short MgSO₄ pad, the crude reaction mixture (1.10 g) is evaporated and crystallized by adding diethyl ether (3 mL) and then pentane (6 mL, slowly). Pale yellow crystals are collected (0.821 g, 76 %). *M*_r = 280.37; ¹H NMR (300 MHz, [D₆]DMSO, 25 °C, HMDS): δ = 1.03 (s, 9H), 2.17 (s, 3H), 5.30 (brs, 1H), 6.81 (dd, 1H, *J* = 9, 1.5 Hz), 6.99 (ddd, 1H, *J* = 7.5, 5, 1 Hz), 7.31 (d, 1H, *J* = 9 Hz), 7.61 (ddd, 1H, *J* = 8, 7.5, 1 Hz), 7.94 (brs, 1H), 8.05 (brd, 1H, *J* = 8 Hz), 8.43 (m, 1H); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = 18.2, 29.9, 56.9, 116.7, 120.5,

121.0, 121.3, 121.6, 126.9, 128.4, 134.7, 136.2, 140.7, 148.1, 155.1; IR (KBr): $\tilde{\nu}$ = 3336, 2965, 1589, 1571, 1441, 1390, 1358, 739 cm^{-1} ; MS: m/z : 280, 223, 196.

Received: March 11, 1998 [Z115761E]
German version: *Angew. Chem.* **1998**, *110*, 2349–2352

Keywords: combinatorial chemistry • cycloadditions • heterocycles • multicomponent reactions

Occurrence of Cationic Intermediates and Deficient Control during the Enzymatic Cyclization of Squalene to Hopanoids**

Catherine Pale-Grosdemange,* Corinna Feil, Michel Rohmer,* and Karl Poralla

Triterpenes belong to a group of natural products for which the theme of enzymic polyene cyclization is rich in variations. Such cyclizations—including the formation of all cyclic isoprenoids, regardless of the series to which they belong—produce the most diverse array of natural products.^[1, 2] Concerning only triterpenes, about 100 different skeletons are found in nature.^[3] Owing to genetic techniques and new purification procedures, highly purified squalene-hop-22(29)-ene cyclase (SHC) is now available without any contamination by cellular lipids.^[4] This cyclase, like lanosterol and cycloartenol cyclase, catalyzes the most sophisticated one-step reaction known in biochemistry.^[5] For the formation of the hopane skeleton, 13 covalent bonds are broken or formed, 9 chiral centers are established, and 5 rings are produced. The reaction is thought to be sensitive to side reactions because of the postulated occurrence of reactive carbocationic intermediates.^[6] Furthermore, exclusion of water from the active site is also a problem for SHC as hopan-22-ol (**3**, diplopterol) is always produced along with hop-22(29)-ene (**2**, diploptene).^[6]

Several minor hydrocarbons are produced along with diploptene (**2**) upon the SHC-catalyzed cyclization of squalene (**1**). The presence of such triterpenes helped explain the intermediacy of tetra- and pentacyclic carbocations during the formation of the hopane skeleton. Upon analyzing the products of the enzymatic cyclization of squalene (**1**) by GLC, peaks for minor products (each representing 0.9–2 % of the area of the peak for diploptene) were observed between the peaks corresponding to squalene and diploptene. The same product distribution also appeared when testing a highly purified SHC without a His tag, which was otherwise necessary for purification on a nickel affinity column. Preliminary GC-MS results showed that all these compounds had a relative molecular mass of 410 and were isomers of squalene and diploptene.

These compounds were separated by thin-layer chromatography on silica gel impregnated with silver nitrate (argenta-

- [1] a) *Curr. Opin. Chem. Biol.* **1997**, *1*, 3–145; b) P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron* **1997**, *53*, 5643–5678; c) F. Balkenhohl, C. von den Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436–2487; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288–2337; d) L. A. Thompson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555–600; e) E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor, M. A. Gallop, *J. Med. Chem.* **1994**, *37*, 1233–1251; 1385–1401.
- [2] a) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123–131; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.
- [3] a) I. Ugi, M. Goebel, B. Gruber, M. Heilingbrunner, C. Heiss, W. Hörl, O. Kern, M. Starnecker, *Res. Chem. Intermed.* **1996**, *22*, 625–644; b) I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 115–122; c) C. Hulme, M. M. Morissette, F. A. Volz, C. J. Burns, *Tetrahedron Lett.* **1998**, *39*, 1113–1116.
- [4] Selected examples: a) H. Bienaymé, K. Bouzid, *Tetrahedron Lett.* **1998**, *39*, 2735–2738; b) A. S. Kiselyov, R. W. Armstrong, *Tetrahedron Lett.* **1997**, *38*, 6163–6166; c) A. Gopalsamy, P. V. Pallai, *Tetrahedron Lett.* **1997**, *38*, 907–910; d) S. Sarshar, D. Siev, A. M. M. Mjalli, *Tetrahedron Lett.* **1996**, *37*, 835–838; e) O. Lack, L. Weber, *Chimia* **1996**, *50*, 445–447; f) P. Wipf, A. Cunningham, *Tetrahedron Lett.* **1995**, *36*, 7819–7822.
- [5] With respect to generation of diversity and intense industrial competition, this may become a serious concern.
- [6] C. G. Newton, *Exp. Opin. Ther. Patents* **1997**, *7*, 1183–1194.
- [7] Other multicomponent reactions can benefit from entropic activation through this bridging strategy. Interestingly, such reactions are also high-yielding and reliable: a) A. Demharter, W. Horl, E. Herdtweck, I. Ugi, *Angew. Chem.* **1996**, *108*, 185–187; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 173–175; b) I. Ugi, A. Demharter, W. Hörl, T. Schmid, *Tetrahedron* **1996**, *52*, 11657–11664.
- [8] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101255. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] A similar multicomponent access to 3-aminoimidazo[1,2-a]pyridines was recently disclosed: a) C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.*, in press; for other routes, see b) J.-L. Moutou, M. Schmitt, V. Collot, J.-J. Bourguignon, *Tetrahedron Lett.* **1996**, *37*, 1787–1790; c) J. C. Teulade, R. Escalé, H. Viols, J. P. Chapat, G. Grassy, A. Carpy, J. M. Léger, *J. Chem. Soc. Perkin Trans. I* **1983**, 2663–2667; d) G. Saint-Ruf, B. Loukalou, C. N'Zouzi, *J. Heterocycl. Chem.* **1981**, *18*, 1565–1570; e) N. W. Bristow, P. T. Charlton, D. A. Peak, W. F. Short, *J. Chem. Soc.* **1954**, 616–629.
- [10] [4 + 1] Cycloaddition of isonitriles with various heterodienes is known, though none of the reported examples are of synthetic value in the context of high-throughput synthesis: a) S. Marcaccini, *Org. Prep. Proced. Int.* **1993**, *25*, 141–208, and references therein; b) C. Buron, L. El Kaïm, A. Uslu, *Tetrahedron Lett.* **1997**, *38*, 8027–8030; c) J. A. Deyrup, M. M. Vestling, W. V. Hagan, H. Y. Yun, *Tetrahedron* **1969**, *25*, 1467–1478.
- [11] a) P. A. Grieco, A. Bahsas, *Tetrahedron Lett.* **1988**, *29*, 5855–5858; b) J. M. Mellor, G. Merriman, H. Ratay, G. Reid, *Tetrahedron Lett.* **1996**, *37*, 2615–2618, and references therein.
- [12] Library syntheses and purification will be reported separately.

[*] Prof. Dr. M. Rohmer, Dr. C. Pale-Grosdemange
Institut Le Bel, Université Louis Pasteur
4 rue Blaise Pascal, F-67070 Strasbourg (France)
Fax: (+33) 3-88-41-61-01
E-mail: mirohmer@chimie.u-strasbg.fr
Dr. C. Feil, Prof. Dr. K. Poralla
Biologisches Institut der Universität
Mikrobiologie/Biotechnologie
Auf der Morgenstelle 28, D-72076 Tübingen
E-mail: poralla@uni-tuebingen.de

[**] We wish to thank Thomas Härtner for production and isolation of the crude fraction of triterpenes, Jean-Daniel Sauer for all NMR measurements, Estelle Nastio and Jacques Blanzat for recording mass spectra, and Dr. Pierre Albrecht (ULP, Strasbourg) for the gift of a neohopene sample. The collaboration was supported by the Deutsche Forschungsgemeinschaft (SFB 323) and a grant to M.R. from the Alexander von Humboldt Foundation.

tion TLC) and identified by GC-MS. Neohop-13(18)-ene (**4**) and eupha-7,24-diene (**8**) were obtained as pure compounds. Their ^1H NMR and mass spectra were identical with those reported in the literature.^[7–9] The structure of **8** was finally confirmed by direct comparison (GC, GC-MS, ^1H NMR) with **8** synthesized from butyrospermol. Neohop-13(18)-ene (**4**) was directly identified by coinjection with a reference sample during the GC experiment and then GC-MS. The two isomeric hydrocarbons **6** and **7** could not be separated from one another. ^1H NMR and mass spectra of **6** were identical with those reported in the literature for dammara-13(17),24-diene isolated from *Polypodium fauriei*, whose structure was confirmed by comparison with the hydrogenated cyclization product of 2,3-dihydrosqualene.^[10] Hydrocarbon **7** was identified as 17-isodammara-12,24-diene by comparison of the ^1H NMR spectrum with that of the 24,25-dihydro derivative 17-isodammara-12-ene, which was previously obtained by enzymatic cyclization of 2,3-dihydrosqualene with a cell-free system from *Alicyclobacillus acidocaldarius*.^[11] Catalytic hydrogenation of the mixture of **6** and **7** selectively reduced the double bond of the side chain, yielding a mixture of 17-isodammara-12-ene and dammar-13(17)-ene; these were identified by comparison with reference compounds (GC-MS, ^1H NMR).^[11] Chemical shifts of the methyl groups from the tetracyclic moiety of **6** were nearly identical with those of the 24,25-dihydro compound. The unsaturated side chain with a Δ^{24} double bond was characterized by the two broad singlets of the methyl groups from this double bond at $\delta = 1.606$ and 1.643 , the broad triplet from vinylic proton H24 at $\delta = 5.10$ ($J = 6.0$ Hz), and the C21 methyl doublet at $\delta = 0.789$ ($J = 7.0$ Hz). For compound **7**, the presence of a Δ^{12} double bond was corroborated by the signal of the olefinic proton H12 appearing as a double doublet at $\delta = 5.20$ ($J = 3.2$ and 5.6 Hz) and by the intense signal at m/z 218 arising from the retro-Diels–Alder product, which is characteristic for Δ^{12} double bonds in a triterpenic skeleton. These last two features were previously observed in the ^1H NMR and mass spectra of dammar-12-ene.^[10]

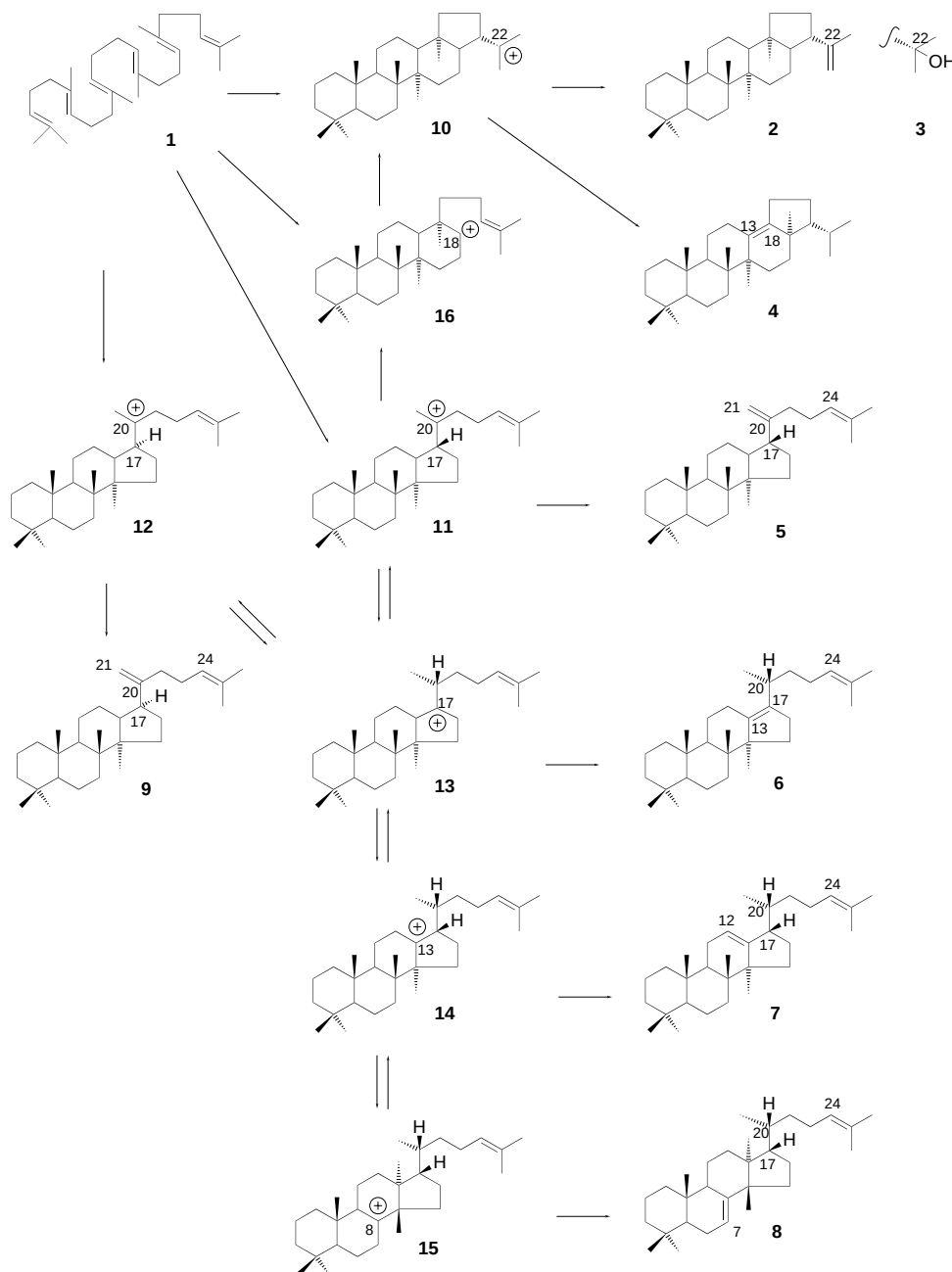
Hydrocarbons **5** and **9** were also obtained as a mixture. ^1H NMR and GC-MS spectra of the minor component **9** were identical with those reported for dammara-20(21),24-diene.^[8] The mass spectrum of **5** was nearly identical with that of **9**,^[8] but the chemical shifts of the five methyl group singlets differed significantly.^[8] The signals from the side-chain protons were similar, however, and indicated the presence of two double bonds in the side chain of **9**. An isopropylidene group corresponding to a Δ^{24} double bond was shown by the two broad singlets of the methyl groups on a double bond at $\delta = 1.618$ and 1.684 , and by the broad triplet of the vinylic proton H24 at $\delta = 5.11$ ($J = 6.7$ Hz). The second double bond was characterized by two olefinic proton singlets at $\delta = 4.87$ and 4.91 (in contrast to an olefinic methylene group) and corresponded to a $\Delta^{20(21)}$ double bond. Hydrocarbon **5** was therefore tentatively identified as 17-isodammara-20(21),24-diene. Its structure is in accordance with the hypothetical biogenetic scheme which can be proposed for the formation of the triterpenoids from *A. acidocaldarius* (Scheme 1). A 17-isodammara derivative resulting from trapping of a cationic intermediate was found as a cyclization product of (3*S*)-29-methylidene-2,3-oxidosqualene by SHC.^[12] Since compounds

from the 17-isodammara series were never found as natural products, definitive identification of **5** requires the synthesis of a reference compound.

Six minor products (**4**–**9**), all resulting from squalene cyclization, were formed in addition to diploptene (**2**) and diplopterol (**3**) from the purified SHC from *A. acidocaldarius* (Scheme 1). These hydrocarbons were not artifacts, resulting from disfunctioning of the enzyme induced by its removal from its natural membrane environment, because they were detected in trace amounts in the hydrocarbon fraction of *A. acidocaldarius*.

The structures of the minor compounds can be deduced from those of carbocationic intermediates possibly involved in the formation of the hopane skeleton (Scheme 1). The pentacyclic neohopa-13(18)-ene (**4**) results from rearrangement induced by the cationic center at C22 of the hopane intermediate **10**. All tetracyclic hydrocarbons arise from cationic 17-isodammara (**11**) or dammarane (**12**) intermediates. On the one hand, cation **11** results from an all-pre-chair conformation of squalene, which is most likely for the formation of the hopane skeleton.^[10] Intervention of a 17-isodammara intermediate is further supported by the structure of the cyclization product of (3*S*)-29-methylidene-2,3-oxidosqualene. Cyclization of this nonnatural substrate of SHC yielded a 17-isodammara derivative resulting from trapping of the isodammara C20 cationic intermediate **11**.^[12] Proton elimination yields 17-isodammara-20(21),24-diene (**5**). On the other hand, the 7-isodammara C20 cation **12** may result either from direct squalene cyclization in a pre-chair-chair-chair-boat conformation^[10] or from the 17-isodammara cation **11** by 1,2-hydride shifts and rotation of the side chain, yielding finally after proton elimination **9** (Scheme 1). The three remaining tetracyclic hydrocarbons **6**, **7**, and **8** resulted from the rearrangement of cation **13** by 1,2-hydride shifts (in the case of **8** by a 1,2-methyl shift) followed by proton elimination.

Formation of tetracyclic triterpenes with a five-membered ring D by SHC may be interpreted in the same way as that of ring C in lanosterol biosynthesis.^[13, 14] Cyclization of artificial substrate analogues such as 20-oxa-2,3-oxidosqualene or of a truncated C₂₀ oxidosqualene analogue by the yeast oxidosqualene cyclase afforded compounds with a five-membered ring C. Their formation is facilitated since it occurs by a Markovnikov process, whereas the expected six-membered ring C would result from an anti-Markovnikov addition. A cationic intermediate with a five-membered ring C was therefore postulated as a regular intermediate in the formation of lanosterol, which results from expansion to the six-membered ring. Computational investigations were in accordance with the likeliness of such a process, but also predicted that the equilibrium between the tertiary cation (Markovnikov) and the nearly isoenergetic secondary cation (anti-Markovnikov) can be readily shifted by selective placement of a nucleophilic group. The involvement of nucleophiles from the protein were proposed,^[15] but a double bond from the substrate could play the same role. A similar process could be imagined for the formation of ring D in the cyclization of squalene into diploptene. In this case, however, for unknown reasons the C20 cationic intermediate (**11** and/or **12**) escapes ring expansion and yields the tetracyclic triterpenes **5**–**9**.



Scheme 1. Hypothetical biogenetic scheme for the formation of triterpenic skeletons by squalene/hopene cyclase of *Alicyclobacillus acidocaldarius*.

Another mode of formation of the five-membered ring D is possible. Cyclization of 2,3-dihydrosqualene by squalene cyclases from *Tetrahymena pyriformis* or from *A. acidocaldarius* yielded tetracyclic triterpenes with a five-membered ring D.^[11] Their carbon skeletons were identical with those of some of the minor compounds described here. This finding suggests that the terminal double bond of squalene may stabilize the secondary C18 cation **16** and is thus required for the formation of a six-membered ring D.^[15] In its absence only the Markovnikov addition occurred, yielding triterpenes derived from dammarane or 17-isodammarane tertiary carbocations. If positioning of the terminal double bond of squalene with respect to the cationic site is not exact,

formation of intermediate **16** may be hampered. This results in the production of the most stable tertiary cationic intermediate **11** or **12**, incomplete cyclization (as in the absence of the double bond), and finally formation of triterpenes of the dammarane and euphane series which represent the signature of the error made by the SHC. Since these alternative cyclization products were isolated from normal bacterial cells, these results suggest that the carbocation intermediates formed during the SHC reaction are sufficiently long-lived to allow alternative cyclization pathways to be followed.

Such a versatility and lack of specificity of SHC was previously demonstrated for the formation of ring A. All tested SHC cyclize squalene, their normal substrate, as well as the two enantiomers of oxidosqualene.^[16–19] Cyclization of the 3*S* enantiomer requires a pre-chair conformation for the formation of ring A, that of the 3*R* enantiomer a pre-boat conformation.^[18] Thus, such cyclizations with different foldings of the substrate are most probably linked to at least small changes in the geometry of the active site and suggests some conformational flexibility of the protein.

Although the X-ray structure of SHC is known,^[20] it is not yet possible to localize precisely squalene in the active site and to understand the interactions inside the catalytic

cavity. Side products have never been observed for the formation of lanosterol. The oxidosqualene cyclase leading to this sterol precursor seems efficiently controlled and has allowed its utilization for the biosynthesis of essential metabolites of higher organisms. In contrast, cyclizations leading to mono- and sesquiterpenes in plants afford side products in significant yields.^[21, 22] Many triterpene cyclases might be supposed to show a similar lack of catalytic specificity, yielding the numerous triterpenic skeletons issued from secondary metabolism in plants. One has just to remember all mono-,^[23] bi-,^[24] tri-,^[25] tetra-,^[7, 8] and pentacyclic^[26] triterpenic hydrocarbons found in ferns and, based on the absence of an oxygen functionality at C3, most probably

derived from squalene cyclization as in the case of bacterial hopanoids.

Experimental Section

A His-tag (6 His residues) was ligated to the N terminus of the SHC cloned from the thermoacidophilic bacterium *Alicyclobacillus acidocaldarius*. This altered enzyme was produced in *Escherichia coli* and purified to homogeneity by complexation chromatography in the last step.^[4]

The NMR spectra were recorded on a Bruker WP400 spectrometer in CDCl₃ at 300 K; CHCl₃ ($\delta = 7.260$) was used as internal standard. The GC-MS measurements were made on a Finnigan TSQ 700 spectrometer. Chromatographic conditions were as those previously described.^[11] Triterpenes were extracted from the enzymatic reaction mixture with hexane/propan-2-ol (3/2). This crude fraction (229 mg) was separated by flash chromatography (CH₂Cl₂/hexane (1/1) followed by CH₂Cl₂) into a hydrocarbon fraction (179 mg) and diplopterol (31 mg).^[27] A further flash chromatography (cyclohexane) yielded a fraction containing all polycyclic triterpenes (112 mg) and unchanged squalene (60 mg). The polycyclic triterpenes were separated by argentation TLC (cyclohexane/toluene (9/1), two migrations),^[28] yielding (in order of increasing polarity) a fraction containing neohop-13(18)-ene (**4**, Scheme 1) and apolar hydrocarbons; a mixture of dammara-12,24-diene (**7**), dammara-13(17),24-diene (**6**), and eupha-7,24-diene (**8**); diploptene (**2**); and finally a mixture of dammara-20(21),24-diene (**9**), a hydrocarbon tentatively identified as 17-isodammara-20(21),24-diene (**5**), and some residual **2**. These fractions were further purified by another argentation TLC. Pure **4** ($R_f = 0.70$, 0.3% yield from the crude reaction mixture) was obtained with cyclohexane as eluent. The mixture of **6**, **7**, and **8** yielded with cyclohexane/toluene (9/1) as eluent a mixture of **6** and **7** in a 54:46 ratio which could not be separated ($R_f = 0.41$, 0.9% yield) and **8** ($R_f = 0.48$, 0.2% yield). The most polar fraction was separated with cyclohexane/toluene (60/40) as eluent into **2** ($R_f = 0.64$) and an inseparable mixture of **5** and **9** ($R_f = 0.25$, 0.6% yield) in a 82:18 ratio. Only spectroscopic data concerning the two new hydrocarbons **5** and **7** are extensively described here.

5 (tentative structure assignment): ¹H NMR: $\delta = 0.803$ (s, CH₃), 0.833 (s, CH₃), 0.845 (s, CH₃), 0.902 (s, CH₃), 0.942 (s, CH₃), 1.618 and 1.684 (2s, 2 × 25-CH₃), 4.87 and 4.91 (2s, 2 × 21-H), 5.11 (brt, $J = 6.7$ Hz, 24-H); GC-MS: m/z (%) = 410 (18, [M⁺]), 395 (3, [M⁺ - CH₃]), 367 (3), 341 (2), 299 (5), 231 (15), 218 (11), 203 (11), 191 (100, cleavage of ring C), 189 (27, cleavage of ring C), 109 (24).

7: ¹H NMR: $\delta = 0.789$ (d, $J = 7.0$ Hz, 20-CH₃), 0.821 (s, 4 α -CH₃), 0.867 (s, 10 β -CH₃), 0.927 (s, 8 β -CH₃), 0.946 (s, 14 α -CH₃), 1.606 and 1.643 (2s, 2 × 25-CH₃), 5.10 (brt, $J = 6$ Hz, 24-H), 5.20 (dd, $J = 3$ and 4 Hz, 12-H); GC-MS: m/z (%) = 410 (100, [M⁺]), 395 (24, [M⁺ - CH₃]), 367 (2), 341 (9, allylic cleavage between C22 and C23), 326 (11), 297 (36 [M⁺ - side chain - 2H]), 284 (21), 218 (32, retro-Diels-Alder reaction induced by the Δ^{12} double bond), 191 (82, cleavage of ring C), 147 (62), 134 (78), 109 (51), 107 (46), 105 (30).

Received: March 30, 1998 [Z11660IE]

German version: *Angew. Chem.* **1998**, *110*, 2355–2358

Keywords: carbocations • cyclases • hopanoids • squalene • terpenoids

- [1] A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890.
- [2] D. E. Cane, *Chem. Rev.* **1990**, *90*, 1089.
- [3] J. Buckingham, *Dictionary of Natural Products on CD-ROM*, Version 5.1, Chapman and Hall, London, **1996**.
- [4] C. Feil, R. Suessmuth, G. Jung, K. Poralla, *Eur. J. Biochem.* **1996**, *242*, 51.
- [5] E. J. Corey, S. P. T. Matsuda, B. Bartel, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 2211.
- [6] I. Abe, M. Rohmer, G. D. Prestwich, *Chem. Rev.* **1993**, *93*, 2189.
- [7] H. Ageta, K. Shiojima, Y. Arai, *Chem. Pharm. Bull.* **1987**, *35*, 2705.
- [8] K. Masuda, K. Shiojima, H. Ageta, *Chem. Pharm. Bull.* **1983**, *31*, 2530.

- [9] I. Abe, M. Rohmer, *J. Chem. Soc. Chem. Commun.* **1991**, 902.
- [10] Y. Arai, K. Masuda, H. Ageta, *Chem. Pharm. Bull.* **1982**, *30*, 4219.
- [11] I. Abe, M. Rohmer, *J. Chem. Soc. Perkin Trans. 1* **1994**, 783.
- [12] I. Abe, T. Dang, Y. F. Zheng, B. A. Madden, C. Feil, K. Poralla, G. D. Prestwich, *J. Am. Chem. Soc.* **1997**, *119*, 11333.
- [13] E. J. Corey, S. C. Virgil, H. Cheng, C. Hunter Baker, S. P. T. Matsuda, V. Singh, S. Sarshar, *J. Am. Chem. Soc.* **1995**, *117*, 11819.
- [14] E. J. Corey, H. Cheng, *Tetrahedron Lett.* **1996**, *37*, 2709.
- [15] C. Jensen, W. L. Jorgensen, *J. Am. Chem. Soc.* **1997**, *118*, 10846.
- [16] C. Anding, M. Rohmer, G. Ourisson, *J. Am. Chem. Soc.* **1976**, *98*, 1274.
- [17] M. Rohmer, C. Anding, G. Ourisson, *Eur. J. Biochem.* **1980**, *112*, 549.
- [18] P. Bouvier, Y. Berger, M. Rohmer, G. Ourisson, *Eur. J. Biochem.* **1980**, *112*, 541.
- [19] M. Rohmer, P. Bouvier, G. Ourisson, *Eur. J. Biochem.* **1980**, *112*, 557.
- [20] K. U. Wendt, K. Poralla, G. E. Schulz, *Science* **1997**, *277*, 1811.
- [21] K.-P. Adam, J. Crock, R. Croteau, *Arch. Biochem. Biophys.* **1996**, *332*, 352.
- [22] C. L. Steele, J. Crock, J. Bohlmann, R. Croteau, *J. Biol. Chem.* **1998**, *273*, 2078.
- [23] Y. Arai, M. Hirohara, H. Ageta, H. Y. Hsu, *Tetrahedron Lett.* **1992**, *33*, 1325.
- [24] K. Shiojima, Y. Arai, K. Masuda, T. Kamada, H. Ageta, *Tetrahedron Lett.* **1983**, *24*, 5733.
- [25] Y. Arai, M. Hirohara, H. Ageta, *Tetrahedron Lett.* **1989**, *30*, 7209.
- [26] G. Berti, F. Bottari, *Progr. Phytochem.* **1969**, *1*, 589.
- [27] W. C. Still, M. Kahn, M. Mitra, *J. Org. Chem.* **1978**, *53*, 2923.
- [28] K. Aitzetmüller, L. A. Gueraldo Goncalves, *J. Chromatogr.* **1990**, *519*, 349.

Crystal Engineering of Organometallic Compounds through Cooperative Strong and Weak Hydrogen Bonds: A Simple Route to Mixed-Metal Systems**

Dario Braga,* Lucia Maini, and Fabrizia Grepioni*

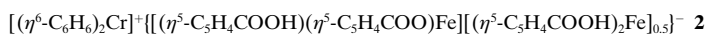
Crystal engineering of organometallic compounds is an emerging field of research.^[1] Much of the excitement arises from the idea of being able to combine the plethora of characteristics provided by functional groups of organic molecules^[2] with the coordination geometry, variable ionic charges, and valence and spin states typical of organometallic complexes to obtain novel crystalline materials.^[3] An intelligent choice of the building blocks may yield materials with magnetic, conducting, superconducting, and nonlinear optical properties.

We now report our success in synthesizing new organometallic crystalline materials by allowing a (rather unconventional) polycarboxylic acid—namely, the neutral organome-

[*] Prof. D. Braga, Dr. F. Grepioni, Dr. L. Maini
Dipartimento di Chimica G. Ciamician
Università di Bologna
Via Selmi 2, I-40126 Bologna (Italy)
Fax: (+39) 51-259456
E-mail: dbrlab@ciam.unibo.it
URL: <http://catullo.ciam.unibo.it>

[**] Crystal Engineering, Part 4. We thank the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (project *Supramolecular Devices*) and the Università di Bologna (project *Innovative Materials*) for financial support. Part 3: D. Braga, A. Angeloni, F. Grepioni, E. Tagliavini, *J. Chem. Soc. Dalton Trans.*, in press

tallic complex $[(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2\text{Fe}] (\text{FeACH}_2)^{[4]}$ —to react with $[(\eta^5\text{-C}_5\text{H}_5)_2\text{Co}]$ and $[(\eta^6\text{-C}_6\text{H}_6)_2\text{Cr}]$ in THF in the presence of oxygen. As previously discussed for the case of polyprotic organic acids,^[5] our crystal engineering strategy is based on the self-assembly of the species carrying strong hydrogen bond donor/acceptor systems, (e.g. FeACH_2 with its two carboxylic groups) around the Cr and Co sandwich complexes. The reaction sequence proceeds by 1) oxidation in the air of solutions of $[(\eta^5\text{-C}_5\text{H}_5)_2\text{Co}]$ and $[(\eta^6\text{-C}_6\text{H}_6)_2\text{Cr}]$ in THF and initial formation of the strongly basic anion O_2^- ; 2) deprotonation of FeACH_2 to yield the anion FeACH^- (or FeAC^{2-}); 3) precipitation of the organometallic salts formed through self-aggregation of the partly deprotonated acid. The precipitates are then recrystallized from nitromethane. Crystalline **1** and **2** have been prepared. The two species contain different electronic and spin states for the metal centers: Fe^{II} and Co^{III} with 18 electrons are present in **1**, whereas Fe^{II} and a paramagnetic Cr^{I} center with 17 electrons are present in **2**. The two crystalline edifices are held together by the complementary contribution of strong neutral $\text{O-H}\cdots\text{O}$ and/or negatively charged $\text{O-H}\cdots\text{O}^{(-)}$ hydrogen bonds between the acid moieties as well as charge-assisted $\text{C-H}^{\delta+}\cdots\text{O}^{\delta-}$ bonds between cations and anions.^[6]



In crystalline **1** the FeACH^- anions form chains (Figure 1 a) through symmetric $\text{O-H}\cdots\text{O}$ interactions between ligands in *transoid* conformation. The $\text{O}-\text{O}$ distances are much shorter than in the $\text{O-H}\cdots\text{O}$ bonds present in neutral crystalline

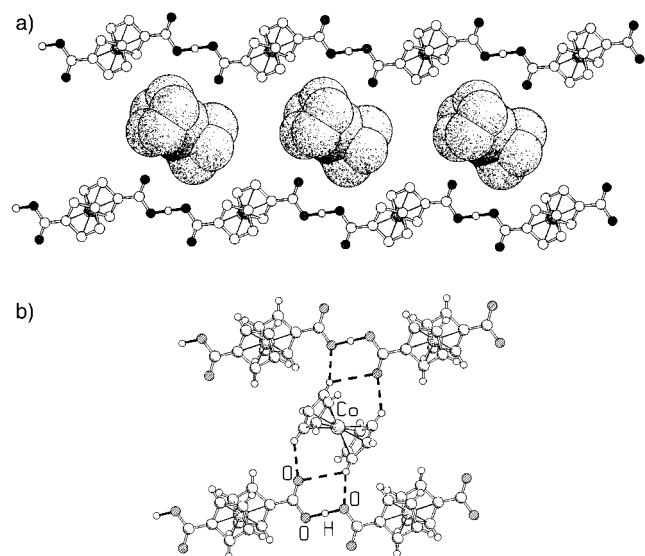


Figure 1. a) In crystalline **1** the FeACH^- anions form parallel chains that enclose the $[(\eta^5\text{-C}_5\text{H}_5)_2\text{Co}]^+$ cations (space-filling representation). The H atoms bound to C atoms are omitted for clarity. b) Schematic representation of the patterns of $\text{O-H}\cdots\text{O}$ interactions connecting the FeACH^- anions and of charge-enhanced $\text{C-H}^{\delta+}\cdots\text{O}^{\delta-}$ hydrogen bonds (dashed lines) between the FeACH^- anions and the cobalticinium cations. The two sets of three $\text{C-H}^{\delta+}\cdots\text{O}^{\delta-}$ hydrogen bonds are directed precisely towards the “unused” lone pairs on the carboxylic oxygen atoms.

FeACH_2 (2.453(3) versus 2.606 Å). Charge-assisted $\text{C-H}^{\delta+}\cdots\text{O}^{\delta-}$ hydrogen bonds link the cobalticinium cations to the FeACH^- chains. Figure 1 b shows how the two sets of three $\text{C-H}^{\delta+}\cdots\text{O}^{\delta-}$ hydrogen bonds on both sides of the cations are directed precisely towards the “unused” lone pairs on the carboxylic oxygen atoms. There are two very short (C)H–O distances (2.192 and 2.254(3) Å) and a longer one (2.523(3) Å) in the bifurcated bond.

Crystalline **2** contains one neutral FeACH_2 molecule for every two FeACH^- anions. The neutral molecule acts as a bridge between hydrogen-bonded dimers formed by two FeACH^- anions. The two $\text{O-H}\cdots\text{O}^{(-)}$ hydrogen bonds (see the bifurcated interaction in Figure 2) are comparable in

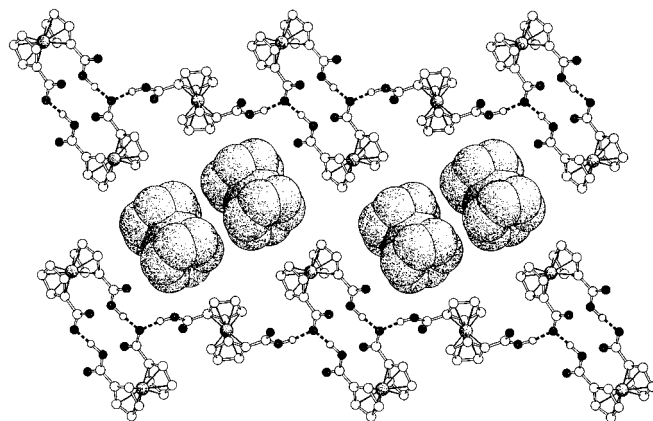


Figure 2. In crystalline **2** neutral FeACH_2 molecules form bridges between dimers of FeACH^- anions linked through negatively charged $\text{O-H}\cdots\text{O}^-$ hydrogen bonds. A space-filling representation is used for the $[(\eta^6\text{-C}_6\text{H}_6)_2\text{Cr}]^+$ cations. The H atoms bound to C atoms are omitted for clarity.

length (2.570(5) and 2.569(5) Å); they are longer than in **1**, but still shorter than in the neutral acid. All “unused” acceptor sites on the oxygen atoms are directed outwards along the chain to attain the maximum number of $\text{C-H}^{\delta+}\cdots\text{O}^{\delta-}$ interactions with the $[(\eta^6\text{-C}_6\text{H}_6)_2\text{Cr}]^+$ cations. There are as many as six (C)H–O distances shorter than 2.5 Å, with one as short as 2.072(5) Å. These values are again indicative of a substantial electrostatic reinforcement of the weak bonds.^[7]

Crystallization from water of the cobaltocene/ FeACH_2 system prepared in 2:1 ratio leads to complete deprotonation of the dicarboxylic acid and formation of **3**. The presence of a large number of water molecules had been previously observed in crystalline $\{[(\eta^5\text{-C}_5\text{H}_5)_2\text{Co}]^+\}_2[\text{L-BTA}]^{2-} \cdot 11\text{H}_2\text{O}$ (BTA = 1*H*-benzotriazole) obtained from complete deprotonation of dibenzoyl-*L*-tartaric acid.^[5b] This behavior suggests that extra donors are required when hydrogen bonds between the acid molecules are not possible owing to a lack of COOH donors.



We have shown here that novel hydrogen-bonded organometallic architectures can be obtained by utilizing organometallic carboxylic acids as building blocks for the construction of anionic hydrogen-bonded frameworks. The acid $[(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2\text{Fe}]$ is very versatile not only because it can

participate in hydrogen-bonded networks as neutral, mono-, and diprotonated species, but also because the conformational freedom allows optimum orientation in space of the functional groups. The acid–base reaction allows a conception for the preparation of a great variety of hydrogen-bonded organometallic crystalline compounds in which metal atoms in different oxidation and spin states can be combined within robust hydrogen-bonded superstructures. Furthermore, the abundance of polarized C–H groups on metal-coordinated ligands, such as C_5H_5 and C_6H_6 , make the use of C–H...O hydrogen bonds also profitable, in particular since they may be reinforced when hydrogen donors and acceptors belong to cations and anions, respectively.^[6]

Experimental Section

$FeACH_2$ (84 mg, 0.3 mmol) was dissolved in anhydrous THF (20 mL), and $(\eta^5-C_5H_5)_2Co$ (57 mg, 0.3 mmol) was added. $FeACH_2$ (71 mg, 0.26 mmol) was dissolved in anhydrous THF (16 mL), and $(\eta^6-C_6H_6)_2Cr$ (54 mg, 0.26 mmol) was added. The oxidation of cobaltocene and bis-benzene chromium was almost instantaneous. In both cases an orange precipitate was formed. After 1 h the slurries were filtered, and the orange powders were recrystallized from nitromethane to afford air-stable orange crystals of **1** and **2**.^[8] $(\eta^5-C_5H_5)_2Co$ (57 mg, 0.3 mmol) was dissolved in water (20 mL) and stirred until complete oxidation to yellow $[(\eta^5-C_5H_5)_2Co][OH]$ had occurred. $FeACH_2$ (8 mg, 0.03 mmol) was added to an aliquot (5 mL) of the solution and stirred for 15 min. The yellow-orange solution was filtered and evaporated to dryness, and the resulting solid was recrystallized from nitromethane to afford well-formed crystals of **3**.^[8]

Received: March 26, 1998 [Z116471E]

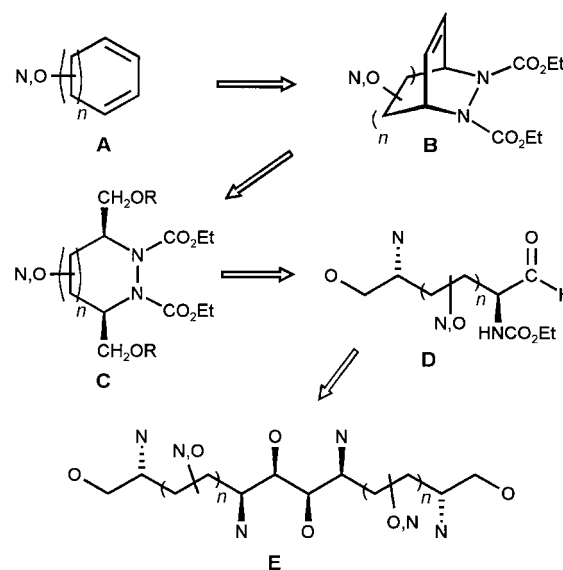
German version: *Angew. Chem.* **1998**, *110*, 2365–2366

Keywords: crystal engineering • hydrogen bonds • sandwich complexes • solid-state structures

From Cycloolefins to Linear C_2 -Symmetrical 1,4-Diamino-2,3-diol Building Blocks—Peptide Mimetics, Biocatalysis, and Pinacol Coupling of α -Amino Aldehydes**

Joachim Armbruster, Stefan Grabowski, Thomas Ruch, and Horst Prinzbach*

C_2 -Symmetrical 1,4-diamino-2,3-diol units of type **E** are central structural elements in numerous bioactive compounds.^[1] A variable synthesis of such building blocks, based on the recently reported route to enantiomerically pure amino aldehydes of type **D** from technical cycloolefins **A**,^[2] and



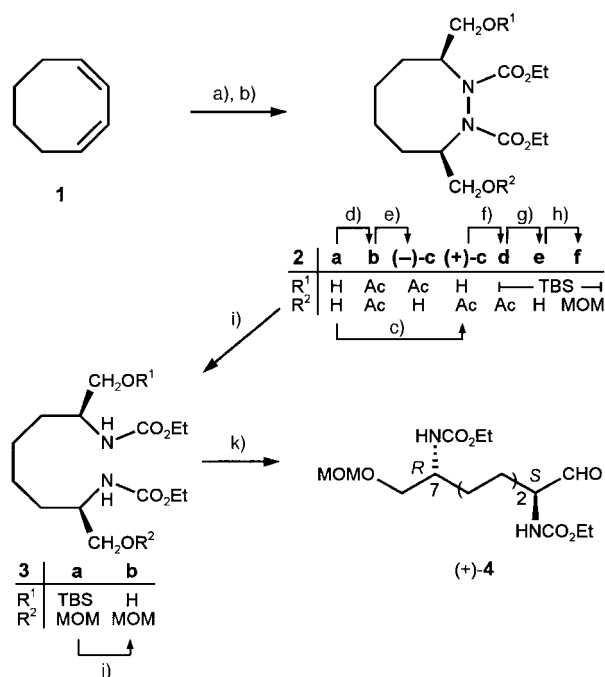
exemplary applications of this synthetic concept in the area of important bioactive compounds are the subjects of this communication.^[1, 3]

The linear, enantiomerically pure C_8 amino aldehyde (+)-**4** (**D**, $n=2$) is prepared by the reaction sequence depicted in Scheme 1:^[2] addition of diethyl azodicarboxylate (DEAD) to 1,3-cyclooctadiene (**1**), ozonolysis, reduction (strictly following a temperature program), and enzymatic asymmetrization, either by esterification of the *meso*-diethyl 3,8-bis(hydroxymethyl)-1,2-diazacyclooctane-1,2-dicarboxylate (**2a**) ($\rightarrow$ (+)-**2c**) or hydrolysis of the diacetate **2b** ($\rightarrow$ (-)-**2c**); lipozyme IM

- [1] a) D. Braga, F. Grepioni, *Chem. Commun.* **1996**, 571; b) D. Braga, F. Grepioni, G. R. Desiraju, *Chem. Rev.*, **1998**, *98*, 1375.
- [2] G. R. Desiraju, *Angew. Chem.* **1995**, *107*, 2541; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2311.
- [3] See, for example, a) C. Elschenbroich, O. Schiemann, O. Burghaus, K. Harms, *J. Am. Chem. Soc.* **1997**, *119*, 7452; b) D. Braga, F. Grepioni, D. Walther, K. Heubach, A. Schmidt, W. Imhof, H. Görls, T. Klettke, *Organometallics* **1997**, *16*, 4910; c) P. J. Davies, N. Veldman, D. M. Grove, A. L. Spek, B. T. G. Lutz, G. van Koten, *Angew. Chem.* **1996**, *108*, 2078; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1959.
- [4] F. Takusagawa, T. F. Koetzle, *Acta Cryst.* **1979**, *B35*, 2888.
- [5] a) D. Braga, F. Grepioni, J. J. Byrne, A. Wolf, *J. Chem. Soc. Chem. Commun.* **1995**, 1023; b) D. Braga, A. L. Costa, F. Grepioni, L. Scaccianoce, E. Tagliavini, *Organometallics* **1997**, *16*, 2070.
- [6] Hydrogen atoms bound to oxygen atoms in crystalline **1** and **2** were observed in the Fourier maps. To evaluate the C–H...O bonds, the C–H distances were normalized to the neutron derived value of 1.08 Å and the program PLATON was used: A. L. Spek, *Acta Crystallogr. Sect. A* **1990**, *46*, C31.
- [7] a) D. Braga, F. Grepioni, *F. Acc. Chem. Res.* **1997**, *30*, 81; b) D. Braga, G. Cojazzi, F. Grepioni, N. Scully, S. M. Draper, *Organometallics* **1998**, *17*, 296.
- [8] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 101304. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[*] Prof. Dr. H. Prinzbach, Dipl.-Chem. J. Armbruster, Dr. S. Grabowski, Dipl.-Chem. T. Ruch
Institut für Organische Chemie und Biochemie der Universität
Albertstrasse 21, D-79104 Freiburg (Germany)
Fax: (+49) 761-203-5987
E-mail: prinzbach@oca.chemie.uni-freiburg.de

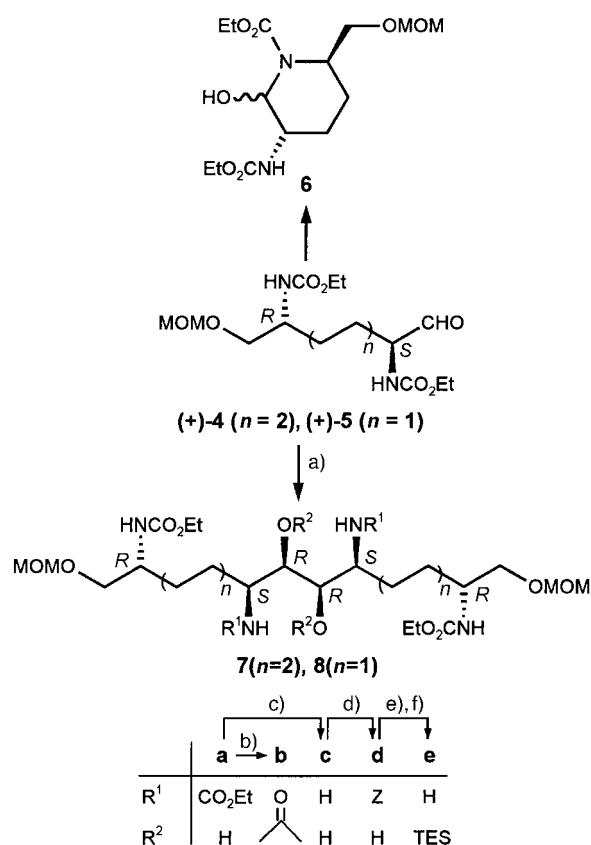
[**] Support by the Fonds der Chemischen Industrie and the BASF AG is gratefully acknowledged. J.A. and S.G. thank the Landesgraduiertenförderung Baden-Württemberg for a stipend. Thanks go to Dr. D. Hunkler for NMR, Dr. J. Wörth for MS, and G. Fehrenbach for HPLC analyses; Dr. H. Jendralla (Hoechst AG) for valuable advice; and Dr. L. Knothe for help with the manuscript.



Scheme 1. a) DEAD, *hν*, 5 d, 87%; b) O₃, EtOH, −48 °C, then NaBH₄, −48 °C, 10 min, room temperature (RT), quenching with acetic acid at −48 °C, 92%; c) lipzyme IM, vinyl acetate, RT, 4 d, 78%, *ee* > 95%; d) Ac₂O, pyridine, DMAP, RT, 12 h, 98%; e) lipzyme IM, phosphate buffer (0.2 N; pH 6.8), *n*-hexane, RT, 8 d, 69%, *ee* = 93%; f) TBSCl, imidazole, DMF, RT, 96%; g) NH₃/MeOH, 0 °C, 4 d, 98%; h) MOMCl, *i*Pr₂NEt, 0 °C, 1 d, 91%; i) Li/NH₃, −78 °C, 1 h, 93%; j) TBAF, THF, RT, 2 h, 98%; k) oxalyl chloride, DMSO, −78 °C, NEt₃, 1 h, quenching with citrate buffer (pH 3.3) at −15 °C, 96%. DEAD = diethyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl, TBAF = tetrabutylammonium fluoride, DMSO = dimethyl sulfoxide.

proved to be the enzyme of choice for both alternatives (70–80% yield each, *ee* ≥ 93%). Manipulation of the protecting groups (so far only practiced with (+)-2c to give 2f), reductive N–N cleavage (3a) as well as the final Swern oxidation 3b → (+)-4 (the absolute configuration 2*S*,7*R* is preliminary^[2]) proceeded with very high yield; under the specified conditions the optical purity is not affected.^[1c, 4] In crystalline form (+)-4 can be kept in stock, whereas in solution (CHCl₃) epimerization at C-2 occurs slowly.

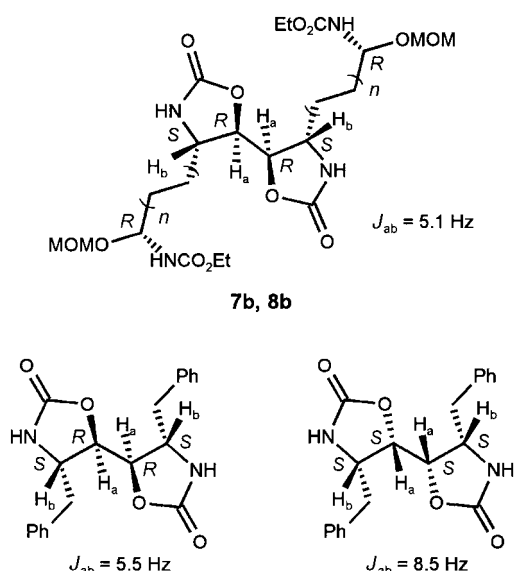
With aldehyde (+)-4 and the C₆ homologue (+)-5^[2] the prospect for stereoselective pinacol coupling was checked by making use of several one-electron reductants (e.g. SmI₂^[5] and C₆Mg^[6]).^[7] Caulton's reagent ([V₂Cl₃(thf)₆][Zn₂Cl₆])^[8] provided the best—for (+)-4 and (+)-5, however, significantly differing—results so far (Scheme 2): In the case of (+)-4 0.27 equiv of reagent (ca. 1 equiv of V²⁺) was sufficient to bring about total conversion. After appropriate workup (addition of the reaction mixture to 0.5 M citrate buffer, pH 4.7), the isolated mixture of dimers (>90%) consisted mainly of 7a; the yield of pure 7a (>80%) collected after crystallization from ethanol compares well with literature reports.^[1c, 4, 9] One of the two side products (ca. 5% each, “dimers” according to mass spectrometry) was identified as a O-MOM-cleaved derivative of 7a; for the second a reliable



Scheme 2. a) With (+)-4: 0.27 equiv of [V₂Cl₃(thf)₆][Zn₂Cl₆], CH₂Cl₂, degassed, anhydrous, N₂ atmosphere, RT, 2 h, then 0.5 M citrate buffer (pH 4.7), >90% mixture of diastereomers (>80% 7a); with (+)-5: a) 1.0 equiv of [V₂Cl₃(thf)₆][Zn₂Cl₆], CH₂Cl₂, RT, 4 h, then 0.5 M citrate buffer (pH 3.3), 60% mixture of diastereomers (80% 8a), 26% 6; b) 0.18 M NaOH in dioxane/water (1/1), RT, 2 h, 99%; c) 0.18 M NaOH in dioxane/water (1/1), 80 °C, 12 h; d) ZCl, *t*BuOH, NaHCO₃, H₂O, RT, 15 min, 78% (based on 7a); e) TESCl, imidazole, DMF, RT, 3 h; f) H₂, Pd/C (5%), toluene, 4 h, 92% (based on 7d). Z = benzyloxycarbonyl, TES = triethylsilyl.

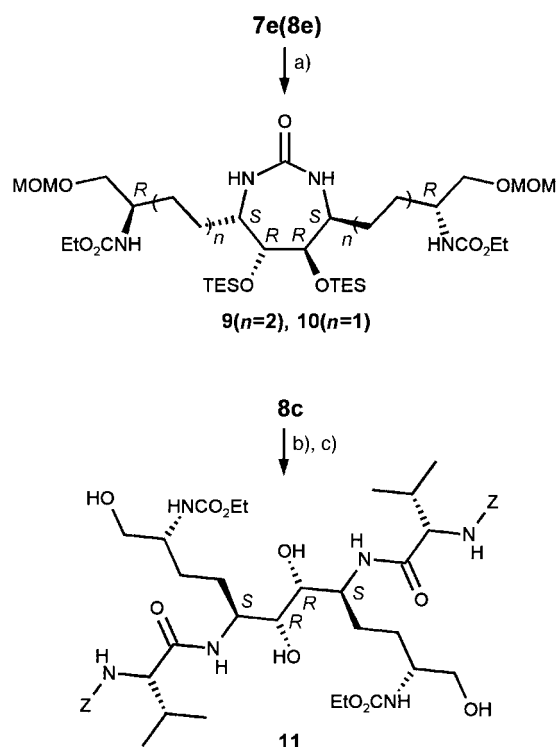
assignment is not yet possible (*S,S,S,S* dimer?). For total conversion of (+)-5 a significant excess of reagent is needed (1.0 equiv, that means 4 equiv of V²⁺). The outcome of the reaction is insofar much more complex, as besides dimerization to give 8a (ca. 45% in addition to ca. 10% of diastereomers) O-MOM cleavage (12%) and cyclization to the azasugar 6 (up to 26%) cannot be avoided (no hint of the *S,S,S,S* dimer). The amount of reagent necessary presumably reflects the complexations induced by the given functionalization pattern and responsible for the competing reaction channels.^[4, 8] The *S,R,R,S* configuration assigned to 7a and 8a is based on a comparison of the bisoxazolidinones 7b and 8b, synthesized from 7a and 8a under base catalysis, with the bisoxazolidinones pictured in Scheme 3, whose absolute configurations of *S,R,R,S* and *S,S,S,S* have been established,^[10] and on the evaluation of the diastereomeric transition states of the dimerization pathways (Pederson^[8]).

From 7a and 8a—examples for potential libraries of structurally varied derivatives—the cyclic ureas 9 and 10 as well as the pseudotetrapeptide 11 are prepared (Scheme 4); they are potential peptide mimetics (see, for example, the structurally related protease inhibitor models DMP 323^[1a] and



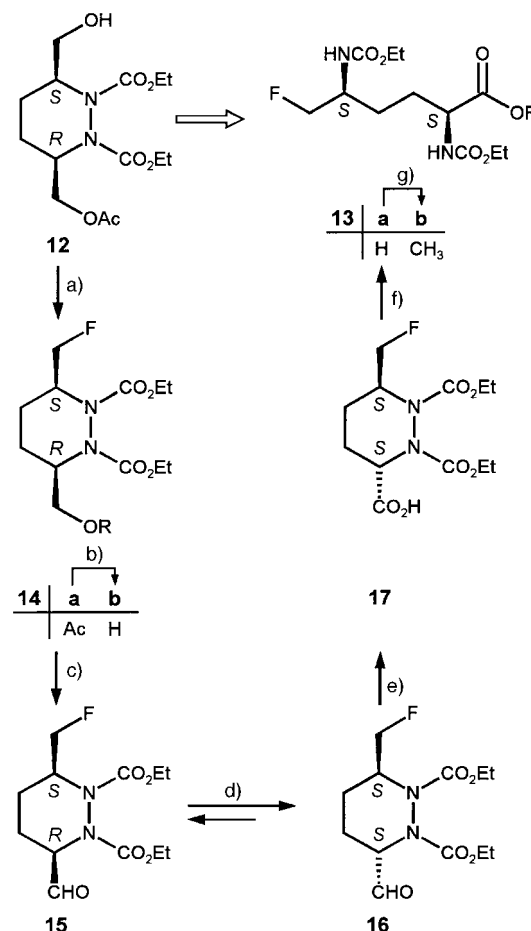
Scheme 3. The assignment of the absolute configuration of **7b** and **8b**.

A 77003^[1b]). It was essential for the efficiency of these syntheses that the central urethane units in **7a** and **8a** could be selectively saponified to **7c** and **8c** with anchimeric assistance of the OH groups. The subsequent steps (**c–e**) to yield **9** and **10** were carried out following known procedures and were unproblematic;^[1c] for the condensation of the highly polar, even in DMF hardly soluble **8c** with *Z*-L-valine, a protocol guaranteeing a low degree of racemization was helpful [activation with the uronium salt TOTU ((Me₂N)₂CON=C(CN)CO₂Et)⁺ BF₄[−]].^[11]



Scheme 4. a) CDI, toluene, RT, 8 h, 53–58%; b) *Z*-valine, *i*Pr₂NEt, TOTU, DMF, RT, 1 h, 67% (based on **8c**); c) MeOH, HCl, 60°C, 2 h, quant. CDI = 1,1'-carbonyldiimidazole.

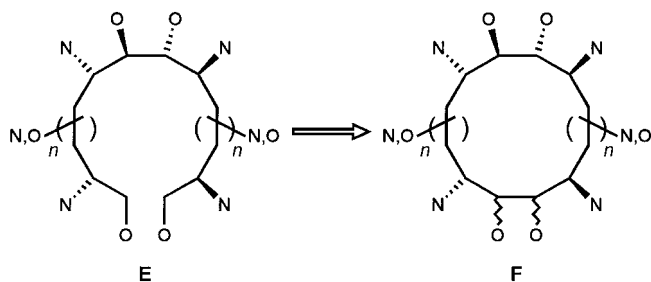
The stereochemical variability of the synthetic concept **A** → **B** → **C** → **D** linked with the 1,2-diazacyclic intermediates of type **C** (*n* = 1)^[2] is exemplified by the advantageous route from **12** to (2*S*,5*S*)-5-fluoromethylornithine (**13a**, an inhibitor of ornithine aminotransferase^[12]) depicted in Scheme 5. Under stereochemical aspects, it is decisive that in the base-



Scheme 5. a) DAST, CH₂Cl₂, RT, 30 min, 74% **14a**; b) MeOH/NH₃ (aq) (4/1), 0°C, 24 h, 80% **14b**; c) oxalyl chloride, DMSO, NEt₃, CH₂Cl₂, −78°C, 45 min, quant.; d) *i*Pr₂NEt, dioxane, 70°C, 12 h; e) NaClO₂, 2-methyl-2-butene, *t*BuOH, aq phosphate buffer, RT, 16 h, 89%; f) Li, NH₃ (aq), THF, −78°C, 15 min, **13a**; g) CH₂N₂, dioxane, RT, 15 min, ca. 50% **13b** (based on **17**). DAST = (diethylamino)sulfur trifluoride.

catalyzed *cis/trans* equilibrium between the 3,6-disubstituted hexahydropyridazine diesters *cis*-**15** (3*a*6e ⇌ 3*e*6*a*) and *trans*-**16** (3*e*6e ⇌ 3*a*6*a*) the latter is highly favored owing to the thermodynamic advantage of axial substitution (NMR;^[13] in support of this, lactonization is fast in *cis*-**14b**, but not in the *trans*-epimer generated from **16**). Whereas the oxidation **16** → **17** with NaClO₂ is straightforward, optimization is still necessary for the subsequent steps **17** → **13b** (preliminarily ca. 50%). This synthetic strategy is clearly applicable to analogous 2*R*,5*R* and 2*R*,5*S* structures.

Further functionalization of the (CH₂CH₂)_{*n*} elements implied in formula **A**, as well as cyclization of the dimers (e.g. **E**) available through this synthetic strategy to the



poly(per)functionalized macrocycles (e.g. **F**), are intensively pursued projects.

Received: April 14, 1998 [Z117281E]

German version: *Angew. Chem.* **1998**, *110*, 2359–2362

Keywords: amino aldehydes • dimerizations • enzyme catalysis • enzyme inhibitors • peptidomimetics

- [1] For example, the HIV protease inhibitors a) DMP323 (DuPont Merck): P. Y. S. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, Y. N. Wong, C.-H. Chang, P. C. Weber, D. A. Jackson, T. R. Sharpe, S. Erickson-Viitanen, *Science* **1994**, *263*, 380; L. T. Rossano, Y. S. Lo, L. Anzalone, Y.-C. Lee, D. J. Meloni, J. R. Moore, T. M. Gale, J. F. Arnett, *Tetrahedron Lett.* **1995**, *36*, 4967; P. J. Jadhav, H.-W. Man, *Tetrahedron Lett.* **1996**, *37*, 1153; b) A77003 (Abbott): W. R. Baker, S. L. Condon, *J. Org. Chem.* **1993**, *58*, 3277; M. V. Hosur, T. N. Bhat, D. J. Kempf, E. T. Baldwin, B. Liu, S. Gulnik, N. E. Wideburg, D. W. Norbeck, K. Appelt, J. W. Erickson, *J. Am. Chem. Soc.* **1994**, *116*, 847; G. T. Wang, S. Li, N. Wideburg, G. A. Krafft, D. J. Kempf, *J. Med. Chem.* **1995**, *38*, 2995; c) HBY 793 (Hoechst): B. Kammermeier, G. Beck, D. Jacobi, H. Jendralla, *Angew. Chem.* **1994**, *106*, 719; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 685; B. Kammermeier, G. Beck, W. Holla, D. Jacobi, B. Napierski, H. Jendralla, *Chem. Eur. J.* **1996**, *2*, 307; S. E. P. Schreiner, A. Pruckner, *J. Org. Chem.* **1997**, *62*, 5380–5384.
- [2] S. Grabowski, H. Prinzbach, *Tetrahedron Lett.* **1996**, *37*, 7955; S. Grabowski, Dissertation, Universität Freiburg, **1997**.
- [3] All new compounds were fully characterized (IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry, elemental analysis); e.g. (+)-**4** ((2*S*,7*R*)-2,7-bis[(ethyloxycarbonyl)amino]-8-methoxymethyloxycotan-1-ol): colorless crystals, m.p. 98 °C (Et₂O/*n*-pentane); $[\alpha]_D^{25} = +4.9$ ($c = 0.4$ in CH₃CN), $[\alpha]_D^{25} = +42.3$ ($c = 0.4$ in CH₃CN); IR (KBr): $\tilde{\nu} = 1547$ (C=O) cm⁻¹ (among other signals); ^1H NMR (400 MHz, CD₃CN): $\delta = 9.47$ (s, 1-H), 5.89 (brd, NH), 5.41 (brd, NH), 4.56 (s, OCH₂O), 4.08 (q, OCH₂CH₃), 4.05 (q, OCH₂CH₃), 3.97 (m, 2-H), 3.63 (m, 7-H), 3.46 (d, 8-CH₂, $J = 5.4$ Hz), 3.30 (s, OCH₃), 1.67–1.26 (m, 4 CH₂), 1.25 (t, OCH₂CH₃), 1.18 (t, OCH₂CH₃); ^{13}C NMR (100.6 MHz, CD₃CN): $\delta = 202.1$ (C-1), 157.4 (C=O), 156.7 (C=O), 97.3 (CH₃O-CH₂O), 70.6 (C-8), 61.7, 61.1 (CH₃CH₂O), 55.5 (CH₂OCH₂O), 55.9, 46.8 (C-2,-7), 32.3, 29.0 (C-3,-6), 26.3, 26.0 (C-4,-5), 15.06, 14.95 (CH₃CH₂O); MS (CI, NH₃): m/z (%): 380 (29) [$M^+ + \text{NH}_4$], 363 (100) [$M^+ + 1$] (among other signals). **10** ((4*S*,5*R*,6*R*,7*S*)-4,7-bis[(3'*R*)-3'-(ethyloxycarbonyl)amino-4'-(methoxymethoxy)butyl]-5,6-bis(triethylsilyloxy)-1,3-diazepin-2-one): ^1H NMR (400 MHz, CDCl₃): $\delta = 5.26$ (brd, NH), 4.56 (s, OCH₂O), 4.47 (brs, NH), 4.06 (m, OCH₂CH₃), 3.71 (4-H, 7-H), 3.54 (dd, 4'-CH₂ A), 3.46 (m, 4'-CH₂ B, 3'-H), 3.40 ("s", 5-H, 6-H), 3.31 (s, OCH₃), 1.74, 1.53 (m, 1'-CH₂, 2'-CH₂), 1.14 (t, OCH₂CH₃), 0.92 (t, SiCH₂CH₃), 0.56 (m, SiCH₂CH₃); ^{13}C NMR (100.6 MHz, CDCl₃): $\delta = 164.8$ (C-2), 156.4 (urethane C=O), 96.8 (OCH₂O), 73.9 (C-5, C-6), 69.8 (C-4', C-4''), 60.7 (OCH₂CH₃), 55.4 (OCH₃), 51.6 (C-4, C-7)*, 50.8 (C-3', C-3'')*, 30.3 (C-1', C-1'')**, 29.2 (C-2', C-2'')**, 14.7 (OCH₂CH₃), 6.9 (SiCH₂CH₃), 5.3 (SiCH₂CH₃); MS (ESI: spray 4–5 kV, capillary 200–250 °C, sheath gas 20 psi): m/z (%): 819.5 (3) [$M^+ + \text{K}$], 803.5 (17) [$M^+ + \text{Na}$], 781.6 (100) [$M^+ + 1$], 749 (5) [$M^+ - \text{OCH}_3$] (among other signals).

- [4] M. T. Reetz, N. Griebenow, *Liebigs Ann.* **1996**, 335.
- [5] G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307; I. L. Chiara, N. Valle, *Tetrahedron: Asymmetry* **1995**, *6*, 1895; T. Sawada, R. Shirai, S. Iwasaki, *Tetrahedron Lett.* **1996**, *37*, 885; I. L. Chiara, M. Martin-Lomas, *Tetrahedron Lett.* **1994**, *35*, 2969; J. P. Guidot, T. LeGall, C. Mioskowski, *Tetrahedron Lett.* **1994**, *35*, 6671.
- [6] *Active Metals* (Ed.: A. Fürstner), VCH, Weinheim, **1996**.
- [7] T. Wirth, *Angew. Chem.* **1996**, *108*, 65; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 61; J. E. McMurry, *Chem. Rev.* **1989**, 1513; A. Fürstner, *Angew. Chem.* **1993**, *105*, 171; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 164.
- [8] A. W. Konradi, S. F. Pedersen, *J. Org. Chem.* **1992**, *57*, 28–32; R. J. Bouma, J. H. Teuben, W. R. Beukema, R. L. Bansemer, J. C. Huffman, K. G. Caulton, *Inorg. Chem.* **1984**, *23*, 2715.
- [9] M. E. Pierce, G. D. Harris, Q. Islam, L. A. Radesca, L. Storace, R. E. Waltermire, E. Wat, P. K. Jadhav, G. C. Emmett, *J. Org. Chem.* **1996**, *61*, 444; D. J. Kempf, T. J. Sowin, E. M. Doherty, S. M. Hannick, L. M. Codacovi, R. F. Henry, B. E. Green, S. G. Spanton, D. W. Norbeck, *J. Org. Chem.* **1992**, *57*, 5692.
- [10] A. K. Ghosh, S. P. McKee, W. J. Thompson, *Tetrahedron Lett.* **1991**, *32*, 5729; D. J. Kempf, D. W. Norbeck, L. M. Codacovi, X. C. Wang, W. E. Kohlbrenner, N. E. Wideburg, D. A. Paul, M. F. Knigge, S. Vasavanonda, A. Craig-Kennard, A. Saldivar, W. Rosenbrook, Jr., J. J. Clement, J. J. Plattner, J. Erickson, *J. Med. Chem.* **1990**, *33*, 2687.
- [11] W. König, G. Breipohl, P. Pokorny, M. Birkner in *Proceedings of the Peptides, 21st European Peptide Symposium 1990* (Eds.: E. Giralt, D. Andreu), ESCOM, Leiden, **1991**, pp. 143–145.
- [12] J. B. Ducep, B. Heintzelmann, K. Jund, B. Lesur, M. Schleimer, P. R. Zimmermann, *Tetrahedron: Asymmetry* **1997**, *8*, 327, and references therein.
- [13] Y. Shvo in *The Chemistry of Functional Groups: Hydrazo-, Azo-, Azoxy-Compounds, Part 2* (Ed.: S. Patai), Wiley, **1975**, p. 1074; see also A. K. Forrest, R. R. Schmidt, G. Huttner, I. Jibril, *J. Chem. Soc. Perkin trans. 1* **1984**, 1981.

The π -Pyrrole Complexation of Alkali Metal Ions by Zirconium *meso*-Octaalkylporphyrinogens: Encapsulation of Li₄H₄ and Li₂O in Sandwich Structures**

Carlo Floriani,* Euro Solari, Giovanna Solari, Angiola Chiesi-Villa, and Corrado Rizzoli

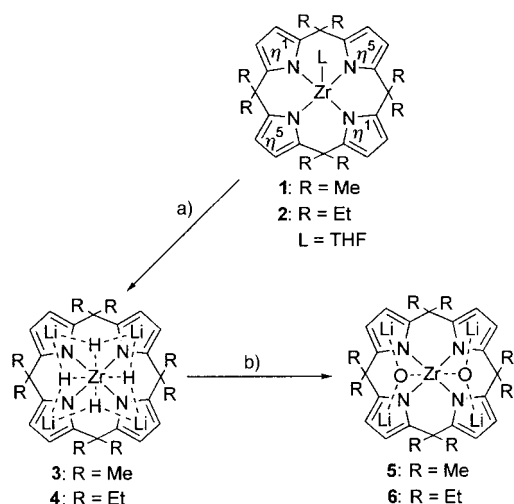
Much attention has been focused on methodologies that allow ionic compounds to be carried into a nonpolar organic phase, either as an ion pair or in an ion-separated form.^[1] For alkali metal salts and polar organometallic compounds, two

[*] Prof. Dr. C. Floriani, Dr. E. Solari, G. Solari
Institut de Chimie Minérale et Analytique
Université de Lausanne
BCH, CH-1015 Lausanne (Switzerland)
Fax: (+41)21-6923905
E-mail: carlo.floriani@icma.unil.ch
Prof. Dr. A. Chiesi-Villa, Dr. C. Rizzoli
Dipartimento di Chimica
Università di Parma (Italy)

[**] This work was supported by the "Fonds National Suisse de la Recherche Scientifique" (Grant No. 20-46'590.96) and Ciba Specialty Chemicals (Basel, Switzerland).

approaches have been devised for achieving their solubility in nonpolar organic solvents. The first one requires the use of a polyoxo crown-type macrocycle for complexing the alkali metal ion,^[1] the second one uses bifunctional complexes.^[2] In the latter case, the carrier binds the alkali metal ion at the basic center and at the same time the corresponding counterion at the acidic site. This event can occur either with the separation of the two ions, or keeping them in the tight ion-pair form.^[2]

meso-Octaalkylporphyrinogen–zirconium assists a number of organic–organometallic transformations, in which it functions as a carrier of polar organometallic compounds.^[2–4] The carrier properties depend on the electron richness of the pyrrolyl anion in metal-porphyrinogen complexes; it acts as a π -binding (η^5 , η^3) site solvating alkali metal ions.^[5, 6] The considerable difference between the π -binding strength of pyrrole units in porphyrinogen and those in the less basic porphyrins should be emphasized, since alkali metal ion π -complexation has never been revealed for the latter.^[7, 8] We report here the best exemplification of the bifunctionality and the π -binding ability of **1** and **2**, which can complex lithium hydride and lithium oxide. One would expect that the reaction of **1** or **2**^[3a] with LiH would lead to different results depending on the solvent conditions and the *meso* substituent R. In the case of **2** (R = Et), when the reaction was carried out in toluene with small amounts of THF, we observed the β -metalation of one of the *meso* ethyl groups.^[4] In the absence of THF (except for that derived from the coordination to Zr in **1** and **2**), we isolated **3** and **4** as green crystalline solids^[9] (see Scheme 1). The synthesis of **4** always presents more problems since the ethyl group undergoes metalation in the presence of even small amounts of THF. The methyl substituent prevents



Scheme 1. Complexation of lithium hydride and lithium oxide by zirconium-*meso*-octaalkylporphyrinogens. a) Toluene, excess LiH; b) H₂O, toluene, –H₂. Projection of the dimers **3**–**6** along the Zr–Zr axis (see Figures 1 and 2).

such a side reaction, and **3** was obtained much more cleanly. The rather low solubility of **3** and **4** in hydrocarbons and their reactivity with the polar solvents normally used prevented their characterization in solution. Both compounds have the

same structure in the solid state, as seen from the X-ray structure determinations, and we report here the structure of **4**^[10] (Figure 1).

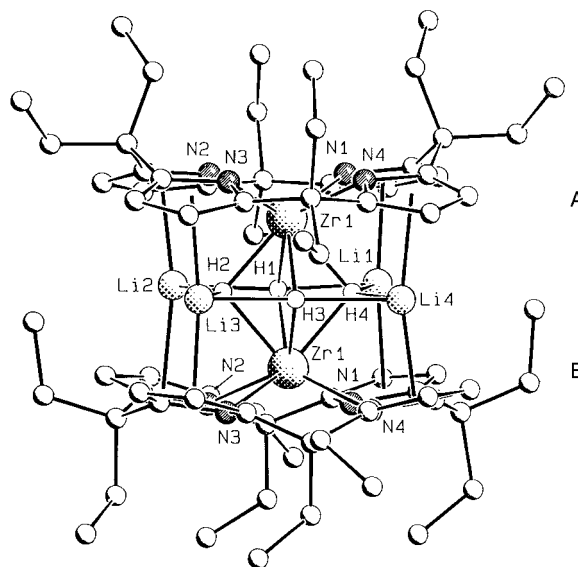


Figure 1. SCHAKAL drawing of complex **4**. Selected bond lengths [Å] and angles [°] (values in square brackets refer to moiety B): Zr1–N1 2.239(3) [2.244(4)], Zr1–N2 2.232(2) [2.240(3)], Zr1–N3 2.246(4) [2.245(3)], Zr1–N4 2.228(3) [2.243(2)]; N3–Zr1–N4 78.8(1) [84.4(1)], N2–Zr1–N4 136.8(1) [138.4(1)], N2–Zr1–N3 85.5(1) [81.2(1)], N1–Zr1–N4 85.7(1) [80.6(1)], N1–Zr1–N3 137.5(1) [137.5(1)], N1–Zr1–N2 79.3(1) [84.2(1)].

The two Zr–porphyrinogen moieties are arranged in an eclipsed sandwich structure that contains the Li₄H₄ plane, which is parallel to the N₄ cores (dihedral angles 2.0° [1.6°]) and perpendicular to the Zr...Zr axis (dihedral angle 1.5°). The two N₄ cores are planar, and parallel to each other (dihedral angle 0.5(1)°). The Zr ions are displaced by 0.817(1) [0.805(1)] Å from the N₄ plane (values in square brackets refer to molecule B). The Zr...Zr separation is 3.058(1) Å. Each hydride ion bridges two Zr atoms at distances ranging from 1.96 to 2.08 and two Li atoms at distances from 2.11 to 2.27 Å; the Li–H distance in lithium hydride is 2.04 Å.^[11a] Both porphyrinogens assume a saddle-shaped conformation, with all the pyrrolyl anions η^1 -bonded to Zr (Zr–N distances range from 2.228(3) to 2.246(3) Å) and η^5 -bonded to lithium (Li– η^5 (C₄H₂N), 2.152(12) Å).

The reaction of **1** with active proton sources should produce a variety of salts that are bifunctionally complexed. Among them a very significant one is lithium oxide, which is derived from the controlled hydrolysis of **3** and **4** in toluene. Complexes **5** and **6** have been obtained as pale yellow crystalline solids. The structure of **5** is shown in Figure 2.^[10] In the centrosymmetric complex **5** the two eclipsed Zr–porphyrinogen moieties sandwich the Li₄O₂ plane that is parallel to the N₄ cores (dihedral angle 0.6(1)°) and perpendicular to the Zr...Zr' axis (dihedral angle 0.4(1)°). The N₄ core is planar; the Zr atom protrudes by 0.798(1) Å towards the oxygen anion. The Zr...Zr' and O...O' separations are 3.315(1) and 2.470(3) Å, respectively. The oxygen atom bridges two Zr atoms and two Li atoms at distances of

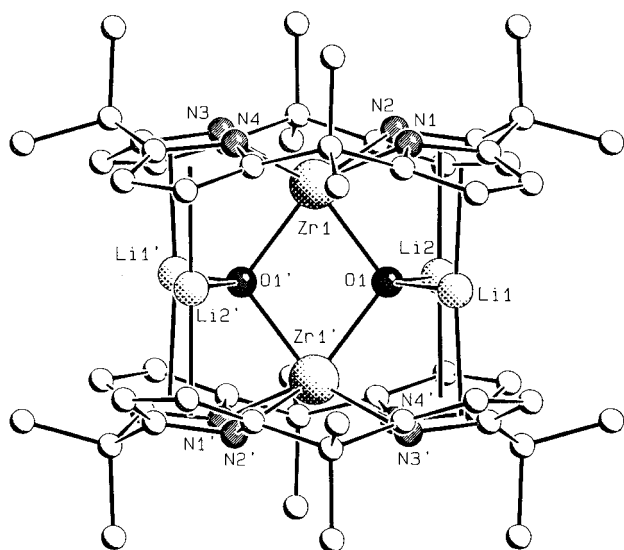


Figure 2. SCHAKAL drawing of complex **5**. Selected bond lengths [Å] and angles [°]: Zr1–O1 2.066(2), Zr1–O1' 2.068(2), Zr1–N1 2.248(2), Zr1–N2 2.252(2), Zr1–N3 2.249(2), Zr1–N4 2.248(2), Li1–O1 1.994(6), Li2–O1 1.967(5), O1–Zr1–O1' 73.4(1), Li1–O1–Li2 119.7(2), Zr1–O1–Zr1' 106.6(1). Prime denotes a transformation of $0.5 - x, 0.5 - y, -z$.

2.067(2) and 1.978(13) Å, respectively; the Li–O distance in lithium oxide is 1.98 Å.^[11b] The rather long Zr–O bond length is expected owing to the absence of a π interaction (see the narrow Zr–O–Zr angle, 73.4(1)°). The porphyrinogen has a saddle-shaped conformation with all the pyrrolyl anions η^1 -bonded to Zr (av Zr–N 2.249(1) Å) and η^5 -bonded to lithium (Li– η^5 (C₄H₅N) 2.181(4)).

Complex **5** reveals how a multicenter interaction led to the complexation of a molecular form of lithium oxide. The synthetic potential of these carrier properties of complexes of high-valent metal centers with *meso*-octaalkylporphyrinogens towards a variety of salts and polar organometallic compounds is currently under investigation.^[2]

Experimental Section

1: ZrCl₄ (14.0 g, 37.0 mmol) was added to a suspension of [Me₈N₄Na₄(thf)₂]^[12] (24.5 g, 37.0 mmol) in THF (200 mL). The mixture was stirred at room temperature for 15 h, then at 60 °C for 4 h. The white fine NaCl powder was filtered off and the orange THF solution was evaporated to dryness. The resulting yellow solid was collected in *n*-hexane, filtered, and dried (79 %). Elemental analysis calcd for **1** (C₃₂H₄₀N₄OZr): C 65.37, H 6.85, N 9.53; found: C 65.67, H 6.79, N 9.59. ¹H NMR ([D₆]benzene, 200 MHz, 298 K): δ = 6.18 (s, 4H; C₄H₅N), 6.01 (s, 4H; C₄H₅N), 3.16 (m, 4H; THF), 1.86 (s, 12H; CH₃), 1.59 (s, 12H; CH₃), 0.89 (m, 4H; THF).

3: LiH (1.0 g, 125 mmol) was added to a suspension of **1** (7.33 g, 12.48 mmol) in toluene (50 mL) and the resulting mixture refluxed for 24 h. A dark blue suspension was obtained, which was then evaporated to dryness and the solid residue was extracted with freshly distilled toluene. A pale green crystalline, light-sensitive solid was collected (49 %). Elemental analysis calcd for **3** (C₃₆H₆₈Li₄N₈Zr₂): C 63.25, H 6.40, N 10.54; found: C 62.90, H 6.57, N 10.14. X-ray quality crystals were grown by slow cooling of a hot toluene solution of **3**. The low solubility of **3** and **4** in innocent solvents prevented their characterization in solution by NMR spectroscopy.

4: Compound **2** (6.52 g, 9.32 mmol) was heated up to 80 °C in the presence of an excess of LiH (0.30 g, 37.5 mmol) in toluene (200 mL) and stirred for two days. A green solution was obtained with a small amount of undissolved solid, which was filtered off. The solvent was evaporated to dryness and the solid collected with *n*-hexane (100 mL) (75 %). It was

recrystallized from hot toluene. Elemental analysis calcd for **4** (C₇₂H₁₀₀Li₄N₈Zr₂): C 67.09, H 7.77, N 8.70; found: C 66.87, H 8.02, N 8.81.

5: A controlled hydrolysis reaction was carried out by allowing a solution of toluene (300 mL) and water (0.10 g, 5.56 mmol) to diffuse through a glass joint into a flask containing a suspension of **3** (3.00 g, 2.82 mmol) in toluene (50 mL). After two days a pale yellow solid was collected (73 %). Elemental analysis calcd for **5** (C₃₆H₆₄Li₄O₂N₈Zr₂): C 61.57, H 5.86, N 10.26; found: C 62.00, H 5.93, N 10.14. X-ray quality crystals were grown in a mixture of toluene and *n*-hexane. ¹H NMR ([D₆]benzene, 200 MHz, 298 K): δ = 5.93 (s, 8H; C₄H₂N), 1.38 (s, 24H; Me). Complex **6** was prepared following the same procedure.

Received: March 18, 1998 [Z11605IE]
German version: *Angew. Chem.* **1998**, *110*, 2367–2369

Keywords: calixpyrroles • ion pairs • lithium • porphyrinogens

- [1] G. Gokel, *Crown Ethers and Cryptands*, Royal Society of Chemistry, Cambridge, **1991**; F. Vögtle, *Supramolecular Chemistry*, Wiley, Chichester, **1991**; C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge **1989**; *Calixarenes, a Versatile Class of Macrocyclic Compounds* (Eds.: J. Vicens, V. Böhmer), Kluwer, Dordrecht, **1991**; B. Dietrich, P. Viout, J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, **1993**.
- [2] C. Floriani, *Pure Appl. Chem.* **1996**, *68*, 1–8, and references therein.
- [3] a) D. Jacoby, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1993**, *115*, 3595–3602; b) D. Jacoby, S. Isoz, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *ibid.* **1995**, *117*, 2793–2804; c) S. De Angelis, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Angew. Chem.* **1995**, *107*, 1200–1202. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1092–1094; d) D. Jacoby, S. Isoz, E. Solari, C. Floriani, K. Schenk, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1995**, *14*, 4816–4824; e) G. Solari, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *ibid.* **1997**, *16*, 508–510.
- [4] D. Jacoby, S. Isoz, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1995**, *117*, 2805–2816.
- [5] S. De Angelis, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Chem. Soc. Dalton Trans.* **1994**, 2467–2469; S. De Angelis, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1994**, *116*, 5691–5701; 5702–5713.
- [6] D. A. Dougherty, *Science*, **1996**, *271*, 163; A. Zanotti-Gerosa, E. Solari, L. Giannini, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Chem. Commun.* **1997**, 183–184, and references therein.
- [7] M. O. Senge, *Angew. Chem.* **1996**, *108*, 2051–2053; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1923–1925, and references therein.
- [8] J. Arnold, *J. Chem. Soc. Chem. Commun.* **1990**, 976–978; J. W. Buchler, J. Hüttermann, J. Löffler, *Bull. Soc. Chem. Jpn.* **1988**, *61*, 71–77; for σ -coordination of alkali metal ions to porphyrins see: J. Arnold, D. Y. Dawson, C. G. Hoffman, *J. Am. Chem. Soc.* **1993**, *115*, 2707–2713.
- [9] We do not have an explanation for the unusual color of such Zr–porphyrinogen complexes, however, it does not arise from any impurity, since it remains the same even after a number of extractions–crystallizations. The rather low solubility in innocent solvents does not allow an easy spectral analysis in solution. For such a case, see: M. W. Renner, J. W. Buchler, *J. Phys. Chem.* **1995**, *99*, 8045–8049.
- [10] Crystal structure analysis of **4**: C₇₂H₁₀₀Li₄N₈Zr₂, *M_r* = 1287.8, triclinic, space group *P* $\bar{1}$, *a* = 14.248(4), *b* = 19.105(2), *c* = 11.760(3) Å, α = 99.46(1), β = 94.72(2), γ = 89.32(1)°, *V* = 3146.9(13) Å³, *Z* = 2, ρ_{calcd} = 1.359 g cm^{−3}, *F*(000) = 1360, MoK α radiation (λ = 0.71069 Å), μ (MoK α) = 3.73 cm^{−1}; crystal dimensions 0.28 × 0.35 × 0.41 mm. For 6922 unique observed reflections [*I* > 2 σ (*I*)] collected at *T* = 295 K on a Rigaku AFC6S diffractometer ($5 < 2\theta < 50^\circ$) the conventional *R* value is 0.036 (*wR*₂ = 0.101 for the 9724 unique reflections having *I* > 0 used in the refinement). Crystal structure analysis of **5**: C₃₆H₆₄Li₄N₈O₂Zr₂, *M_r* = 1091.4, monoclinic, space group *C2/c*, *a* = 21.691(2), *b* = 12.911(1), *c* = 18.942(2) Å, β = 98.91(1)°, *V* = 5240.7(9) Å³, *Z* = 4,

$\rho_{\text{calc}} = 1.383 \text{ g cm}^{-3}$, $F(000) = 2256$, $\text{MoK}\alpha$ ($\lambda = 0.71069 \text{ \AA}$, $\mu(\text{MoK}\alpha) = 4.38 \text{ cm}^{-1}$; crystal dimensions $0.23 \times 0.29 \times 0.34 \text{ mm}$. For 2505 unique observed reflections [$I > 2\sigma(I)$] collected at $T = 295 \text{ K}$ on a Rigaku AFC6S diffractometer ($6 < 2\theta < 50^\circ$) the conventional R value is 0.026 ($wR2 = 0.043$ for the 4570 unique reflections having $I > 0$ used in the refinement). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101526. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [11] a) A. F. Wells, *Structural Inorganic Chemistry 5th ed.*, Oxford University Press, Oxford, 1986, p. 344; b) *ibid.* p. 534.
[12] The synthesis and structure of $[\text{Me}_8\text{N}_4\text{Na}_4(\text{thf})_2]$ will be reported in a forthcoming paper. The alternative use of the sodium instead of the lithium porphyrinogen is dictated by easier separation of NaCl from the reaction mixture.

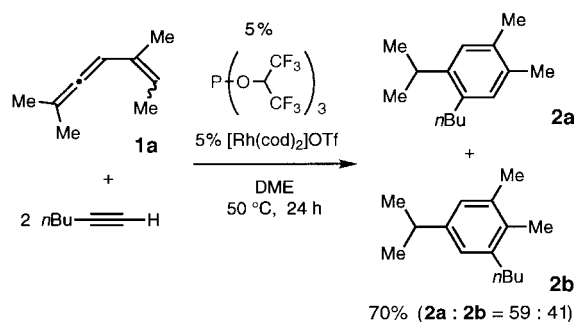
Rhodium-Catalyzed Intermolecular [4+2] Cycloaddition of Unactivated Substrates**

Masahiro Murakami,* Minoru Ubukata, Kenichiro Itami, and Yoshihiko Ito*

Cycloaddition reactions have played a prominent role in the construction of complex cyclic compounds.^[1] In particular, [4+2] Diels–Alder cycloaddition is arguably the most important synthetic tool for the preparation of six-membered rings.^[2] Virtually the only requirement for [4+2] cycloaddition reactions to be effective is that the two components have complementary electronic properties. This is typically achieved by employing an electron-rich 1,3-diene and an electron-deficient dienophile. In fact, 1,3-dienes and dienophiles in which the multiple bonds are not activated by electron-withdrawing or electron-releasing substituents fail to undergo cycloaddition except under the most severe conditions. The use of transition metal catalysts has proven to be a valuable solution to this limitation. Complexation of unactivated substrates to such catalysts promotes both inter-^[3] and intramolecular^[4] [4+2] cycloadditions. Recently, we developed new [4+1] and [4+2] cycloaddition reactions of unactivated vinylallenes based on our study of their bonding interactions with transition metals.^[5–7] Here we report a rhodium-catalyzed intermolecular [4+2] cycloaddition reaction between a vinylallene and an ordinary alkyne which proceeds under mild conditions without the need for electron-withdrawing or electron-releasing substituents. With this method, 1,3,5-tri-

substituted benzene derivatives can be synthesized in a highly regioselective manner.

We first examined the reaction of vinylallene **1a** with the unactivated dienophile 1-hexyne in the presence of $[\text{Rh}(\text{dppe})(\text{cod})]\text{PF}_6$ (dppe = 1,2-bis(diphenylphosphanyl)ethane, cod = (Z,Z)-1,5-cyclooctadiene), a potent catalyst for the [4+1] cycloaddition of vinylallene with carbon monoxide.^[5a] However, [4+2] cycloaddition failed to occur even under forcing conditions,^[8] which led us to examine the electronic perturbation of the catalyst.^[9] Screening of various combinations of catalyst precursors and phosphorus ligands under different reaction conditions revealed that a complex prepared in situ from $[\text{Rh}(\text{cod})_2]\text{OTf}$ and $\text{P}[\text{OCH}(\text{CF}_3)_2]_3$, one of the most strongly electron-accepting ligands available, efficiently catalyzed the [4+2] cycloaddition.^[10] 1,2-Dimethoxyethane (DME) was the solvent of choice. Thus, a mixture of **1a**, 1-hexyne (2 equiv), $[\text{Rh}(\text{cod})_2]\text{OTf}$ (5 mol %), and $\text{P}[\text{OCH}(\text{CF}_3)_2]_3$ (5 mol %) in DME was heated at 50°C for 24 h (Scheme 1). Isomerization (i.e. aromatization) ensued after cycloaddition to afford the corresponding tetrasubstituted benzene in 70% yield as a mixture of regioisomers (**2a** and **2b**).



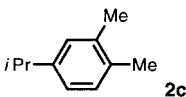
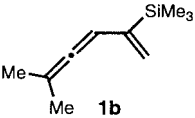
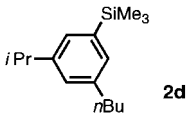
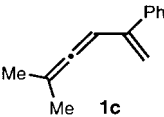
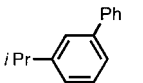
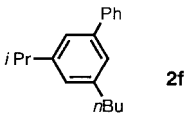
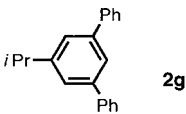
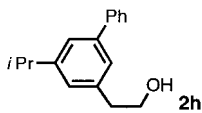
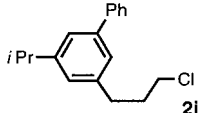
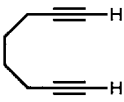
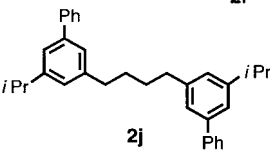
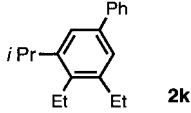
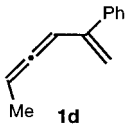
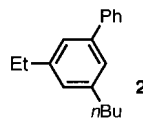
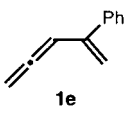
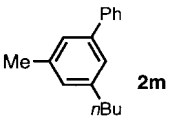
Scheme 1. [4+2] Cycloaddition of vinylallene **1a** with 1-hexyne.

A variety of substrates were allowed to react under the standard reaction conditions to produce the corresponding aromatic compounds (Table 1).^[11] It is noteworthy that synthetically useful results were obtained with substrates lacking directive heteroatom functionalities. For example, ethyne was found to be a reactive dienophile. Furthermore, when a terminal alkyne and a vinylallene lacking substituents at the vinylic terminus were used, 1,3,5-trisubstituted benzene derivatives (**2d**, **2f–j**) were produced in a highly regioselective manner.^[12] Hydroxyl and chloro functionalities are compatible with the present reaction conditions (**2h**, **2i**). In the case of 1,7-octadiyne, a tethered bis-benzene derivative (**2j**) was obtained in 82% yield, without formation of the [2+2+2] cycloadduct.^[13] An internal alkyne could also be employed in the reaction. Vinylallenes in which the allenic terminus is monosubstituted (**1d**) and nonsubstituted (**1e**) gave lower yields of the corresponding cycloadducts (**2l**, **2m**). These results can be explained in terms of the preference for η^2 over η^4 coordination. With **1d** and **1e**, η^2 coordination at the allenic π bond distal to the vinyl group would be favored over η^4 coordination owing to steric reasons.^[5a, 14]

[*] Prof. M. Murakami, Prof. Y. Ito, M. Ubukata, K. Itami
Department of Synthetic Chemistry and Biological Chemistry
Kyoto University
Yoshida, Kyoto 606–8501 (Japan)
Fax: (+81) 75-753-5668

[**] Support from Monbusho is gratefully acknowledged. K.I. thanks the Japan Society for the Promotion of Science for a predoctoral fellowship.

Table 1. [4+2] Cycloaddition of vinylallenes with alkynes.

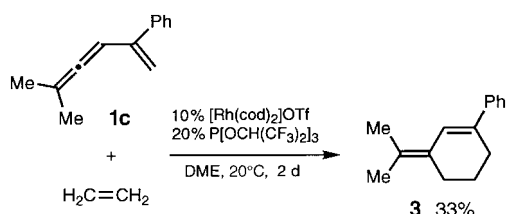
Vinylallene	Alkyne	Amount of alkyne	$T[^\circ\text{C}]$	$t[\text{h}]$	Product	Yield [%] ^[a]
1a	$\text{H}-\text{C}\equiv\text{C}-\text{H}$	10^6 Pa	20	16	 2c	93
 1b	$n\text{Bu}-\text{C}\equiv\text{C}-\text{H}$	2 equiv	20	3	 2d	87
 1c	$\text{H}-\text{C}\equiv\text{C}-\text{H}$	10^6 Pa	20	16	 2e	81
1c	$n\text{Bu}-\text{C}\equiv\text{C}-\text{H}$	1.5 equiv	20	2	 2f	84
1c	$\text{Ph}-\text{C}\equiv\text{C}-\text{H}$	2 equiv	70	40	 2g	48
1c	$\text{Ph}-\text{C}\equiv\text{C}-\text{H}$	2 equiv	70	72		55 ^[b]
1c	$\text{H}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{OH}$	2 equiv	20	4	 2h	94
1c	$\text{H}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$	2 equiv	20	4	 2i	93
1c		0.3 equiv	70	23	 2j	82 ^[b, c]
1c	$\text{Et}-\text{C}\equiv\text{C}-\text{Et}$	1.3 equiv	60	13	 2k	65 ^[d]
 1d	$n\text{Bu}-\text{C}\equiv\text{C}-\text{H}$	5 equiv	20	48	 2l	24
 1e	$n\text{Bu}-\text{C}\equiv\text{C}-\text{H}$	5 equiv	20	96	 2m	15

[a] Yield of isolated product based on **1**. [b] 2 equiv of $\text{P}[\text{OCH}(\text{CF}_3)_2]_3$ based on Rh. [c] Yield of isolated product based on 1,7-octadiyne. [d] 5 equiv of $\text{P}[\text{OCH}(\text{CF}_3)_2]_3$ based on Rh.

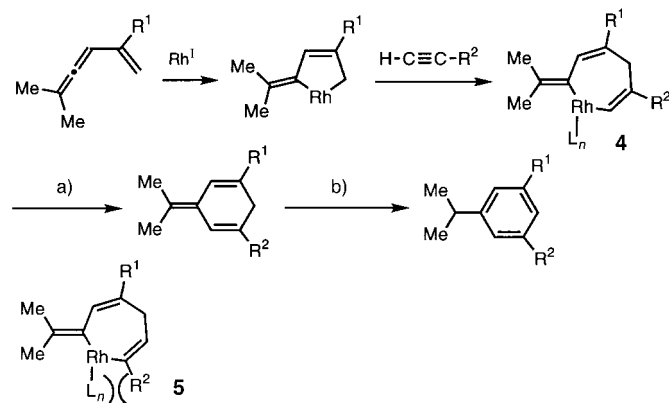
Under the present conditions, even ethene, one of the most sluggish dienophiles, underwent cycloaddition with **1c** to give cyclohexene **3** at temperatures as low as 20°C , albeit in low yield (33 %, Scheme 2).

A plausible mechanism for the production of **2** is shown in Scheme 3. A five-membered rhodacycle is initially formed

from the vinylallene substrate.^[5a, b] After coordination of the alkyne to the rhodium center, C–C bond formation takes place to afford a seven-membered rhodacycle. The regiochemical outcome observed with terminal alkynes can be regarded as a consequence of the selective formation of **4** by insertion of an alkyne into the $\text{Rh}-\text{C}_{\text{sp}^3}$ bond. Competing



Scheme 2. [4+2] Cycloaddition of vinylallene **1c** with ethene (2×10^6 Pa).



Scheme 3. Proposed mechanism of the rhodium-catalyzed [4+2] cycloaddition; a) reductive elimination, b) aromatization.

formation of a seven-membered rhodacycle with the alternative alkyne orientation (**5**) would be disfavored because of repulsive steric interactions between the alkyne substituent R^2 and the ligands on the metal. This interpretation also accounts for the nonregioselective cyclization of **1a**; the preference for an intermediate analogous to **4** would be balanced due to an additional steric interaction between the alkyne substituent R^2 and the methyl group at the vinylic terminus of **1a**.^[15] Finally, reductive elimination followed by isomerization completes the formation of the substituted arenes.

In summary, intermolecular [4+2] cycloaddition reactions of vinylallenes with alkynes, without the necessity of activating heteroatoms, is successfully mediated by use of an electronically tuned rhodium catalyst. Although the precise reason of the beneficial effect of employing an electron-accepting ligand is unclear, the present work indicates that optimization of a ligand set by electronic tuning will offer great potential for the regulated incorporation of unreactive substances, including readily available carbon feedstocks such as ethene and ethyne, into carbon skeletons.

Experimental Section

2a and **2b**: A mixture of $[\text{Rh}(\text{cod})_2]\text{OTf}$ (9.6 mg, 20.5 μmol), $\text{P}[\text{OCH}(\text{CF}_3)_2]_3$ (10.9 mg, 20.5 mmol), **1a** (50.0 mg, 409 μmol), and 1-hexyne (67.2 mg, 818 μmol) in DME (2 mL) was stirred at 50 °C for 24 h. After the mixture was cooled, the solvent was removed under vacuum. The residue was subjected to gel permeation chromatography to afford a mixture of **2a** and **2b** (58.2 mg, 70 %). **2a**: ^1H NMR (300 MHz, CDCl_3): δ = 0.94 (t, J = 7.3 Hz, 3H), 1.22 (d, J = 6.8 Hz, 6H), 1.35–1.45 (m, 2H), 1.48–1.58 (m, 2H), 2.20 (s, 3H), 2.23 (s, 3H), 2.57 (t, J = 7.9 Hz, 2H), 3.11 (septet, J = 6.8 Hz, 1H), 6.90 (s, 1H), 7.01 (s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ = 14.0, 19.2, 19.5, 22.9, 24.2, 28.2, 32.2, 34.3, 126.5, 130.8, 133.4, 134.0, 137.0, 143.8. **2b**: ^1H NMR (300 MHz, CDCl_3): δ = 0.95 (t, J = 7.3 Hz, 3H), 1.23 (d, J = 6.8 Hz, 6H), 1.35–1.45 (m, 2H), 1.48–1.58 (m, 2H), 2.16 (s, 3H), 2.27 (s, 3H), 2.60 (t, J = 7.7 Hz, 2H), 2.81 (septet, J = 6.8 Hz, 1H), 6.86

(s, 1H), 6.87 (s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ = 14.0, 14.7, 20.8, 22.9, 24.1, 33.0, 33.6, 34.0, 125.0, 125.5, 131.7, 136.6, 140.9, 145.7. Elemental analysis calcd for $\text{C}_{15}\text{H}_{24}$ (204.36): C 88.16, H 11.84; found: C 87.91, H 11.72.

Received: March 12, 1998 [Z11581 IE]
German version: *Angew. Chem.* **1998**, *110*, 2362–2364

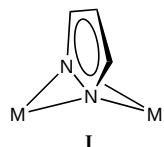
Keywords: alkynes • cycloadditions • P ligands • rhodium • vinylallenes

- [1] W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, **1990**, pp. 1–208.
- [2] W. Oppolzer in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, Oxford, **1991**, pp. 315–399.
- [3] a) A. Carbonaro, A. Greco, G. Dall'Asta, *J. Org. Chem.* **1968**, *33*, 3948; b) H. Siegel, H. Hopf, A. Germer, P. Binger, *Chem. Ber.* **1978**, *111*, 3112; c) H. tom Dieck, R. Diercks, *Angew. Chem.* **1983**, *95*, 801; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 778; d) I. Matsuda, M. Shibata, S. Sato, Y. Izumi, *Tetrahedron Lett.* **1987**, *28*, 3361; e) S. Saito, M. M. Salter, V. Gevorgyan, N. Tsuboya, K. Tando, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 3970; f) V. Gevorgyan, A. Takeda, Y. Yamamoto, *ibid.* **1997**, *119*, 11313.
- [4] a) P. A. Wender, T. E. Jenkins, *J. Am. Chem. Soc.* **1989**, *111*, 6432; b) R. S. Jolly, G. Luedtke, D. Sheehan, T. Livinghouse, *ibid.* **1990**, *112*, 4965; c) T. Mandai, S. Suzuki, A. Ikawa, T. Murakami, M. Kawada, J. Tsuji, *Tetrahedron Lett.* **1991**, *32*, 7687; d) L. McKinstry, T. Livinghouse, *Tetrahedron* **1994**, *50*, 6145; e) P. A. Wender, T. E. Jenkins, S. Suzuki, *J. Am. Chem. Soc.* **1995**, *117*, 1843; f) P. A. Wender, T. E. Smith, *J. Org. Chem.* **1995**, *60*, 2962; g) D. J. R. O'Mahony, D. B. Belanger, T. Livinghouse, *Synlett* **1998**, 443.
- [5] a) M. Murakami, K. Itami, Y. Ito, *Angew. Chem.* **1995**, *107*, 2943; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2691; b) *J. Am. Chem. Soc.* **1996**, *118*, 11672; c) *ibid.* **1997**, *119*, 2950; d) *ibid.* **1997**, *119*, 7163.
- [6] For other examples of cycloaddition of vinylallenes, see a) M. S. Sigman, B. E. Eaton, *J. Am. Chem. Soc.* **1996**, *118*, 11783; b) T. Mandai, J. Tsuji, Y. Tsujiguchi, *ibid.* **1993**, *115*, 5865; c) C. Darcel, C. Bruneau, P. H. Dixneuf, *Synlett* **1996**, 218; d) see also ref. [3b, 4c].
- [7] For other examples of vinylallene complexes, see C. E. Kerr, B. E. Eaton, J. A. Kaduk, *Organometallics* **1995**, *14*, 269, and references therein.
- [8] The palladium(0) complex $[\text{Pd}(\text{PPh}_3)_4]$ which successfully promoted the intermolecular [4+2] cycloaddition between vinylallene and 1,3-diene^[5d] was ineffective for the reaction of **1a** with 1-hexyne.
- [9] a) P. W. N. M. van Leeuwen, C. F. Roobeek, *Tetrahedron*, **1981**, *37*, 1973; b) P. W. N. M. van Leeuwen, C. F. Roobeek, *J. Organomet. Chem.* **1983**, 258, 343.
- [10] For the acceleration of cycloaddition reactions by the use of electron-accepting phosphite ligands, see references [4b, d–g]. In the present cycloaddition, electron-accepting $\text{P}[\text{OCH}(\text{CF}_3)_2]_3$ might facilitate reductive elimination of **4** in Scheme 3.
- [11] The use of two or more equivalents of $\text{P}[\text{OCH}(\text{CF}_3)_2]_3$ (based on rhodium) gave better yields of **2** in some cases, especially when heating was required.
- [12] The stereochemistries were determined by ^1H NMR NOE studies.
- [13] R. Grigg, R. Scott, P. Stevenson, *Tetrahedron Lett.* **1982**, *23*, 2691.
- [14] M. Murakami, K. Itami, M. Ubukata, I. Tsuji, Y. Ito, *J. Org. Chem.* **1998**, *63*, 4.
- [15] The nonregioselective reaction with **1a** is hardly explained by assuming insertion of an alkyne into the $\text{Rh}-\text{C}_{\text{sp}^2}$ bond.

Unprecedented μ - η^2 : η^2 -Pyrazolate Coordination in $[\{\text{Yb}(\eta^2$ -*t*Bu₂pz)(μ - η^2 : η^2 -*t*Bu₂pz)(thf) $\}_2]$ **

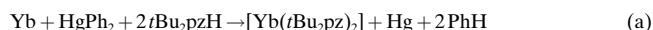
Glen B. Deacon,* Ewan E. Delbridge, Brian W. Skelton, and Allan H. White

Pyrazolate (pz) ions coordinate^[1–5] as bridging (*exo*-bidentate) ligands (commonly for *d*-block elements), chelating (*endo*-bidentate or η^2) ligands (both for *f*-block elements,^[6–8] and, recently, for *d*-block^[9]), and less commonly as unidentate ligands,^[1–5, 9c] whilst η^5 -binding has been postulated but never observed.^[1, 2, 5] The possibility of the formally electron-deficient μ - η^2 : η^2 -pyrazolate binding **1** has never been considered. We now report the synthesis and X-ray structure of a ytterbium(II) pyrazolate, $[\text{Yb}(\eta^2$ -*t*Bu₂pz)(μ - η^2 : η^2 -*t*Bu₂pz)(thf) $\}_2$ (*t*Bu₂pz = 3,5-di-*tert*-butylpyrazolate; thf = tetrahydrofuran) **1**, which exhibits this unexpected

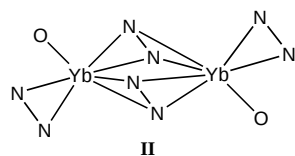


coordination mode. Only one lanthanoid(II) pyrazolate complex has previously been reported, namely $[\text{Yb}(\eta^2$ -Ph₂pz)₂(dme) $\}_2$ (Ph₂pz = 3,5-diphenylpyrazolate; dme = 1,2-dimethoxyethane) **2**,^[8] which has solely η^2 -pyrazolate ligands.

3,5-Di-*tert*-butylpyrazolatoytterbium(II) was prepared by redox transmetalation/ligand exchange [Eq. (a)] in tetrahydrofuran, and gave **1** on crystallization from light petroleum.



A similar preparation followed by crystallization from DME gave **2**,^[8] but the solubility properties of the initial product precluded the crystallization from light petroleum that is a key factor in obtaining **1** (see below). X-ray crystallography^[10] revealed **1** to be a centrosymmetric dimer with the metals bridged by two chelating pyrazolate groups



(Figure 1). Each ytterbium atom is seven-coordinate with one tetrahydrofuran, one terminal η^2 -*t*Bu₂pz and two bridging η^2 : η^2 -*t*Bu₂pz ligands (see **II**). η^2 -Pyrazolate groups have previously been observed only as terminal ligands,^[2–9] whilst known bridging pyrazolates are attached to each metal atom by a single nitrogen atom.^[1–5] The structure of **1** strikingly contrasts that

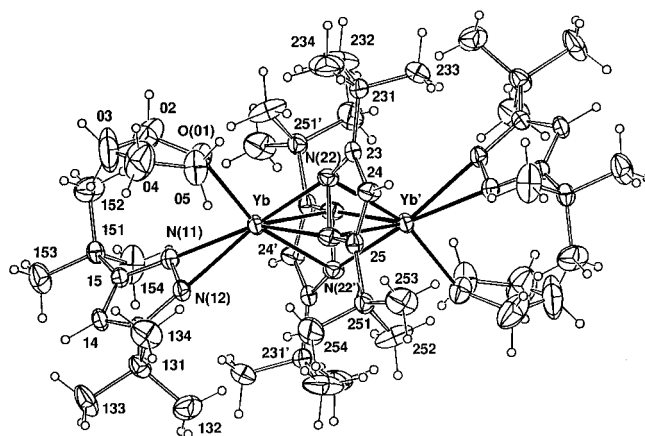


Figure 1. ORTEP plot of $[\{\text{Yb}(\text{tBu}_2\text{pz})_2(\text{thf})\}_2]$ showing 20% thermal ellipsoids for the non-hydrogen atoms; the hydrogen atoms were given an arbitrary radius of 0.1 Å. Selected bond lengths [Å] and angles [°]: Yb–N(11) 2.404(6), Yb–N(12) 2.378(5), Yb–N(21) 2.494(8), Yb–N(22) 2.529(7), Yb–O(01) 2.437(9), Yb–N(21') 2.563(8), Yb–N(22') 2.641(9), N(11)–N(12) 1.39(1), N(21)–N(22) 1.421(9); N(11)–Yb–N(12) 33.8(3), N(11)–Yb(21) 147.0(2), N(11)–Yb–N(22) 163.4(3), N(11)–Yb–O(01) 85.7(3), N(11)–Yb–N(21') 113.6(3), N(11)–Yb–N(22') 105.2(3), N(12)–Yb–N(21) 113.2(2), N(12)–Yb–N(22) 138.2(3), N(12)–Yb–O(01) 87.9(3), N(12)–Yb–N(21') 133.2(3), N(12)–Yb–N(22') 108.9(2), N(21)–Yb–N(22) 32.9(2), N(21)–Yb–O(01) 97.7(3), N(21)–Yb–N(21') 88.7(3), N(21)–Yb–N(22') 80.7(3), N(22)–Yb–O(01) 78.8(3), N(22)–Yb–N(21') 81.6(2), N(22)–Yb–N(22') 91.3(2), O(01)–Yb–N(21') 131.3(2), O(01)–Yb–N(22') 162.5(2), N(21')–Yb–N(22') 31.6(2).

of **2**, which is monomeric with eight-coordinate ytterbium and only η^2 -pyrazolate ligands. The Yb...Yb' axis of **1** intersects the *N,N,N',N'* plane at 78.3(1)°, whereas N–N bonds of previous bridging pyrazolato ligands are near parallel to the M...M axis. Not unexpectedly, the Yb–N_{terminal} distances (Figure 1) are shorter (by ca. 0.1–0.25 Å) than the Yb–N_{bridging} distance, whilst the Yb–N_{terminal} distance is 0.03 Å shorter in **1** than **2**, marginally less than the 0.06 Å expected^[11] for the difference in coordination number. There is some asymmetry in the bridging with the nitrogen atoms of each μ - η^2 : η^2 -*t*Bu₂pz ligand 0.07–0.11 Å closer to one ytterbium. The asymmetry in the bridging is also reflected in tilting of the bridging pyrazolate towards the more weakly bound ytterbium center. This is shown by the intersection angle of 116.7° between the Yb–Yb' axis and the C(24)–cen(2) (cen(2) = center of N(21)–N(22)) axis, instead of 90° for fully symmetrical bridging. It is unlikely that the tilting indicates π - η^5 -pz–Yb' bonding, but weak agostic π -C...Yb interactions between Yb' and C(23) and C(25) are plausible. Subtraction of the ionic radius for seven-coordinate Yb²⁺ ions (1.08 Å)^[11] from Yb'...C(2n)^[12] (*n* = 3,4,5) gives 2.24, 2.46, and 2.14 Å, respectively. The two smallest values are near the upper limit (2.16 Å) of similarly derived values for complexes with inter- or intramolecular π -arene–Ln coordination (Ln = lanthanoid),^[13] though they are significantly longer than values derived from Ln–C bonds of arene–Ln^{II} complexes.^[13]

The ¹H NMR spectrum of **1** in C₇D₈ showed two *t*Bu and two H4 resonances at room temperature, and the ¹³C{¹H} NMR spectrum revealed two resonances for each carbon atom in *t*Bu₂pz, consistent with the presence of both η^2 - and μ - η^2 : η^2 -*t*Bu₂pz ligands. However, neither the *t*Bu nor the H4

[*] Prof. Dr. G. B. Deacon, E. E. Delbridge

Chemistry Department

Monash University

Clayton, Victoria 3168 (Australia)

Fax: (+61) 3-9905-4597

E-mail: glen.deacon@sci.monash.edu.au

Dr. B. W. Skelton, Prof. Dr. A. H. White

Department of Chemistry

The University of Western Australia

Nedlands, Western Australia 6907 (Australia)

Fax: (+61) 8-9380-1005

[**] This work was supported by the Australian Research Council and an Australian Postgraduate Award to E.E.D.

proton resonances were of equal intensity (cf. $[\{\text{Yb}(\text{OR})(\mu\text{-OR})\}_2]$, $\text{R} = 2,6\text{-}t\text{Bu}_2\text{-4-MeC}_6\text{H}_2$ ^[14]), and very complex changes occurred on cooling (reversed on warming). Accordingly, some structural modification, possibly involving partial dissociation of THF, occurs on dissolution in C_7D_8 . Nevertheless, the spectra at the two lowest temperatures investigated (213 and 193 K) showed two equal intensity H4 resonances, consistent with a symmetrical dimer. The ^{171}Yb chemical shift at room temperature is within the range^[15] for dimeric Yb^{II} complexes and close to the value of $\delta = 536$ ^[15] for $[\{\text{Yb}(\text{NR}'_2)(\mu\text{-OR})\}_2]$ ($\text{R}' = \text{SiMe}_3$).

Crystallization from light petroleum appears to be a vital factor in isolation of **1**, and probably causes loss of THF from a monomeric $[\text{Yb}(t\text{Bu}_2\text{pz})_2(\text{thf})_n]$ species. (Compound **1** in $\text{C}_4\text{D}_8\text{O}$ shows only single $t\text{Bu}$ and H4 resonances in the ^1H NMR spectrum.) Adoption of $\mu\text{-}\eta^2\text{-}\eta^2$ bonding enables the Yb^{II} center to attain a higher degree of coordination saturation than is possible with the alternative arrangements of a five-coordinate monomer, $[\text{Yb}(\eta^2\text{-}t\text{Bu}_2\text{pz})_2(\text{thf})]$, or a five-coordinate $\mu\text{-}\eta^1\text{-}\eta^1$ -bridged dimer. Moreover the latter structure would lead to severe steric repulsion between the 3- and 5- $t\text{Bu}$ substituents of the bridging ligands and the terminal ligands, whereas adverse steric interactions are reduced with the $\mu\text{-}\eta^2\text{-}\eta^2$ - $t\text{Bu}_2\text{pz}$ ligands. 3,5-Disubstituted ($t\text{Bu}$, Ph) pyrazolates are insufficiently bulky to stabilize low-coordinate (≤ 6) Ln^{III} complexes,^[7] and ytterbium is eight-coordinate in **2**.^[8]

Experimental Section

The compound described here is extremely air- and moisture-sensitive and consequently all operations were carried out in an inert atmosphere (purified Ar or N_2). Yb metal powder (3.46 g, 20.0 mmol), HgPh_2 (1.96 g, 5.56 mmol), and $t\text{Bu}_2\text{pzH}$ (2.0 g, 11.1 mmol) in THF (30 mL) were heated at 60°C for 30 h. Filtration of the red solution to remove excess Yb and precipitated Hg followed by evaporation of THF yielded a red solid which on crystallization from light petroleum at -20°C afforded large red crystals of **1** (2.58 g 77%). IR (Nujol): $\tilde{\nu} = 3122$ w, 1601 w, 1562 w, 1500 s, 1432 s, 1404 ms, 1358 s, 1315 m, 1296 m, 1248 vs, 1231 s, 1206 s, 1104 vw, 1037 s, 1006 s, 991 s, 917 m, 882 m, 802 s, 782 s, 732 m, 724 s, 664 w, 626 m cm^{-1} ; ^1H NMR (300 MHz, $[\text{C}_7\text{D}_8]$, 0.02 M, 297 K): $\delta = 6.25$ (s) and 6.13 (s) (total integration 4H, H4 pz), 3.40 (vbr, 8H; $\alpha\text{-THF}$), 1.44 (s) and 1.33 (s) (total integration 80H, $t\text{Bu}$; $\beta\text{-THF}$); ^1H NMR (300 MHz, $[\text{C}_4\text{D}_8\text{O}]$, 0.05 M, 297 K): $\delta = 5.89$ (s, 4H, H4 pz), 1.29 (s, 72H; $t\text{Bu}$); ^{13}C [^1H] NMR (50 MHz, $[\text{C}_6\text{D}_6]$, 0.02 M, 297 K): $\delta = 30.6$, 31.4 (CH_3), 32.1, 32.2 ($\text{C}(\text{CH}_3)_3$), 96.9, 100.2 ($\text{C}3, \text{C}5$), 162.5, 164.0 ($\text{C}4$); ^{171}Yb NMR (52.5 MHz, 0.05 M in PhMe): $\delta = 557$ ($\Delta\nu_{1/2} = 44$ Hz) (relative to $[(\text{C}_5\text{Me}_5)_2\text{Yb}(\text{thf})_2]$); Vis/near IR (4.14×10^{-3} M in THF; λ_{max} (ϵ)) = 386 (383), 429sh (283) nm; elemental analysis calcd for $\text{C}_{52}\text{H}_{92}\text{N}_8\text{O}_2\text{Yb}_2$: C 51.73, H 7.68, N 9.28, Yb 28.66; found: C 51.30, H 7.54, N 9.21, Yb 28.28.

Received: March 12, 1998 [Z115771E]
German version: *Angew. Chem.* **1998**, *110*, 2372–2373

Keywords: lanthanides • N ligands • ytterbium

- [1] S. Trofimenko, *Chem. Rev.* **1972**, *72*, 497–509.
- [2] S. Trofimenko, *Prog. Inorg. Chem.* **1986**, *34*, 115–210.
- [3] A. P. Sadimenko, S. S. Bassoon, *Coord. Chem. Rev.* **1996**, *147*, 247–297.
- [4] G. La Monica, G. A. Ardizzone, *Prog. Inorg. Chem.* **1997**, *46*, 151–238.
- [5] J. E. Cosgriff, G. B. Deacon, *Angew. Chem.* **1998**, *110*, 298–299; *Angew. Chem. Int. Ed.* **1998**, *37*, 286–287.
- [6] C. W. Eigenbrot, K. N. Raymond, *Inorg. Chem.* **1981**, *20*, 1553–1556; C. W. Eigenbrot, K. N. Raymond, *Inorg. Chem.* **1982**, *21*, 2653–2660.

- [7] J. E. Cosgriff, G. B. Deacon, B. M. Gatehouse, H. Schumann, R. Weimann, *Chem. Ber.* **1996**, *129*, 953–958 and references therein.
- [8] G. B. Deacon, E. E. Delbridge, B. W. Skelton, A. H. White, *Eur. J. Inorg. Chem.* **1998**, 543–545.
- [9] a) D. Röttger, G. Erker, M. Grehl, R. Frölich, *Organometallics* **1994**, *13*, 3897–3902; b) I. A. Guzei, A. G. Baboul, G. P. A. Yap, A. L. Rheingold, H. B. Schlegel, C. H. Winter, *J. Am. Chem. Soc.* **1997**, *119*, 2287–2288; c) I. A. Guzei, G. P. A. Yap, C. H. Winter, *Inorg. Chem.* **1997**, *36*, 1738–1739.
- [10] Crystal structure analysis of **1**: Air-sensitive red crystals, $\text{C}_{52}\text{H}_{92}\text{N}_8\text{O}_2\text{Yb}_2$, $M_r = 1207.44$, triclinic, space group $P\bar{1}$ with $a = 13.588(3)$, $b = 12.169(6)$, $c = 10.034(7)$ Å, $\alpha = 108.43(5)^\circ$, $\beta = 100.76(3)^\circ$, $\gamma = 104.68(3)^\circ$, $V = 1457(1)$ Å³, $Z = 1$, $\rho_{\text{calcd}} = 1.376$ g cm⁻³, $F(000) = 616$, $\mu_{\text{Mo}} = 32.3$ cm⁻¹, $A_{\text{min,max}}^* = 1.45$, 2.10. A single crystal $0.12 \times 0.22 \times 0.25$ mm was covered in a heavy oil and sealed into a glass capillary under purified argon. From 5121 diffractometer reflections ($2\theta_{\text{max}} = 50^\circ$, $2\theta/\theta$ scan mode; monochromatic $\text{MoK}\alpha$ radiation; $\lambda = 0.71073$ Å; $T \approx 295$ K; 10233 total reflections merged ($R_{\text{int}} = 0.038$), 3436 “observed” ($I > 3\sigma(I)$)) used after Gaussian absorption correction in the final least squares refinement (anisotropic thermal parameters for non-hydrogen atoms, x, y, z, and U_{iso} constrained for H atoms). R , R_w on $|F|$ were 0.048, 0.049 (statistical weights). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101244. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [11] R. D. Shannon, *Acta Crystallogr. Sect. A* **1976**, *32*, 751–767.
- [12] C(23) $\cdots$ Yb' 3.32(1), C(24) $\cdots$ Yb' 3.64 (1), C(25) $\cdots$ Yb' 3.22(1), cf. C(23') $\cdots$ Yb 3.83(1), C(24') $\cdots$ Yb 4.43(1), C(25') $\cdots$ Yb 3.77(1) Å.
- [13] G. B. Deacon, Q. Shen, *J. Organomet. Chem.* **1996**, *511*, 1–17; G. N. Cloke, *Chem. Soc. Rev.* **1993**, *22*, 17–24.
- [14] J. R. van den Hende, P. B. Hitchcock, M. F. Lappert, *J. Chem. Soc. Chem. Commun.* **1994**, 1413–1414.
- [15] J. R. van den Hende, P. B. Hitchcock, S. A. Holmes, M. F. Lappert, *J. Chem. Soc. Dalton Trans.* **1995**, 1435–1440.

Lithium Ephedrinat Mediated Aldol Reaction of Arylacetonitriles: Thermodynamic Control of Enantioselectivity**

Paul R. Carlier,* Weldon W.-F. Lam, Nan Chi Wan, and Ian D. Williams

A reaction in which enantioselectivity is thermodynamically controlled is termed an “asymmetric transformation”.^[1] Both homogeneous (“first kind”) and crystallization-induced (“second kind”) asymmetric transformations are synthetically attractive, since they offer the possibility of converting a racemic mixture into its enantiomers in quantitative yield. The aldol reaction would appear to be a logical choice for the

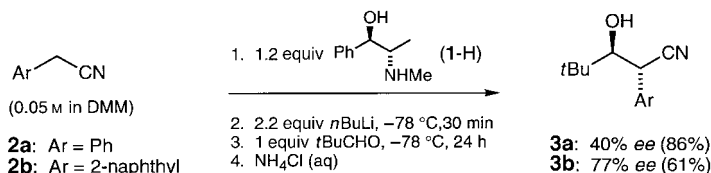
[*] Prof. Dr. P. R. Carlier, W. W.-F. Lam, Dr. N. C. Wan, Prof. Dr. I. D. Williams^[+]
Department of Chemistry
Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong (China)
Fax: (+852) 2358-1594
E-mail: chpaul@ust.hk

[+] X-ray structure analysis

[**] This work was supported by the Research Grants Council of Hong Kong (HKUST 588/95P).

development of asymmetric transformations, given the documented facility of retro-aldol pathways. However, to date, no reversible enantioselective aldol reactions are known.

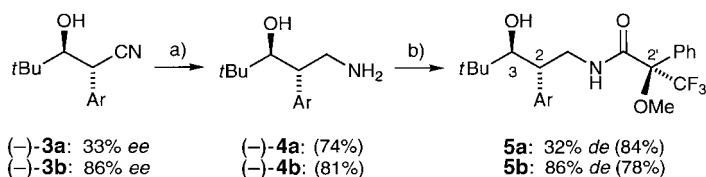
Herein we report the first example of a thermodynamically controlled enantioselective aldol reaction: Lithium ephedrinates (**1-Li**) mediates the addition of arylacetonitriles **2** to aldehydes with up to 86% *ee*. The β -hydroxynitriles *rac*-**3** are readily synthesized by the *anti*-selective aldol reaction of arylacetonitriles,^[2] and are useful precursors for γ -amino alcohol neuronal reuptake inhibitors such as **4b**.^[3] The use of nitriles in enantioselective aldol reactions is currently limited to acetonitrile^[4] and 2-cyanopropionates.^[5] To enable asymmetric synthesis of β -hydroxynitriles derived from **2**, we explored the use of a wide range of nonbasic, monobasic, and dibasic chelating chiral ligands. The best results were afforded by the use of 1.2 equivalents of **1-Li** (generated in situ by the addition of *n*BuLi to (1*R*,2*S*)-(-)-ephedrine (**1-H**)) in a 0.05 M solution of the nitrile in dimethoxymethane (DMM), as illustrated in Scheme 1 for the reaction of **2a** and **2b** with



Scheme 1. Aldol reaction of **2a** and **2b** with pivalaldehyde mediated by **1-Li**.

pivalaldehyde. In both cases the (2*S*,3*S*)-(-)-alcohols **3a** and **3b** are formed as pure *anti* compounds; the enantiomeric excesses were low (40% for **3a**) to moderate (77% for **3b**).

The absolute configurations were determined in the following way. Single-crystal X-ray determination of the (1*S*)-(+)-10-camphorsulfonic acid salt of (+)-*ent*-**4b**^[6] (obtained by resolution of *rac*-**4b**, crystals from ethanol/water) established that (+)-*ent*-**4b** possessed the 2*R*,3*R* configuration. Reduction of (-)-**3b** afforded (-)-**4b**, thus indicating the 2*S*,3*S* configuration for (-)-**3b** (Scheme 2). Conversion of



Scheme 2. a) $\text{LiAlH}_4/\text{AlCl}_3$, Et_2O ; NaOH (aq). b) Chloride salt of (+)- α -methoxy- α -trifluoromethylphenylacetyl chloride (1.1 equiv), CH_2Cl_2 , NaOH (aq).

(-)-**3b** (86% *ee*) into the corresponding (*R*)-Mosher amide **5b** confirmed that reduction of **3b** was stereoselective.^[7] Compound (-)-**3a** was assigned the 2*S*,3*S* configuration on the basis of its levorotation and the similarity of the ^1H NMR spectrum of the major (*R*)-Mosher amide **5a** to that of (2*S*,3*S*,2'*R*)-**5b**.

β -Amino alkoxides have been used previously as chiral controllers in 1,2-additions^[8] and aldol reactions.^[4, 9] However,

our use of a 24-hour reaction time at -78°C in the present case is unusual, and stems from the observation that initial enantioselectivities are near zero. The effect of reaction time on the enantiomeric excess in different reactions of **2a** and pivalaldehyde (0.025 M)^[10] is depicted in Table 1. As can be

Table 1. Effect of reaction time on yield and enantiomeric excess of **3a** ($[\mathbf{2a}]_0 = 0.025 \text{ M}$).^[a]

<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	73	7
2	81	16
6	67	29
12	83	33
24	79	36
48	72	32

[a] The values were determined from six individual reactions. [b] Yield of **3a** after chromatography (pure *anti* product according to ^1H NMR spectroscopy). [c] Determined by HPLC (Daicel Chiralcel OD).

seen, the yield is essentially maximized after 1 h, but the enantiomeric excess rises to a maximum value of approximately 34% after 12 h (curve A, Figure 1). Schlosser et al.

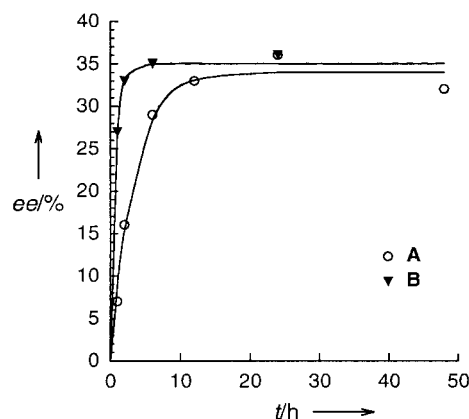
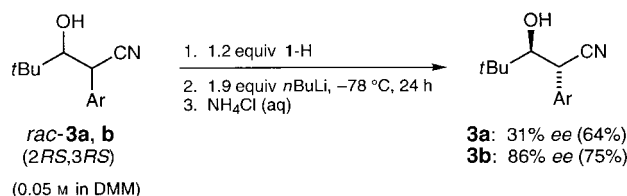


Figure 1. Enantiomeric excess of **3a** as a function of reaction time ($[\mathbf{2a}]_0 = 0.025 \text{ M}$). Curve A: data from separate reactions (Table 1). Curve B: data from a single reaction.

observed a similar dependence of the enantiomeric excess on the reaction time for the carboxylation of sparteine-ligated lithium *N*-BOC-*N*-methylbenzylamine (BOC = *tert*-butoxy-carbonyl).^[11] As a check, another reaction was performed, and aliquots of the reaction mixture were periodically withdrawn and analyzed directly; these data are shown in curve B of Figure 1. These two series of experiments clearly indicate that enantioselectivity is thermodynamically controlled and that the aldol reaction is reversible.

We have previously established that diastereoselectivity in the reaction of lithiated **2a** and cyclohexanecarbaldehyde in THF at -78°C within 30 min is kinetically controlled.^[2c] The change to thermodynamic control in the present case is most likely due to the 48-fold increase in the reaction time, but the assistance of DMM or **1-Li** cannot be ruled out. As a final proof that the aldol reaction of nitriles was reversible over a 24-hour period at -78°C , racemic *anti*-aldols *rac*-**3a, b** were individually resubjected to the reaction conditions (Scheme 3



Scheme 3. Deracemization of *rac*-**3a** and *rac*-**3b** mediated by **1-Li**.

and Experimental Section). Surprisingly, no deracemization^[12] took place in the presence of even a slight excess of *n*BuLi. However, reactions performed with “substoichiometric” amounts of base (1.9 equiv) were successful: **3a** and **3b** are recovered with 31 % and 86 % *ee*, respectively, values close to those obtained in the corresponding aldol reactions (Scheme 1). Additional evidence for operation of a retro-aldol pathway is provided by the observation of small amounts of starting nitriles **2a** and **2b** (3–8 %) in the crude product mixture. No precipitate was observed during the reaction, which indicates that **3a** and **3b** are formed as a result of an asymmetric reaction of the first kind.

At this point it is possible to outline a possible mechanism for asymmetric induction. Lithium alkoxides, including **1-Li**,^[13] are known to be aggregated in ether solvents. We propose that the lithium alkoxides of both **3** and *ent*-**3** form mixed aggregates with **1-Li**. These mixed aggregates are diastereomeric and differ in energy; retro-aldol reaction establishes the equilibrium concentration of these diastereomers, which upon quenching gives rise to enantiomerically enriched **3**.

Noncovalently linked chiral controllers have been successfully applied in a great number of crystallization-driven asymmetric transformations.^[1, 14] However, effective use of noncovalently linked chiral controllers in homogeneous asymmetric transformations is rarely achieved. In reactions which deracemize a single stereogenic center Pirkle et al.,^[15] Hoppe et al.,^[14] and Hoffmann et al.^[16] have achieved asymmetric induction approaching 80 % *ee*. Beak et al. have achieved up to 98 % *ee* (at 10 % conversion) by using a limiting reagent to “quench” a homogeneous asymmetric transformation of an organolithium compound.^[17] The current work is noteworthy in view of the high enantiomeric excess obtained (86 %), and the fact that two stereogenic centers are simultaneously deracemized.

Experimental Section

Deracemization of *rac*-3b: An oven-dried 50-mL flask was charged with *rac*-**3b**^[2a] (126.5 mg, 0.5 mmol) and **1-H** (100 mg, 0.6 mmol) and purged with N_2 . Then 10 mL of DMM (freshly distilled from Na/benzophenone) were added, and the solution was cooled to -78°C . *n*BuLi (2.31 M in hexane, 0.4 mL, 0.92 mmol) was added, and after 24 hours at -78°C the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (1.0 mL). Standard workup and column chromatography (EtOAc/hexane 15/85) afforded 94.3 mg of **3b** (75 %). The spectral data matched that of *rac*-**3b**.^[2b] HPLC analysis indicated 86 % *ee* (Daicel Chiralcel OD, EtOH/hexane 5/95, 1 mL min⁻¹; $t_{\text{ret}} = 13.0$ (2*S*,3*S*), 16.6 min (2*R*,3*R*)). Recrystallization (toluene/hexane) gave 48 mg of **3b** (34 %) with 95 % *ee*; $[\alpha]_{\text{D}} = -74.0^{\circ}$ (21 $^{\circ}\text{C}$, $c = 1.01$ in CHCl_3).

Received: March 30, 1998 [Z11652IE]
German version: *Angew. Chem.* **1998**, *110*, 2374–2376

Keywords: aldol reactions • asymmetric synthesis • lithium • nitriles • retro reactions

- [1] E. L. Eliel, S. H. Wilen, L. N. Mander in *Stereochemistry of Carbon Compounds*, Wiley, New York, **1994**; pp. 364–374, 1192–1193.
- [2] a) P. R. Carlier, K. M. Lo, M. M.-C. Lo, P. C.-K. Lo, C. W.-S. Lo, *J. Org. Chem.* **1997**, *62*, 6316–6321; b) P. R. Carlier, K.-M. Lo, M. M.-C. Lo, I. D. Williams, *J. Org. Chem.* **1995**, *60*, 7511–7517; c) P. R. Carlier, K.-M. Lo, *J. Org. Chem.* **1994**, *59*, 4053–4055.
- [3] P. R. Carlier, M. M.-C. Lo, P. C.-K. Lo, E. Richelson, M. Tatsumi, I. J. Reynolds, T. A. Sharma, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 487–492.
- [4] K. Soai, Y. Hirose, S. Sakata, *Tetrahedron: Asymmetry* **1992**, *3*, 677–680.
- [5] R. Kuwano, H. Miyazaki, Y. Ito, *Chem. Commun.* **1998**, 71–72.
- [6] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101395. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [7] The diastereomeric purity of (*R*)-Mosher amides **5a** and **5b** was determined by ^1H NMR spectroscopy (300 MHz, CDCl_3). The best resolution was observed for the NH signal (t , $J = 5.8$ Hz): **5a**: $\delta = 6.98$ (major), 6.79 (minor, from *ent*-**4a**); **5b**: $\delta = 7.01$ (major), 6.81 (minor, from *ent*-**4b**). (*R*)-Mosher amides derived from enantiomerically pure **4b** and *ent*-**4b** gave single NH resonances at $\delta = 7.01$ and 6.81, respectively, confirming that the ^1H NMR spectroscopic determination of the diastereomeric excess is not affected by the presence of amide rotamers.
- [8] A. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowski, J. F. Remenar, D. B. Collum, *J. Am. Chem. Soc.* **1998**, *120*, 2028–2038.
- [9] a) J. Mulzer, P. De Lasalle, A. Chucholowski, U. Blaschek, G. Brüntrup, I. Jibril, G. Huttner, *Tetrahedron* **1984**, *40*, 2211–2218; b) E. Juaristi, A. K. Beck, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson, D. Seebach, *Synthesis* **1993**, 1271–1289.
- [10] Subsequent process optimization established that maximum enantiomeric excesses at obtained at a nitrile concentration of 0.05 M (Scheme 1).
- [11] M. Schlosser, D. Limat, *J. Am. Chem. Soc.* **1995**, *117*, 12342–12343.
- [12] The term “deracemization” is sometimes used to refer to kinetically controlled enantioselective protonation of an achiral enolate. We use the term to describe a thermodynamically controlled conversion of a racemic mixture into an enantiomerically enriched material.
- [13] M. A. Nichols, A. T. McPhail, E. M. Arnett, *J. Am. Chem. Soc.* **1991**, *113*, 6222–6233.
- [14] D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 2282–2316.
- [15] W. H. Pirkle, D. S. Reno, *J. Am. Chem. Soc.* **1987**, *109*, 7189–7190.
- [16] R. W. Hoffmann, W. Klute, *Chem. Eur. J.* **1996**, *2*, 694–700.
- [17] A lower enantiomeric excess (84 % *ee*) is obtained at 100 % conversion, which reflects the actual ratio (92:8) of diastereomeric sparteine-ligated organolithium complexes: S. Thayumanavan, A. Basu, P. Beak, *J. Am. Chem. Soc.* **1997**, *119*, 8209–8216.

Hydrogenation of White Phosphorus to Phosphane with Rhodium and Iridium Trihydrides**

Maurizio Peruzzini,* José Antonio Ramirez, and Francesco Vizza*

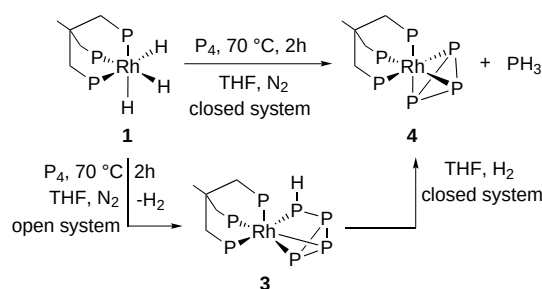
In memory of Ya. A. Dorfman

The reaction of white phosphorus with transition metal fragments results in complexes containing a large variety of P_x ligands ($1 \leq x \leq 12$) most of which have been studied during the last two decades.^[1] Nonetheless, there are still few examples of the functionalization of the P_4 molecule and of its fragmentation mediated by transition metals.^[2] In particular, with the only exception of the thermal reaction of white phosphorus and Cp_2MoH_2 in toluene,^[3] reactions of white phosphorus with transition metal hydrides have received little attention. As these reactions generate potentially unusual phosphorus–hydrogen compounds,^[4] we decided to study the reactivity of white phosphorus towards the transition metal hydrides [(triphos)MH₃] (M = Rh (**1**),^[5a] Ir (**2**);^[5b] triphos = 1,1,1-tris(diphenylphosphanylmethyl)ethane).

In keeping with the well-documented ability of **1** and **2** to behave as hydrogenating reagents toward different organic substrates,^[6] we accumulated strong evidence for the stoichiometric hydrogenation of one of the phosphorus atoms of P_4 to produce phosphane PH_3 . A mechanism which encompasses the formation of the intermediate species [(triphos)MH($\eta^1:\eta^1-P_4$)] and [(triphos)M($\eta^1:\eta^2-HP_4$)] is proposed here.

White phosphorus dissolved in tetrahydrofuran (THF) under dinitrogen reacts with the rhodium trihydride [(triphos)RhH₃] (**1**) at about 70 °C to afford an orange solution. After evaporation of the solvent under reduced pressure yellow microcrystals of the novel complex [(triphos)Rh($\eta^1:\eta^2-HP_4$)] (**3**) are obtained (Scheme 1). On carrying out the same experiment in a closed system in the presence of dihydrogen ($p(H_2) \geq 1$ atm), the known *cyclo*-triphosphorus complex [(triphos)Rh(η^3-P_3)]^[7] (**4**) is formed in high yield.

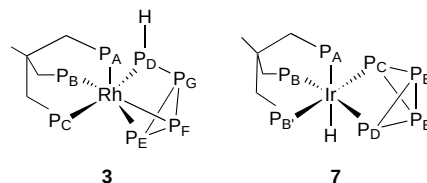
It was unambiguously shown by multinuclear and multi-dimensional NMR spectroscopy that **3** contains the unprecedented hydrogen tetraphosphide HP_4^- ion as a η^3 -six-electron ligand. Key experimental evidences were the $^{31}P\{^1H\}$ NMR spectrum, which exhibited a temperature-invariant eight-nuclei ABCDEFGX spin system and the $^{31}P-^{31}P$ 2D COSY NMR spectrum, which allowed us to unravel the network of



Scheme 1. Reaction of white phosphorus with [(triphos)RhH₃].

several P–P connections. The presence of the monohydrophosphido moiety was clearly supported by a combination of ^{31}P DEPT (DEPT-90 and DEPT-135) and heteronuclear $^1H-^{31}P$ HMQC NMR experiments. In particular, the 2D NMR experiment points to a strong one-bond correlation between the P_D resonance ($\delta = -280.22$) and the doublet of multiplets centered at $\delta = 0.01$ in the ^1H NMR spectrum. The $^1J(H,P)$ coupling constant of approximately 120 Hz matches well with the values reported by Baudler and co-workers for the extremely reactive alkali metal salts of the HP_4^- ion.^[8]

By monitoring the reaction of **1** with P_4 by $^{31}P\{^1H\}$ NMR spectroscopy (in a sealed NMR tube, N_2 (or H_2) atmosphere, $[D_8]THF$, 2 h, 70 °C) it is found that, irrespective of the gas used, one of the four phosphorus atoms of the P_4 molecule is completely hydrogenated to PH_3 (singlet at $\delta = -244.77$ which transforms into a quartet with $^1J(H,P)$ 186.9 Hz in the



proton-coupled ^{31}P NMR spectrum). The remaining phosphorus atoms are efficiently scavenged by the (triphos)Rh moiety through the formation of the stable η^3 -*cyclo*-triphosphorus complex **4**.

Mechanistic information on the hydrogenation of P_4 is provided by in situ NMR experiments at lower temperature. Thus, when **1** in $[D_8]THF$ is treated with P_4 at approximately 40 °C (Rh: P_4 = 1:2) under dinitrogen, the selective transformation of **1** into **3** occurs. During the process a resonance at $\delta = 4.75$ ascribable to H_2 grows in intensity in the proton spectrum before slowly disappearing. On heating at 70 °C the fast disappearance of the dihydrogen resonance is accompanied by the formation of PH_3 and **4**. A separate NMR experiment carried out with $[D_3]1$ under dinitrogen indicated the total incorporation of the deuterium labels into the phosphane, confirming that all of the three hydride ligands are transferred from rhodium to one P atom.

The high stability of the $Rh(\eta^3-P_3)$ complex means that the present hydrogenation of P_4 to PH_3 cannot be catalytic. In fact, only a stoichiometric amount of phosphane is observed when a solution of **1** and P_4 (Rh: P_4 = 1:10) in $[D_8]THF$ is pressurized in a sapphire 10-mm NMR tube with up to 30 atm of H_2 and heated to 90 °C (HP-NMR experiment).

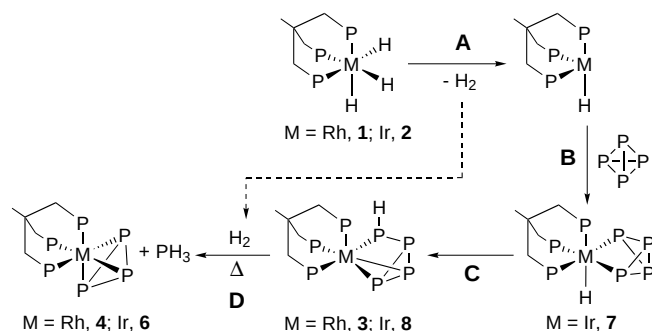
[*] Dr. M. Peruzzini, Dr. F. Vizza
Istituto per lo Studio della Stereochimica ed Energetica dei Composti di Coordinazione, ISSECC, CNR
Via Jacopo Nardi, 39-50132 Firenze (Italy)
Fax: (+390)55-2478366
E-mail: peruz@cacao.issecc.fi.cnr.it
vizza@cacao.issecc.fi.cnr.it

Dr. J. A. Ramirez
Departament de Química Inorgànica
Facultat de Químicas, Dr. Moliner, 50
Universitat de València, 46100 Burjassot (Spain)

[**] This work was supported by the European Commission (INCO-Copernicus project ERB IC15CT960746). Thanks are expressed to Dr. Pierluigi Barbaro (ISSECC-CNR) for running the $^1H-^{31}P$ 2D-HMQC NMR experiment on complex **3**, and to Dr. Claudio Bianchini and Dr. Carlo Mealli (ISSECC-CNR) for helpful suggestions.

A deeper insight into the hydrogenation process of P_4 was obtained by conducting the phosphorylation reaction in the presence of the kinetically more inert iridium complexes [(triphos)IrH₃] (**2**) and [(triphos)IrH₂(C₂H₅)]^[9] (**5**). Although **2** is also an efficient promoter for the transfer of three hydrogen atoms and leads to both PH₃ and [(triphos)Ir(η³-P₃)]^[7] (**6**), no reaction occurs before 120 °C (experiment in a sealed NMR tube). At this temperature, the formation of phosphane and **6** is probably too fast to allow the detection of any intermediate species. However, on replacing **2** with the dihydridoethyl complex **5**, which reductively eliminates ethane rather than H₂,^[9] pale yellow air-sensitive microcrystals of the bicycletetraphosphane (P₄²⁻) complex [(triphos)IrH(η¹:η¹-P₄)] (**7**) were obtained. Complex **7** is formed by oxidative addition of P₄, this being probably the first basic step of the whole process.^[10] On dissolving **7** in [D₈]THF under dinitrogen a very slow reaction takes place at room temperature to afford [(triphos)Ir(η¹:η²-HP₄)] (**8**).^[11] Moreover, on saturating a solution containing **8** with H₂, PH₃ and the *cyclo*-P₃ complex **6** are formed after heating at around 70 °C.^[12]

The present study provides good evidence for the direct hydrogenation of white phosphorus to PH₃ and *cyclo*-P₃ when promoted by rhodium and iridium trihydrides. A plausible mechanism is depicted in Scheme 2. The highlights of the process are: A) the generation of the transient [(triphos)MH] complex by thermal reductive elimination of H₂ from



Scheme 2. Mechanism for the stoichiometric hydrogenation of P₄ promoted by [(triphos)MH₃] complexes.

[(triphos)MH₃]; B) the oxidative addition of P₄ to afford the hydrido-(η¹:η¹-P₄) complexes [(triphos)MH(η¹:η¹-P₄)]; C) the intramolecular migration of the hydride ligand from metal to phosphorus to yield the hydrogen tetraphosphide complexes [(triphos)M(η¹:η²-HP₄)]; and D) the final addition of H₂ to the HP₄ ligand with concomitant P–P bond cleavage.^[13] Although we do not yet know how the dihydrogen molecule is transferred to the PH phosphorus atom during the last reaction step, a possible mechanism which is under investigation involves the metal-mediated heterolytic splitting of an η²-H₂ ligand followed by the stepwise addition of H⁺ and H⁻ to the HP₄ ligand.^[14]

Experimental Section

3: A solution of **1** (0.73 g, 1.00 mmol) and white phosphorus (0.25 g, 2.02 mmol) in THF (50 mL) was refluxed under dinitrogen for 2 h. After the solvent and the volatile components had been evaporated under

vacuum, the residue was washed with ethanol (2 × 5 mL) and pentane (2 × 5 mL). The yellow microcrystalline material was collected by filtration under dinitrogen and washed with pentane (2 × 5 mL) before being dried under a stream of dinitrogen (yield: 0.62 g, 73 %). Elemental analysis calcd for C₄₁H₄₀P₇Rh: C 57.77, H 4.73, P 25.43; found: C 57.56, H 4.70, P 25.28. IR (Nujol): $\tilde{\nu}$ = 2213 cm⁻¹ (w, PH); ¹H NMR (500.13 MHz, [D₈]THF, 20 °C, TMS): δ = 0.01 (ddbrm, ¹J(H,P) = 119.9, ²J(H,P) = 28.3 Hz, 1H; PH); ³¹P{¹H} NMR (81.01 MHz, [D₈]THF, 20 °C, 85 % H₃PO₄, ABCDEFGX spin systems (X = ¹⁰³Rh): δ = 15.96 (m, J(P_A,P_B) 12.5, J(P_A,P_C) 31.6, J(P_A,P_D) 19.1, J(P_A,P_E) 28.3, J(P_A,P_F) 3.1, J(P_A,P_G) 7.1, J(P_A,Rh) 121.1 Hz, 1P, P_A), 2.81 (m, J(P_B,P_C) 40.0, J(P_B,P_D) 42.2, J(P_B,P_E) 5.4, J(P_B,P_F) 5.4, J(P_B,P_G) 7.1, J(P_B,Rh) 112.5 Hz, 1P, P_B), -3.33 (m, J(P_G,P_C) 7.1, J(P_G,P_D) 119.5, J(P_G,P_E) 144.5, J(P_G,P_F) 155.0, J(P_G,Rh) 7.0 Hz, 1P, P_G), -10.78 (m, J(P_C,P_D) 50.2, J(P_C,P_E) ≈ 0, J(P_C,P_F) ≈ 0, J(P_C,Rh) 78.8 Hz, 1P, P_C), -180.12 (m, J(P_E,P_D) 24.4, J(P_E,P_F) 321.9, J(P_E,Rh) 20.0 Hz, 1P, P_E), -184.98 (m, J(P_F,P_D) 24.4, J(P_F,Rh) 20.0 Hz, 1P, P_F), -280.22 (m, J(P_D,Rh) 6.4 Hz, 1P, P_D).

7: A solution of **5** (0.70 g, 0.82 mmol) and white phosphorus (0.20 g, 1.61 mmol) in THF (or benzene) (50 mL) was refluxed under nitrogen for 5 h. Workup as above gave **7** as pale yellow microcrystals (yield: 0.73 g, 77 %). Elemental analysis calcd for C₄₁H₄₀P₇Ir: C 52.29, H 4.28, P 23.02; found: C 52.24, H 4.31, P 22.80. IR (Nujol): $\tilde{\nu}$ = 2061 cm⁻¹ (m, IrH); ¹H NMR (200.13 MHz, [D₆]benzene, 20 °C, TMS): δ = -7.09 (dqint, ²J(H,P_{trans}) = 141.3 Hz, ²J(H,P_{cis}) = 8.7 Hz, 1H; IrH); ³¹P{¹H} NMR (81.01 MHz, [D₈]THF, 20 °C, 85 % H₃PO₄, ABB'CDEE' spin systems: δ = -31.65 (m, ²J(P_B,P_A) = ²J(P_B,P_A) = 16.9, ³J(P_B,P_E) = ³J(P_B,P_E) = -14.3, ³J(P_B,P_E) = ³J(P_B,P_E) = 18.3 Hz, 2P, P_B and P_E), -28.40 (m, ²J(P_A,P_C) = ²J(P_A,P_D) = -5.9 Hz, 1P, P_A), -251.28 (m, ¹J(P_C,P_D) = 160.8, ¹J(P_C,P_E) = ¹J(P_C,P_E) = 133.0 Hz, 1P, P_C), -255.02 (m, ¹J(P_D,P_E) = ¹J(P_D,P_E) = 141.3 Hz, 1P, P_D), -272.7 (m, ¹J(P_E,P_E) = 72.7 Hz, 2P, P_E and P_E).

Received: February 19, 1998 [Z11498IE]
German version: *Angew. Chem.* **1998**, *110*, 2376–2378

Keywords: iridium • P ligands • phosphanes • phosphorus • rhodium

- Reviews: a) M. Di Vaira, M. Peruzzini, P. Stoppioni, *Polyhedron* **1987**, *6*, 351–382; b) O. J. Scherer, *Comments Inorg. Chem.* **1987**, *6*, 1–22; c) O. J. Scherer, *Angew. Chem.* **1990**, *102*, 1137–1155; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1104–1122; d) M. Scheer, E. Herrmann, *Z. Chem.* **1990**, *29*, 41–55; e) O. J. Scherer in *Multiple Bonds and Low Coordination in Phosphorus Chemistry* (Eds.: M. Regitz, O. J. Scherer), Thieme, Stuttgart, Germany, **1990**; chap 3.
- a) O. J. Scherer, J. Braun, P. Walter, G. Heckmann, G. Wolmershäuser, *Angew. Chem.* **1991**, *103*, 861–863; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 850–852; b) C. E. Laplaza, W. M. Davis, C. C. Cummins, *Angew. Chem.* **1995**, *107*, 2181–2183; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2042–2044; c) M. J. A. Johnson, A. L. Odom, C. C. Cummins, *Commun.* **1997**, 1523–1524; d) J. E. Davies, M. C. Klunduck, M. J. Mays, P. R. Raithby, G. P. Shields, P. K. Tompkin, *J. Chem. Soc. Dalton Trans.* **1997**, 715–719; e) J. E. Davies, M. J. Mays, E. J. Pook, P. R. Raithby, P. K. Tompkin, *Chem. Commun.* **1997**, 1997–1999; f) O. J. Scherer, C. Vondung, G. Wolmershäuser, *Angew. Chem.* **1997**, *109*, 1360–1362; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1303–1305.
- a) J. C. Green, M. L. H. Green, G. E. Morris, *J. Chem. Soc. Chem. Commun.* **1974**, 212–213. b) E. Cannillo, A. Coda, K. Prout, J.-C. Daran, *Acta Crystallogr. Sect. B* **1977**, *33*, 2608–2610.
- Reviews on phosphorus–hydrogen compounds: a) M. Baudler, *Angew. Chem.* **1982**, *94*, 520–540; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 492–512; b) M. Baudler, *Z. Chem.* **1984**, *24*, 352–366; c) M. Baudler, *Angew. Chem.* **1987**, *99*, 429–451; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 419–441. A μ -PH₂ complex resulting from the stepwise addition of NaOH and HBF₄ to a μ -η²-P₂ dimolybdenum complex has been recently reported: J. E. Davies, M. S. Mays, P. R. Raithby, G. P. Shields, P. K. Tompkin, *Chem. Commun.* **1997**, 361–362.
- a) J. Ott, L. M. Venanzi, C. A. Ghilardi, S. Midollini, A. Orlandini, *J. Organomet. Chem.* **1985**, *291*, 89–100; b) P. Janser, L. M. Venanzi, F. J. Bachechi, *J. Organomet. Chem.* **1985**, *296*, 229–242.

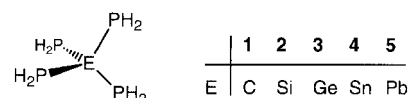
- [6] C. Bianchini, A. Meli, M. Peruzzini, F. Vizza, A. Albinati, *Organometallics* **1990**, 9, 2283–2291.
- [7] a) C. Bianchini, C. Mealli, A. Meli, L. Sacconi, *Inorg. Chim. Acta* **1979**, 37, L54–L55; b) M. Di Vaira, P. Stoppioni, L. Sacconi, *J. Organomet. Chem.* **1983**, 250, 183–195.
- [8] M. Baudler, C. Adamek, S. Opiela, H. Budziewicz, D. Ouzounis, *Angew. Chem.* **1988**, 100, 1110–1112; *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 1059–1061.
- [9] P. Barbaro, C. Bianchini, A. Meli, M. Peruzzini, F. Vizza, *Organometallics* **1991**, 10, 2227–2238.
- [10] Complexes containing the bicyclotetraphosphane ligand: Zr, Hf: a) O. J. Scherer, M. Swarowsky, H. Swarowsky, G. Wolmershäuser, *Angew. Chem.* **1988**, 100, 738–739; *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 694–695; Co: b) O. J. Scherer, M. Swarowsky, G. Wolmershäuser, *Organometallics* **1989**, 8, 841–842; c) M. Scheer, U. Becker, J. C. Huffman, M. C. Chisholm, *J. Organomet. Chem.* **1993**, 461, C1–C3; Rh: d) A. P. Ginsberg, W. E. Lindsell, K. J. McCullough, C. R. Sprinkle, A. J. Welch, *J. Am. Chem. Soc.* **1986**, 108, 403–416; e) M. Scheer, C. Troitzsch, P. G. Jones, *Angew. Chem.* **1992**, 104, 1137–1139; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1377–1379; f) M. Scheer, C. Troitzsch, L. Hilfert, M. Dargatz, E. Kleinpeter, P. G. Jones, J. Sieler, *Chem. Ber.* **1995**, 128, 251–257; Ir: g) M. Scheer, U. Becker, E. Matern, *Chem. Ber.* **1996**, 129, 721–724; Pt: h) M. Scheer, M. Dargatz, A. Rufinska, *J. Organomet. Chem.* **1992**, 440, 327–333.
- [11] After 12 days at room temperature a ^{31}P NMR analysis of a solution of **7** in a sealed NMR tube prepared under dinitrogen had the following composition: **7**, 35%; **8**, 28%; **6**, 12%; unknown iridium compounds 25%. The NMR spectroscopic properties of **8** are virtually the same as those for **3**. $^{31}\text{P}\{^1\text{H}\}$ NMR ($[\text{D}_8]\text{THF}$, 25 °C, 202.42 MHz): ABCDEFG spin system, $\delta_{\text{A}} = -19.60$, $\delta_{\text{B}} = -30.73$, $\delta_{\text{C}} = -45.63$, $\delta_{\text{D}} = -268.33$ (transforms into a doublet of multiplets in the proton-coupled ^{31}P spectrum: $^1J(\text{HP}) \approx 118$ Hz), $\delta_{\text{E}} = -217.65$, $\delta_{\text{F}} = -221.72$, $\delta_{\text{G}} = 28.87$.
- [12] On hydrogenation of **7**, the reductive elimination of P_4 with formation of the trihydride **2** becomes competitive with respect to the hydrogenation reaction of P_4 . This finding supports the hypothesis that hydrogen migration from the metal to one of the P atoms of P_4 is mandatory to bring about the final dihydrogen transfer to give PH_3 and *cyclo*- P_3 .
- [13] Homolytic P–P bond cleavage of P_4 has been considered recently in the photochemical reaction of P_4 with $[\text{Cp}''(\text{CO})_2\text{Fe}]_2$ ($\text{Cp}'' = 1,3\text{-tBu}_2\text{C}_5\text{H}_3$): O. J. Scherer, G. Schwarz, G. Wolmershäuser, *Z. Anorg. Allg. Chem.* **1996**, 622, 951.
- [14] The molecular hydrogen complex $[(\text{triphos})\text{Ir}(\eta^2\text{-H}_2)(\text{H})_2]\text{BPh}_4$; which is relevant to this hypothesis, has been recently described: C. Bianchini, S. Moneti, M. Peruzzini, F. Vizza, *Inorg. Chem.* **1997**, 36, 5818–5825.

Synthesis and Crystal Structure Analysis of Tetraphosphanylsilane and Identification of Tetraphosphanylgermane**

Matthias Driess,* Christian Monsé, Roland Boese, and Dieter Bläser

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

The ease with which the phosphanyl group (PH_2) can be functionalized by electrophilic and nucleophilic reagents provides facile access to a wide range of molecular phosphorus compounds. Polyphosphanyl–element compounds without organic substituents are also very promising as potential single-source precursors for chemical vapor deposition (CVD) for the synthesis of metastable element phosphides and for surface refining. Element hydrides substituted solely by PH_2 groups are not yet known, however. We have therefore been concerned with the synthesis of tetraphosphanyl compounds with elements of Group 14 (**1–5**). Whereas nothing is



yet known about the existence of these (expectedly) extremely reactive molecules, in the case of the polyphosphanylsilanes only $\text{HSi}(\text{PH}_2)_3$ ^[1] and related organotriphosphanylsilanes^[2] could be isolated. An excellent nucleophilic transfer reagent for the PH_2 group is the tetraphosphanylalanato ion in $[\text{LiAl}(\text{PH}_2)_4]$, which reacts even at -80°C with halogen–element compounds under halogen/ PH_2 exchange.^[1,3] According to earlier studies, the reaction of SiX_4 and GeX_4 ($\text{X} = \text{halide}$) with $[\text{LiAl}(\text{PH}_2)_4]$ does not lead to **2** and **3**, but to a mixture of SiH- and GeH- containing phosphanyl derivatives.^[4] In contrast, we ascertained that the title compounds **2** and **3** are indeed accessible when mild reaction conditions are employed and the reaction products rapidly worked-up. Whereas **2** was for the first time isolated and characterized by means of NMR and IR spectroscopy as well as by X-ray structure analysis, **3** has only been identified by gas chromatography and mass spectrometry as yet.

The reaction of SiCl_4 with $[\text{LiAl}(\text{PH}_2)_4]$ in tetraethylene glycol dimethyl ether at -30°C leads to an orange solution,

[*] Prof. Dr. M. Driess, Dipl.-Chem. C. Monsé
Lehrstuhl für Anorganische Chemie I der Universität
Fakultät für Chemie
Universitätsstrasse 150, D-44801 Bochum (Germany)
Fax: (+49) 234-7094378
E-mail: driess@ibm.anch.ruhr-uni-bochum.de

Prof. Dr. R. Boese, Dipl.-Ing. D. Bläser
Institut für Anorganische Chemie der Universität Essen (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Universität Bochum, and the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen. We would like to thank Prof. Dr. W. Sander, Dipl.-Chem. A. Kuhn, and Priv.-Doz. Dr. C. van Wüllen (Universität Bochum) for recording the matrix IR spectra and carrying out ab initio MO calculations, and Prof. Dr. J. Hahn (Universität Köln) for the NMR spectrum simulations.

from which **2** can be isolated in 18% yield. Compound **2** is colorless with a melting point of -25°C , and can be stored without problem under vacuum or inert gas at temperatures below -10°C . Contact with atmospheric oxygen leads to spontaneous combustion or even explosion. In the EI mass spectrum the molecular ion was detected at $m/z = 160$ with a relative intensity of approximately 30%. The ^1H NMR spectrum shows a doublet of multiplets of higher order at $\delta = 2.04$. The M part of the $\text{A}[\text{MX}_2]_4$ spin system ($\text{A} = {}^{29}\text{Si}$, $\text{M} = {}^{31}\text{P}$, $\text{X} = {}^1\text{H}$) in the ${}^{31}\text{P}$ NMR spectrum (Figure 1) is a triplet of complex multiplets at characteristic high field ($\delta = -205.0$). The ${}^{31}\text{P}$ nuclei in **2** are somewhat more strongly

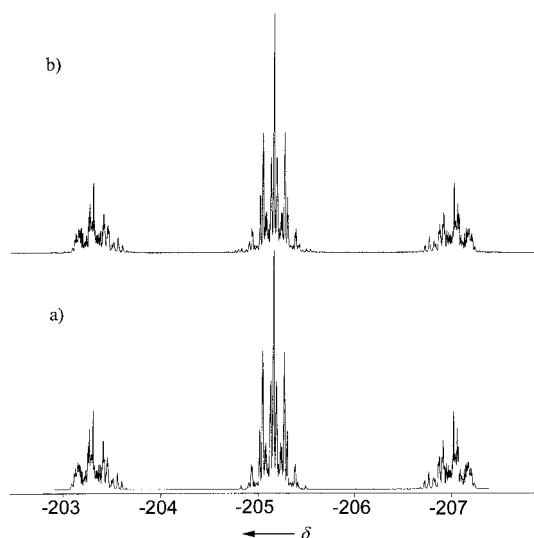


Figure 1. ${}^{31}\text{P}$ NMR spectra of **2**. a) measured; b) simulated.

shielded than those in $\text{HSi}(\text{PH}_2)_3$ ($\delta = -216$).^[4] Analysis of the multiplet by spectrum simulation^[5] results in coupling constants of ${}^1J(\text{P},\text{H}) = 185.51$, ${}^2J(\text{P},\text{P}) = 14.28$, ${}^2J(\text{H},\text{H}) = 0.37$, and ${}^4J(\text{P},\text{H}) = 4.35$ Hz. As expected, the ${}^{29}\text{Si}\{^1\text{H}\}$ NMR spectrum (Figure 2) has a quintet at $\delta = -12.17$ (${}^1J(\text{Si},\text{P}) = 52.5$ Hz), which in the ${}^1\text{H}$ -coupled spectrum is additionally split into a nonet of quintets (${}^2J(\text{Si},\text{H}) = 7.5$ Hz).

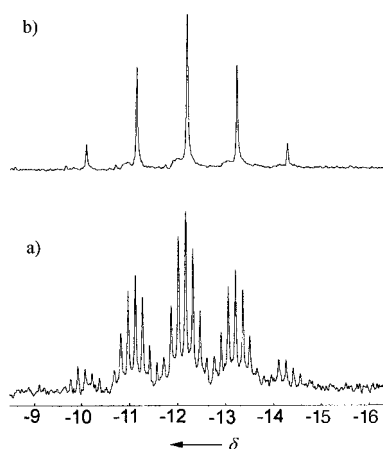


Figure 2. ${}^{29}\text{Si}$ NMR spectra of **2**. a) ${}^{29}\text{Si}$ NMR spectrum; b) ${}^{29}\text{Si}\{^1\text{H}\}$ NMR spectrum.

A single crystal of **2** suitable for X-ray structure analysis was obtained by in situ crystallization on a diffractometer at -30°C .^[6] Compound **2** crystallized in the monoclinic space group $P2_1/c$ with four independent molecules in the unit cell. In the structure refinement, the H atoms on the pyramidally coordinated phosphorus atom were initially localized by a difference Fourier synthesis, but then refined with restrictions.^[6] This resulted in a local C_1 symmetry, with the P atoms forming an ideal tetrahedron around the Si atom (av P-Si-P $109.46(5)^{\circ}$, Figure 3). The sum of the bond angles at

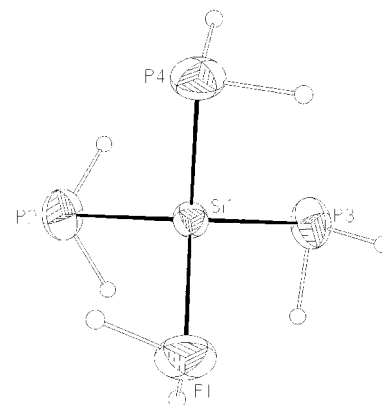


Figure 3. Structure of **2** in the crystal (50% probability ellipsoids). Bond lengths [$\text{\AA}$] and angles [$^{\circ}$]: Si1–P1 2.239(1), Si1–P2 2.243(1), Si1–P3 2.241(1), Si1–P4 2.237(1); P4–Si1–P1 $109.75(5)$, P1–Si1–P3 $111.59(5)$, P1–Si1–P2 $109.60(5)$, P4–Si1–P3 $108.81(5)$, P4–Si1–P2 $108.28(5)$, P3–Si1–P2 $108.74(5)$.

phosphorus amounts to 277° . The average Si–P bond length of $2.240(1)$ $\text{\AA}$ is practically identical with that found in other silylphosphanes.^[8] The structure calculated with the B3LYP density function without symmetry restrictions has C_1 symmetry, and the bond lengths and angles are in excellent agreement with the experimental values (Si–P 2.227, 2.225, and 2.230 $\text{\AA}$; av P-Si-P 109.4° ; H–P 1.43 $\text{\AA}$). However, conformations with higher symmetry (D_2 , D_{2d} , or S_4) are almost identical in energy with the C_1 -symmetrical form and the rotation barriers of the PH_2 groups are only about 3–5 kcal mol^{-1} . This implies that various conformations that may be present in solution cannot be observed on the NMR time scale. The ${}^1\text{H}$ and ${}^{31}\text{P}$ NMR spectra of **2** in $[\text{D}_8]\text{toluene}$ do indeed remain identical between -80 and 80°C . In contrast, the packing of **2** in the crystal (Figure 4) favors local C_1 symmetry, and inversion-symmetrical molecule pairs are formed with two $\text{P}(3)\text{-H}\cdots\text{P}(4')$ or $\text{P}(4)\text{-H}\cdots\text{P}(3')$ interactions. The longer $\text{H}\cdots\text{P}$ distances of 2.97 $\text{\AA}$ lie in the range of the sum of the van der Waals radii of 3.0 $\text{\AA}$, the $\text{P-H}\cdots\text{P}$ angles are 154° and the $\text{P}\cdots\text{P}'$ distances about 4.3 $\text{\AA}$.

Calculations at the MP2/6-31G* level^[7] of the gas-phase structure of such a dimer resulted, however, in weak *repulsive* Gibbs energies of association, irrespective of whether they were based on the crystallographically determined or geometrically optimized atomic sites for the H atoms on phosphorus, while at the same time holding the (experimental) distances of the Si and P atoms. In agreement with this, vibrational spectroscopy studies on **2** in an argon matrix at the

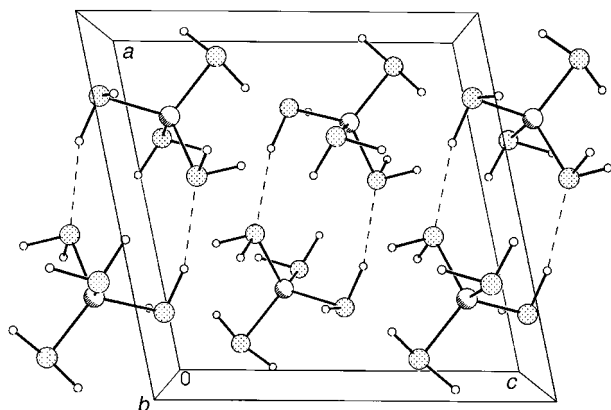


Figure 4. Packing and pair formation of **2** in the crystal.

temperature interval from 8 to 55 K gave no indication of the voluntary formation of a dimer.

Owing to the strongly oxidizing effect of tetravalent germanium, PH_3 and an insoluble yellow solid are formed spontaneously on reaction of GeCl_4 with $\text{Li}[\text{Al}(\text{PH}_2)_4]$ in ethylene glycol dimethyl ether at -45°C . After filtration and removal of PH_3 , the clear reaction solution contains only tetraphosphanylgermane (**3**) and triphosphanylgermane ($\text{HGe}(\text{PH}_2)_3$, **6**) in the ratio 1:2.5, as determined by GC-MS. In the EI mass spectrum of **3**, the molecular ion peak is at $m/z=206$ with a relative intensity of 10% and a correct isotope distribution. The new compounds **2**, **3**, and **6** are indeed thermolabile single-source precursors for CVD processes. They react at the relatively low temperature of 80°C under cleavage of PH_3 to readily form Si and Ge phosphides. We will report on these elsewhere.

Experimental Section

2: SiCl_4 (11.46 g, 67.4 mmol) was added to a solution of $\text{Li}[\text{Al}(\text{PH}_2)_4]$ (0.25 M, 75 mmol) in tetraethylene glycol dimethyl ether (300 mL) at -30°C over a period of 10 min under continuous stirring. The solution turned orange. The volatile components (PH_3 , $\text{HSi}(\text{PH}_2)_3$, and **2**) were removed under vacuum (10^{-3} Torr) at 20°C and collected in a cold trap at -196°C . These were then fractionated by condensation in a series of cold traps at -10 , -60 , and -196°C . Compound **2** was collected in the trap at -10°C , $\text{HSi}(\text{PH}_2)_3$ at -60°C , and PH_3 at -196°C . Yield: 1.94 g (12.1 mmol, 18%); m.p. -25°C ; ^1H NMR (250 MHz, C_6D_6 , 25°C): $\delta = 2.04$ (dm); ^{31}P NMR (101 MHz, C_6D_6 , 25°C): $\delta = -205.0$ (tm, $^1J(\text{P,H}) = 185.51$, $^2J(\text{P,P}) = 14.28$, $^2J(\text{H,H}) = 0.37$, $^4J(\text{P,H}) = 4.35$ Hz); ^{29}Si NMR (49 MHz, C_6D_6 , 25°C): $\delta = -12.17$ (n of quint, $^1J(\text{Si,P}) = 52.5$, $^2J(\text{Si,H}) = 7.5$ Hz); IR (Ar matrix, -218°C): $\tilde{\nu} = 2289$ (vs), 1183 (vs), 840 (w), 721 (m), 633 (m), 566 (w), 478 cm^{-1} (vs); MS (EI): m/z (%): 160 (30) [M^+], 127 (100) [$M^+ - \text{PH}_2$], 93 (61) [$\text{SiPH}(\text{PH}_2)^+$], 61 (17) [SiPH_2^+].

3/6: GeCl_4 (0.60 g, 2.8 mmol) was added dropwise under stirring to a solution of $\text{Li}[\text{Al}(\text{PH}_2)_4]$ (0.31 M, 3.1 mmol) in ethylene glycol dimethyl ether (10 mL) at -45°C . The release of gas (PH_3) was accompanied by formation of a yellow suspension, which was filtered. According to GC-MS, the clear filtrate contained only **3** and **6** in the ratio 1:2.5. **3:** MS(EI): m/z (%) = 206 (10) [M^+], 173 (100) [$M^+ - \text{PH}_2$], 137 (100) [GeP_2H^+], 107 (82) [GePH^+], 74 (19) [Ge^+], 67 (19) [P_2H_3^+]. **6:** MS(EI): m/z (%): 174 (23) [M^+], 140 (90) [$M^+ - \text{PH}_3$], 107 (100) [$M^+ - \text{PH}_2\text{PH}_3$], 74 (40) [Ge^+].

Received: March 30, 1998 [Z11658IE]
German version: *Angew. Chem.* **1998**, *110*, 2389–2391

Keywords: germanium • NMR spectroscopy • phosphorus • silanes • silicon

- [1] A. D. Norman, *J. Am. Chem. Soc.* **1968**, *90*, 6556.
- [2] M. Baudler, G. Scholz, W. Oehlert, *Z. Naturforsch. B* **1989**, *44*, 627.
- [3] A. E. Finholt, C. Helling, V. Imhof, L. Nielsen, E. Jacobsen, *Inorg. Chem.* **1963**, *2*, 504; M. Driess, K. Merz, H. Pritzkow, R. Janoschek, *Angew. Chem.* **1996**, *108*, 2688; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2507.
- [4] A. D. Norman, D. C. Wingleth, *Inorg. Chem.* **1970**, *9*, 98.
- [5] The spectrum simulation was carried out with the program Perch, Version 1/96, University of Kuopio (Finland).
- [6] A single crystal of **2** was formed in a capillary tube with a diameter of 0.3 mm on a four-circle diffractometer at 242 K by miniaturized zone melting with focused infra-red radiation.^[9] **2:** monoclinic, space group $P2_1/c$, $a = 10.659(3)$, $b = 7.137(2)$, $c = 10.832(3)$ Å, $\beta = 101.72(2)^\circ$, $V = 806.8(4)$ Å³, $Z = 4$, $\rho = 1.318\text{ g cm}^{-3}$, $\Theta_{\text{max}} = 30^\circ$; of 2464 measured reflections, 2316 were independent ($R_{\text{merg}} = 0.0379$) and 1752 observed ($I > 2\sigma(I)$). The intensities were measured on a Nicolet R3m/V four-circle diffractometer (MoK α radiation, $\lambda = 0.71073$ Å, ω scan, $T = 123$ K). The structure was solved by direct methods,^[10a] and refined with all measured reflections against F^2 .^[10b] The Si and P atoms were anisotropic, and hydrogen-atom positions were determined from a difference Fourier and refined as riding groups with P–H distances taken from the sum of the covalent radii (1.42 Å) with group isotropic temperature factors. A refinement without imposing certain restrictions led to unreasonably small P–H distances. $R1 = 0.0479$, $wR2 = 0.1306$ (all data), 50 parameters. Models with higher local symmetry (D_{2d} or S_4) led to significantly higher R values ($R1 > 0.10$). Further details on the crystal structure investigation can be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-408423.
- [7] GAUSSIAN 94, Revision B.3., M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1995**.
- [8] Review: W. S. Sheldrick in *The Chemistry of Organic Silicon Compounds* (Eds.: Z. Rappoport, S. Patai), Wiley, New York, **1989**, p. 254.
- [9] R. Boese, M. Nussbaumer in *In Situ Crystallisation Techniques in Organic Crystal Chemistry* (Ed.: D. W. Jones), Oxford University Press, Oxford, **1994**, pp. 20–37.
- [10] a) G. M. Sheldrick, *SHELXS86*, Universität Göttingen, **1986**; b) G. M. Sheldrick, *SHELXL93*, Universität Göttingen, **1993**.

Rate Enhancement of the Radical 1,2-Acyloxy Shift (Surzur–Tanner Rearrangement) by Complexation with Lewis Acids**

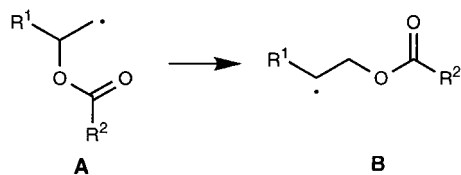
Emmanuel Lacôte and Philippe Renaud*

Owing to their mildness and their compatibility with many functional groups, radical reactions have become a very powerful tool for organic synthesis.^[1] For instance, unique

[*] Prof. P. Renaud, E. Lacôte
Institut de chimie organique
Université de Fribourg
Pérolles, CH-1700 Fribourg (Switzerland)
Fax: (+41) 263-009-739
E-mail: philippe.renaud@unifr.ch

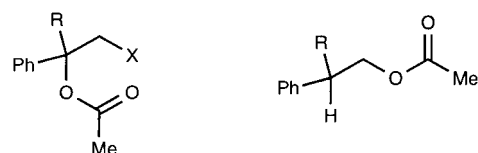
[**] This work was supported by the fonds national suisse de la recherche scientifique. We thank Prof. H. Zipse for drawing our attention to his calculation results and for helpful suggestions.

radical rearrangements have found synthetic applications. Among them, the 1,2-acyloxy shift of β -(acyloxy)alkyl radicals (Surzur–Tanner rearrangement, **A** $\rightarrow$ **B**) is particularly interesting since it has no equivalent in ionic chemistry.^[2] As a



consequence, since its discovery by Surzur in 1967^[3] and a seminal study by Tanner in 1969,^[4] this rearrangement has attracted considerable attention from a mechanistic^[5] as well as a synthetic point of view.^[6] However, for many β -(acyloxy)alkyl radicals, the rate of rearrangement is too slow for synthetic purposes. Recently, Zipse reported calculations indicating that the rate of the 1,2-acyloxy migration should be enhanced by protic acids.^[7] This hypothesis was underlined in a recent review,^[2] and Giese has reported that intramolecular protonation of acetate groups may be responsible for the rate acceleration of a closely related fragmentation of α -hydroxy- β -(acetoxy)alkyl radicals.^[8] Our experience with Lewis acids in radical reactions^[9, 10] led us to investigate their ability to accelerate the rate of the 1,2-acyloxy shift. We report here the first evidence that Lewis acids can efficiently enhance the rate of this rearrangement. This represents, to the best of our knowledge, the first example of a Lewis acid mediated acceleration of a radical rearrangement (with the exception of cyclization reactions).^[11]

Our investigation started with the acetate **1**, which has been thoroughly investigated by Beckwith et al.^[12] Under standard radical reaction conditions (0.02 M Bu₃SnH, AIBN (azobisisobutyronitrile), refluxing benzene), only the reduced compound **2** could be detected; no rearranged product **3** is observed.^[13] Interestingly, in the presence of stoichiometric amounts of Lewis acids such as Et₂AlCl or methylaluminum bis(di-2,6-*tert*-butyl-4-methylphenoxide) (MAD), the migration product **3** was detected. However, the yield was low and poorly reproducible due to Lewis acid induced cationic decomposition of both starting material and products. A reagent less prone to ionization—that is, the secondary benzylic acetate **4**—was chosen next.^[14] As anticipated, better yields (up to 76%) were obtained in the presence of Lewis acids, but only the product of direct reduction **5** was observed; no rearranged product **6** was detected.



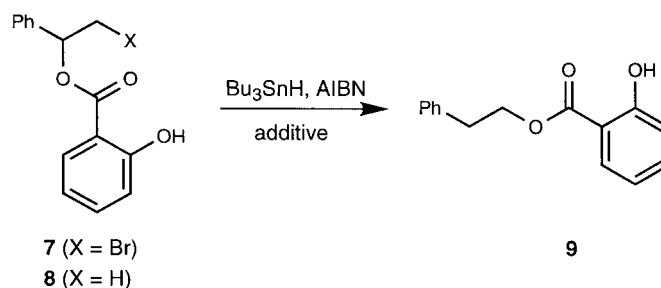
We attribute the inefficiency of the Lewis acids to the presence of only a small amount of complexed radical precursor. To favor the formation of the complex by means of chelation, we decided to use the salicylate **7** instead of the acetate **4** as radical precursor. The results of the radical reactions are reported in Table 1.

Table 1. Radical reduction of **7** with Bu₃SnH in refluxing benzene to provide **8** and **9**. Procedure A: 0.02 M Bu₃SnH; procedure B: Bu₃SnH added over 12 h with a syringe pump.

Entry	Additive ^[a]	Proce- dure	Yield[%]	8:9 ^[b]
1	–	A	88	97:3
2	–	B	78	75:25
3	MeAl(<i>Op</i> -Tol) ₂	A	68	62:38
4	MeAl(<i>Op</i> -Tol) ₂	B	73	12:88
5	La(OTf) ₃ , NEt ₃	A	78	91:9
6	Yb(OTf) ₃ , NEt ₃	A	69	95:5
7	Sc(OTf) ₃ , NEt ₃	A	75	75:25
8	Sc(OTf) ₃ , DIPA	A	62	76:24
9	Sc(OTf) ₃ , TMEDA	A	66	74:26
10	Sc(OTf) ₃ , quinuclidine	A	86	70:30
11	Sc(OTf) ₃ , 2,6-lutidine	A	71	67:33
12	Sc(OTf) ₃ , 2,6-lutidine	B	76	17:83 ^[c]
13	Sc(OTf) ₃ , 2,6-lutidine (10% cat.)	A	86	98:2
14	Sc(OTf) ₃ , 2,6-lutidine, TEMPO	A	no reaction	–

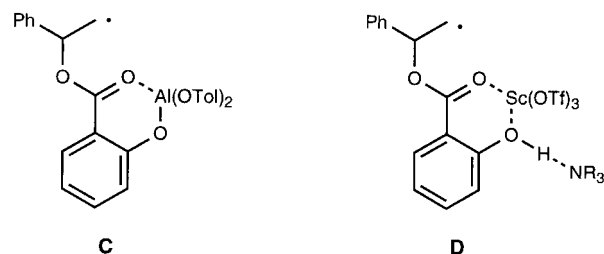
[a] Tol = tolyl. [b] The ratios were determined by ¹H NMR spectroscopy (360 MHz). [c] 1.0-mmol scale; on a 0.5-mol scale, the ratio was 12:88.

To allow a facile comparison of the additive effects, we used an easily reproducible standard one-pot procedure (A: 0.02 M each Bu₃SnH and **7**). A second procedure (B: 0.02 M **7** and slow addition of Bu₃SnH over 10 h) was used to optimize the

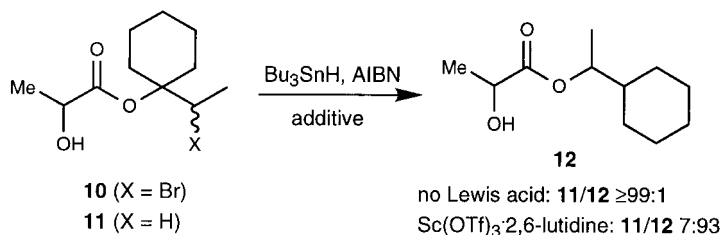


amount of rearranged product **9**. In the absence of Lewis acid, the product of direct reduction **8** was the major product with both procedures (**8:9** = 97:3 and 75:25, respectively; entries 1 and 2). Different aluminum Lewis acids were tested, and interesting effects were obtained with methylaluminum bis(4-methylphenoxide). With this additive, the aluminum tris(aryloxy) was formed in situ, as proven by the evolution of methane. With procedure A, the ratio **8:9** reached 62:38 (68% yield, entry 3). In contrast, procedure B gave **9** as the major product (**8:9** = 12:88, entry 4) without loss of yield. Comparison of entries 1/3 and 2/4 indicates that an approximate 20-fold enhancement in the rate of the rearrangement occurs upon complexation (assuming that the rate of reduction is not influenced by the complexation). Besides aluminum compounds, zinc(II) and magnesium(II) derivatives were investigated; all of them induced a rapid decomposition of the

starting bromide **7**. Trivalent lanthanides^[15] which have been applied with success in radical reactions^[16] were tested, but only minor effects were noticed (entries 5 and 6). Interestingly, scandium(III) triflate (triflate = trifluoromethanesulfonate (Tf)) was found to be an effective promoter of the rearrangement (entries 7–11). The nature of the coligand proved to be important. Good results were obtained with tertiary amines, but no rate enhancement of the rearrangement was observed with less basic coadditives such as dimethyl sulfoxide (DMSO) and hexamethyl phosphoramide (HMPA). A screening of different amines (entries 7–11; DIPA = diisopropylamine, TMEDA = tetramethylethylenediamine) showed that 2,6-lutidine was the coadditive of choice. By the one-pot procedure, a **8:9** ratio of 67:33 (entry 11) was obtained, which is similar to the result observed with methylaluminum bis(4-methylphenoxide) (entry 3). Upon slow addition of Bu₃SnH (procedure B), the major product was the rearranged compound **9** (**8:9** = 17:83, entry 12). As expected, stoichiometric amounts of scandium(III) triflate are necessary for the maximum rate enhancement. In the presence of 10 mol % of the Lewis acid, no rate enhancement was perceptible (entry 13). With both scandium(III) triflate and methylaluminum bis(4-methylphenoxide), the presence of a free *ortho*-OH group was necessary for a rate enhancement. Methylation of the phenol fully inhibits the effect of additives.^[17] This is in accord with the formation of an aluminum tris(aryloxy) of type **C** or a scandium complex of type **D**. The radical nature of the rearrangement was confirmed by the absence of reaction when 20 mol % of the radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) was used (entry 14).^[18]



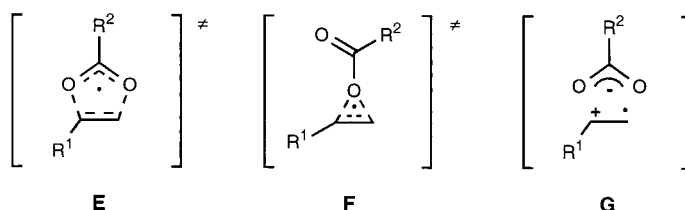
An even greater increase in the rearrangement rate was observed in the lactate series starting with bromide **10**. In the absence of Lewis acid, the one-pot procedure A furnished exclusively the reduced compound **11** (**11:12** ≥ 99:1) in 75 % yield. The use of one equivalent of scandium(III) triflate/2,6-lutidine led to preferential formation of the rearranged product **12** (**11:12** = 7:93) in 54 % yield. This represents an



increase in the reaction rate by three orders of magnitude.^[19] Interestingly, under Lewis acidic conditions, it was possible to

run the rearrangement at –20 °C (**11:12** = 25:75) in 60 % yield. This is, to our knowledge, the lowest temperature at which a 1,2-acyloxy shift was observed.^[20]

Three mechanisms have been proposed for the acyloxy shift: five-electron five-center shift (**E**), three-electron three-center shift (**F**), and in-cage fragmentation to a carboxylate and an alkene radical cation (**G**).^[2] Because of the polarization of the transition states or intermediates **E**–**G**, all three pathways are expected to be favored by complexation with Lewis acids. However, Zipse's recent calculations indicated that the three-center mechanism proceeding via intermediate **F**, which resembles the addition of a carboxylic acid to an olefin radical cation, is favored by protonation of the ester carbonyl group.^[7]



In conclusion, aluminum and scandium Lewis acid, when used in stoichiometric amounts, can efficiently accelerate the β-(acyloxy)alkyl radical rearrangement. The idea of favoring one mechanism, the three-center shift via **F**, upon complexation is particularly interesting when considering the stereochemical aspect of such rearrangements. Further study of the stereochemical outcome of the reaction, with either chiral substrates or chiral Lewis acids, is under way in our laboratory.

Received: March 2, 1998 [Z11538IE]

German version: *Angew. Chem.* **1998**, *110*, 2369–2371

Keywords: aluminum • Lewis acids • radical reactions • rearrangements • scandium

- [1] a) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Oxford, **1988**; b) W. B. Motherwell, D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, **1992**; c) D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1996**.
- [2] A. L. J. Beckwith, D. Crich, P. J. Duggan, Q. Yao, *Chem. Rev.* **1997**, *97*, 3273–3312.
- [3] J. M. Surzur, P. Teissier, *C. R. Acad. Sci. Fr. Ser. C* **1967**, *264*, 1981–1984.
- [4] D. D. Tanner, F. C. P. Law, *J. Am. Chem. Soc.* **1969**, *91*, 7535–7537.
- [5] a) L. R. C. Barclay, D. Griller, K. U. Ingold, *J. Am. Chem. Soc.* **1982**, *104*, 4399–4403; b) L. R. C. Barclay, J. Luszyk, K. U. Ingold, *J. Am. Chem. Soc.* **1984**, *106*, 1793–1796; c) P. Kocovsky, I. Stary, F. Turecek, *Tetrahedron Lett.* **1986**, *27*, 1513–1516; d) H.-G. Korth, R. Sustmann, K. S. Gröninger, M. Leisung, B. Giese, *J. Org. Chem.* **1988**, *53*, 4364–4369; e) A. L. J. Beckwith, P. J. Duggan, *J. Chem. Soc. Perkin Trans. 2* **1992**, 1777–1783; f) A. L. J. Beckwith, P. J. Duggan, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1673–1679; g) D. Crich, F. Filzen, *J. Org. Chem.* **1995**, *60*, 4834–4837; h) A. L. J. Beckwith, P. J. Duggan, *J. Am. Chem. Soc.* **1996**, *118*, 12838–12839; i) H. Zipse, *J. Chem. Soc. Perkin Trans. 2* **1997**, 1797–1800.
- [6] a) B. Giese, S. Gilges, K. S. Gröninger, C. Lamberth, T. Witzel, *Liebigs Ann. Chem.* **1988**, 615–617; b) T. Gimisis, G. Ialongo, M. Zamboni, C. Chatgililoglu, *Tetrahedron Lett.* **1995**, *36*, 6781–6784; c) Y. Itoh, K.

- Haraguchi, H. Tanaka, K. Matsumoto, K. T. Nakamura, T. Miyasaka, *Tetrahedron Lett.* **1995**, 36, 3867–3870.
- [7] H. Zipse, *J. Am. Chem. Soc.* **1997**, 119, 1087–1093.
- [8] S. N. Müller, R. Batra, M. Senn, B. Giese, M. Kisel, O. Shadiro, *J. Am. Chem. Soc.* **1997**, 119, 2795–2803.
- [9] a) P. Renaud, P.-A. Carrupt, M. Gerster, K. Schenk, *Tetrahedron Lett.* **1994**, 35, 1703–1706; b) P. Renaud, N. Moufid, L. H. Kuo, D. P. Curran, *J. Org. Chem.* **1994**, 59, 3547–3552; c) P. Renaud, M. Gerster, *J. Am. Chem. Soc.* **1995**, 117, 6607–6608; d) M. Gerster, P. Renaud, *Angew. Chem.* **1996**, 108, 2523–2525; *Angew. Chem. Int. Ed.* **1996**, 35, 2396–2399; e) M. Gerster, L. Audergon, M. Moufid, P. Renaud, *Tetrahedron Lett.* **1996**, 37, 6335–6338; f) A.-R. Fhal, P. Renaud, *Tetrahedron Lett.* **1997**, 38, 2661–2664.
- [10] P. Renaud, M. Gerster, *Angew. Chem.* **1998**, 110, in press; *Angew. Chem. Int. Ed.* **1998**, 37, in press.
- [11] Acceleration of radical cyclizations was recently reported: T. Ooi, Y. Hokke, K. Maruoka, *Angew. Chem.* **1997**, 109, 1230–1231; *Angew. Chem. Int. Ed.* **1997**, 36, 1181–1183. The rate of cyclization of aminyl radicals is also influenced by the Lewis acids: C. Hau, O. M. Musa, F. N. Martinez, M. Newcomb, *J. Org. Chem.* **1997**, 62, 2704–2710; for more examples, see reference [10].
- [12] A. L. J. Beckwith, C. B. Thomas, *J. Chem. Soc. Perkin Trans. 2* **1973**, 861–872.
- [13] The product of phenyl migration (neophyl rearrangement) is not observed under these conditions.
- [14] Compound **4** was prepared according to the procedure of Beckwith et al.^[12] For physical data and elemental analysis, see C. S. Marvel, N. S. Moon, *J. Am. Chem. Soc.* **1940**, 62, 45–49.
- [15] S. Kobayashi, *Synlett* **1994**, 689–701.
- [16] a) M. P. Sibi, C. P. Jasperse, J. Ji, *J. Am. Chem. Soc.* **1995**, 117, 10779–10780; b) M. P. Sibi, J. Ji, *Angew. Chem.* **1996**, 108, 198–200; *Angew. Chem. Int. Ed.* **1996**, 35, 190–192.
- [17] In the absence of Lewis acids, the *ortho*-methoxybenzoate rearranged slightly slower (procedure B: the ratio of rearrangement to direct reduction products was 84:16) than the hydroxy-substituted compound **7** (procedure B: the ratio of rearrangement to direct reduction products was 75:25; Table 1, entry 2). This small difference may be attributed to intramolecular protonation.
- [18] The hypothesis of an ionic rearrangement followed by a radical reaction was discarded since treatment of **7** with MeAl(OPh)₂ or Sc(OTf)₃ left the bromide unchanged.
- [19] A low diastereoselectivity (< 60% *ds*) was observed.
- [20] Most reported 1,2-acyloxy shifts have been conducted at temperatures higher than 60 °C.

Transition Metal Complexes with Organoazide Ligands: Synthesis, Structural Chemistry, and Reactivity**

Michael Barz, Eberhardt Herdtweck, and Werner R. Thiel*

Organoazides are important starting materials for a multitude of organic reactions,^[2] such as in the synthesis of alkylamines from alkyl alcohols or halides

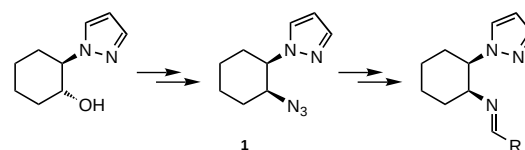
[*] Priv.-Doz. Dr. W. R. Thiel, Dr. M. Barz, Dr. E. Herdtweck
Anorganisch-chemisches Institut
der Technischen Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+49) 89-28913473
E-mail: thiel@arthur.anorg.chemie.tu-muenchen.de

[**] Ligands with Cycloalkane Backbones, part 7. The authors wish to thank Prof. W. A. Herrmann and the Deutsche Forschungsgemeinschaft for support of this work. Part 6: reference [1]

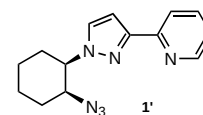
($R-X \rightarrow RN_3 \rightarrow R-NH_2$) or heterocycles (e.g. [2+3] cycloaddition).^[3] The most remarkable aspect in the reactivity of organoazides is the loss of dinitrogen, which can occur thermally, photochemically, or by acid or transition metal catalysis.^[4] The highly reactive nitrenes (“R–N”) that are generated from the RN_3 fragment, can rearrange to the corresponding imines, insert into C–C bonds, form amines by intra- or intermolecular hydrogen abstraction (“R–N” $\rightarrow$ R–NH₂), or undergo cycloaddition in the presence of unsaturated substrates (e.g. “R–N” + C₂H₄ $\rightarrow$ R–N(C₂H₄)).^[5]

An illustrative example of the stabilization of a “nitrene fragment” at a transition metal center was described by Bergman and Proulx with the reaction of [Cp₂TaCH₃(PMe₃)] with phenylazide, which led to the formation of the tantalum imido complex [Cp₂TaCH₃(=N–C₆H₅)].^[6] In the intermediate [Cp₂TaCH₃(N₃–C₆H₅)], the transition metal center is coordinated by the terminal nitrogen atom (N3) of the azido functionality. This compound was, to our knowledge, the only structurally characterized transition metal complex bearing a RN_3 ligand.^[7] This is surprising since many coordination complexes of the azide ion (N₃[–]) are known.^[8] Here we report the first structurally characterized organoazide complexes, which are coordinated by the alkylated nitrogen atom (N1) to the transition metal center.

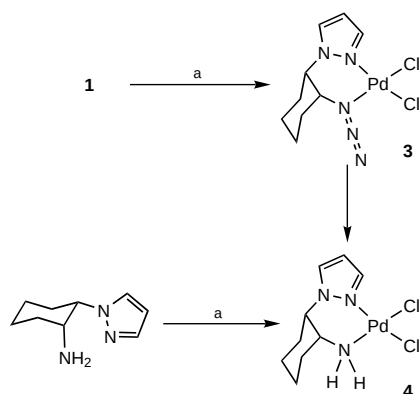
For some time we have investigated new chiral chelating ligands for applications in enantioselective catalysis, where the donor centers are linked by 1,2-disubstituted cycloalkanes.^[1, 9] The cyclohexaneazide **1** was obtained as a key



intermediate during the synthesis of new multidentate imine ligands following this strategy.^[9c] Surprisingly, hydrogenation of **1** to the corresponding amine with palladium/charcoal in ethanol proceeds rather slowly, in contrast to the behavior of the analogous pyrazolyl pyridine derivative **1'**.^[10] Therefore, investigation of the reactivity of **1** in solution in the presence of transition metal ions like Pd^{II} and Cu^{II}, which are known to be efficient catalysts for the decomposition of organoazides,^[4] appeared promising.



Reaction of **1** with CuCl₂ · 2H₂O in methanol leads quantitatively to the dinuclear Cu^{II} complex [{CuCl₂(**1**)₂}] (**2**), which is thermally and photochemically (daylight) stable, and crystals suitable for X-ray structure analysis could be obtained by recrystallization from methanol. Reaction of **1** with [PdCl₂(NCC₆H₅)₂] in CH₂Cl₂ gives the Pd^{II} complex [PdCl₂(**1**)] (**3**) after dissociation of the benzonitrile ligands. In contrast to **2**, **3** is not stable in CH₂Cl₂ and decomposes slowly, even in the absence of light, to yield the amine complex **4**, which is also accessible from the corresponding amine^[9c] and [PdCl₂(NCC₆H₅)₂] (Scheme 1).



Scheme 1. Synthesis of **3** and **4**. a) $[\text{PdCl}_2(\text{NCC}_6\text{H}_5)_2]$, CH_2Cl_2 , 15 min, room temperature. The conversion of **3** into **4** is slow.

Since **3** is stable in the solid state, crystals suitable for X-ray structure analysis could be obtained. The metal centers in complexes **2**^[11] and **3**^[12] are coordinated by the alkylated nitrogen atom of the azide fragment, which leads to the formation of stable six-membered metallacycles. Semiempirical calculations (AM1^[13]) for the formation of adducts between the Lewis acids BMe_3 , CH_3^+ , and H^+ and the model bases methylazide and phenylazide showed greater stability for an electrophilic attack at the carbon-substituted nitrogen atom N1 (Table 1).

Table 1. Calculated (AM1^[12]) differences of the enthalpies of formation ($\delta\Delta G = \Delta G_{\text{N1}} - \Delta G_{\text{N3}}$ [kcal mol⁻¹]) for the adducts of BMe_3 , CH_3^+ , and H^+ with N1 and N3 of methylazide and phenylazide.

	BMe_3	CH_3^+	H^+
$\text{CH}_3\text{-N}_3$	-2.71	-11.18	-18.50
$\text{C}_6\text{H}_5\text{-N}_3$	-0.10	-9.66	-16.81

Accordingly, the spectroscopic and structure chemical data of $[\text{Cp}_2\text{TaCH}_3(\text{N}_3\text{C}_6\text{H}_5)]$ prove that this compound cannot be considered an azide adduct of a Ta^{III} complex, but a Ta^{V} derivative bearing a phenyl diimine substituted imido ligand.^[6] In contrast, complexes **2** and **3** are classical coordination compounds of the organoazide **1**, which is also confirmed by the bonding parameters (Figures 1 and 2).

A search in a structure database^[7a] showed that the bonding parameters of organoazides vary relatively broadly. The N3–N4 distances in **2** and **3** (ca. 1.251 Å) are slightly longer than those of free aliphatic azides, whereas the N4–N5 distances (ca. 1.126 Å) are slightly shorter than the mean value for aliphatic azides. This observation can be explained by a decrease in double-bond character of the bond between N3 and N4 and a slightly increased triple-bond character of the bond between N4 and N5, as expected for an organoazide fragment coordinated with the alkylated nitrogen atom. The bending at the central nitrogen atom N4 (174.5(2)° in **2** and 177.1(4)° in **3**) is not as pronounced as in free aliphatic azides. The sterically demanding pyrazolyl substituent in both complexes is oriented equatorially at the cyclohexane ring, and the N_3 group occupies an axial position. An analogous conformation was found in the free chelating ligand **1**.^[9c] In **2**, the Cu^{II}

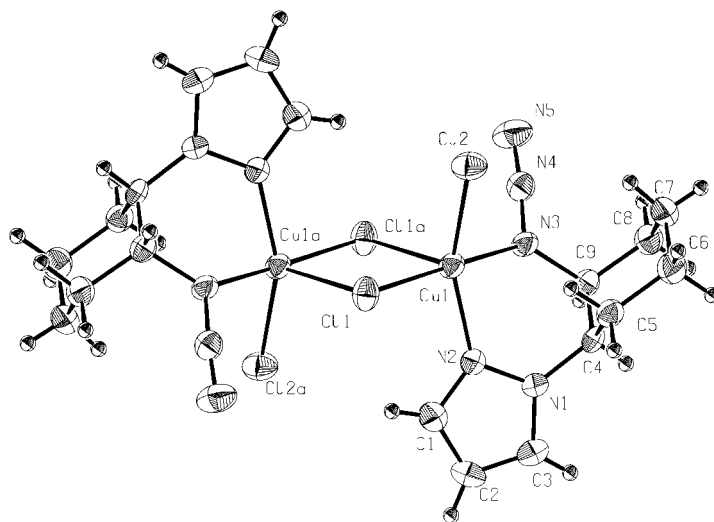


Figure 1. Structure of **2** in the crystal (PLATON plot^[14]). Selected distances [Å] and bond and torsion angles [°]: Cu1–Cl1 2.2758(7), Cu1–Cl1a 2.7006(8), Cu1–Cl2 2.2130(7), Cu1–N2 1.985(2), Cu1–N3 2.079(2), N3–N4 1.251(3), N4–N5 1.123(3); Cu1–Cl1–Cu1a 89.27(2), Cl1–Cu1–Cl1a 90.73(2), Cl1–Cu1–Cl2 94.32(2), Cl1a–Cu1–Cl2 103.90(2), Cl1–Cu1–N2 92.73(5), Cl1–Cu1–N3 174.26(6), Cl1a–Cu1–N2 100.53(5), Cl1a–Cu1–N3 84.62(5), Cl2–Cu1–N2 154.45(6), Cl2–Cu1–N3 90.08(5), N2–Cu1–N3 84.83(7), Cu1–N3–N4 115.06(13), N4–N3–C9 114.93(17), N3–N4–N5 174.5(2); N1–C4–C9–N3 59.7(2).

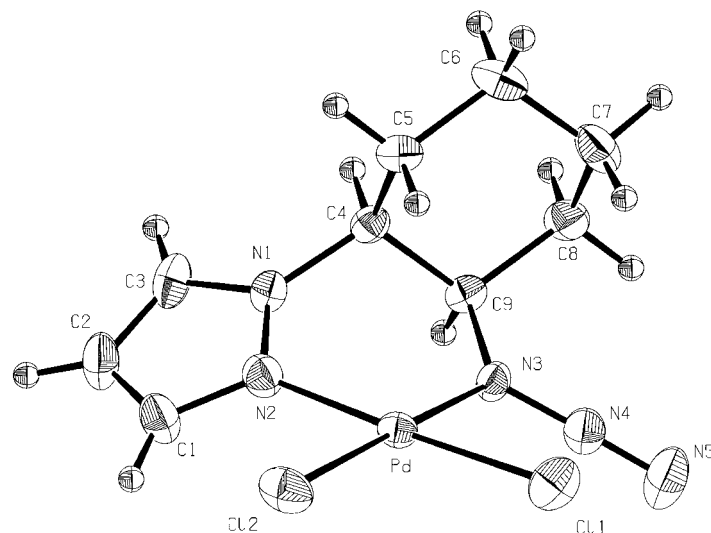
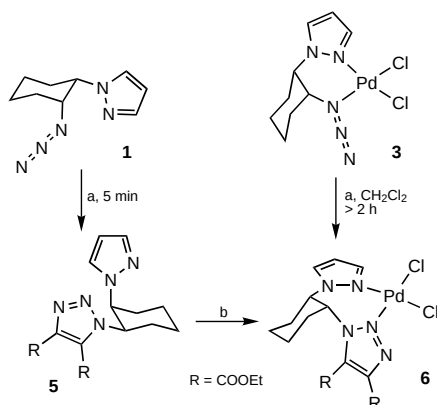


Figure 2. Structure of **3** in the crystal (PLATON plot^[14]). Selected distances [Å] and bond and torsion angles [°]: Pd–Cl1 2.2735(12), Pd–Cl2 2.2805(11), Pd–N2 2.017(3), Pd–N3 2.056(3), N3–N4 1.251(5), N4–N5 1.129(5); Cl1–Pd–Cl2 91.81(4), Cl1–Pd–N2 176.91(10), Cl1–Pd–N3 89.55(9), Cl2–Pd–N2 90.89(10), Cl2–Pd–N3 177.12(11), N2–Pd–N3 87.82(13), Pd–N3–N4 118.2(2), N4–N3–C9 114.3(3), N3–N4–N5 177.1(4); N1–C4–C9–N3 -62.9(4).

center is coordinated in a distorted trigonal-bipyramidal mode, with the donor sites Cl(1a), Cl(2), and N(2) in equatorial positions on the coordination polyhedron. There are three different Cu–Cl distances: two relatively short bonds between Cu^{II} and the terminal chloro and one bridging chloro ligand, and one relatively long bond between Cu^{II} and the second chloro ligand of the central planar Cu_2Cl_2 unit. In complex **3**, the Pd^{II} center is coordinated in a (distorted) square-planar geometry. All bond angles between *cis*-oriented

donor atoms and Pd^{II} are approximately 90°. The Pd–N2 (pyrazole) bond is significantly shorter than the Pd–N3 (azide) bond.

Initial investigations into the reactivity of coordinated organoazides showed that **3** undergoes [2+3] cycloaddition with diethyl acetylenedicarboxylate, which is a typical reaction for azides. *cis*-1-Pyrazolyl-2-triazolylcyclohexane (**5**) is generated from the azide **1** and EtOOC–C≡C–COOEt in a rapid and exothermal reaction (Scheme 2). The ¹H NMR spectroscopic data of **5** show that the bulky triazolyl substituent occupies an equatorial position on the cyclohexane ring.



Scheme 2. Synthesis of **5** and **6**. a) EtOOC–C≡C–COOEt, 40 °C. b) [PdCl₂(NCC₆H₅)₂], CH₂Cl₂, 15 min, room temperature.

The Pd^{II} complex **6**, which can also be synthesized from **5** and [PdCl₂(NCC₆H₅)₂], is obtained as a mixture of two conformers which are in equilibrium in solution: pyrazolyl equatorial, triazolyl axial and pyrazolyl axial, triazolyl equatorial, respectively (Scheme 2 only shows one of these conformers). The interconversion barrier of 67 ± 2 kJ/mol between these conformers was determined by ¹H NMR spectroscopy.

A triazaphospha tetracycle has been postulated as an intermediate in the decomposition of organoazides in the presence of tertiary phosphanes, a reaction which ultimately leads to phosphorane imines.^[15] If the decomposition of organoazides in the presence of transition metals follows an analogous intramolecular mechanism, the inclusion of the organoazide fragment in a chelating ligand should decrease the rate of the decomposition for steric reasons. At present we are investigating the reactivity of **1** in the presence of Lewis acidic, d²-configured transition metal centers. In these cases, **1** should yield, under evolution of N₂, d⁰ imine complexes with a second chiral (hemilabile) donor, which will be of potential interest for catalysis.

Experimental Section

2: A solution of **1**^[9c] (0.19 g, 1.00 mmol) and CuCl₂·2H₂O (0.17 g, 1.00 mmol) in MeOH (20 mL) was heated to 50 °C for several minutes. After removal of the solvent in vacuo, **2** was obtained as a green microcrystalline solid, which was washed twice with Et₂O (20 mL) and

dried in vacuo. Yield: 0.32 g (97 %); correct elemental analysis; IR (KBr): $\tilde{\nu}$ = 2148 cm⁻¹ (ν_{N_3}).

3: A solution of [PdCl₂(NCC₆H₅)₂]^[16] (0.38 g, 1.00 mmol) in CH₂Cl₂ (20 mL) was treated with a solution of **1** (0.19 g, 1.00 mmol) in CH₂Cl₂ (10 mL). After 15 min of stirring at room temperature, the solution was filtered to remove traces of elemental palladium, the solvent was reduced to 15 mL, and the solution was layered with Et₂O (30 mL). **3** crystallized as orange prisms. In a side reaction, **4** was formed under evolution of gas as a tan-orange, microcrystalline solid. Yield: 0.45 g; correct elemental analysis when the amount of **4** determined by NMR spectroscopy is taken into account; ¹H NMR (400.13 MHz, 25 °C, CDCl₃): δ = 7.43 (br, 1H), 7.38 (br, 1H), 6.14 (m), 5.21 (brd, 1H, $1 \times {}^3J_{HH}$ = 11.5, $2 \times {}^3J_{HH}$ = 3.0–4.0 Hz), 4.70 (ddd, 1H, $3 \times {}^3J_{AH}$ = 3.0–4.0 Hz), 2.20–1.40 (m, 8H); ¹³C{¹H} NMR (100.25 MHz, 25 °C, CDCl₃): δ = 142.2, 131.4, 107.0, 63.1, 60.3, 25.4, 24.3, 18.6, 18.7; IR (KBr): $\tilde{\nu}$ = 2147 cm⁻¹ (ν_{N_3}).

5: **1** (2.41 g, 12.6 mmol) and diethyl acetylenedicarboxylate (2.14 g, 12.6 mmol) were heated in a 50-mL flask under vacuo for a short period until reaction ceased (quantitative yield by GC). After chromatography (neutral Al₂O₃, Et₂O) and removal of the solvent, the oily residue was crystallized from hexane/Et₂O. Yield: 3.09 g (68 %), colorless crystals. M.p. 71 °C; correct elemental analysis; ¹H NMR (400.13 MHz, 25 °C, CDCl₃): δ = 7.33 (d, 1H, ${}^3J_{HH}$ = 1.5 Hz), 6.87 (d, 1H, ${}^3J_{HH}$ = 1.50 Hz), 5.99 (dd), 5.56 (ddd, 1H, $3 \times {}^3J_{HH}$ = 4.0 Hz), 4.70 (ddd, 1H, $2 \times {}^3J_{AH}$ = 4.0, $1 \times {}^3J_{HH}$ = 12.0 Hz), 4.31 (m, 4H), 2.71 (m, 1H), 2.30–2.01 (m, 5H), 1.68–1.56 (m, 2H), 1.33 (t, ${}^3J_{HH}$ = 7.0 Hz, 6H); ¹³C{¹H} NMR (100.25 MHz, 25 °C, CDCl₃): δ = 160.1, 158.6, 139.5, 138.5, 132.2, 126.8, 105.4, 62.8, 61.6, 61.6, 59.2, 29.6, 26.0, 24.5, 20.2, 14.1, 13.8.

6: A solution of [PdCl₂(NCC₆H₅)₂] (0.38 g, 1.00 mmol) in CH₂Cl₂ (20 mL) was treated with a solution of **4** (0.36 g, 1.00 mmol) in CH₂Cl₂ (10 mL). After 15 min of stirring at room temperature, the solution was filtered to remove traces of elemental palladium. Then the solvent was removed in vacuo and the product precipitated by rapid addition of Et₂O (50 mL). Yield: 0.52 g (96 %), yellow-orange solid, correct elemental analysis; ¹H NMR (400.13 MHz, 60 °C, CDCl₃): δ = 7.60 (br, 1H), 7.65–6.85 (br, 1H), 6.20 (br, 1H), 4.70–4.20 (br, 6H), 3.20–1.05 (br, 14H); ¹³C{¹H} NMR (100.25 MHz, 60 °C, CDCl₃): δ = 159.6, 158.0, 141.8, 137.7, 133.7, 132.8, 108.9, 64.2, 64.0, 62.8, 61.4, 29.8, 26.4, 25.1, 18.6, 13.7, 13.5.

Received: March 13, 1998 [Z11586IE]
German version: *Angew. Chem.* **1998**, *110*, 2380–2383

Keywords: azides • copper • palladium

- [1] M. Barz, H. Glas, W. R. Thiel, *Synthesis*, in press.
- [2] *The Chemistry of the Azido Group*, (Ed.: S. Patai), Interscience, London, **1971**.
- [3] R. A. Abramovitch, E. P. Kyba in ref. [2], p. 222.
- [4] T. Sheradsky in ref. [2], p. 332.
- [5] *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed. 1952, vol. X/3, **1965**, p. 813.
- [6] G. Proulx, R. G. Bergman, *J. Am. Chem. Soc.* **1995**, *117*, 6382–6383.
- [7] a) Cambridge Structural Database, Version 2.3.7, UNIX 97/2. In version 98/1 we found two other structures showing a terminally coordinating organoazide. b) G. Proulx, R. G. Bergman, *Organometallics* **1996**, *15*, 684. c) T. A. Hanna, H. M. Baranger, R. G. Bergman, *Angew. Chem.*, **1996**, *108*, 693; *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 653.
- [8] a) K. Vrieze, G. van Koten in *Comprehensive Coordination Chemistry*, Vol. 2, (Ed.: G. Wilkinson), Pergamon, **1987**, p. 225–242; b) U. Müller, *Struct. Bonding* **1973**, *14*, 141.
- [9] a) M. Barz, E. Herdtweck, W. R. Thiel, *Tetrahedron: Asymmetry* **1996**, *7*, 1717–1722; b) C. L. Thurner, M. Barz, M. Spiegler, W. R. Thiel, *J. Organomet. Chem.* **1997**, *541*, 39–49; c) M. Barz, M. U. Rauch, W. R. Thiel, *J. Chem. Soc. Dalton Trans.* **1997**, 2155–2161; d) H. Glas, M. Spiegler, W. R. Thiel, *Eur. J. Inorg. Chem.* **1998**, 275–281.
- [10] H. Glas, W. R. Thiel, unpublished results.
- [11] X-ray structure analysis of **2**: green prisms from MeOH, Mo_{K α} radiation (λ = 0.71073 Å), STOE IPDS diffractometer, structure solution with Patterson methods (SHELXS-86), refinement with

SHELXL-93, all hydrogen-atom positions were found in the Fourier map and freely refined, $C_{18}H_{26}Cl_4Cu_2N_{10}$, $M = 651.4 \text{ g mol}^{-1}$, orthorhombic, space group $Pbca$ (no. 61), $a = 8.396(1)$, $b = 18.756(1)$, $c = 15.781(1) \text{ \AA}$, $V = 2485.1(4) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 1.741 \text{ g cm}^{-3}$, $\mu = 21.7 \text{ cm}^{-1}$, $T = 20^\circ\text{C}$, 30426 observed reflections, 1949 independent reflections used for refinement (1595 with $I > 4\sigma(I)$), 206 parameters refined, $R1 = 0.0255$, $\omega R2 = 0.0522$, $GOF = 0.96$, max./min. residual electron density $0.29/-0.25 \text{ e \AA}^{-3}$.^[12b]

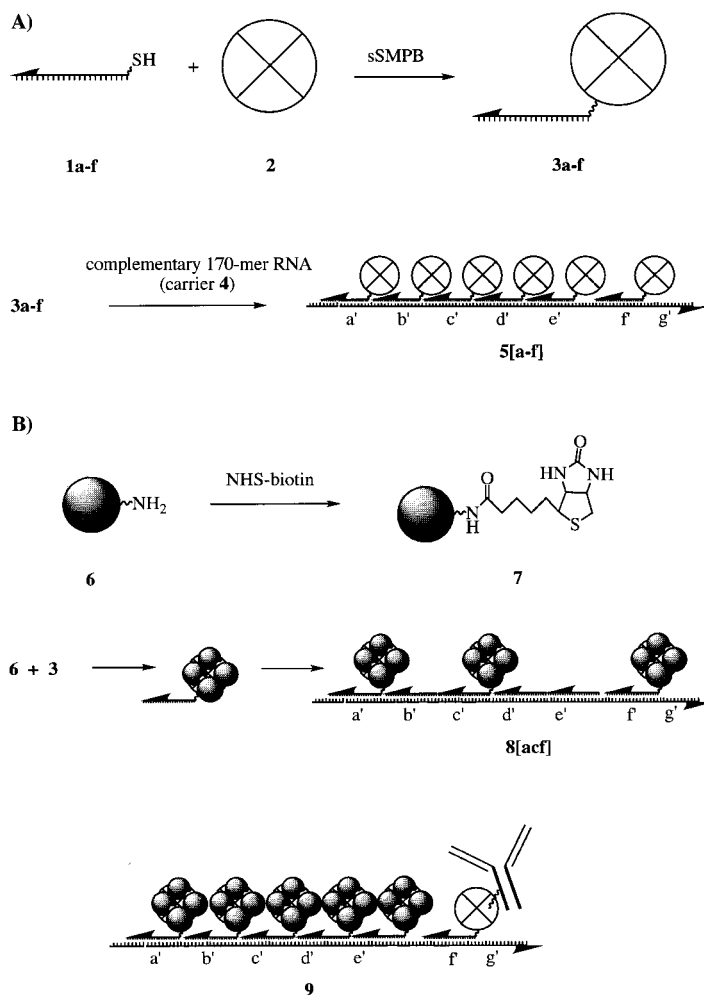
- [12] a) X-ray structure analysis of **3**: orange prisms from $\text{CH}_2\text{Cl}_2/\text{pentane}$, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), Enraf-Nonius MACH3 diffractometer, structure solution with Patterson methods (SHELXS-86), refinement with SHELXL-93, all hydrogen atoms were calculated in idealized positions, $C_9H_{13}Cl_2N_3Pd$, $M = 368.6 \text{ g mol}^{-1}$, monoclinic, space group $P2_1/n$ (no. 14), $a = 8.4828(6)$, $b = 9.4916(8)$, $c = 16.2852(15) \text{ \AA}$, $\beta = 94.087(8)^\circ$, $V = 1307.9(2) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 1.872 \text{ g cm}^{-3}$, $\mu = 18.1 \text{ cm}^{-1}$, $T = -110^\circ\text{C}$, 2735 observed reflections, 2644 independent reflections used for refinement (2086 with $I > 4\sigma(I)$), empirical absorption correction $T_{\text{min}} = 0.939$, $T_{\text{max}} = 1.000$, 154 parameters refined, $R1 = 0.0534$, $\omega R2 = 0.0667$, $GOF = 1.05$, max./min. residual electron density $0.62/-0.69 \text{ e \AA}^{-3}$. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101257. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [13] The AM1 calculations were performed on a Silicon Graphics O2 Workstation with the MOPAC 6.0 package and the INSIGHT II Graphical User Interface (Biosym). a) M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909; b) M. J. S. Dewar, E. G. Zoebisch, *Theochem.* **1988**, *49*, 1–21; c) M. J. S. Dewar, C. Jie, E. G. Zoebisch, *Organometallics* **1988**, *7*, 513–521.
- [14] A. L. Spek, *Acta Crystallogr. Sect. A* **1990**, *46*, C34–C34.
- [15] Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron* **1992**, *48*, 1353–1406.
- [16] J. R. Doyle, P. E. Slade, H. B. Jonassen, *Inorg. Synth.* **1960**, *6*, 216–219.

Covalent DNA–Streptavidin Conjugates as Building Blocks for Novel Biometallic Nanostructures**

Christof M. Niemeyer,* Wolfgang Bürger, and Jörg Peplies

The generation of nanoscale structural and functional devices by self-assembly of small molecular building blocks is an important goal of nanotechnology.^[1] Owing to its unique recognition capabilities, physicochemical stability, and mechanical rigidity, DNA is a promising construction material^[2–4] for the fabrication of nanostructured scaffolds^[3] and for the precise spatial positioning of conducting polymers,^[5] pro-

teins,^[6] and nanocrystalline gold clusters.^[7–9] Recently, we reported the synthesis of covalent conjugates of single-stranded DNA and streptavidin (STV).^[6] In these adducts, the protein's native binding capacity for four biotin molecules is supplemented by a highly specific binding site for complementary nucleic acids, and the conjugates can thus be utilized as biomolecular adapters for positioning biotinylated components along a nucleic acid backbone. Here we report on the self-assembly of DNA–STV adducts **3** to form supramolecular aggregates **5** and the utilization of the adapters for the fabrication of nanostructured biometallic aggregates **8** and **9** from biotin-derivatized metal colloids (Scheme 1).



Scheme 1. Schematic representation of the DNA–protein hybrids. A) Generation of supramolecular aggregates from DNA–STV conjugates **3**, obtained by covalent coupling of 5'-thiol-modified oligonucleotides **1** and streptavidin **2**. The 3'-end of the oligonucleotide is indicated by an arrowhead, and the spacer chains between DNA and protein by wavy lines. The conjugates **3** with nucleotide sequences **a–f** self-assemble in the presence of RNA **4**, which contains complementary sequence sections, to form supramolecular aggregates **5**. B) Fabrication of biometallic aggregates by means of DNA–STV adapters **3**. Monoamino-modified 1.4-nm gold clusters **6** are converted into biotin derivatives, and the biotinylated clusters **7** are coupled with DNA–STV adducts **3**. The resulting hybrids are assembled in the presence of helper oligonucleotides **1** and RNA carrier **4** to form supramolecular aggregates **8**. (The letters in brackets indicate the protein components bound to the carrier.) Similarly, an antibody-containing aggregate **9** was constructed from gold-labeled **3a–e** and a conjugate from **3f** and biotinylated IgG, previously coupled in separate reactions.

[*] Dr. C. M. Niemeyer, Dipl.-Chem. W. Bürger, J. Peplies
Universität Bremen, FB2-UFT
Biotechnologie und Molekulare Genetik
Leobener Strasse, D-28359 Bremen (Germany)
Fax: (+49) 421-218-7578
E-mail: cmn@biotec.uni-bremen.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Tönjes-Vagt Stiftung. We thank the staff of the Institut für Werkstoffphysik und Strukturfor-

Six DNA–STV hybrid molecules **3** were synthesized from 5'-thiol-modified oligonucleotides with different base sequences **1a–f** and recombinant STV (**2**) by means of the heterobispecific cross-linker, sulfosuccinimidyl-4(*p*-maleimidophenyl)butyrate (sSMPB).^[6] The nucleic acid sequences of the adapters **3a–f** were chosen from a region with about 170 base pairs of the antisense strand of bacteriophage M13mp18 DNA, and were recently studied with regard to their hybridization characteristics.^[10] An RNA molecule **4** containing sequence sections complementary to **3a–f** in the order 5'-a'-b'-c'-d'-e'-f'-g'-3' was prepared by in vitro transcription as a template for the supramolecular assembly of the adapters.

To investigate the organization of multiple protein components along the carrier molecule and to analyze the resulting aggregates **5**, an instrumental modification of the electrophoretic gel-shift assay,^[11] widely applied for the study of biomolecular interactions, was designed. Labeling of the DNA–protein aggregates with a 5'-fluorescein-derivatized oligonucleotide probe (G18), which is complementary to binding site g' of the RNA carrier, allows the DNA–protein aggregates to be analyzed with an automated DNA sequencer. Due to the high sensitivity and quantifiability of fluorescence detection, as well as a remarkably enhanced separation performance for compounds of high molecular weight compared to conventional electrophoresis, this method is highly suitable for the analysis of supramolecular DNA–protein aggregates and the investigation of the self-assembly processes.

In an initial series of experiments, the successive assembly of an aggregate of six DNA–STV adducts was investigated. A mixture of RNA carrier **4**, fluorescent probe G18, and an excess of hybrid **3a** (Figure 1 A, lane 1) showed bands of the free probe, the RNA–G18 heteroduplex, and a single species of higher molecular weight, which was assigned to the aggregate **4·3a·G18**. In spite of the excess of **3a**, no products with higher molecular weight are formed; this suggests that aggregation occurs exclusively by specific Watson–Crick base pairing. In contrast, the addition of further adducts complementary to the carrier strand, such as **3b** (Figure 1 A, lane 2), led to the formation of new species with lower electrophoretic mobility. Subsequently, supramolecular aggregates consisting of up to six protein components, that is, defined molecular assemblies with relative molecular weights of greater than 400 kDa were assembled (Figure 1 A, lanes 3–6). Quantification of the fluorescence bands indicated an increase in the aggregation yield with increasing number of bound conjugates **3**. This is an indication for cooperative effects during the self-assembly process, which are the result of increasing disruption of the secondary structures of the nucleic acid carrier and the associated increase in stability of the DNA–protein aggregates.^[12] To further examine this phenomenon, several distinct aggregates were assembled and compared to control reactions in which free sequence stretches of the carrier backbone were saturated with “helper oligonucleotides”^[12] (Figure 1 B). In the case of aggregates containing two protein components (e.g., **5[ad]** and **5[bd]**) the presence of helper oligonucleotides resulted not only in a doubling of the signal intensities, but also led to completion of the previously incomplete common aggregation of both protein components. These results

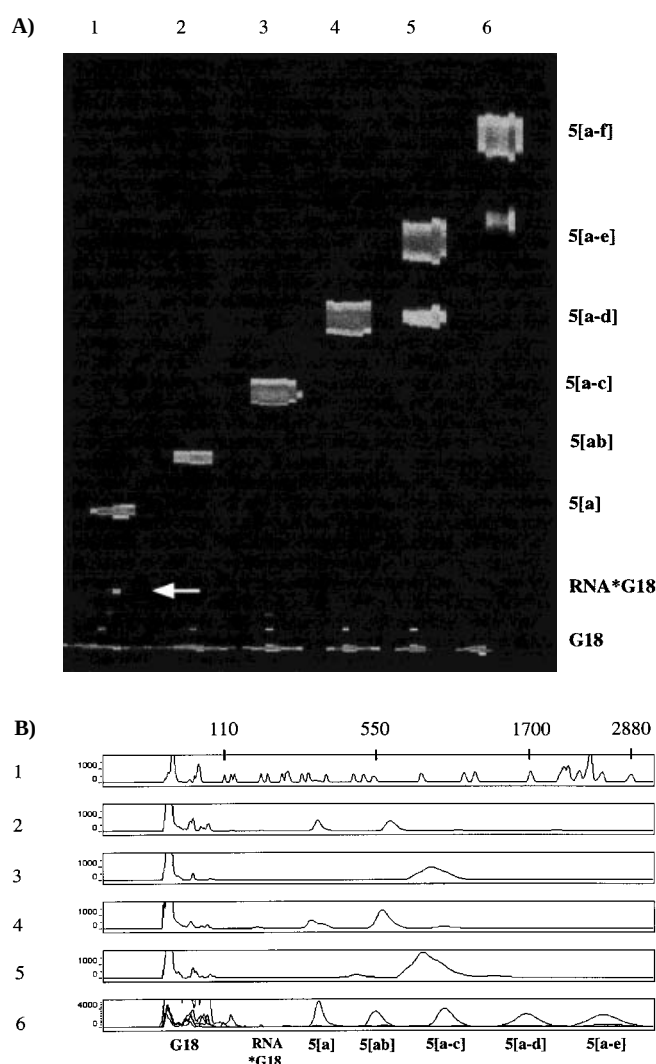


Figure 1. Investigation of the supramolecular self-assembly of DNA–STV hybrids **3** by fluorescence gel-shift analysis. A) Lanes 1–6 correspond to successive construction of oligomeric aggregates **5**. The weak band of uncomplexed RNA **4** in lane 1 is indicated by an arrow. An increasing number of protein components bound to **4** leads to an increasing signal strength (gray scale representation of the originally blue fluorescence bands). Pentameric and hexameric DNA–protein aggregates (lanes 5 and 6) display enhanced dissociation, likely due to the absence of cations that stabilize the double helix during electrophoresis. B) Line plots of the gel-shift analysis of complexes **5[ad]** and **5[bd]** (lanes 2 and 4, respectively). The formation of ternary complexes is incomplete. Therefore, binary aggregates of similar electrophoretic mobility (**5[a]** and **5[d]**) are present in lane 2 in addition to the ternary aggregate **5[ad]**. The presence of helper oligonucleotides that are complementary to free sequence sections of the carrier leads to completion of aggregation and also reduces the electrophoretic mobility of **5[ad]** (lane 3) and **5[bd]** (lane 5). Lane 1: DNA molecular weight marker (GeneScan-2500 Rox, length in base pairs). Lane 6: overlay plot of five lanes for the successive assembly of a pentameric aggregate, analogous to the gel-shift analysis shown in A).

demonstrate that oligonucleotide-directed assembly of molecular devices can be significantly improved by minimizing secondary structure in the nucleic acid backbone.^[13]

Stimulated by recent reports on oligonucleotide-directed organization of gold clusters,^[7–9] we examined the applicability of biomolecular adapters **3** for the fabrication of nanostructured metal aggregates. For this purpose, preparative quantities of supramolecular aggregates **5** were prepared from

combinations of the individual DNA–STV components and separated from nonaggregated compounds by gel-filtration chromatography. Calibration of the filtration column gave approximate molecular weights of the aggregates **5[acf]** and **5[a–f]** of 240 and 440 kDa, respectively. Commercially available 1.4-nm gold clusters **6** with a single amino substituent were used as metal components. Following derivatization with *N*-hydroxysuccinimidylbiotin, the biotinylated metal colloids **7** were coupled to the DNA–STV adapters. The presence of gold particles within the protein hybrids was verified during chromatographic isolation by means of the characteristic absorption at 420 nm.

On analysis of the biometallic aggregates by transmission electron microscopy (TEM), multiple gold clusters bound to a single STV molecule could not be differentiated. Average particle sizes of 1.3 ± 0.2 , 2.3 ± 0.3 , 3.6 ± 0.3 , and 4.5 ± 0.3 nm were observed, depending on the coupling stoichiometry between **3** and **7**. According to model calculations,^[14] these dimensions are consistent with mono-, di-, tri-, and tetra-adducts of **7** with STV. Transmission electron micrographs of gold-labeled aggregates reveal stretched and sharply bent structures (Figure 2). Aggregates consisting of three protein

components, **8[acf]**, have particle sizes of 4.5 nm and two different interparticle distances of approximately 5 ± 2 and 10 ± 3 nm (Figure 2A). These results are in agreement with the schematic aggregate structure (Scheme 1), since both nucleic acid spacer regions are flexible due to the presence of several gaps in the backbone of the double helix.

Subsequently a functional protein component was incorporated into the biometallic aggregates. To generate the IgG-containing construct **9** (IgG = immunoglobulin), DNA–STV hybrid **3f** was coupled with a biotinylated antibody against IgG from mice, and hybrids **3a–e** were coupled with biotinylated gold clusters. Following organization of the components along RNA carrier **4** and subsequent chromatographic purification, the functionality of the product aggregate was tested by coating TEM grids with mouse IgG and briefly bringing them into contact with a solution of **9**. In control experiments with grid-immobilized rabbit IgG, no metal colloids were observed, but TEM images of antigen-coated surfaces showed clear accumulations of clusters in which isolated chainlike structures were evident (Figure 3B). The metal aggregates have average particle sizes and interparticle distances of 4.6 ± 0.3 and 2.7 ± 0.4 nm, respectively. This leads to an estimated length of the nucleic acid domain within single DNA–STV components of about 7.3 nm, which is consistent with the theoretical value of 7.1 nm of a double helix with 21 base pairs. The length of the three chainlike structures is 33 ± 2 nm, which correlates with the theoretical value of about 37 nm for a double helix with 108 base pairs when the flexibility of the 1.2-nm spacers between oligonucleotide and STV is taken into account.

These experiments demonstrate the applicability of covalent conjugates of oligonucleotides and streptavidin as versatile and convenient adapters for the fabrication of novel nanostructured molecular assemblies. Further fundamental studies of structure, stability, formation, and modification of supramolecular aggregates based on nucleic acids will show whether biotechnological applications such as sensor and switching devices, synthetic multienzyme complexes, and interface structures between electronic and biological systems can be realized.

Experimental Section

Covalent DNA–STV Adducts were synthesized from 5'-thiolated oligonucleotides (NAPS, Göttingen) and recombinant STV (Boehringer Mannheim) by means of the heterobispecific cross-linker sSMPB (Pierce) in about 10–15% yield.^[6] The nucleotide sequences of **1a–f** are as follows: 5'-thiol-TCCTGTGTGAAATTGTTATCCGCT-3' (**1a**); 5'-thiol-GTAATCATGATGTCATAGCTGTT-3' (**1b**); 5'-thiol-CCGGGTACCGAGCTCGAATTC-3' (**1c**); 5'-thiol-CAGGTCGACTCTAGAGGATCC-3' (**1d**); 5'-thiol-AGTGCCAAGCTTGCATGCCTG-3' (**1e**); 5'-thiol-GTTTCCCAAGTCACGACGTGTTAA-3' (**1f**). For the preparation of RNA carrier **4**, a double-stranded DNA fragment with 189 base pairs was synthesized from M13mp18 DNA by polymerase chain reaction (PCR) with primers M13T7 (5'-GTAATCATGATGTCATAGCTGTTGTAATCATGATGTCATAGCTGTT-3') and M13G3 (5'-GTAATCATGATGTCATAGCT-3'). Primer M13T7 contains the promoter region of T7-RNA polymerase (underlined). In vitro transcription of the purified PCR product yields approximately 10 molar equivalents of the corresponding 170-mer RNA. The latter was characterized by conventional

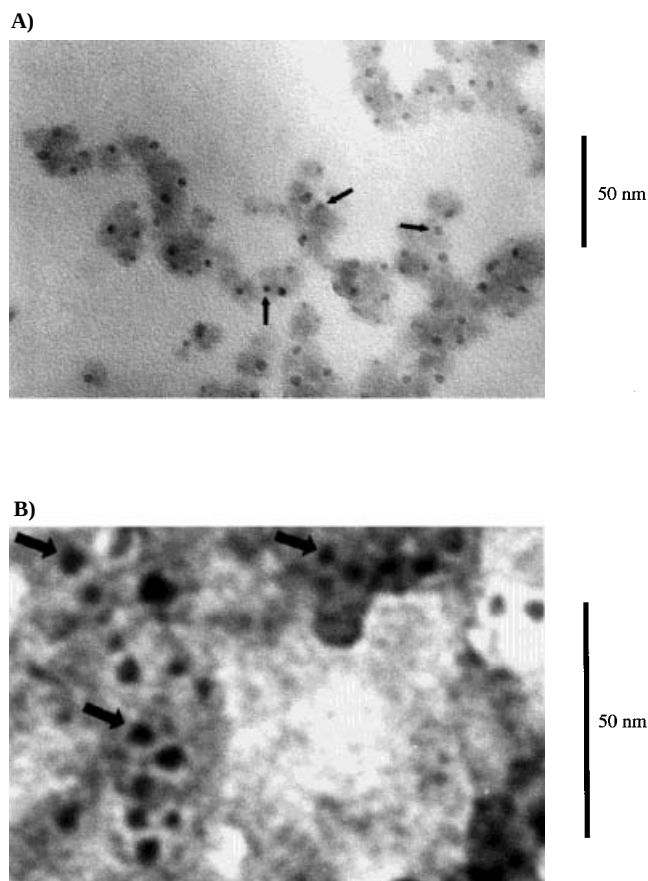


Figure 2. TEM images of supramolecular aggregates labeled with gold clusters. A) DNA–protein aggregate containing three DNA–STV adapters **8[acf]**. The central particles of typical aggregates are indicated by arrows. B) Aggregate **9** containing five gold-labeled adapters **3a–e**, anti-mouse IgG-coupled **3f**, and RNA. Since optical differentiation of the four STV-bound clusters was not achieved, the individual gold-labeled adapters are visible as spherical structures of high contrast. The shady areas in the background result from immobilized protein matrices (poly-D,L-lysine in A) and mouse IgG in B).

electrophoresis (10% acrylamide gel containing 7 M urea) in the presence of a DNA molecular weight standard (GIBCO).

Fluorescence gel-shift analysis was carried out with an ABI Prism 377 DNA sequencing instrument (Perkin Elmer). The nucleotide sequence of the 5'-fluorescein-derivatized G18 oligonucleotide probe (NAPS) is 5'-fluorescein-GTA ATG GTC ATAGCT GTT-3'. In a typical experiment, 3 pmol of the hybrid component (3 μ M stock solution in tris(hydroxymethyl)amino-methane (tris) buffer, pH 7.3, 150 mM NaCl) was mixed with 0.5 pmol of RNA **4** and 0.5 pmol of G18 probe and the mixture incubated for 30 min at 37 °C. If no temperature-sensitive components are present, the aggregation may also be carried out for 2 min at 50 °C. A volume of 1 μ L of the mixture was applied to a non-denaturing 4% acrylamide gel, and electrophoresis was carried out at 750 V, 50 mA for 3.5 h at 20 °C. The fluorescence bands were analyzed with ABI Prism GeneScan 2.0.2 software (Perkin Elmer).

Amino-modified 1.4-nm gold clusters (20 nmol; Monoamino-Nanogold, Nanoprobes) in 100 μ L of phosphate buffer were treated with 10 equiv of NHS-biotin (Pierce) for 60 min at room temperature and subsequently purified by chromatography on a Superdex Peptide FPLC column (Pharmacia). Coupling with **3** was performed by mixing typically 100 pmol of the DNA-STV hybrids with 2–8 molar equivalents of **7** followed by incubation for 60 min. The assembly was carried out by the addition of 100 pmol of RNA **4** and incubating the mixture for 60 min. In some cases, unlabeled aggregates **5** were prepared and purified by chromatography (Superdex-200, Pharmacia) and subsequently treated with **7**. The purified biometallic aggregates were concentrated by ultrafiltration (Centricon, Millipore) and quantified photometrically. To prepare aggregate **9**, **3a–e** were coupled with **7** and **3f** with biotinylated goat anti-mouse IgG (Dianova) in separate reactions prior to the addition of RNA. For TEM analysis, 400-mesh copper grids with a thin carbon coating (Plano) were coated with proteins (mouse or rabbit IgG or poly-D,L lysine, Boehringer-Mannheim, 1 mg mL⁻¹ in phosphate-buffered NaCl solution). For immobilization, a 5- μ L drop of the gold-labeled aggregates (1–10 nm) was deposited on the grids for 2 min. TEM analysis was carried out with a Philips EM 420 instrument operating at 120 kV.

Received: December 29, 1997

Revised version: April 9, 1998 [Z11301 IE]

German version: *Angew. Chem.* **1998**, *110*, 2391–2395

Keywords: DNA hybridization • nanostructures • supra-molecular chemistry

- [1] a) R. P. Feynman in *Miniaturization* (Ed.: H. D. Gilbert), Reinhold, New York, **1961**, p. 282; b) K. E. Drexler, *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 5275; c) J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, Germany **1995**, p. 193; d) D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154.
- [2] N. C. Seeman, *J. Theor. Biol.* **1982**, *99*, 237.
- [3] N. C. Seeman, *Acc. Chem. Res.* **1997**, *30*, 357.
- [4] C. M. Niemeyer, *Angew. Chemie* **1997**, *109*, 603; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 585.
- [5] B. H. Robinson, N. C. Seeman, *Protein Eng.* **1987**, *1*, 295.
- [6] C. M. Niemeyer, T. Sano, C. L. Smith, C. R. Cantor, *Nucl. Acids Res.* **1994**, *22*, 5530.
- [7] C. A. Mirkin, R. L. Letsinger, R. C. Mucic, J. J. Storhoff, *Nature* **1996**, *382*, 607.
- [8] A. P. Alivisatos, K. P. Johnsson, X. Peng, T. E. Wilson, C. J. Loweth, M. P. Bruchez Jr., P. G. Schultz, *Nature* **1996**, *382*, 609.
- [9] R. Elghanian, J. J. Storhoff, R. C. Mucic, R. L. Letsinger, C. A. Mirkin, *Science* **1997**, *277*, 1078.
- [10] A comparative study of the hybridization kinetics of **1a–f** and **3a–f** revealed dramatic differences in affinity of sequences **a–f**: The hybridization efficiency at room temperature decreases in the order **a** > **b**, **f** > **c**, **d** > **e** and correlates with the structural properties of the oligonucleotides. The coupling with STV results in minor changes of the sequence-specific binding properties: The rates of association and dissociation of **3a–f** are up to five times slower than those of **1a–f**. C. M. Niemeyer, W. Bürger, R. J. M. Hoedemakers, *Bioconjugate Chem.* **1998**, *9*, 168.

- [11] *Current Protocols in Molecular Biology*, Vol. 2, Wiley, New York, **1996**.
- [12] This effect was previously observed, for example, for the binding of 12-mer oligonucleotides to an RNA molecule: G. Godard, J.-C. Francois, I. Duroux, U. Asseline, M. Chassignol, N. Thuong, C. Helene, T. Saison-Behmoaras, *Nucleic Acids Res.* **1994**, *22*, 4789.
- [13] Although the denaturation temperature of STV is higher than 75 °C (M. González, L. Bagatolli, I. Echabe, J. Arrondo, C. Argaraña, C. R. Cantor, G. Fidelio, *J. Biol. Chem.* **1997**, *11288*), due to the thermal instability of many biomolecules and the gold clusters **6**, the oligonucleotide-directed assembly of proteins requires moderate temperatures. The RNA **4** forms secondary structures at these temperatures with similar stability ($\Delta G \approx -44.6$ kcal mol⁻¹) to the oligonucleotide double helices ($\Delta G = -34.2$ to -44.7 kcal mol⁻¹[10]). Thus, thermodynamic stability of binary aggregates **5** is, depending on the sequences, influenced to a varying extent by the presence of helper oligonucleotides. Experiments in which the aggregation temperature and time were varied suggest that the system reaches thermodynamic equilibrium under the conditions described. Therefore, the influence of helper oligonucleotides depends on the base sequence and the number of DNA-STV hybrids. While the formation of binary aggregates is increased by a factor of up to 20 (e.g., for **5[d]**, **5[e]**), depending on the sequence, a comparison of ternary aggregates reveals an increase in signal intensity by a factor of up to three, depending on the building blocks applied. The rates of increase are consistent with the calculated secondary structure of **4**, and this indicates that the sequence section d'-e'-f', in particular, is engaged in a stable double-helical domain. Aggregates consisting of four or more protein components are scarcely influenced by helper oligonucleotides.
- [14] The dimensions of the protein are approximately 4 × 4.2 × 5.6 nm, and the four biotin-binding sites inside the molecule form a distorted tetrahedron with edge lengths of about 2.3 nm on average: P. C. Weber, D. H. Ohlendorf, J. J. Wendoloski, F. R. Salemme, *Science* **1989**, *243*, 85. After labeling of avidin with similar 1-nm gold clusters, a distance between the biotin binding sites of about 2 nm was determined: D. E. Safer, J. Hainfeld, J. S. Wall, J. E. Reardon, *Science* **1982**, *218*, 290.

Synthesis of an ansa-Zirconocene via a Novel S₄-Symmetric Spirobis(silastannaindacene) Compound**

Mario Hüttenhofer, Frank Schaper, and Hans H. Brintzinger*

The utilization of chiral ansa-zirconocenes as catalysts for numerous reactions^[1, 2] demands a diastereoselective synthetic access to these complexes.^[3] One approach to this goal involves the diastereoselective reaction of ZrCl₄ with a silyl-bridged bis(cyclopentadienylstannyl) ligand unit^[4, 5] or a substituted 8-sila-4-stannatetrahydroindacene, a cyclic stan-

[*] Prof. H. H. Brintzinger, M. Hüttenhofer, F. Schaper
Fakultät für Chemie der Universität
Fach M 737, 78457 Konstanz (Germany)
Fax: (+49) 7531-883-137
E-mail: hans.brintzinger@uni-konstanz.de

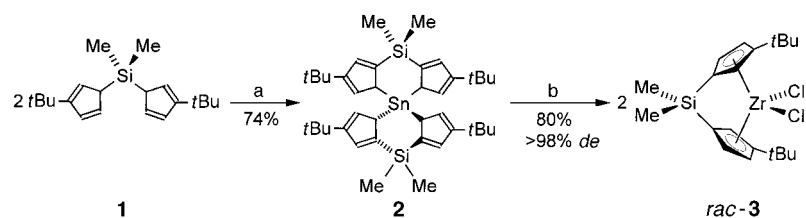
[**] ansa-Metallocene Derivatives, part 42. This work was supported by BASF AG, BMBF, and the Fonds der Chemischen Industrie. We thank Dr. Armin Geyer and Monika Cavegn for NMR spectra. Part 42: S. Martin, H. H. Brintzinger, *Inorg. Chim. Acta*, in press

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

nylene ligand derivative.^[6] A serious draw-back of these organotin-based zirconocene syntheses is the necessity to separate the *rac* and *meso* forms of the stannyl or stannylene intermediates, which are generally obtained with little or no diastereoselectivity.^[4–6] To utilize the stereoselective transfer of Sn-bound cyclopentadienyl units to ZrCl_4 ^[4–7] for a practicable ansa-zirconocene synthesis, we have searched for diastereoselective routes to cyclic silastannaindacene precursors and have found that this aim can be achieved in a straightforward manner with the tin amide $\text{Sn}(\text{NMe}_2)_4$ as a metalating agent.^[8]

The reaction of $\text{Sn}(\text{NMe}_2)_4$ with two equivalents of the *tert*-butyl-substituted bicyclopentadienylsilane **1**^[9] present as a 1:1 mixture of its *rac* and *meso* isomers in diethyl ether, gave one product exclusively (Scheme 1): After removal of the solvent in vacuo and treatment of the residue with pentane, compound **2** was obtained as a yellow crystalline solid in 74 % overall yield. Its identity was established as 2,2',6,6'-tetra-*tert*-butyl-4,4'-spirobis(8-sila-4-stannatetrahydro-*s*-indacene) by NMR spectroscopy and X-ray diffractometry.^[10, 11]

Both methods reveal that compound **2** has an approximate S_4 -symmetric structure.^[12] As in other silastannaindacenes,^[4, 6] the more electronegative Si atoms are bonded to the sp^2 -



Scheme 1. Stereoselective formation of *rac*-**3** via the bicyclic tin compound **2** a) $\text{Sn}(\text{NMe}_2)_4$, Et_2O , room temperature; b) ZrCl_4 , toluene, room temperature.

hybridized cyclopentadienyl C atoms, while the Sn atom is bonded to the sp^3 C centers. Both of the central six-rings, which are joined at the Sn spiro center, assume a twist geometry—as required by the axial symmetry of the molecular structure (Figure 1). Remarkably, the two C_2 -symmetric six-rings are of opposite configuration: While the two asymmetry centers in one of the six-rings are *R,R*-configured, those in the other six-ring have an *S,S* configuration. The preference for the *R,R,S,S* isomer over all the other diastereomers for complex **2**^[13] appears to be a special case of the general phenomenon of chirality-directed self-assembly of organometallic and other coordination compounds: Other examples have also been found where S_4 -symmetric assemblies with two chelating ligands of opposite configuration are more stable than species with two ligands of identical configuration, presumably because of reduced interligand repulsion.^[14]

When (*R,R,S,S*)-**2** is treated with two equivalents of ZrCl_4 in toluene, transmetalation to the ansa-zirconocene **3** occurs in approximately 12 h. This reaction leads exclusively to the racemic form of **3**,^[9] which is obtained, after removal of SnCl_4 in vacuo, in around 80 % isolated yield. This observation is in accord with the stereoselectivity established previously for Sn/Zr exchange reactions of this type.^[4–7]

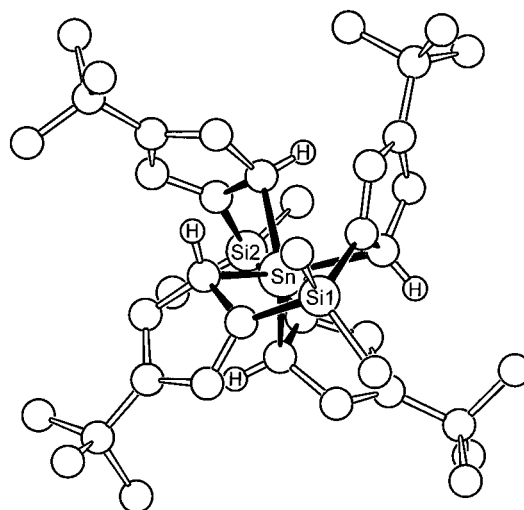


Figure 1. Idealized S_4 -symmetric geometry of (*R,R,S,S*)-**2**.^[12] Hydrogen atoms are only shown at stereogenic centers, the carbon atoms are unlabeled. The spiro-connected six-rings are represented by dark bonds.

Our results document that racemic ansa-zirconocenes can be obtained stereoselectively from a mixture of ligand diastereomers in a short sequence of smooth, high-yield reactions by the appropriate choice of reagents. Extensions of this methodology to other types of chiral ansa-metalloenes are presently under investigation.

Experimental Section

All manipulations were performed on argon/vacuum apparatus or in a glove box under nitrogen. Solvents were dried and distilled over sodium/benzophenone. $\text{Me}_2\text{Si}(3\text{-}t\text{BuC}_5\text{H}_4)_2$ ^[9] and $\text{Sn}(\text{NMe}_2)_4$ ^[8] were prepared according to literature methods. NMR spectra were recorded on Bruker AC250 and Bruker DRX 600 spectrometers. ^1H NMR chemical shifts were determined by comparison with residual ^1H solvent peaks and reported relative to $\delta(\text{Me}_4\text{Si}) = 0$.

Caution! Mixtures of tin amides with halogenated hydrocarbon solvents are potentially explosive.^[15]

2: A solution of $\text{Sn}(\text{NMe}_2)_4$ (1.0 mL, 6 mmol) in Et_2O (50 mL) was added over 30 min to a solution of $\text{Me}_2\text{Si}(3\text{-}t\text{BuC}_5\text{H}_4)_2$ (3.3 g, 11 mmol)^[9] in Et_2O (100 mL). The reaction mixture was stirred for 16 h. The solvent was reduced to 80 mL to remove the dimethylamine, and the mixture was stirred until the NMR signals of $\text{Sn}(\text{NMe}_2)_4$ were no longer observed. The solvent was removed and replaced by pentane (30 mL). A light-yellow precipitate was collected by filtration and washed with small amounts of cold pentane. The remaining mother liquor was reduced in volume and stored at -30°C to yield further precipitate. In total, 2.9 g (74 %) of compound **2** were obtained. ^1H NMR (600 MHz, CDCl_3 , 25°C): $\delta = 7.04$ (s, $^4J(\text{H},\text{Sn}) = 17$ Hz, 4H, $\text{C}_5\text{-H}$), 6.12 (s, $^3J(\text{H},\text{Sn}) = 9$ Hz, 4H, $\text{C}_5\text{-H}$), 3.50 (s, $^2J(\text{H},\text{Sn}) = 103$ Hz, 4H, $\text{C}_5\text{-H}$), 1.23 (s, 36H, $\text{C}(\text{CH}_3)_3$), 0.37 (s, 12H, SiCH_3); ^{13}C NMR (broad-band decoupled, CDCl_3 , 150 MHz, 25°C): $\delta = 154.2$ (C_5 , sp^2), 145.2 (C_5 , sp^2), 137.4 (C_5 , sp^2), 126.6 (C_5 , sp^2), 58.9 (C_5 , sp^3 , $^1J(\text{C},\text{Sn}) = 90$ Hz), 32.1 ($\text{C}(\text{CH}_3)_3$), 31.1 ($\text{C}(\text{CH}_3)_3$), -2.2 (SiCH_3); ^{119}Sn NMR (broad-band decoupled, 223.6 MHz, CDCl_3 , 25°C , Me_4Sn): $\delta = -45.3$; elemental analysis calcd (%) for $\text{C}_{40}\text{H}_{60}\text{Si}_2\text{Sn}$: C 67.12, H 8.45; found: C 67.17, H 8.78.

rac-3: A solution of **2** (0.62 g, 0.85 mmol) in toluene (250 mL) was added dropwise to a well-stirred suspension of ZrCl_4 (0.4 g, 1.7 mmol) in toluene (200 mL), and the reaction mixture stirred for 16 h. The toluene was removed in vacuo, the residue was taken up in pentane, and any insoluble impurities were removed by filtration. The pentane and SnCl_4 were removed in vacuo to give 0.64 g (80 %) of pure *rac*-**3** as a yellow residue. ^1H

NMR (C_6D_6 , 250 MHz, 25 °C, see ref. [9]): δ = 6.72 (m, 2H), 5.67 (m, 4H), 1.39 (s, 18H), 0.19 (s, 6H).

Received: February 10, 1998 [Z114571E]
German version: *Angew. Chem.* **1998**, *110*, 2378–2380

Keywords: metallocenes • spiro compounds • stereoselective synthesis • tin • zirconium

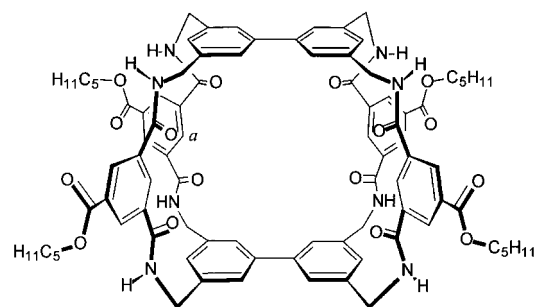
- [1] J. P. Morken, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1378; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1263; R. B. Grossmann, R. A. Doyle, S. L. Buchwald, *Organometallics* **1991**, *10*, 3301; R. B. Grossmann, W. M. Davis, S. L. Buchwald, *J. Am. Chem. Soc.* **1991**, *113*, 2321; T. K. Hollis, W. Odenkirk, N. P. Robinson, J. Whelan, B. Bosnich, *Tetrahedron* **1993**, *49*, 5415.
- [2] M. Bochmann, *J. Chem. Soc. Dalton Trans.* **1996**, 255; H. H. Brintzinger, D. Fischer, R. Mülhaupt, B. Rieger, R. M. Waymouth, *Angew. Chem.* **1995**, *107*, 1255; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1143.
- [3] R. B. Grossmann, J. C. Tsai, W. M. Davis, A. Gutiérrez, S. L. Buchwald, *Organometallics* **1994**, *13*, 3892; R. L. Halterman, *Chem. Rev.* **1992**, 965; W. W. Ellis, T. K. Hollis, W. Odenkirk, J. Whelan, R. Ostrander, A. L. Rheingold, B. Bosnich, *Organometallics* **1993**, *12*, 4391; M. E. Huttenlocher, J. Diebold, U. Rief, H. H. Brintzinger, A. M. Gilbert, T. J. Katz, *Organometallics* **1992**, *11*, 3600; G. M. Diamond, S. Rodewald, R. F. Jordan, *Organometallics* **1995**, *14*, 5; G. M. Diamond, R. F. Jordan, J. L. Petersen, *Organometallics* **1996**, *15*, 4045; S. T. Chacon, E. B. Coughlin, L. M. Henling, J. E. Bercaw, *J. Organomet. Chem.* **1995**, *497*, 171.
- [4] I. E. Nifant'ev, P. V. Ivchenko, *Organometallics* **1997**, *16*, 713; I. E. Nifant'ev, M. V. Borzov, A. V. Churakov, *Organometallics* **1992**, *11*, 3942.
- [5] L. Resconi, F. Piemontesi, I. Camurati, D. Balboni, A. Sironi, M. Moret, H. Rychlicki, R. Zeigler, *Organometallics* **1996**, *15*, 5046.
- [6] a) M. Hüttenhofer, M. H. Prosenc, U. Rief, F. Schaper, H. H. Brintzinger, *Organometallics* **1996**, *15*, 4816; b) M. Hüttenhofer, Dissertation, Universität Konstanz, **1997**.
- [7] L. A. Paquette, M. R. Sivik, *Organometallics* **1992**, *11*, 3503.
- [8] K. Jones, M. F. Lappert, *J. Chem. Soc.* **1965**, 1944.
- [9] H. Wiesenfeldt, A. Reinmuth, E. Barsties, K. Evertz, H. H. Brintzinger, *J. Organomet. Chem.* **1989**, *369*, 359.
- [10] The ^1H and ^{13}C NMR spectra of **2** in $CDCl_3$ are in accord with the expected S_4 symmetry: The number of signals observed is only one fourth of that expected for an unsymmetrical molecule (see Experimental Section). The signal assigned to the H atom at C1 exhibits a large ^1H – $^{117/119}Sn$ coupling of 103 Hz (see ref. [6a]).
- [11] Colorless monoclinic prisms of **2** ($C_4H_{60}Si_2Sn \cdot 0.5O(C_2H_5)_2$) were obtained by crystallization from diethyl ether at 4 °C. Further details on the crystal structure investigation of **2** may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-380134.
- [12] The molecular geometry of **2** in the solid state is distorted from the idealized S_4 symmetry represented in Figure 1 in that the Si(1)–Sn axis deviates from the Sn–Si(2) axis by 18°. This distortion might be caused by packing effects related to the cocrystallization of a diethyl ether molecule.
- [13] Compound **2** is thermally stable; even after several days in solution there were no indications of any rearrangement having occurred.
- [14] K. Bernauer, H. Stoeckli-Evans, D. Hugi-Cleary, H. J. Hilgers, H. Abdul-el-Khalek, J. Porret, J. J. Sauvain, *Helv. Chim. Acta* **1992**, *75*, 2327; K. Bernauer, F. Gretillat, H. Stoeckli-Evans, R. Warmuth, *Helv. Chim. Acta* **1993**, *76*, 545.
- [15] J. Lorberth, *J. Organomet. Chem.* **1969**, *16*, 235.

A Tricyclic Polyamide Receptor for Carbohydrates in Organic Media**

Anthony P. Davis* and Richard S. Wareham

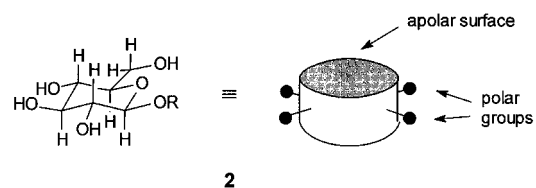
Carbohydrates are important^[1] but especially challenging substrates for supramolecular chemistry. Their structures are complex, yet lack (in the general case) individual features, such as ionic or strongly hydrophobic units, able to partake in strong and specific noncovalent interactions.^[2] The problem intensifies in hydroxylic solvents, where a receptor must distinguish its target from a large excess of similarly functionalized competitors. With the exception of boron-based systems which operate through covalent bond formation,^[3] there are still no effective synthetic receptors for carbohydrates in aqueous solution.^[4] Of the many published systems for operation in organic media,^[5, 6] only a few can tolerate significant quantities of hydroxylic cosolvents.^[6]

We now report a new carbohydrate receptor **1**, which shows unusual levels of affinity and selectivity in chloroform, and remains effective even in the presence of 8% CD_3OH . The design of **1** was inspired by carbohydrate-binding proteins,



1

which commonly place aromatic surfaces against patches of carbohydrate CH groups while accepting the hydroxyl groups into networks of hydrogen bonds.^[1d, 7] The intended target of **1**, the β -D-glucopyranosyl unit **2**, possesses axial CH groups and equatorially directed hydroxyl groups (Figure 1). The



2

Figure 1. Target molecule of the receptor **1** with axial hydrophobic and equatorial polar groups.

[*] Prof. A. P. Davis, Dr. R. S. Wareham
Department of Chemistry, Trinity College
Dublin 2, (Ireland)
Fax: (+353) 1-6712826
E-mail: adavis@mail.tcd.ie

[**] Financial support for this work was provided by the EU Human Capital and Mobility and Training and Mobility for Researchers programmes. We are grateful to Peter Ashton (University of Birmingham) for mass spectra and to Prof. C. S. Wilcox for access to the HOSTEST binding analysis program.

complementary cavity should therefore have parallel arene rings, appropriately spaced, linked by moieties capable of hydrogen-bond donation and/or acceptance. Other perceived design requirements were sufficient rigidity that self-complementary features in the receptor could not meet and satisfy each others' demands, and externally directed functionality which could be used to control solubility.

The tricyclic structure of **1** with two biphenyl and eight amide groups appeared to fit these criteria quite well. Molecular modeling^[8] on the analogous tetramethyl ester indicated that the cavity defined by the biphenyl and benzene-1,3-dicarboxamide units was sufficiently large to accept a β -D-glucose molecule (Figure 2), forming up to six intermolecular hydrogen bonds and several CH- π interactions. Modeling in

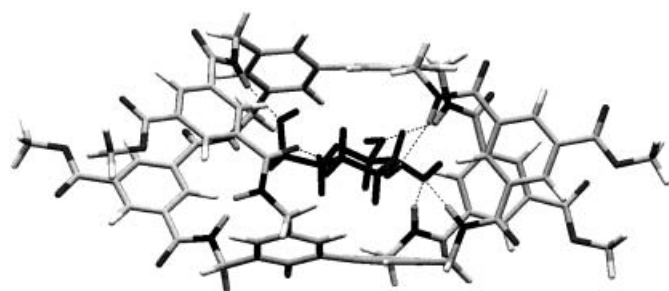
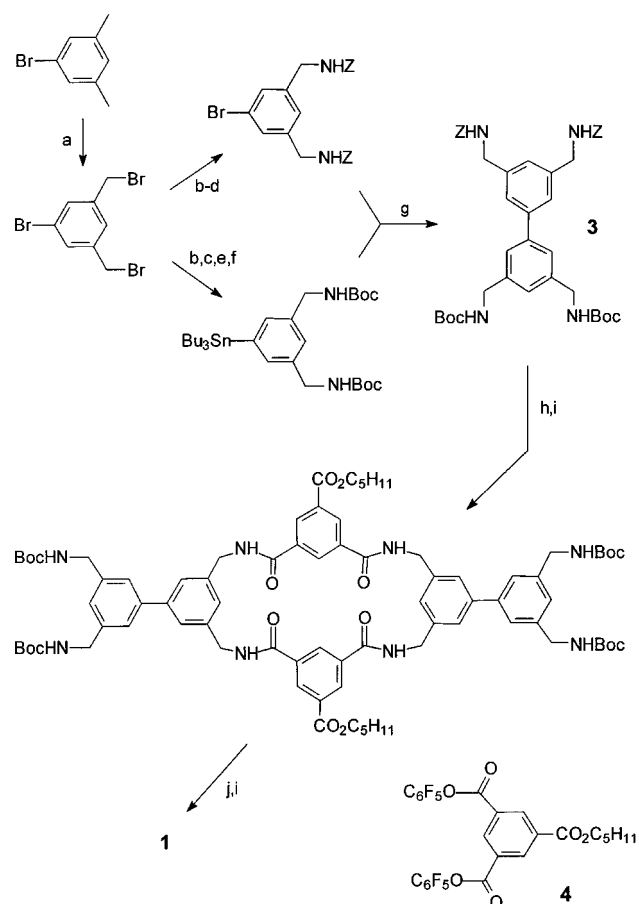


Figure 2. Baseline conformation resulting from a 1000 step Monte Carlo molecular mechanics study of **1**, modeled as the analogous tetramethyl ester, plus β -D-glucopyranose.^[7] The six intermolecular hydrogen bonds are shown as broken lines. Hydrogen atoms on C1, C2, and C3 of the carbohydrate are positioned to form close CH- π interactions with the host.

the absence of substrate did reveal low-energy conformations possessing up to three intramolecular hydrogen bonds and no substantial cavities. However, these could only be accessed at the cost of two or three *syn*-amide linkages, representing strain energy available to open the cavity during the binding process. The peripheral pentyl ester groups seemed likely to confer solubility in organic solvents, and could in principle be hydrolyzed to allow studies in water.

The synthesis of **1** proceeded via the asymmetrically protected biphenyl intermediate **3** (Scheme 1).^[9] Key steps were the [2+2] macrocyclizations involving bispentafluorophenyl ester **4**. Competition from [1+1] cyclizations was not observed, presumably due to steric/stereoelectronic effects.

Although quite soluble in CDCl_3 , **1** could not be studied by NMR spectroscopy in this solvent because of strongly broadened spectra. However, spectra acquired in $\text{CDCl}_3/\text{CD}_3\text{OH}$ (92:8) were well resolved and could be used for binding studies. Addition of octyl pyranosides **5–7** to **1** in this solvent system caused various changes in the ^1H NMR spectrum of the host. Interestingly, the signal due to amide NH moved upfield^[10] by about 0.2 ppm and split into two multiplets of equal size. The creation of two NH environments is an expected consequence of the interaction of **1** (D_{2h} symmetry) with a chiral substrate.^[11] The signals due to the benzylic methylene groups were also split into two broad multiplets, while that due to the inward-directed aromatic CH (position *a* in formula of **1**) moved downfield by about 0.3 ppm. The motions of the latter were consistent with 1:1



Scheme 1. Synthesis of **1**: a) NBS, AIBN, HCOOMe , $h\nu$; b) potassium phthalimide, DMF; c) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, then HCl aq.; d) $\text{PhCH}_2\text{O}(\text{CO})\text{Cl}$, THF, $i\text{Pr}_2\text{NEt}$; e) $(\text{Boc})_2\text{O}$, THF, $i\text{Pr}_2\text{NEt}$; f) $(\text{SnBu}_3)_2$, $\text{Pd}(\text{OAc})_2$, PPh_3 , toluene, reflux; g) $[\text{Pd}_2(\text{dba})_3]$, tri-(2-furyl)phosphane, NMP, 50°C ; h) H_2 , 10% Pd/C, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$; i) **4**, $i\text{Pr}_2\text{NEt}$, THF-DMF, high dilution; j) TFA, CH_2Cl_2 . AIBN = 2,2'-azobis(2-methylpropionitrile), Boc = *tert*-butoxycarbonyl, dba = dibenzylidenacetone, NBS = *N*-bromosuccinimide, NMP = *N*-methyl-2-pyrrolidinone, TFA = trifluoroacetic acid, Z = benzyloxycarbonyl.

binding, and could be analyzed to yield the data shown in Table 1. We were pleased to record quite substantial binding

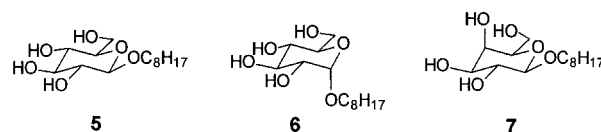


Table 1. Results from ^1H NMR titrations of **1** with octyl pyranosides **5–7**.^[a]

Pyranoside	K_a [M^{-1}]	$-\Delta G^\circ$ [kJ mol^{-1}]	$\Delta\delta$ [ppm] ^[b]
5	980 ($\pm 2\%$)	17.4	0.32
6	20 ($\pm 23\%$)	7.8	0.30
7	220 ($\pm 5\%$)	13.6	0.27

[a] In $\text{CDCl}_3/\text{CD}_3\text{OH}$ (92:8). $[\textbf{1}] =$ in the range 0.66 to about 0.52 mM for titrations with **5** and **7**, and between 2.2 and 1.53 mM for titrations with **6**. ^1H NMR spectrum of **1** was independent of concentration within this range. Guest concentrations 0.066–2.75 mM (**5**), 0.86–15.0 mM (**6**), 0.066–3.61 mM (**7**). $T = 303$ K. Association constants K_a were calculated from movements of the signal due to ArH^a using HOSTEST version 5.0.^[13a] Uncertainties are standard deviations calculated by using the Monte Carlo error analysis incorporated in the program. [b] Limiting change in chemical shift of ArH^a .

constants (K_a) for **5** and **7**, considering the presence of competing methanol, and a remarkable selectivity of about 45 between anomers **5** and **6**.

This success in a hydroxylic medium prompted a return to chloroform, the solvent which would best allow comparison of **1** with other systems. With no recourse to NMR spectroscopy, we investigated fluorescence spectroscopy as an indicator of complexation. On excitation at 285 nm **1** emits fluorescence between 350 and 450 nm (maximum at 387 nm). Addition of **5–7** appears to reduce intensity by two mechanisms, one which exhibits saturation and one which is linear with concentration. As illustrated in Figure 3, titration data could

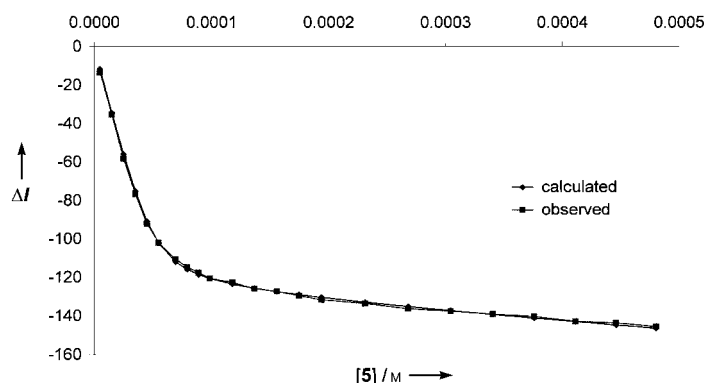


Figure 3. Experimental and calculated values for the fluorescence binding study of **1**+**5**.

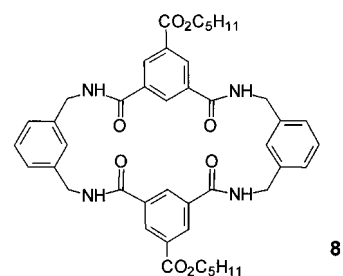
be reproduced to good accuracy by assuming that the first of these processes corresponded to 1:1 complex formation. The binding constants implied by the analyses are listed in Table 2. The selectivity between **5** and **6** is maintained, while the K_a for **5** is raised to $300\,000\text{ M}^{-1}$.

Table 2. Results from fluorescence titrations of **1** with octyl pyranosides **5–7**.^[a]

Pyranoside	K_a [M^{-1}] ^[b]	$-\Delta G^\circ$ [kJ mol^{-1}]	$-\Delta I$ [%] ^[c]
5	$300\,000 (\pm 6\%)$	30.7	36.4
6	$13\,000 (\pm 8\%)$	23.1	18.8
7	$110\,000 (\pm 12\%)$	28.3	22.8

[a] In CHCl_3 . [**1**] $\approx 0.05\text{ mM}$, guest concentrations $0.005\text{--}0.48\text{ mM}$ (**5** and **7**), $0.005\text{--}0.23\text{ mM}$ (**6**). [b] Calculated using specially written nonlinear least-squares curve-fitting programs implemented within Excel version 5.0 and Systat version 5.2. The programs made allowance for bimolecular (Stern–Vollmer) quenching of both **1** and complex by free pyranoside at a common rate, and gave the same results to a high level of accuracy. Uncertainties are asymptotic standard errors delivered by the Systat program. [c] Potential limiting change in fluorescence on complex formation (excluding Stern–Vollmer effect).

The geometries of the complexes between **1** and **5–7** remain uncertain. Although the exceptional binding constants and selectivities may imply that the strongly bound carbohydrates (**5** and **7**) enter the cavity of **1** as anticipated, we have as yet no direct indication that this is the case.^[12] However, control experiments on macrocycle **8** suggest that the complete structure of **1** is required for full effect. The behavior of **8** with **5** in CDCl_3 is complicated by dimerization



($K_{\text{dim}} = 600\text{ M}^{-1}$) and multiple stoichiometries, but appears to be compatible with K_a for 1:1 binding of just 850 M^{-1} .^[13]

Finally, a useful and important test for the recognition of carbohydrates is their extraction into nonpolar organic media. This may be said to mimic transport across biological membranes, and has practical implications for carbohydrate separation^[3c] and detection,^[3a,b] and for the moderation of carbohydrate reactivities.^[14] Although boron-based receptors^[3] and certain “unstructured” organic systems^[15] appear to be broadly effective, preorganized organic receptors have been restricted to less challenging substrates such as ribose,^[5e,i] fucose,^[5e] or methyl glucoside.^[5d,f] All reported attempts to extract hexoses with such receptors have been unsuccessful.^[5e,i] When **1** was stirred with an excess of glucose in CDCl_3 , significant quantities of the carbohydrate could be detected by TLC after filtration of the solution ($0.45\text{ }\mu\text{m}$ microfil). No glucose was detected in a control run in the absence of **1**. Complex formation was confirmed by fluorescence spectroscopy ($\Delta I = -25\%$) and by ^1H NMR spectroscopy after evaporation and re-solution in $(\text{CD}_3)_2\text{SO}$. Integration of the latter spectrum indicated that $0.8\text{--}0.9$ equivalents of glucose had been solubilized in the CDCl_3 . The ratio of β - to α -anomers was approximately 7:1, substantially different to the equilibrium ratios in $(\text{CD}_3)_2\text{SO}$ (55:45) and D_2O (65:35),^[16] and presumably reflecting the preference of **1** for the β -pyranosyl unit.

The success of **1** gives reason to hope that tricyclic polyamide receptors with related structures may prove effective even under aqueous conditions.

Received: February 24, 1998 [Z11511 IE]
German version: *Angew. Chem.* **1998**, *110*, 2397–2401

Keywords: carbohydrates • hydrogen bonds • molecular recognition • receptors • supramolecular chemistry

- [1] For leading references to the biological significance of carbohydrate recognition, see: a) S. D. Rosen, C. R. Bertozzi, *Curr. Opin. Cell Biol.* **1994**, *6*, 663; b) N. Sharon, H. Lis, *Essays Biochem.* **1995**, *30*, 59; c) Y. C. Lee, R. T. Lee, *Acc. Chem. Res.* **1995**, *28*, 321; d) W. I. Weis, K. Drickhamer, *Annu. Rev. Biochem.* **1996**, *65*, 441; e) R. U. Lemieux, *Acc. Chem. Res.* **1996**, *29*, 373.
- [2] The alkanol hydroxyl group, characteristic of carbohydrates, is of course capable of hydrogen-bond donation and acceptance, and can also ligate to metal ions. However, it is considerably less basic or acidic than many other groups involved in biochemical recognition, and forms correspondingly weaker interactions. See for example; D. H. Williams, *Aldrichimica Acta* **1991**, *24*, 71.
- [3] a) T. D. James, P. Linnane, S. Shinkai, *Chem. Commun.* **1996**, 281; b) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, *108*, 2038; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1911; c) B. D. Smith, *Supramol. Chem.* **1996**, *7*, 55.

- [4] Studies in aqueous media have either registered very low binding constants, or have employed carbohydrate substrates with hydrophobic appendages. For examples, see: Y. Aoyama, Y. Nagai, J. Otsuki, K. Kobayashi, H. Toi, *Angew. Chem.* **1992**, *104*, 785; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 745; A. V. Eliseev, H.-J. Schneider, *J. Am. Chem. Soc.* **1994**, *116*, 6081; K. Kobayashi, Y. Asakawa, Y. Kato, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, *114*, 10307; B.-L. Poh, C. M. Tan, *Tetrahedron* **1993**, *49*, 9581; J. Jimenez-Barbero, E. Junquera, M. Martinpastor, S. Sharma, C. Vicent, S. Penades, *J. Am. Chem. Soc.* **1995**, *117*, 11198; S. A. Staley, B. D. Smith, *Tetrahedron Lett.* **1996**, *37*, 283.
- [5] Reports from this laboratory: a) R. P. Bonar-Law, A. P. Davis, B. A. Murray, *Angew. Chem.* **1990**, *102*, 1497; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1407; b) K. M. Bhattarai, R. P. Bonar-Law, A. P. Davis, B. A. Murray, *J. Chem. Soc. Chem. Commun.* **1992**, 752; c) A. P. Davis, S. Menzer, J. J. Walsh, D. J. Williams, *Chem. Commun.* **1996**, 453; d) K. M. Bhattarai, A. P. Davis, J. J. Perry, C. J. Walter, S. Menzer, D. J. Williams, *J. Org. Chem.* **1997**, *62*, 8463. Representative examples from other laboratories: e) Y. Aoyama, Y. Tanaka, S. Sugahara, *J. Am. Chem. Soc.* **1989**, *111*, 5397; f) Y. Kikuchi, Y. Tanaka, S. Sutar, K. Kobayashi, H. Toi, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, *114*, 10302; g) R. Liu, W. C. Still, *Tetrahedron Lett.* **1993**, *34*, 2573; h) C.-Y. Huang, L. A. Cabell, E. V. Anslyn, *J. Am. Chem. Soc.* **1994**, *116*, 2778. i) M. Inouye, T. Miyake, M. Furusyo, H. Nakazumi, *J. Am. Chem. Soc.* **1995**, *117*, 12416; j) G. Das, A. D. Hamilton, *J. Am. Chem. Soc.* **1994**, *116*, 11139.
- [6] a) S. Anderson, U. Neidlein, V. Gramlich, F. Diederich, *Angew. Chem.* **1995**, *107*, 1722; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1596; b) U. Neidlein, F. Diederich, *Chem. Commun.* **1996**, 1493; c) P. B. Savage, S. H. Gellman, *J. Am. Chem. Soc.* **1993**, *115*, 10448; d) R. P. Bonar-Law, J. K. M. Sanders, *J. Am. Chem. Soc.* **1995**, *117*, 259; e) T. Mizutani, T. Murakami, N. Matsumi, T. Kurahashi, H. Ogoshi, *J. Chem. Soc. Chem. Commun.* **1995**, 1257. The receptors in references [6a–c] exploit strong hydrogen bonds to ionic centers, while those in references [6d,e] employ Zn–O interactions.
- [7] F. A. Quiñocho, *Pure Appl. Chem.* **1989**, *61*, 1293.
- [8] MacroModel V5.5; F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440. Calculations employed the MM2* force field and CHCl₃/GB/SA solvation.
- [9] **1**: ¹H NMR (400 MHz, [D₆]DMSO): δ = 0.91 (t, J = 7.0 Hz, 12H, CH₃), 1.38 (m, 16H, CH₂CH₂CH₃), 1.76 (quintet, J = 7.0 Hz, 8H, CH₂CH₂CH₂CH₂), 4.33 (t, J = 6.5 Hz, 8H, CO₂CH₂), 4.43 (dq, J = 18.0, 5.0 Hz, 16H, CH₂NH), 7.26 (s, 4H, biaryl ArH), 7.81 (s, 8H, biaryl ArH), 8.15 (s, 4H, spacer ArH), 8.46 (s, 8H, spacer ArH), 9.09 (t, J = 5.0 Hz, 4H, NH); ¹³C NMR (100.6 MHz, DMSO-d₆): δ = 13.83 (CH₃), 21.77 (CH₂), 27.60 (CH₂), 27.84 (CH₂), 43.73 (NHCH₂), 65.26 (CO₂CH₂), 124.87 (Ar CH), 129.11 (Ar CH), 130.27 (2 × Ar CH), 130.38 (Ar C), 135.26 (Ar C), 136.70 (Ar C), 139.76 (Ar C), 164.77 (CO), 164.80 (CO); LSI-MS: m/z: 1517.7 [MH⁺] (100), 534.9 (20), 460.9 (68).
- [10] This unexpected direction of shift may be due to displacement of methanol by the carbohydrate, giving a structure in which not all NH groups are maximally hydrogen-bonded. Alternatively, a conformational change may take place, altering the position of the NH protons in relation to the arene rings.
- [11] At first sight it might be thought that, at fast exchange, all eight NH protons would be equivalent. However, the carbohydrate substrate lacks any element of symmetry, and therefore creates eight different NH environments on interaction with the receptor. Coalescence of these eight signals would require fast exchange between eight equivalent binding orientations. The symmetry of **1** allows only four such orientations, and the NH protons are therefore split into two groups of four.
- [12] Data from the ¹H NMR studies in CDCl₃/CD₃OH (92:8) suggest that the carbohydrate protons experience upfield shifts of about 0.2–0.3 ppm on complexation. These modest shifts might imply attachment to the exterior of **1**, or might reflect competing shielding/deshielding effects from the arene rings defining the cavity.
- [13] ¹H NMR titrations analyzed by HOSTEST 5.0. See: a) C. S. Wilcox in *Frontiers in Supramolecular Chemistry and Photochemistry* (Eds.: H.-J. Schneider, H. Dürr), VCH, Weinheim, **1990**, p. 123.
- [14] Y. Tanaka, C. Khare, M. Yonezawa, Y. Aoyama, *Tetrahedron Lett.* **1990**, *31*, 6193.
- [15] Inverse micelles: N. Greenspoon, E. Wachtel, *J. Am. Chem. Soc.* **1991**, *113*, 7233; T. Kida, D. Furue, A. Masuyama, Y. Nakatsuji, I. Ikeda, *Chem. Lett.* **1996**, 733. “Unimolecular inverse micelles”: K. Kobayashi, F. Ikeuchi, S. Inaba, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, *114*, 1105.
- [16] F. Franks, P. J. Lillford, G. Robinson, *J. Chem. Soc. Faraday Trans. 1* **1989**, *85*, 2417.

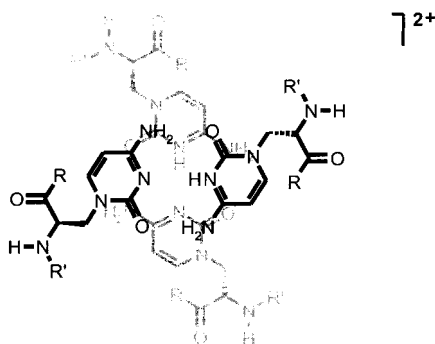
Oligomers with Intercalating Cytosine – Cytosine⁺ Base Pairs and Peptide Backbone: DNA i-Motif Analogues**

Ulf Diederichsen*

The ends of chromosomes are built up of telomeric DNA with an up to 1000-fold repeating guanine-rich DNA and complementary cytosine-rich sequence.^[1] The organization of guanine strands in tetrads based on a guanine donor/acceptor pattern that allows for simultaneous pairing by the Watson–Crick and Hoogsteen sides is a familiar structural motif.^[2] Surprisingly, however, the cytosine-rich oligomers are also able to form tetramers since pyrimidine molecules lack a Hoogsteen side they contribute less to the complex stability through stacking interactions. Nevertheless, at pH 4.5–6.5 the semiprotonated C–C⁺ base pairs are formed in the reverse Watson–Crick mode with three hydrogen bonds building up a parallel double strand; two C–C⁺ pairing double strands intercalate and stabilize the structure in a four-stranded complex.^[3–5] The interaction of consecutive base pairs is provided only by the stacking of the exocyclic carbonyl and amino groups that are oriented with opposed dipoles (Scheme 1). This base-pair arrangement makes a considerable contribution to the stabilization of the pairing complex as indicated by a base-pair distance of only 3.1 Å. DNA tetramers containing C–C⁺ pairing were called i-motif in reference to intercalating double strands, and were described by Gehring et al. in an NMR structural analysis of the DNA oligomer d(TCCCCC) that forms an i-motif^[3] and by Chen et al. with an X-ray structure of d(C₄).^[4] In the meantime, the intercalating C–C⁺ double strands that form C tetrads were established as a structural motif.^[5] Unwinding of the double helix is required to facilitate intercalation and leads to a helical twist of only 12.4–16° in the DNA i-motif. As part of

[*] Dr. U. Diederichsen
Institut für Organische Chemie und Biochemie der Technischen Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+49) 89-2891-3210
E-mail: ud@linda.org.chemie.tu-muenchen.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft (Di 542 2-1, Di 542 3-1), the Fonds der Chemischen Industrie, and the Leonhard-Lorenz-Stiftung. I am grateful to Professor H. Kessler, Garching, for generous support.



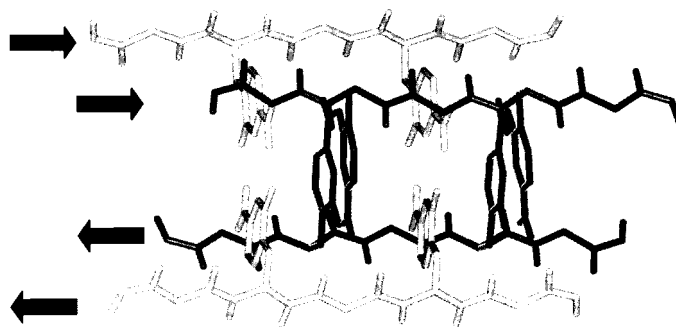
Scheme 1. Arrangement of consecutive C–C⁺ base pair planes of an alanyl-PNA tetrad analogous to the DNA i-motif.

our ongoing investigation of alanyl-PNA (PNA = peptide nucleic acids),^[6] cytosine–cytosine self-pairing gained our interest because we expected alanyl-PNA to be a suitable i-motif analogue by mimicking backbones that are close to linear.

Alanyl-PNA consists of a regular peptide backbone with an alternating configuration of the alanyl amino acids, which have nucleobases connected in the β position of the side chain. This arrangement leads to the favorable formation of double strands with an extended backbone. The linearity of alanyl-PNA pairing complexes is structurally inherent since the distance of two consecutive side chains is close to the stacking distance of 3.4 Å that is found in DNA. An alternating configuration of the nucleobases is required for orientation of the nucleobases on the same side of the backbone.

To study C–C pairing we synthesized the octamers H-(AlaC-AlaC)₄-Lys-NH₂ (**1**) and H-(AlaC-AlaC)₄-Lys-NH₂ (*ent-1*; AlaC = β -(cytosine-1-yl)alanine amino acids; amino acids with D configuration are underlined; lysine amide was introduced for solubility reasons).^[7] The nucleobase distance hampers intercalation since further extension of the backbone is not possible. In contrast, the oligomers H-(Gly-AlaC)₄-Lys-NH₂ (**2**) and H-(Gly-AlaC)₄-Lys-NH₂ (*ent-2*) contain a glycine unit as every second amino acid thus providing a spacer that facilitates the intercalation of linear double strands (Scheme 2). Because of the pairing selectivity of alanyl-PNA the oligomers had to be synthesized in both enantiomeric forms: since the reverse Watson–Crick mode offers the only possibility for C–C pairing, antiparallel strand orientation with base pairs formed by heterochiral nucleobases or parallel backbone orientation with homochiral base pairs were required.^[6]

We examined the formation of pairing complexes and their stability by temperature-dependent UV spectroscopy by measuring the cooperative destacking of nucleobases as a sigmoidal increase in absorption (hyperchromicity) with raising temperature. The self-pairing tendency of oligomers **1**, *ent-1*, **2**, and *ent-2* as well as pairing of the equimolar mixtures of the enantiomers **1** + *ent-1* or **2** + *ent-2* was examined at pH 7 (100 mM NaCl, 10 mM Na₂HPO₄/H₃PO₄) and pH 4.5 (100 mM NaCl, 80 mM tris-acetate).^[8] At pH 7 none of the oligomers showed any indication of pairing, which is in agreement with the lack of pyrimidine–pyrimidine recogni-



Scheme 2. Part of the alanyl-PNA tetrad formed analogous to the DNA i-motif: Oligomers H-(Gly-AlaC)₄-Lys-NH₂ (**2**) and H-(Gly-AlaC)₄-Lys-NH₂ (*ent-2*) pair in an antiparallel double strand. Two of these double strands stabilize by interpenetration.

tion in alanyl-PNA.^[6] Further, self-pairing of **1** or *ent-1* as well as the parallel pairing of enantiomers **1** + *ent-1* at pH 4.5 was not observed. Therefore, eight C–C⁺ base pairs with three hydrogen bonds each are not sufficient for double-strand formation. On the other hand, a stable pairing complex (T_m = 34 °C, 17% hyperchromicity, each 14 μ M; Figure 1a) was found when intercalation of the antiparallel C–C⁺ pairing double strands **2** and *ent-2* was facilitated. Complexation was reversible with hysteresis and was also concentration depend-

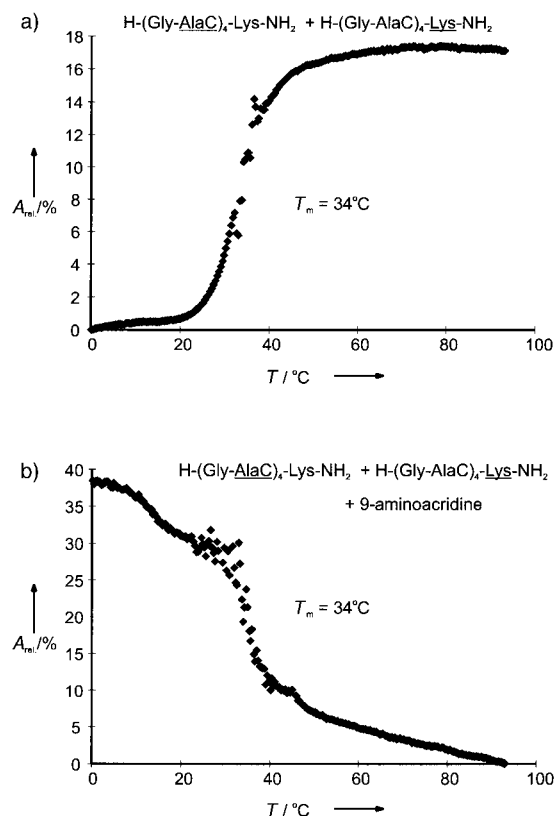
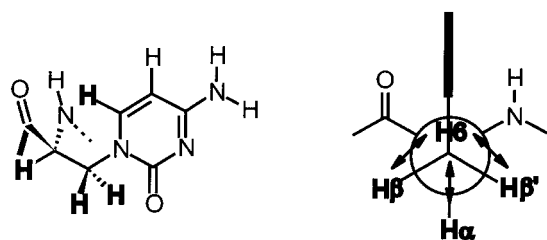


Figure 1. UV melting curves of a) an equimolar mixture of enantiomers **2** and *ent-2* (each 14 μ M, 100 mM NaCl, 80 mM tris-acetate, pH 4.5, 260 nm) and b) of pairing complex **2** + *ent-2* in the presence of 9-aminoacridine (each 15 μ M **2**, *ent-2*; 150 μ M acridine, 100 mM NaCl, 80 mM tris-acetate, pH 4.5, 260 nm).

ent. Pairing was not observed with oligomer concentrations of lower than $10\text{ }\mu\text{M}$ each. Furthermore, self-pairing of alanyl-PNA **2** or *ent-2* was not observed. This is in agreement with parallel double strand orientation being disfavored in the alanyl-PNA series.^[9] The alanyl-PNA tetraplex **2** + *ent-2* is more stable than the corresponding DNA i-motif. The melting stabilities of DNA were determined under the same conditions as $T_m = 23^\circ\text{C}$ (30% hyperchromicity, $14\text{ }\mu\text{M}$) for the tetramer $d(C_4)$ and $T_m = 48^\circ\text{C}$ (35% hyperchromicity, $11\text{ }\mu\text{M}$) for hexamer $d(C_6)$ (not shown).

In contrast to the nonoccurrence of the double strand of **1** with eight C–C⁺ base pairs, the pairing complex **2** + *ent-2* was formed with high stability. This indicates—in analogy to the DNA i-motif—an organization of the latter into a tetrad based on intercalation of double strands, with each forming four C–C⁺ base pairs. The special stacking orientation of the semiprotonated base pairs with opposed dipole orientation of the exocyclic amino and carbonyl functionalities seems to be decisive for the difference in pairing of a C–C⁺ double strand and a tetramer. In contrast to the DNA i-motif, the alanyl-PNA tetrad is based on antiparallel pairing double strands. By comparison of the overall charge of C–C⁺ pairing oligomers three cases can be realized: the DNA i-motif has a negative net charge, the self-pairing DNA dimer with an ethylene bridge between positions 3' and 5'^[10] is neutral, whereas alanyl-PNA **2** + *ent-2* has an overall positive charge.

Further evidence for **2** + *ent-2* organization in tetrads was obtained by gel filtration HPLC (Pharmacia Superdex-Pep-tide PC 3.2/30). In addition to the main peak with a retention time of 19.0 min a second small peak could be observed at 8.6 min when an aqueous buffer solution (100 mM NaCl, 80 mM tris-acetate, pH 4.5; flowrate 0.1 mL min^{-1}) was used as eluent. The latter signal most likely corresponds to the tetrameric species. In 2D NMR experiments of the **2** + *ent-2* complex (500 MHz, D₂O, each 2 mM, 100 mM NaCl, 80 mM tris-acetate) only peaks corresponding to the spin system of one oligomer were observed, as expected for the highly symmetric tetramer. Furthermore, ROESY cross-peaks were found between the proton on C6 (H6) of the nucleobase and the H β protons as well as with the H α proton of the corresponding nucleo amino acid. Qualitatively this indicates a conformation of the nucleo amino acids with the nucleobase oriented antiperiplanar to H α with the H–C6 pointing towards the backbone (Scheme 3).



Scheme 3. The most likely preferred conformation of the nucleo amino acids in the pairing complex **2** + *ent-2*. The observed ROEs (ROE = rotating frame Overhauser enhancement) between H6 and H α , H β , and H β' are indicated by arrows.

The UV melting curve of **2** + *ent-2* in the presence of ten equivalents of 9-aminoacridine showed that a degrading of the tetramer occurs, as observed by a hypochromic effect ($T_m = 34^\circ\text{C}$, about 25% hypochromicity, reversible with hysteresis, each $15\text{ }\mu\text{M}$ alanyl-PNA, $150\text{ }\mu\text{M}$ acridine; Figure 1b). This effect is likely to be caused by the association of the acridine to the single or double strand, in a similar manner as has been described for the DNA dimer $d(AC)$.^[11] In contrast, the addition of 9-aminoacridine did not affect the melting curve of DNA $d(C_4)$ under comparable conditions.

Overall, the C–C⁺ pairing in the alanyl-PNA tetrad represents a DNA i-motif analogue. Because of the inherent linearity of the alanyl-PNA backbone, alanyl-PNA was expected to be a suitable i-motif mimic. This C–C⁺ pairing is the only exception to pyrimidine–pyrimidine recognition in the alanyl-PNA series. Since the i-motif was not observed for RNA, the sugar moiety and the internucleotide linkage were thought to be essential for formation of the i-motif.^[12] The alanyl-PNA analogue indicates that the i-motif is not limited to nucleic acids. Finally, the unusual stacking of base pairs in the i-motif was found to be a prerequisite for the formation of a tetrameric structure.

Received: March 4, 1998 [Z11550IE]

German version: *Angew. Chem.* **1998**, *110*, 2395–2397

Keywords: base pairing • DNA structures • intercalations • peptide nucleic acids

- [1] D. Voet, J. G. Voet, *Biochemistry*, 2. ed., Wiley, New York, **1995**.
- [2] a) C. Kang, X. Zhang, R. Ratliff, R. Moyzis, A. Rich, *Nature* **1992**, *356*, 126; b) F. W. Smith, J. Feigon, *Nature* **1992**, *356*, 164; c) P. Schultze, F. W. Smith, J. Feigon, *Structure* **1994**, *2*, 221.
- [3] K. Gehring, J.-L. Leroy, M. Guéron, *Nature* **1993**, *363*, 561.
- [4] L. Chen, L. Cai, X. Zhang, A. Rich, *Biochemistry* **1994**, *33*, 13540.
- [5] a) J. L. Leroy, K. Gehring, A. Kettani, M. Guéron, *Biochemistry* **1993**, *32*, 6019; b) J.-L. Leroy, M. Guéron, J.-L. Mergny, C. Hélène, *Nucleic Acids Res.* **1994**, *22*, 1600; c) C. Kang, I. Berger, C. Lockshin, R. Ratliff, R. Moyzis, A. Rich, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 11636; d) S. Ahmed, A. Kintanar, E. Henderson, *Nat. Struct. Biol.* **1994**, *1*, 83; e) I. Berger, C. Kang, A. Fredian, R. Ratliff, R. Moyzis, A. Rich, *Struct. Biol.* **1995**, *2*, 416; f) J.-L. Leroy, M. Guéron, *Structure* **1995**, *3*, 101; g) I. Berger, M. Egli, A. Rich, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 12116.
- [6] a) U. Diederichsen, *Angew. Chem.* **1996**, *108*, 458; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 445; b) U. Diederichsen, *Angew. Chem.* **1997**, *109*, 1966 *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1886; c) U. Diederichsen, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1743; d) U. Diederichsen, *Med. Chem. Lett.* **1998**, *8*, 145.
- [7] For synthesis of the nucleo amino acid Boc-AlaC(Z)-OH (Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl) by the nucleophilic ring opening of the Boc-serine lactone with *N*⁴-benzyloxycytosine, see ref. [6b] and P. Lohse, B. Oberhauser, B. Oberhauser-Hofbauer, G. Baschang, A. Eschenmoser, *Croatica Chem. Acta* **1996**, *69*, 535. Oligomerization by solid-phase peptide synthesis (SPPS) was carried out on a 4-methylbenzhydrylamine–polystyrene support loaded with L- or D-lysine(Z)-OH. Activation with *O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) provided coupling yields in excess of 95%. All oligomers were characterized by ¹H NMR spectroscopy and ESI-MS: **1**: m/z : 1587.4 [MH^+], 794.3 [MH_2^+]; *ent-1*: m/z : 794.0 [MH_2^+]; **2**: m/z : 1094.4 [MH^+], 548.1 [MH_2^+]; *ent-2*: m/z : 1094.2 [MH^+], 548.3 [MH_2^+].
- [8] The following temperature program was used to control the heating block for the UV melting curves: $80^\circ\text{C} \rightarrow -2^\circ\text{C}$ (20 min) $\rightarrow -2^\circ\text{C}$ (240 min) $\rightarrow 95^\circ\text{C}$ (180 min) $\rightarrow -2^\circ\text{C}$ (180 min) $\rightarrow -2^\circ\text{C}$ (240 min)

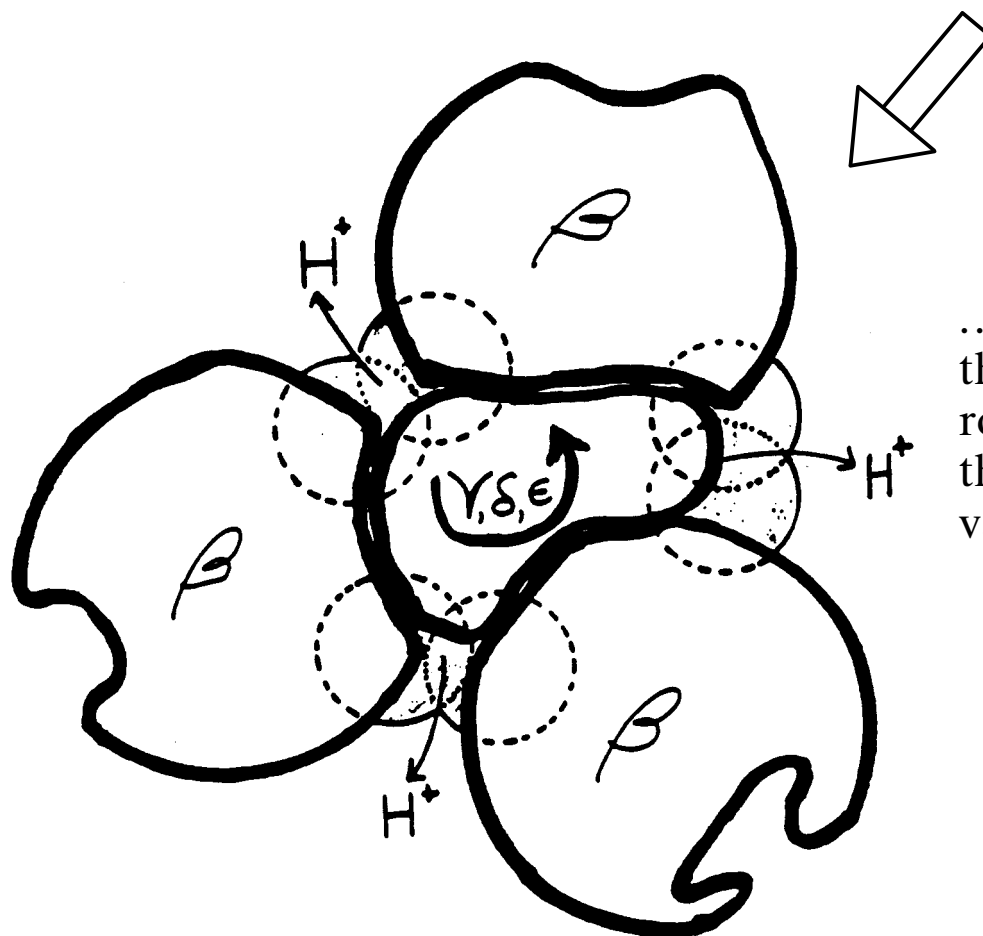
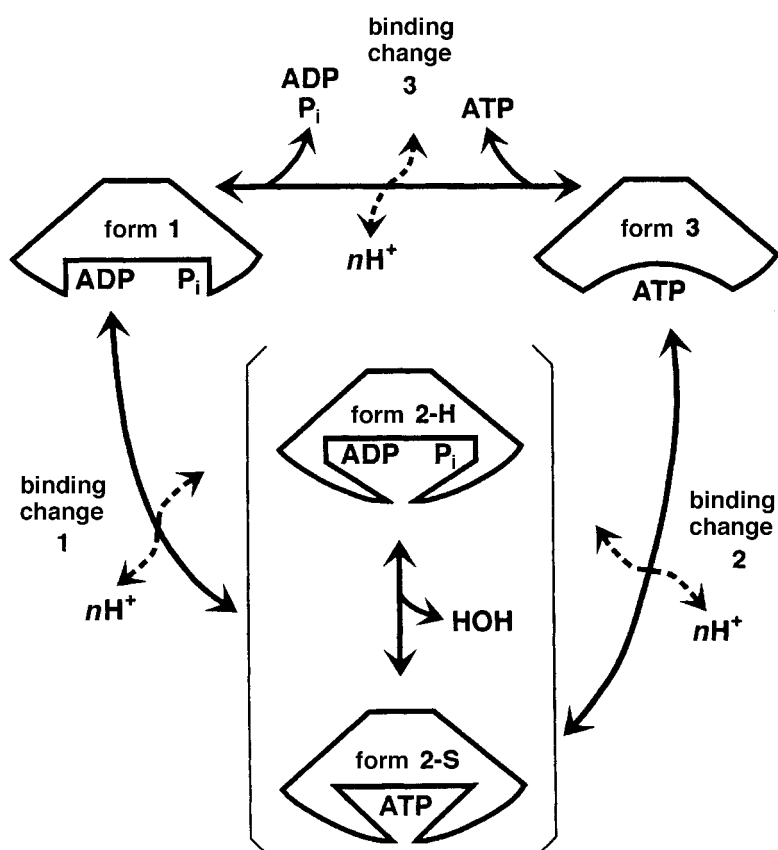
→95 °C (180 min) → −2 °C (180 min). The temperature was measured directly in solution.

- [9] U. Diederichsen, unpublished results. Since interpenetrated C–C⁺ base pairs prefer a separation of 3.1 Å and alanyl-PNA with an extended backbone would provide a base-pair distance of 3.6 Å, it is likely that tetrad **2+ent-2** lowers the distance by inclining the backbone axes or by helication. This would give a preference for the antiparallel backbone orientation; see J. Hunziker, H.-J. Roth, M.

Böhringer, A. Giger, U. Diederichsen, M. Göbel, R. Krishnan, B. Jaun, C. Leumann, A. Eschenmoser, *Helv. Chim. Acta* **1993**, 76, 259.

- [10] M. Egli, P. Lubini, M. Bolli, M. Dobler, C. Leumann, *J. Am. Chem. Soc.* **1993**, 115, 5855.
 [11] E. Westhof, M. Sundaralingam, *Proc. Natl. Acad. Sci. USA* **1980**, 77, 1852.
 [12] a) S. Robidoux, M. J. Damha, *J. Biomol. Struct. Dyn.* **1997**, 15, 529.
 b) D. Collin, K. Gehring, *J. Am. Chem. Soc.* **1998**, 120, 4069.

The recognition of binding changes of catalytic sites of the ATP synthase ...



... was followed by the postulate of a rotational catalysis that has now been validated.

Energy, Life, and ATP (Nobel Lecture)**

Paul D. Boyer*

Overview

I have a deep appreciation for the unusual and unexpected chain of events that has brought me the Nobel Award. It is my good fortune to be a spokesman for a considerable number of outstanding researchers in the field of bioenergetics, whose efforts have revealed an unusual and novel mechanism for one of nature's most important enzymes. Over 50 years ago a vital cellular process called oxidative phosphorylation was demonstrated. The process was recognized as the major way that our bodies capture energy from foods to be used for a myriad of essential cellular functions, but how it occurred was largely unknown. The intervening years have seen much progress. Today I will tell you how contributions of my research group in the 1970s led to new hypotheses that helped overcome the limitations of old paradigms which were no longer applicable. We gained further support of the hypotheses and clarified other aspects of the process in the 1980s and early 1990s. Then—as John Walker, my corecipient, will relate^[123]—the X-ray structural data from his group became available. The structural information about the catalytic portion of the enzyme for the phosphorylation supported the most novel and least accepted aspect of our hypotheses. Now on this occasion, John and I can tell you how a truly remarkable molecular machine accomplishes the oxidative phosphorylation that was left unexplained for over half a century.

A key player in the process is called ATP, the abbreviation for adenosine triphosphate. At the time I was a graduate student, Fritz Lipmann^[1] recognized the broad role ATP played in biological energy capture and use. The adenosine portion, for our purposes, can be regarded as a convenient handle to bind the ATP to enzymes. It is the three phosphate groups attached in a row, particularly the last two, that participate in energy capture. When the energy stored in ATP

is used, the terminal anhydride bond is split, forming adenosine diphosphate (ADP) and inorganic phosphate (P_i). The resynthesis of ATP, coupled to energy input, is catalyzed by an enzyme called ATP synthase, which is present in abundance in intracellular membranes of animal mitochondria, plant chloroplasts, bacteria, and other organisms. The ATP made by your ATP synthase is transported out of the mitochondria and used for the function of muscle, brain, nerve, kidney, liver, and other tissues, and for transport and for making a host of compounds that the cell needs. The ADP and phosphate formed when ATP is used return to the mitochondria, and ATP is made again using the energy from the oxidations. I estimate that the net synthesis of ATP is the most prevalent chemical reaction that occurs in your body. Indeed, because plants and microorganisms capture and use energy by the same reaction, and the amount of biomass is large, the formation and use of ATP is the principal net chemical reaction occurring in the whole world. This is obviously a very important reaction. How does it occur?

All living cells contain hundreds of large, specialized protein molecules called enzymes. These catalyze the hundreds of chemical reactions that are necessary for the cell to function. Among these are the reactions by which energy is captured by the mitochondria, which are packed into muscle, brain, and other cells. Inside the mitochondria and imbedded in its membranes are enzymes that catalyze oxidation of the food you eat. They essentially burn it, using oxygen and producing carbon dioxide and water, in a series of small steps, each catalyzed by a special enzyme. The oxygen you are breathing now is carried by the hemoglobin of your red blood cells, then it reaches the mitochondria where it oxidizes iron atoms that are part of a specialized enzyme, which in turn oxidizes other enzymes in a respiratory chain. The blood stream carries the carbon dioxide produced to the lungs for exhaling. The sequence of oxidations liberates protons and promotes a charge that tends to force protons across the membrane. Similarly, in chloroplasts light energy is coupled to the formation of proton-motive force. This proton-motive force, as shown by the 1978 nobelist Peter Mitchell,^[2] causes protons (hydrogen ions) to be translocated through the ATP synthase accompanied by formation of ATP. The important and very difficult question that remained unanswered for many years was how the ATP synthase uses the proton-motive force to make ATP.

[*] Prof. P. D. Boyer
Department of Chemistry and Biochemistry
University of California at Los Angeles
611 Circle Drive East, Los Angeles, CA 90095-1570 (USA)
Fax: (+1) 310-206-7286
E-mail: pdboyer@ucla.edu

[**] Copyright© The Nobel Foundation 1998. We thank the Nobel Foundation, Stockholm, for permission to print this lecture.

ATP Synthase

First I will summarize what is now known about the ATP synthase, then convey aspects of how this knowledge was attained. The enzyme uses a novel mechanism that has catalytic steps different from any that had been seen before with other enzymes. A sketch that depicts the enzyme function is available on the Nobel Foundation internet site.^[124] A similar sketch was provided in a recent paper from Richard Cross's laboratory.^[3] The ATP synthase has three copies each of large α and β subunits, with three catalytic sites located mostly on the β subunit at the interface of the α and β subunits. A γ subunit core and smaller δ and ϵ subunits complete a portion known as F_1 , with a subunit composition in order of decreasing size designated as $\alpha_3\beta_3\gamma\delta\epsilon$. This portion of the enzyme was first isolated in the laboratory of a splendid investigator, Efraim Racker, and shown to act as an ATPase.^[4] Several leading investigators in the bioenergetic field were trained in Racker's laboratory. The F_1 -ATPase^[*] catalyzes ATP hydrolysis, but not ATP synthesis. The rest of the enzyme, which is imbedded in the membrane, is known as F_0 ; in *E. coli* the F_0 contains a large subunit *a*, two copies of a subunit *b*, and probably 12 copies of a much smaller *c* subunit. The F_0 of the mitochondrial enzyme is much more complex. The designation F_1F_0 -ATPase is sometimes used in the literature for the complete ATP synthase.

During net ATP synthesis the three catalytic sites on the enzyme, acting in sequence, first bind ADP and phosphate, then undergo a conformational change so as to make a tightly bound ATP, and then change conformation again to release this ATP. These changes are accomplished by a striking rotational catalysis driven by a rotating inner core of the enzyme, which in turn is driven by the protons crossing the mitochondrial membrane. I share the view that revealing the mechanism of the ATP synthase is a fine achievement of modern biochemistry. I am also keenly aware that this achievement comes from the sum of the research of many members of the bioenergetics community, who deserve a major share in the recognition of the accomplishment. But the

Nobel awards tend to make heroes of only one or a few of those responsible. It is my good fortune to be addressing you today because my research group, strongly dependent on the information provided by others, gained the first insights into three unusual features of the ATP synthase catalysis. These unusual features are energy-linked binding changes that include release of a tightly bound ATP, sequential conformational changes of three catalytic sites to accomplish these binding changes, and a rotary mechanism that drives the conformational changes. These features had not been recognized previously in enzymology.

Early Probes

In the mid 1950s, some twelve years after receiving my Ph.D., some experiments on how ATP is made were conducted in my laboratory. One concerned the capture of energy in glycolysis. We found that the oxidation of glyceraldehyde 3-phosphate could occur without the participation of inorganic phosphate,^[5] suggesting participation of an acyl enzyme intermediate. Extension of these experiments, and salient findings in Racker's group,^[6] demonstrated that a sulfhydryl group on the enzyme was acylated and the acyl enzyme was cleaved by inorganic phosphate to form 1,3-diphosphoglycerate, which in turn transferred a phosphoryl group to ADP to make ATP. The demonstration that two covalent intermediates, the acyl enzyme and the phosphorylated substrate, preceded ATP formation made it seem logical to seek for similar intermediates in oxidative phosphorylation. As we and others learned years later, this was not a useful approach.

Of more relevance to ATP synthase were experiments with ^{18}O and ^{32}P , initiated because of the demonstration by Mildred Cohn that mitochondria would catalyze a rapid exchange of phosphate oxygen atoms with those of water.^[7] We found from the ^{32}P experiments that the overall reaction of oxidative phosphorylation was dynamically reversible.^[8] The ^{18}O experiments revealed the striking finding that the exchange of inorganic phosphate oxygen atoms with water was occurring even more rapidly. As illustrated in Figure 1, we attributed this to the formation of a covalent intermediate, which was then cleaved by inorganic phosphate. We tried unsuccessfully

[*] Abbreviations used for the F_1 -ATPase from various sources: from heart mitochondria MF₁, from chloroplasts CF₁, from *E. coli* EcF₁, and from Kagawa's thermophilic bacterium TF₁.



Paul D. Boyer was born on July 31, 1918 in Provo, Utah. He received a B.S. degree in chemistry from Brigham Young University in 1939, and a Ph.D. in biochemistry from the University of Wisconsin in 1943. After two years at Stanford University on a war research project for stabilization of serum albumin, he became an Assistant Professor at the University of Minnesota, where he initiated studies on oxidative phosphorylation. Since 1963 he has been a Professor in the Department and Biochemistry at the University of California, Los Angeles, where he also served as founding Director of the Molecular Biology Institute. In 1955 he was a Guggenheim fellow for studies in Sweden and received the American Chemical Society Award in Enzyme Chemistry. He has honorary doctorate degrees from the Universities of Stockholm, Minnesota, and Wisconsin. He received the Rose Award of the American Society of Biochemistry and Molecular Biology in 1989 and shared the 1997 Nobel Prize in Chemistry.

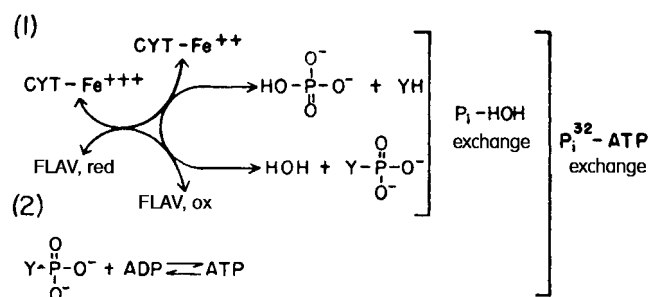


Figure 1. Exchange of phosphate oxygen atoms between $^{32}\text{P}_i$ and ATP as well as between P_i and HOH for the overall reaction $\text{ADP} + ^{32}\text{P}_i \rightleftharpoons \text{ATP} + \text{HOH}$ along with the dynamic reversal of oxidative phosphorylation (adapted from ref. [7]). In this early study covalent intermediates were proposed to explain why oxygen exchange was more rapid than reversal of the overall reaction. FLAV = flavin, CYT = cytochrome.

to separate out fractions from mitochondria that would catalyze the first step leading to the formation of an intermediate in oxidative phosphorylation. It was some sixteen years later that we found the simple explanation that no intermediate was formed, and that the rapid ^{18}O exchange resulted from the rapid and reversible formation of a tightly bound ATP.

In the 1960s we embarked on another, only partially successful, series of experiments. By using ^{32}P as a sensitive tracer, we found in mitochondria a ^{32}P -labeled protein that was an intermediate between inorganic phosphate and ATP. We identified this as a previously unrecognized phosphorylated protein, with a phosphoryl group attached to a histidine residue. We mistakenly thought we had identified an intermediate in oxidative phosphorylation, but subsequently found it to be an intermediate in GTP or ATP formation by the succinyl CoA synthetase of the citric cycle.^[9] We were reaching for a gold but got a bronze instead.

^{18}O Exchanges and a New Concept

For several years we mostly studied other problems, including taking a look at active transport in *E. coli*. This study gave evidence for an intermediate and unidentified energized state,^[10] but we did not characterize this state or pay enough attention to the rumblings coming from Peter Mitchell's laboratory. It was difficult for me to accept proton-motive force as a driving agent for ATP formation when I could not visualize a logical way this could occur. But the lure of the ATP synthase continued, and we tried to get leads with photophosphorylation by spinach thylakoid membranes as well as oxidative phosphorylation by heart mitochondria. The use of the ^{18}O -exchange measurements to study the process provided a crucial insight. The types of exchange that can be measured are readily understood with the aid of the diagram in Figure 2. The box represents a catalytic site. ADP and P_i can bind and be converted into a tightly bound ATP. The water formed freely interchanges with medium water. Reversal of this reaction results in the incorporation of one water oxygen atom into the bound P_i . If the P_i can tumble freely at the catalytic site, when bound ATP is again formed

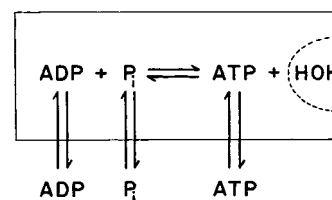


Figure 2. Binding, interconversion, and release steps for oxygen exchanges.

there are three chances out of four that it will contain a water oxygen atom. Various exchanges of phosphate oxygen atoms with water oxygen atoms are measurable, as shown in Table 1. The oxygen exchanges thus provide sensitive probes of reaction steps that otherwise might be hidden.

Table 1. Exchanges of phosphate oxygen atoms with water oxygen atoms catalyzed by ATP synthase.

Exchange	Measurement
intermediate $\text{P}_i \rightleftharpoons \text{HOH}$	hydrolysis of $[\gamma\text{-}^{18}\text{O}]\text{ATP}$ and determination of ^{18}O in P_i formed
intermediate $\text{ATP} \rightleftharpoons \text{HOH}$	synthesis of ATP from $[\text{P}_i\text{-}^{18}\text{O}]\text{P}_i$ and determination of ^{18}O in ATP formed
medium $\text{P}_i \rightleftharpoons \text{HOH}$	determination of loss of ^{18}O from $[\text{P}_i\text{-}^{18}\text{O}]\text{P}_i$ when P_i binds, undergoes exchange, and returns to the reaction medium
medium $\text{ATP} \rightleftharpoons \text{HOH}$	determination of loss of ^{18}O from $[\gamma\text{-}^{18}\text{O}]\text{ATP}$ when ATP binds, undergoes exchange, and returns to the reaction medium

The ^{18}O probes revealed a puzzling aspect, namely that the intermediate $\text{P}_i \rightleftharpoons \text{HOH}$ exchange was unusually insensitive to uncouplers of oxidative phosphorylation. As shown in Figure 3, even though the potent uncoupler S-13 allowed oxidation to proceed without net ATP synthesis, the rapid exchange of phosphate and water oxygen atoms continued. The significance of this was not grasped for some time. But one day, while listening to a seminar that I did not understand, the oxygen-exchange data churned in my mind. It became clear to me that the results could be explained if the energy from oxidations was not used to *make* the ATP molecule, but instead was used to bring about a *release* of a tightly bound ATP. The reversible formation of the tightly bound ATP molecule could continue at the catalytic site without involving proton-motive force, and give rise to the uncoupler-insensitive oxygen exchange. We now had a new concept for oxidative phosphorylation and were anxious to call it to the attention of the field. The editors of the *Journal of Biological Chemistry* declined the opportunity to publish this new concept. I used the privilege of my recent membership in the National Academy of Sciences^[11] (Figure 4) to publish this first feature of what was to become the binding change mechanism of ATP synthesis. Independently, Slater's group, based on the presence of tightly bound nucleotides on the isolated $\text{F}_1\text{-ATPases}$, also suggested that energy input might be involved in their release.^[12]

Our feeling that the new concept was valid was strengthened by companion studies with the ATPase activity of muscle

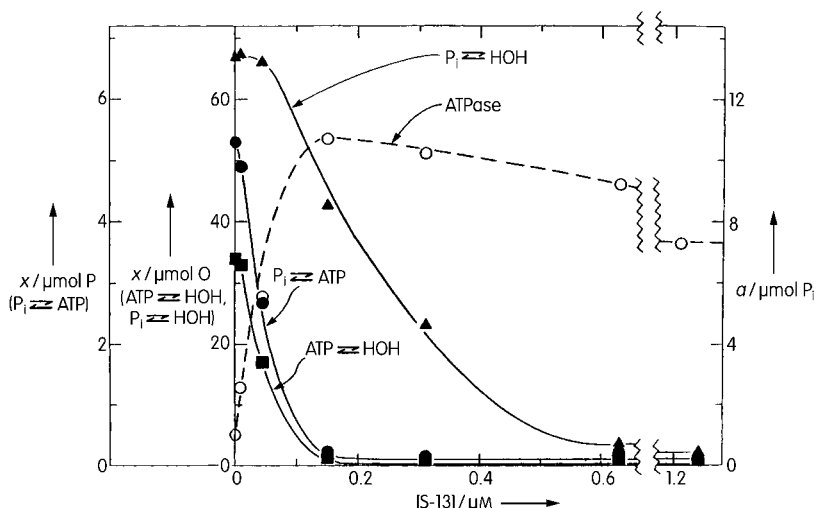


Figure 3. The insensitivity of phosphate oxygen atom exchange to an uncoupler of oxidative phosphorylation as compared to other measured reactions. Various uncouplers gave similar results; in this experiment an uncoupler known as S-13 was used. a = ATPase activity, given in micromoles of released P_i ; x = exchange, given in micromoles of P ($P_i \rightleftharpoons ATP$) or O ($ATP \rightleftharpoons HOH$, $P_i \rightleftharpoons HOH$).

Reprinted from
Proc. Nat. Acad. Sci. USA
Vol. 70, No. 10, pp. 2837–2839, October 1973

A New Concept for Energy Coupling in Oxidative Phosphorylation Based on a Molecular Explanation of the Oxygen Exchange Reactions

(protein conformational change/uncouplers/mitochondria)

PAUL D. BOYER, RICHARD L. CROSS, AND WILLIAM MOMSEN

The Molecular Biology Institute and The Department of Chemistry, University of California, Los Angeles, Calif. 90024

Contributed by Paul D. Boyer, June 25, 1973

ABSTRACT The $P_i \rightleftharpoons HOH$ exchange reaction of oxidative phosphorylation is considerably less sensitive to uncouplers than the $P_i \rightleftharpoons ATP$ and $ATP \rightleftharpoons HOH$ exchanges. The uncoupler-insensitive $P_i \rightleftharpoons HOH$ exchange is inhibited by oligomycin. These results and other considerations suggest that the relatively rapid and uncoupler-insensitive $P_i \rightleftharpoons HOH$ exchange results from a rapid, reversible hydrolysis of a tightly but noncovalently bound ATP at a catalytic site for oxidative phosphorylation, concomitant with interchange of medium and bound P_i . Such tightly bound ATP has been demonstrated in sub-mitochondrial particles in the presence of uncouplers, P_i , and ADP, by rapid labeling from ^{32}P , under essentially steady-state phosphorylation conditions. These results lead to the working hypothesis that in oxidative phosphorylation energy from electron transport causes release of preformed ATP from the catalytic site. This release could logically involve energy-requiring protein conformational change.

Figure 4. The beginning of the binding change mechanism. Portion of the publication presenting a new concept for oxidative phosphorylation.^[11]

myosin. Data from my and from Koshland's laboratories^[13, 14] had shown that myosin could catalyze both a medium $P_i \rightleftharpoons HOH$ and an intermediate $P_i \rightleftharpoons HOH$ exchange. It seemed possible that myosin might be able to spontaneously form a tightly bound ATP from medium ADP and P_i . Experiments showed this to be the case.^[15] This and other salient properties of myosin had also been revealed in contemporary studies by Trentham and associates.^[16, 17] Importantly, the oxygen exchange could be quantitatively accounted for by the rate of formation and cleavage of the bound ATP.

Not all bioenergeticists readily accepted the concept that a prime function of energy input was to bring about the release of a tightly bound ATP. For example, Mitchell preferred a mechanism in which the protons migrated to the catalytic site and induced the formation of ATP from ADP and P_i . It

seemed logical to me that proton translocation was linked to ATP release indirectly through conformational changes in the protein.^[18] Without my being informed, my publication was accompanied by a rebuttal from Mitchell,^[19] and I thus presented a more complete model for conformational coupling.^[20] With time this indirect manner in which proton translocation drives ATP formation has become generally accepted, but this does not detract from Mitchell's salient recognition of proton-motive force as a means of capturing energy for ATP synthesis and active transport.

Catalytic Cooperativity

We were now launched on an exciting period of research. As we probed mitochondrial oxidative phosphorylation further by ^{32}P and ^{18}O isotope exchanges, some puzzling aspects emerged. For example, when submitochondrial particles capable of oxidative phosphorylation were hydrolyzing ATP, a lively medium $ATP \rightleftharpoons HOH$ exchange occurred. Removal of product ADP stopped this exchange (Figure 5), although the reversal of ATP hydrolysis was still occurring on the enzyme. Somehow the lack of

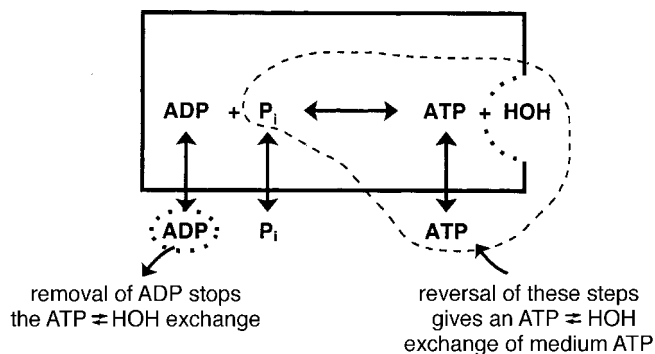


Figure 5. Catalysis of the synthesis and hydrolysis of ATP by sub-mitochondrial particles. Removal of medium ADP stops the medium $ATP \rightleftharpoons HOH$ oxygen exchange.

medium ADP to bind to the enzyme was stopping the release of ATP. It was not apparent how this could occur if the simple scheme of Figure 2 was used to explain the oxygen exchanges. Similarly, during net synthesis of ATP, removal of the medium ATP stopped the medium $P_i \rightleftharpoons HOH$ exchange. An explanation for why these oxygen exchanges were blocked, and for other related observations, was suggested by one of my graduate students, Celik Kayalar from Turkey. Celik said he could account for these results if the catalytic sites had to work cooperatively, so that ATP could not be released from one site unless ADP and P_i were available to bind at another site, or that P_i could not be released from one catalytic site unless ATP were available to bind at another catalytic site. Celik, together with Jan Rosing from Holland, demonstrated and characterized sequential and cooperative participation of

catalytic sites with the synthase in submitochondrial particles capable of or during oxidative phosphorylation.^[21, 22] In addition, their results gave evidence that the binding changes accompanying proton translocation also promoted the tight binding of P_i .

Adolfsen and Moudrianakis suggested that site–site cooperativity might occur with the separated F_1 -ATPase, based on the observation that a tightly bound ADP was released when ATP was cleaved by a bacterial F_1 -ATPase.^[23] Experiments in my laboratory revealed that, as we had found with the ATP synthase, a strong cooperativity of catalytic sites occurs with the isolated ATPase. When the MF_1 hydrolyzes relatively high concentrations of ATP, the P_i formed contains only slightly more than the one water oxygen atom required for the hydrolysis (Figure 6). But as the ATP concentration is

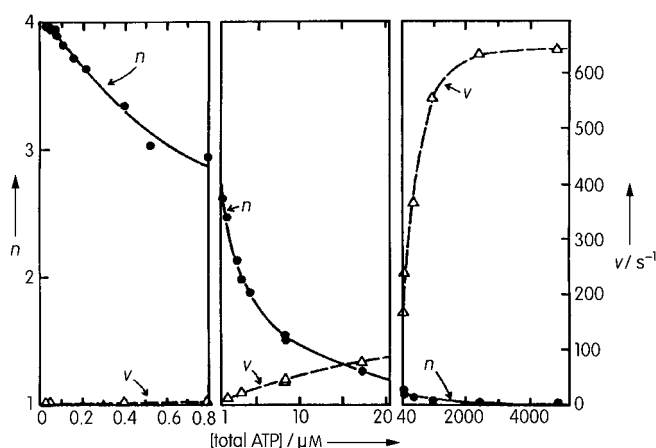


Figure 6. Effect of decrease in ATP concentration on the number of water oxygen atoms incorporated in each phosphate released ($n = O$ pro P_i) and on net hydrolysis velocity v as catalyzed by the MF_1 -ATPase (adapted from ref. [10]).

lowered, an instructive change occurs. The hydrolysis velocity is of course lowered, but the number of water oxygen atoms appearing in each P_i formed increases to almost four. It can be calculated that nearly 400 reversals of bound ATP hydrolysis occur before the P_i formed is released.^[10] The bound ADP and P_i formed cannot be released until ATP is available to bind at another catalytic site.^[*]

Experiments had now made it seem likely that an unexpected catalytic cooperativity was a prominent feature of the ATP synthase. At that time the prevailing view was that the enzyme had only two catalytic sites, and a diagram

depicting a bi-site mechanism appeared in my 1977 review article in the *Annual Review of Biochemistry*.^[25] We recognized, however, that if the enzyme were found to have three catalytic sites, a tri-site mechanism, as currently known to occur, would be likely.^[22, 26] The crucial point was that a tightly bound ATP could not be released until ADP and P_i bound at a second or a second and third catalytic site and the binding changes driven by proton translocation occur. This positive cooperativity meant that a low substrate concentrations, during either net synthesis or hydrolysis of ATP, a tightly bound ATP should still be present at a catalytic site. We undertook experiments to find if this was so. These tests were made with submitochondrial particles^[27] or chloroplast thylakoids^[28] so that net ATP formation was occurring with ADP concentrations far below the apparent K_m of ADP for maximal phosphorylation rates. About one tightly bound ATP committed to net ATP formation was found on each synthase. Such data give good evidence that strong positive catalytic cooperativity takes place under conditions where ATP synthesis is actually occurring. Additional findings from our and from other laboratories consistent with or favoring the catalytic cooperativity are summarized elsewhere.^[29]

In 1982 Feldman and Sigman demonstrated that the CF_1 -ATPase or the ATP synthase on chloroplast thylakoids, which have a tightly bound ADP in the catalytic site, would slowly form an equilibrium concentration of bound ATP from relatively high concentrations of medium P_i .^[30, 31] Their characterization of this single-site catalysis supported our concept of tight ATP formation without coupling to proton-motive force. Factors that promote formation of ATP at catalytic sites of myosin and F_1 -ATPases likely include the very tight preferential binding of ATP and, as suggested by deMeis,^[32] low water activity.

Also in 1982, the acceptance of catalytic cooperativity by the field was considerably enhanced by the determination in Penefsky's laboratory of the rate constants for the interconversion, binding, and release steps for MF_1 exposed to ATP at molar concentrations less than the molarity of the enzyme, conditions that gave what was termed uni-site catalysis.^[33, 34] An additional important contribution from the same laboratory was the demonstration that the hydrolysis of a trinitrophenyl-ATP bound at a single catalytic site was markedly increased by the binding of a second trinitrophenyl-ATP.^[35]

A number of researchers subsequently found a slow uni-site catalysis with different F_1 -ATPases. However, an inability to see a definite uni-site catalysis with TF_1 raised the question as to whether the cooperativity we had observed was a general phenomenon of F_1 -ATPases.^[36] That slow uni-site catalysis was indeed occurring was demonstrated by the increase in intermediate $P_i \rightleftharpoons HOH$ exchange as ATP concentration was lowered.^[37] For a number of years there appeared to be a general acceptance that a slow uni-site rate occurs and that the catalytic rate is markedly accelerated when ATP binds to additional sites. It was thus somewhat surprising when a quite recent claim appeared that MF_1 depleted of bound nucleotides did not show a slow uni-site catalysis.^[38] However, this claim is not experimentally sound; slow uni-site catalysis occurs with either native or nucleotide depleted MF_1 .^[39, 40]

[*] We missed obtaining this striking result about a decade earlier. At that time Efraim Racker came to my laboratory with some F_1 -ATPase so we could find if it catalyzed an oxygen exchange when ATP was hydrolyzed. We conducted the reaction at a relatively high ATP concentration, and found the incorporation of only one water oxygen atom, as required for the cleavage reaction. Harvey Penefsky made a similar observation.^[24] If we had measured what happened as the ATP concentration was lowered, we would have revealed the catalytic site cooperativity then. But we had no reason to suspect that the enzyme catalysis for each substrate cleaved would change so dramatically with substrate concentration. The strong catalytic cooperativity that we later demonstrated had not been described previously for any other enzyme.

Related Experiments

My laboratory group at this time also had an experimental interest in the Na^+/K^+ -ATPase that Prof. Skou presents.^[125] There was uncertainty whether the phosphoryl group that became attached to the enzyme as an intermediate in the catalysis was on a glutamyl or an aspartyl residue. We developed a borohydride reduction method that established that the group was attached to an aspartyl residue.^[41, 42] We also discovered that the enzyme in the presence of K^+ and Mg^{2+} catalyzed a rapid exchange of oxygen atoms of P_i with water oxygen atoms, attributable to a dynamic reversal of enzyme phosphorylation.^[43] This was and remains^[44] a useful way to probe this step of the reaction sequence. The related Ca^{++} -activated sarcoplasmic reticulum ATPase was likewise found to catalyze a rapid $\text{P}_i \rightleftharpoons \text{HOH}$ exchange.^[45]

Our attention was also directed toward the capacity of yeast pyrophosphatase to catalyze a $\text{P}_i \rightleftharpoons \text{HOH}$ exchange.^[46] We revealed that this exchange was due to a reversible formation of an enzyme-bound pyrophosphate,^[47] and the details of the exchange process were elucidated.^[47, 48] It was important to us that rapid mixing experiments showed that the rate of formation and cleavage of the bound pyrophosphate accounted for the oxygen exchange.^[47] As mentioned above, this was shown previously for the bound ATP and oxygen exchange catalyzed by myosin. For the pyrophosphatase exchange, Hackney developed a theoretical analysis of the distribution of ^{18}O -labeled species of P_i ^[49] that was to serve us well in studies we had underway on oxidative phosphorylation. The $\text{P}_i \rightleftharpoons \text{HOH}$ exchange catalyzed by the sarcoplasmic reticulum ATPase was also shown by rapid mixing and quenching experiments to result from the dynamic reversal of the formation of the phosphorylated enzyme intermediate.^[50] Such results, and the demonstration by Wimmer and Rose that the $\text{ATP} \rightleftharpoons \text{HOH}$ exchange catalyzed by mitochondria resulted from the reversible cleavage of the terminal $\text{P}-\text{O}-\text{P}$ bond,^[51] gave us confidence that in oxidative phosphorylation and photophosphorylation the oxygen exchanges we observed were due to the reversible hydrolysis of tightly bound ATP.

The Number of Catalytic Sites

Meanwhile studies in other laboratories were revealing the subunit stoichiometry of the F_1 -ATPase. As noted in a review by Penefsky covering literature up through 1978,^[24] considerable controversy remained. The difficulty of obtaining satisfactory molecular weights and subunit quantitation made it hard to get a clear choice between the presence of two or three copies of the major α and β subunits. Reports that measurements with EcF_1 and TF_1 isolated from bacteria grown on ^{14}C -labeled amino acids^[52, 53] favored a stoichiometry of $\alpha_3\beta_3\gamma_1$ seemed convincing to us. Reports on the composition of CF_1 strongly supported the presence of three each of the large subunits.^[54] On the basis of these and other developments, the field soon widely accepted the composition of F_1 -ATPases as $\alpha_3\beta_3\gamma\delta\epsilon$. All of our further experiments have been based on such a stoichiometry of subunits.

The number of nucleotide binding sites on the enzyme remained controversial until about a decade ago. Both α and β subunits were shown to have nucleotide binding sites. Reports in 1982 for MF_1 ^[55] and in 1983 for EcF_1 ^[56] gave good evidence for the presently accepted values of six potential nucleotide binding sites per enzyme. However, as late as 1987 claims were still made for only three nucleotide binding sites on CF_1 ^[57] and four for the liver F_1 .^[58] Subsequent data for CF_1 ^[59, 60] and the liver enzyme,^[61] as well as the highly conserved sequence of the β subunits, support the present view that all F_1 -ATPases have six nucleotide binding sites, although differing considerably in affinity.

Chemical derivatization studies, such as those in Bragg's laboratory^[62] and summarized in reviews^[29, 63] showed that all three β subunits, although with identical amino acid sequence, had distinctly different chemical properties. Such heterogeneity was a prominent reason why we considered it likely that all three β subunits passed through different conformations during catalysis. The participation of all three β subunits in a cooperative, sequential manner was supported, but not proven, by observations (over twenty are given in an earlier review)^[29] that derivatization of only one site per enzyme would nearly or completely block catalysis. We were also impressed by studies in Futai's laboratory showing that one defective mutant β subunit stopped catalysis,^[64] and by related mutational studies in Senior's laboratory^[65] that favored the participation of three equivalent β subunits for catalysis.

There has, however, been considerable delay in reaching a general acceptance that three catalytic sites participate in an equivalent manner. A single catalytic and two regulatory sites has been proposed.^[66, 67] Various models with only two catalytic sites have been suggested,^[68–73] as well as a 1991 model with four functioning catalytic sites arranged in two alternate pairs.^[74, 75] A 1989 review by Tiedge and Schafer^[76] stresses symmetrical considerations and favors equivalent β subunit participation. Various models, and a 1991 review favoring a two-site model,^[77] were appraised in a review prepared in 1992, in which I attempted to consider any experiments not in harmony with the binding change mechanism.^[29] The conclusion I reached is that very likely three sites participate in an equivalent manner. Subsequent events^[78] have strengthened this conclusion, although some doubts of which I am not aware may remain. The probability that three sites participate equivalently has guided experiments in my laboratory since the presence of three β subunits first seemed likely.

Rotational Catalysis

Toward the end of the 1970s we initiated experiments that led to the postulation of the third feature of the binding change mechanism. The presence of three copies of the major α and β subunits and single copies of the γ , δ , and ϵ subunits made it unlikely that all three β subunits could have identical interactions with single copy subunits. In particular, interactions with the larger γ subunits seemed likely to be crucial. McCarty's laboratory had reported that, with chloroplasts, light increased the reactivity of SH groups on the γ subunit

and that modifications in the γ subunits increased the leakage of protons across the coupling membrane.^[79, 80] This and other evidence suggested that the γ subunit interacted strongly with the catalytic β subunit. The growing information about the synthase gave a base for the interpretation of additional experiments with ^{18}O that were underway in my laboratory.

Water highly labeled with ^{18}O had become more readily available, and by NMR spectroscopy, as demonstrated by Cohn,^[81] or mass spectrometry we could measure what we designated as the ^{18}O isotopomers of P_i , containing 0, 1, 2, 3, or 4 ^{18}O atoms. Then when ATP synthesis or hydrolysis occurs with highly ^{18}O -labeled substrates, under conditions where appreciable oxygen exchange occurs, the distribution of isotopomers formed can be measured. If all the catalytic sites involved behave identically, the distributions of ^{18}O isotopomers would conform to a statistically predicted pattern. The results observed in a typical experiment for hydrolysis of ^{18}O -ATP by F_1 -ATPase are given in Figure 7.^[82] They show that the distribution of isotopomers conforms very closely to that expected for identical behavior of all catalytic sites. The data rule out the possible participation of two types of catalytic sites. As shown by one example in Figure 7, this would give a markedly different distribution of isotopomers. Importantly, experiments with the net ATP synthesis by chloroplast and mitochondrial ATP synthases also showed that all catalytic sites behave identically.^[83–85] The tests were sensitive and revealing; if steps of substrate binding, interconversion, or release or their concentration dependencies differed among catalytic sites, this should have been revealed in the ^{18}O experiments.

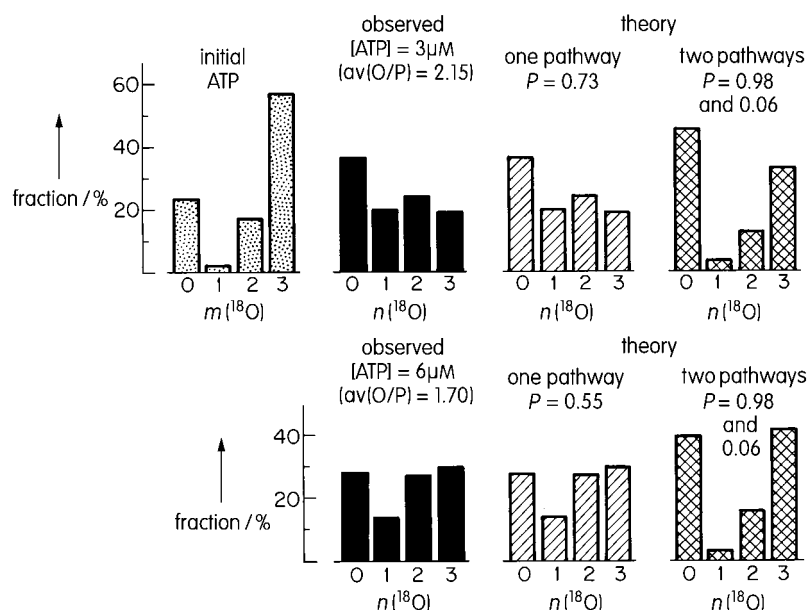


Figure 7. Distribution of ^{18}O isotopomers of P_i formed from $[\gamma\text{-}^{18}\text{O}]\text{ATP}$ by MF_1 -ATPase hydrolysis at two relatively low ATP concentrations (top: $3\ \mu\text{M}$, bottom: $6\ \mu\text{M}$). The observed average number of water oxygen atoms incorporated (O/P ratio) and the distribution of species with 0 to 4 ^{18}O atoms are shown. Also shown is the theoretical distribution for one pathway as expected if the probability P for exchange instead of release of bound P_i was 0.73 (with $3\ \mu\text{M}$ ATP) and 0.55 (with $6\ \mu\text{M}$ ATP). This is compared to the expected distributions if two pathways were operative, one with a high and one with a low probability of exchange, that would give the observed total amount of oxygen exchange. $m(^{18}\text{O})$ = number of ^{18}O atoms per γ -phosphate group on ATP; $n(^{18}\text{O})$ = number of ^{18}O atoms per product P_i . Adapted from ref. [82].

I was again confronted with unexplained results. Although it might be possible to bring a similar residue or residues on minor subunits into contact with each of the three β subunits, the interactions would not be expected to be identical. The situation might be analogous to the family of serine proteases, where markedly different sequences can appropriately position a serine residue. But the resulting proteases do not conduct their catalyses identically. To me, there seemed only one way that all catalytic sites could proceed sequentially and identically, with modulation by one or more single-copy, minor subunits. This was by a rotational catalysis, in which large catalytic subunits moved rotationally around a smaller asymmetric core. Such consideration, together with what was known about the structure of the enzyme, resulted in the postulate of rotational catalysis, presented at Gordon Research Conferences and elsewhere.^[86–88] A sketch of our view as presented at that time is shown in Figure 8.^[88] The internal

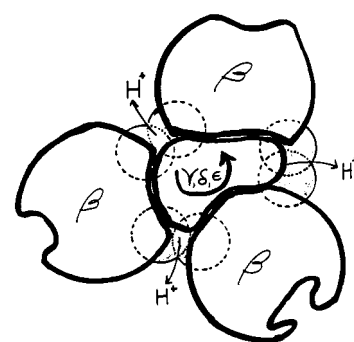


Figure 8. A sketch of possible rotational catalysis as used in 1980 for presentations and discussions.

core was likened to a cam shaft that modulated the conformation of the β subunits. The probability that the core was asymmetric was strengthened when data on the amino acid sequence became available;^[89] this gave no indications of possible tripartite symmetry of the minor subunits.

Later other suggestions were made of possible rotational features in the ATP synthase catalysis. Increased information about the structure of the F_0 portion of the synthase made some type of circular motion in the F_0 attractive. Cox et al. suggested rotational movement of circularly arranged c subunits.^[90, 91] Hoppe and Sebald visualized an oligomeric core of c subunits rotating against subunit a or b ,^[92] a suggestion that still seems pertinent. Mitchell proposed a rotational model that exposed catalytic sites to a proton channel through the γ subunit.^[93]

The homogeneity of catalysis demonstrated by the ^{18}O technique also, to my mind, ruled out postulates, as mentioned earlier, that only two β subunits were involved in catalysis, with the other serving a regulatory function. Considerations of the need for symmetry in subunit

interactions made it unlikely that two sites could alternate in catalysis identically. Their interactions on one side could not be identical with those on another side at the same stages of catalysis.

We attempted some assessments of subunit positional interchange as required by a rotational catalysis. After labeling of one β subunit with radioactive dicyclohexylcarbodiimide (DCCD), the MF_1 -ATPase still retained some activity. A different β subunit reacted with 2-azido-ATP. After catalytic turnover, the reactivity toward DCCD and 2-azido-ATP was randomized, as expected if a change in relative position and conformation had occurred.^[94] In another approach, we observed that a mild cross-linking of subunits stopped catalysis, and that cleavage of the cross-linker restored activity.^[95] There was a report from another laboratory that cross-linking of the β and γ subunits did not stop catalysis,^[96] which I regarded as inconclusive.^[29] None of these experiments were as edifying as those that came later from other laboratories (see below). It seemed apparent that an adequate evaluation of the possibility of rotational catalysis would need to await the knowledge of the three-dimensional structure of the F_1 -ATPase. In a review I prepared in the spring of 1992, I summarized the case for rotational catalysis at that stage.^[29] This included the need for a second attachment between F_0 and F_1 to act as a stator, and the suggestion that present evidence indicated that the δ subunit of the *E. coli* enzyme, or the analogous oligomycin sensitivity conferring protein (OSCP) of mitochondria, could help serve this function, a prediction that has found support in recent experiments.^[97, 98] Attachment of a stator to the exterior of an α subunit might be partly responsible for the asymmetry of the α subunits, an asymmetry that is retained during catalysis.^[99] This may be analogous to the symmetry of the internal rotation of a motor not being disrupted upon bolting of the motor to a bench.

The occurrence of a rotational catalysis was dramatically supported by the X-ray structure for the major portion of MF_1 , attained by Abrahams, Leslie, Lutter, and Walker.^[100] This structure served as the base for innovative demonstrations of rotation in the laboratories of Cross,^[3, 101, 102] Capaldi,^[103–105] and Kagawa.^[97] Sabbert et al. demonstrated rotation by sophisticated fluorescent techniques,^[106, 107] and Noji et al. demonstrated rotation visually.^[108] Such developments allowed me to title a recent review “The ATP Synthase—A Splendid Molecular Machine”.^[78] These more recent aspects of the ATP synthase story are more appropriately the subject of my able corecipient John Walker’s lecture. But before you have the opportunity to hear from him, I want to discuss some additional important and unsettled facets of the ATP synthase catalysis.

Some Additional Aspects

Acceptance of the binding change mechanism over the past two decades has been fostered by clarification of a number of unusual aspects of the synthase action, some of which are mentioned here. The number and properties of nucleotide binding sites needed clarification. With the use of the 2-azido-

ATP, introduced for studies with F_1 -ATPases by Abbot et al.,^[109] we established where catalytic and noncatalytic sites resided with the F_1 -ATPase from different sources.^[59, 110–112] The characteristics of the inhibition of the F_1 -ATPase by Mg^{2+} and tightly bound ADP—which had harassed our, and many other, earlier studies—were established.^[113, 114] A role for the noncatalytic nucleotides in enabling the inhibition to be overcome was uncovered.^[115, 116]

A direct estimation of how many catalytic sites were filled during photophosphorylation was accomplished.^[117] The results gave evidence that near maximal rates of ATP synthesis were attained when a second, and not a second and a third, site were loaded with substrates. The consideration of these results, other earlier data, and recent experiments on site filling in MF_1 have led to refinements in how I consider the binding change mechanism to operate. Salient points from earlier data are that the rate of ATP formation during uni-site catalysis is much slower than the rate of ATP formation when rapid photophosphorylation is occurring, and that during photophosphorylation about one tightly bound ATP per synthase is present. In previous depictions of the mechanism (Figure 9), after a binding change a site is depicted as having a

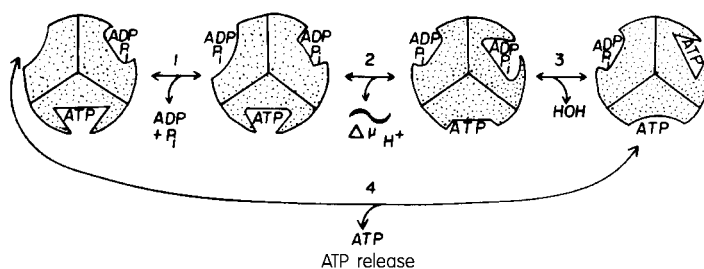


Figure 9. A typical tri-site model for cooperativity including tightly bound ADP and P_i as intermediates.

tightly bound ADP and P_i that is being reversibly converted into tightly bound ATP while waiting for the next binding change. We now propose that during active net ATP synthesis the interconversion of sites is as depicted in Figure 10. As a site to which ADP and P_i have added is converted into a tight site, the capacity for the rapid formation of the terminal covalent bond in ATP is also acquired, such that essentially all the bound ADP and P_i are converted into bound ATP. A site with tightly bound ADP and P_i , as in Figure 9, is not an intermediate. The next rapid binding change brings about the release of the ATP to the medium.

All ATP made by oxidative phosphorylation^[118] or photophosphorylation^[84, 119] contains about 0.4–1.1 water oxygen atoms. This means that some rapid reversal of ATP formation has occurred. Indeed, during net oxidative phosphorylation by mitochondria, rapid reversal of the overall process is demonstrated by ^{32}P measurements.^[9, 118] Thus, it seems likely that the rapid incorporation of some water oxygen atoms results from the reversal of a binding change step of Figure 10. The much slower uni-site catalysis that can occur in the absence of medium nucleotides may occur with the forms indicated in the lower portion of Figure 10. With time, the P_i drops off, and the remaining synthase retains a tightly bound ADP. This is the

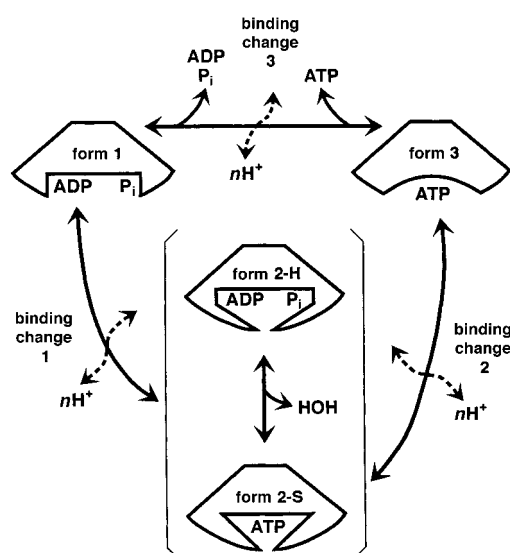


Figure 10. A proposal of how a catalytic site on the ATP synthase is modified by successive binding changes. When ADP + P_i add to create form 1, and adequate proton-motive force is present, both rapid formation and tight binding of ATP arise during binding change 1. Most of the site assumes the conformation of form 2-S, and the ATP becomes loosely bound in binding change 2. When ATP adds to form 3, and no proton-motive force is present, both rapid formation and tight binding of ADP + P_i arise during binding change 2. Most of the site assume the conformation of form 2-H, and the ADP + P_i become loosely bound during binding change 1. Both site occupancy on forms 1 and 3 and proton-motive force modulate the quasiequilibrium of form 2.

ADP that in presence of Mg^{2+} results in a strong inhibition of ATPase activity. However, when proton-motive force is applied, such tightly bound ADP is released to the medium without delay in the first binding change.^[120]

Other recent experiments pertinent to site occupancy during ATP hydrolysis by MF_1 were based on competition between ATP and trinitrophenyl-ATP (TNP-ATP). They revealed that TNP-ATP could bind strongly to a third catalytic site for ATP which had a dissociation constant K_d in the millimolar concentration range. The near maximal ATPase rate was attained at considerably less than 1 mM ATP.^[121] This result, and further characterization of the transition from uni-site to multi-site catalysis and initial velocity measurements, are best explained by the filling of only two catalytic sites being necessary for near maximal rates of ATP hydrolysis.^[40] Interestingly, ADP had a considerably higher affinity than ATP for the third empty site of the MF_1 . Our present hypothesis about catalytic site occupancy during rotational catalysis is depicted in Figure 11. During rapid synthesis one site has a bound ATP, and a site to its left (as viewed from above, the F_1 portion of the synthase) can preferentially bind ADP and P_i . When adequate proton-motive force is present, rapid ATP synthesis ensues. The filling of a third site with ADP and P_i at higher substrate concentrations results in little rate acceleration. During net ATP hydrolysis, when proton-motive force is weak or absent, the preferential binding of ATP to a site to the right of the tight ATP site can result in a near maximal hydrolysis rate. Filling of the third site at millimolar concentrations of ATP gives little rate acceleration. Nature appears to have designed a way

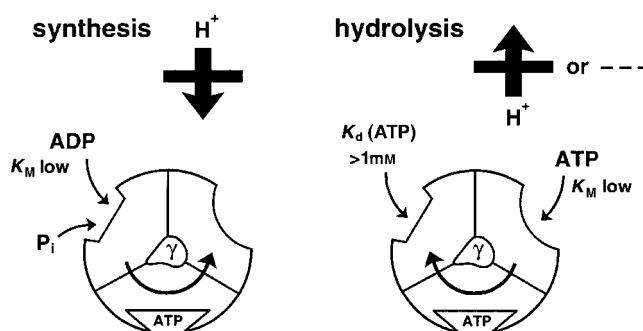


Figure 11. A proposal that near maximum rates of hydrolysis by F_1 -ATPase or synthesis by ATP synthase occurs with the filling of only two sites.

that ATP synthesis occurs with ADP addition to a site that has low affinity for ATP, helping to obviate ATP inhibition of its own synthesis.

The recognition of the principal features of the ATP synthase catalysis creates many opportunities for gaining a better understanding of this remarkable enzyme. I will be an interested spectator in these developments. I believe that societies will, and should continue to, devote some of their resources to basic scientific research, even if the only return is the satisfaction that comes from the knowledge of how living processes occur. An additional justification is that such knowledge underlies past and future gains for attaining a healthy life. As summarized by Ernster,^[122] the oxygen we use to make ATP is also a toxic substance, resulting in production of harmful free radicals. The mitochondrion is particularly susceptible to such damage, and knowledge of the enzymes involved in energy capture and use may give insight into, and help find how to prevent, unwanted damage.

A final acknowledgment: I am exceptionally fortunate to have been a biochemist over the past decades when so much has been accomplished in my field. Participation in a series of researches that has revealed an unusual rotational catalysis by a vital enzyme has been warmly gratifying. I am indebted to the society that has made this possible, to my wife, Lyda, for her devotion and guidance given freely to help me and our children find our way, and to the universities and government agencies that provided the environment and the financial support for my researches.

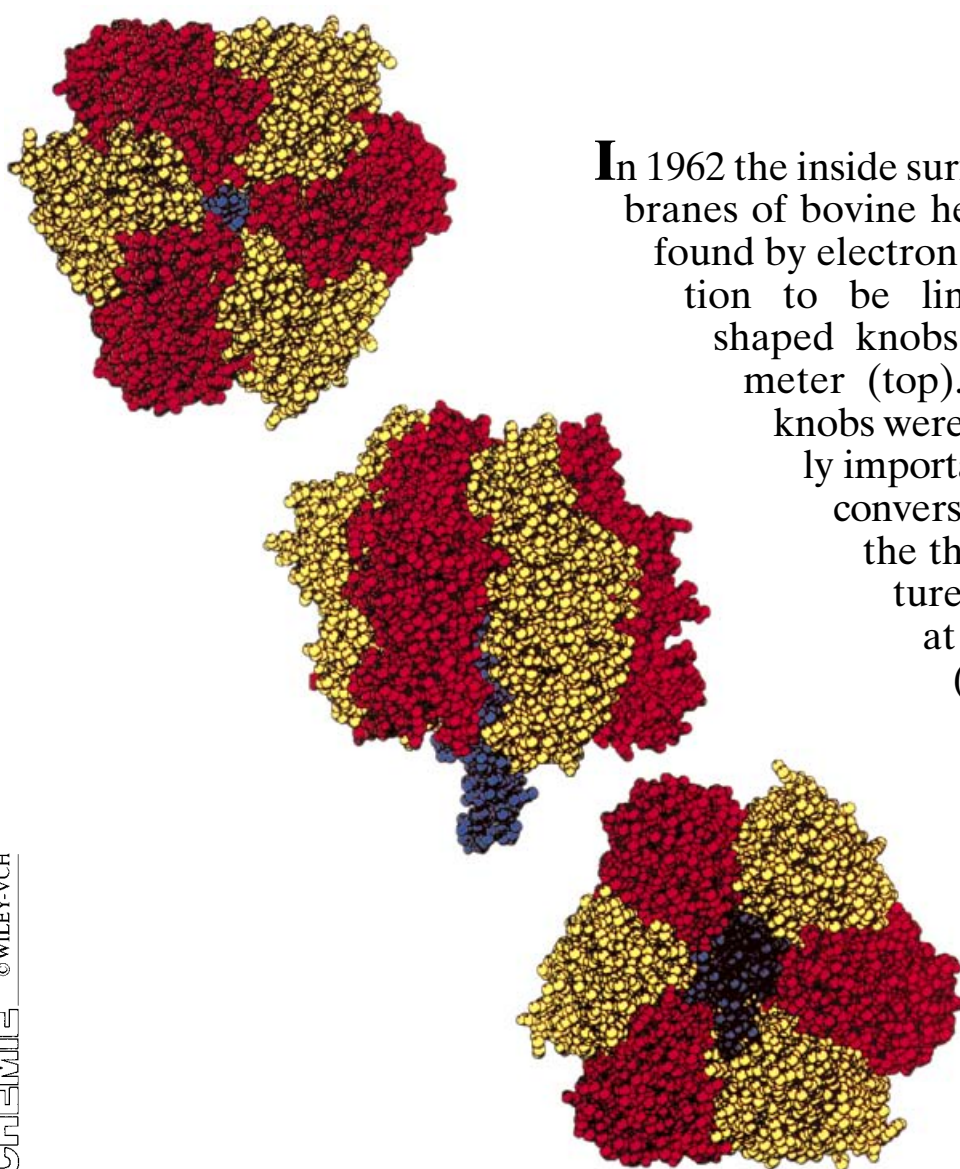
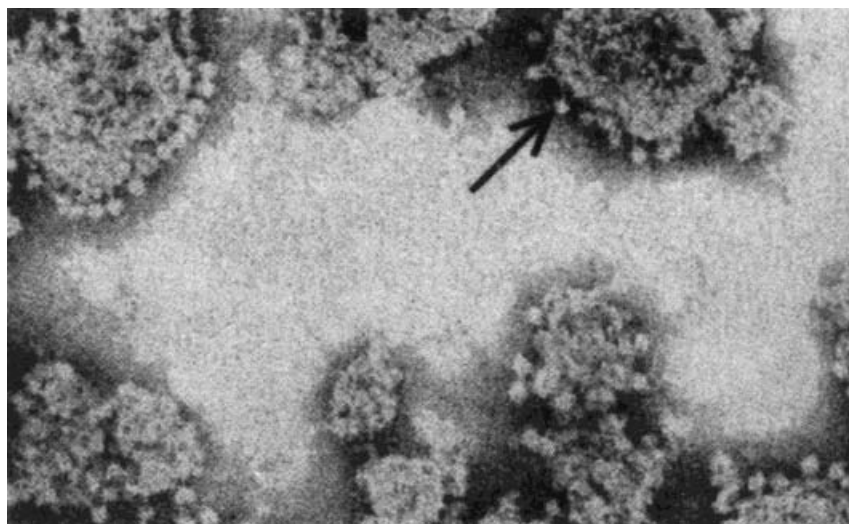
Received: April 17, 1998 [A277IE]
German version: *Angew. Chem.* **1998**, *110*, 2424–2436

Keywords: ATP • bioenergetics • enzyme catalysis • Nobel lecture • phosphorylations

- [1] F. Lipmann, *Adv. Enzymol.* **1941**, *1*, 99–152.
- [2] P. Mitchell, *Science* **1979**, *206*, 1148–1159.
- [3] T. M. Duncan, V. V. Bulygin, Y. Zhou, M. L. Hutcheon, R. L. Cross, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 10964–10968.
- [4] H. S. Penefsky, M. E. Pullman, A. Datta, E. Racker, *J. Biol. Chem.* **1960**, *235*, 3330–3336.
- [5] H. L. Segal, P. D. Boyer, *J. Biol. Chem.* **1953**, *204*, 265–280.
- [6] I. Krinsky, E. Racker, *J. Biol. Chem.* **1952**, *198*, 721–730.

- [7] M. Cohn, *J. Biol. Chem.* **1953**, 201, 739–744.
- [8] P. D. Boyer, A. S. Falcone, W. H. Harrison, *Nature* **1954**, 174, 401–404.
- [9] C. C. O'Neal, P. D. Boyer, *J. Biol. Chem.* **1984**, 259, 5761–5767.
- [10] W. L. Klein, P. D. Boyer, *J. Biol. Chem.* **1972**, 247, 7257–7265.
- [11] P. D. Boyer, R. L. Cross, W. Momsen, *Proc. Natl. Acad. Sci. USA* **1973**, 70, 2837–2839.
- [12] D. A. Harris, J. Rosing, R. J. van de Stadt, E. C. Slater, *Biochim. Biophys. Acta* **1973**, 314, 149–153.
- [13] M. E. Dempsey, P. D. Boyer, E. S. Benson, *J. Biol. Chem.* **1963**, 238, 2708–2715.
- [14] H. M. Levy, N. Sharon, E. Lindemann, D. E. Koshland, *J. Biol. Chem.* **1960**, 235, 2628–2633.
- [15] R. G. Wolcott, P. D. Boyer, *J. Supramol. Struct.* **1975**, 3, 154–161.
- [16] C. R. Bagshaw, J. F. Eccleston, F. Eckstein, R. S. Goody, H. Gutfreund, D. R. Trentham, *Biochem. J.* **1974**, 141, 351–364.
- [17] C. R. Bagshaw, D. R. Trentham, R. G. Wolcott, P. D. Boyer, *Proc. Natl. Acad. Sci. USA* **1975**, 72, 2592–2596.
- [18] P. D. Boyer, *FEBS Lett.* **1975**, 50, 91–94.
- [19] P. Mitchell, *FEBS Lett.* **1975**, 50, 95–97.
- [20] P. D. Boyer, *FEBS Lett.* **1975**, 58, 1–6.
- [21] J. Rosing, C. Kayalar, P. D. Boyer, *J. Biol. Chem.* **1977**, 252, 2478–2485.
- [22] C. Kayalar, J. Rosing, P. D. Boyer, *J. Biol. Chem.* **1977**, 252, 2486–2491.
- [23] R. Adolfsen, E. N. Moudrianakis, *Arch. Biochem. Biophys.* **1976**, 172, 425–433.
- [24] H. S. Penefsky, *Adv. Enzymol. Relat. Areas Mol. Biol.* **1979**, 49, 223–280.
- [25] P. D. Boyer, *Annu. Rev. Biochem.* **1977**, 46, 955–966.
- [26] C. Kayalar, Dissertation, University of California, Los Angeles, **1977**.
- [27] M. Gresser, J. Cardon, G. Rosen, P. D. Boyer, *J. Biol. Chem.* **1979**, 254, 10649–10653.
- [28] G. Rosen, M. Gresser, C. Vinkler, P. D. Boyer, *J. Biol. Chem.* **1979**, 254, 10654–10661.
- [29] P. D. Boyer, *Biochim. Biophys. Acta* **1993**, 1140, 215–250.
- [30] R. I. Feldman, D. S. Sigman, *J. Biol. Chem.* **1982**, 257, 1676–1683.
- [31] R. Feldman, D. S. Sigman, *J. Biol. Chem.* **1983**, 258, 12178–12183.
- [32] L. de Meis, *Biochim. Biophys. Acta* **1989**, 973, 333–349.
- [33] C. Grubmeyer, R. Cross, H. S. Penefsky, *J. Biol. Chem.* **1982**, 257, 12092–12100.
- [34] R. L. Cross, C. Grubmeyer, H. S. Penefsky, *J. Biol. Chem.* **1982**, 257, 12101–12105.
- [35] T. Hisabori, E. Muneyuki, M. Odaka, K. Yokoyama, K. Mochizuki, M. Yoshida, *J. Biol. Chem.* **1992**, 267, 4551–4556.
- [36] M. K. Yohda, M. Yoshida, *J. Biochem.* **1987**, 102, 875–883.
- [37] V. N. Kasho, M. Yoshida, P. D. Boyer, *Biochemistry* **1989**, 28, 6949–6954.
- [38] D. B. Reynafarje, P. L. Pedersen, *J. Biol. Chem.* **1996**, 271, 32546–32550.
- [39] Y. Milgrom, R. L. Cross, *J. Biol. Chem.* **1997**, 272, 32211–32214.
- [40] Y. Milgrom, M. B. Murataliev, P. D. Boyer, *Biochem. J.* **1998**, 330, 1037–1043.
- [41] C. Degani, P. D. Boyer, *J. Biol. Chem.* **1973**, 248, 8222–8226.
- [42] C. Degani, A. S. Dahms, P. D. Boyer, *Ann. N. Y. Acad. Sci.* **1974**, 242, 77–79.
- [43] P. D. Boyer, L. de Meis, M. G. C. Carvalho, D. D. Hackney, *Biochemistry* **1977**, 16, 136–140.
- [44] V. N. Kasho, M. Stengelin, I. N. Smirnova, L. D. Faller, *Biochemistry* **1997**, 36, 8045–8052.
- [45] T. Kanazawa, P. D. Boyer, *J. Biol. Chem.* **1973**, 248, 3163–3172.
- [46] M. Cohn, *J. Biol. Chem.* **1958**, 230, 369–379.
- [47] C. A. Janson, C. Degani, P. D. Boyer, *J. Biol. Chem.* **1979**, 254, 3743–3749.
- [48] D. D. Hackney, P. D. Boyer, *Proc. Natl. Acad. Sci. USA* **1978**, 75, 3133–3137.
- [49] D. D. Hackney, *J. Biol. Chem.* **1980**, 255, 5320–5328.
- [50] P. D. Boyer, L. de Meis, M. G. C. Carvalho, D. D. Hackney, *Biochemistry* **1977**, 16, 136–140.
- [51] M. J. Wimmer, I. A. Rose, *J. Biol. Chem.* **1977**, 252, 6769–6775.
- [52] P. D. Bragg, C. Hou, *Arch. Biochem. Biophys.* **1975**, 167, 311–321.
- [53] Y. Kagawa, N. Sone, M. Yoshida, H. Hirata, H. Okamoto, *J. Biochem.* **1976**, 80, 141–151.
- [54] S. Merchant, S. L. Shaner, B. R. Selman, *J. Biol. Chem.* **1983**, 258, 1026–1031.
- [55] R. L. Cross, C. M. Nalin, *J. Biol. Chem.* **1982**, 257, 2874–2881.
- [56] J. G. Wise, T. M. Duncan, L. R. Latchney, D. N. Cox, A. E. Senior, *Biochem. J.* **1983**, 215, 343–350.
- [57] R. E. McCarty, G. G. Hammes, *Trends Biochem. Sci.* **1987**, 12, 234–237.
- [58] N. Williams, J. Hüllihen, P. L. Pedersen, *Biochemistry* **1987**, 26, 162–169.
- [59] Z. Xue, J. M. Zhou, T. Melese, R. L. Cross, P. D. Boyer, *Biochemistry* **1987**, 26, 3749–3753.
- [60] G. Girault, G. Berger, J. M. Galmiche, F. Andre, *J. Biol. Chem.* **1988**, 263, 14690–14695.
- [61] K. J. Guerrero, P. D. Boyer, *Biochem. Biophys. Res. Commun.* **1988**, 154, 854–860.
- [62] P. D. Bragg, C. Hou, *Biochim. Biophys. Acta* **1990**, 1015, 216–222.
- [63] P. V. Vignais, J. Lunardi, *Annu. Rev. Biochem.* **1985**, 54, 977–1014.
- [64] T. Noumi, M. Taniai, H. Kanazawa, M. Futai, *J. Biol. Chem.* **1986**, 261, 9196–9201.
- [65] R. Rao, A. E. Senior, *J. Biol. Chem.* **1987**, 262, 17450–17454.
- [66] J. H. Wang, V. Joshi, J. C. Wu, *Biochemistry* **1986**, 25, 7996–8001.
- [67] J. H. Wang, J. Cesana, J. C. Wu, *Biochemistry* **1987**, 26, 5527–5533.
- [68] A. Di Pietro, F. Penin, C. Godinot, D. C. Gautheron, *Biochemistry* **1980**, 19, 5671–5678.
- [69] D. A. Bullough, J. G. Verburg, A. Yoshida, W. A. Allison, *J. Biol. Chem.* **1987**, 262, 11675–11683.
- [70] D. Leckband, G. G. Hammes, *Biochemistry* **1987**, 26, 2306–2311.
- [71] J. P. Issartel, A. Dupuis, J. Junardi, P. V. Vignais, *Biochemistry* **1991**, 30, 4726–4730.
- [72] X. Ysern, L. M. Amzel, P. L. Pedersen, *J. Bioenerg. Biomemb.* **1988**, 29, 423–450.
- [73] P. Fromme, P. Gräber, *FEBS Lett.* **1989**, 259, 33–36.
- [74] A. B. Shapiro, R. E. McCarty, *J. Biol. Chem.* **1991**, 266, 4194–4200.
- [75] A. B. Shapiro, K. D. Gibson, H. A. Scheraga, R. E. McCarty, *J. Biol. Chem.* **1991**, 266, 17277–17285.
- [76] H. Tiedge, G. Schafer, *Biochim. Biophys. Acta* **1989**, 977, 1–9.
- [77] J. A. Berden, A. F. Hartog, C. M. Edel, *Biochim. Biophys. Acta* **1991**, 1057, 151–156.
- [78] P. D. Boyer, *Annu. Rev. Biochem.* **1997**, 66, 717–749.
- [79] R. E. McCarty, J. Fagan, *Biochemistry* **1973**, 12, 1503–1507.
- [80] J. V. Moroney, R. E. McCarty, *J. Biol. Chem.* **1979**, 254, 8951–8955.
- [81] M. Cohn, A. Hu, *Proc. Natl. Acad. Sci. USA* **1978**, 75, 200–205.
- [82] R. L. Hutton, P. D. Boyer, *J. Biol. Chem.* **1979**, 254, 9990–9993.
- [83] D. D. Hackney, P. D. Boyer, *J. Biol. Chem.* **1978**, 253, 3164–3170.
- [84] D. D. Hackney, G. Rosen, P. D. Boyer, *Proc. Natl. Acad. Sci. USA* **1979**, 76, 3646–3650.
- [85] W. E. Kohlbrener, P. D. Boyer, *J. Biol. Chem.* **1983**, 258, 10881–10886.
- [86] P. D. Boyer, W. E. Kohlbrener, in *Energy Coupling in Photosynthesis* (Eds.: B. Selman, S. Selman-Reiner), Elsevier/North Holland, New York, **1981**, pp. 231–240.
- [87] M. J. Gresser, J. A. Myers, P. D. Boyer, *J. Biol. Chem.* **1982**, 257, 12030–12038.
- [88] P. D. Boyer, in *Biochemistry of Metabolic Processes* (Eds.: D. L. F. Lennon, F. W. Stratman, R. N. Zahlten), Elsevier, New York, **1983**, pp. 465–477.
- [89] H. Kanazawa, T. Kayano, K. Mabuchi, M. Futai, *Biochem. Biophys. Res. Commun.* **1981**, 103, 604–612.
- [90] G. B. Cox, D. A. Jans, A. L. A. Fimmel, F. Gibson, L. Hatch, *Biochim. Biophys. Acta* **1984**, 768, 201–208.
- [91] G. B. Cox, A. L. Fimmel, F. Gibson, L. Hatch, *Biochim. Biophys. Acta* **1986**, 849, 62–69.
- [92] J. Hoppe, W. Sebald, *Biochim. Biophys. Acta* **1984**, 768, 1–27.
- [93] P. Mitchell, *FEBS Lett.* **1985**, 181, 1–7.
- [94] T. Melese, P. D. Boyer, *J. Biol. Chem.* **1985**, 260, 15398–15401.
- [95] R. P. Kandpal, P. D. Boyer, *Biochim. Biophys. Acta* **1987**, 890, 97–105.
- [96] K. M. Musier, G. G. Hammes, *Biochemistry* **1987**, 26, 5982–5988.
- [97] W. Kagawa, T. Hamamoto, *J. Bioenerg. Biomembr.* **1996**, 28, 421–431.
- [98] I. Ogilvie, R. Aggeler, R. A. Capaldi, *J. Biol. Chem.* **1997**, 272, 19621–19624.

- [99] F. A. S. Kironde, R. L. Cross, *J. Biol. Chem.* **1987**, 262, 3488–3495.
- [100] J. P. Abrahams, A. G. W. Leslie, R. Lutter, J. E. Walker, *Nature* **1994**, 370, 621–628.
- [101] Y. Zhou, T. M. Duncan, V. V. Bulgin, M. L. Hutcheon, R. L. Cross, *Biochim. Biophys. Acta* **1996**, 1275, 96–100.
- [102] R. L. Cross, T. M. Duncan, *J. Bioenerg. Biomembr.* **1996**, 28, 403–408.
- [103] R. Aggeler, R. A. Capaldi, *J. Biol. Chem.* **1996**, 271, 13888–13891.
- [104] C. Tang, R. A. Capaldi, *J. Biol. Chem.* **1996**, 271, 3018–3024.
- [105] Z. Feng, R. Aggeler, M. Haughton, R. A. Capaldi, *J. Biol. Chem.* **1996**, 271, 17986–17989.
- [106] D. Sabbert, S. Engelbrecht, W. Junge, *Nature* **1996**, 381, 623–625.
- [107] D. Sabbert, S. Engelbrecht, W. Junge, *Proc. Natl. Acad. Sci. USA* **1997**, 94, 2312–2317.
- [108] H. Noji, R. Yasuda, M. Yoshida, K. Kinoshita, Jr., *Nature* **1997**, 386, 299–302.
- [109] M. S. Abbott, J. J. Czarnecki, B. R. Selman, *J. Biol. Chem.* **1984**, 259, 12271–12278.
- [110] R. L. Cross, D. Cunningham, C. G. Miller, Z. Xue, J. M. Zhou, P. D. Boyer, *Proc. Natl. Acad. Sci. USA* **1987**, 84, 5715–5719.
- [111] Z. Xue, C. G. Miller, J. M. Zhou, P. D. Boyer, *FEBS Lett.* **1987**, 223, 391–394.
- [112] J. G. Wise, B. J. Hicke, P. D. Boyer, *FEBS Lett.* **1987**, 223, 395–401.
- [113] K. J. Guerrero, Z. Xue, P. D. Boyer, *J. Biol. Chem.* **1990**, 265, 16280–16287.
- [114] M. B. Murataliev, Y. M. Milgrom, P. D. Boyer, *Biochemistry* **1991**, 30, 8305–8310.
- [115] Y. M. Milgrom, L. L. Ehler, P. D. Boyer, *J. Biol. Chem.* **1991**, 266, 11551–11558.
- [116] M. B. Murataliev, P. D. Boyer, *Eur. J. Biochem.* **1992**, 209, 681–687.
- [117] J. M. Zhou, P. D. Boyer, *J. Biol. Chem.* **1993**, 268, 1531–1538.
- [118] D. A. Berkich, G. D. Williams, P. T. Masiakos, M. B. Smith, P. D. Boyer, K. F. LaNoue, *J. Biol. Chem.* **1991**, 266, 123–129.
- [119] M. Avron, N. Sharon, *Biochem. Biophys. Res. Commun.* **1960**, 2, 336–339.
- [120] J. Rosing, D. J. Smith, C. Kayalar, P. D. Boyer, *Biochem. Biophys. Res. Commun.* **1976**, 72, 1–8.
- [121] M. B. Murataliev, P. D. Boyer, *J. Biol. Chem.* **1994**, 269, 15431–15439.
- [122] L. Ernster, *Chem. Scr.* **1986**, 26, 525–534.
- [123] J. E. Walker, *Angew. Chem.* **1998**, 110, 2438–2450; *Angew. Chem. Int. Ed.* **1998**, 37, 2308–2319.
- [124] Internet address: <http://www.nobel.se>
- [125] J. C. Skou, *Angew. Chem.* **1998**, 110, 2452–2461; *Angew. Chem. Int. Ed.* **1998**, 37, 2320–2328.



In 1962 the inside surface of the inner membranes of bovine heart mitochondria was found by electron microscopic examination to be lined with mushroom-shaped knobs about 100 Å in diameter (top). At that time, these knobs were thought to be probably important in biological energy conversion. On the basis of the three-dimensional structure of bovine F₁-ATPase at atomic resolution (below), the mechanism of ATP synthase is well understood today.

ATP Synthesis by Rotary Catalysis (Nobel lecture)**

John E. Walker*

Biological energy comes from the sun. Light energy harvested by photosynthesis in chloroplasts and phototropic bacteria is stored in carbohydrates and fats. This stored energy can be released by oxidative metabolism in the form of adenosine triphosphate (ATP), and used as fuel for other biological processes. ATP is a high-energy product of both photosynthesis and oxidative metabolism, and in textbooks it is often referred to as the chemical currency of biological energy.

In the 1960s and early 1970s the field of oxidative metabolism was dominated by a debate about the nature of the intermediate between nicotinamide adenine dinucleotide (NADH (reduced form), a key product from carbohydrate and fat metabolism) and ATP itself. Many bioenergeticists believed in and sought evidence for a high-energy covalent chemical intermediate. The issue was resolved by Peter Mitchell, the Nobel Laureate in Chemistry in 1978. He established that in mitochondria, energy is released from NADH by the electron transport chain and used to generate a chemical potential gradient for protons across the inner membrane of the organelle. He referred to this gradient as the proton-motive force (pmf, also designated as $\Delta\mu_{H^+}$). It was demonstrated that the pmf is harnessed by the ATP-synthesizing enzyme (ATP synthase) to drive the synthesis of ATP from ADP and inorganic phosphate, not only in mitochondria, but also in eubacteria and chloroplasts.^[1]

Because of Peter Mitchell's efforts, the pmf became established as a key intermediate in biological energy conversion. In addition to being employed in ATP synthesis, it is also used by various membrane-bound proteins to drive the transport of sugars, amino acids, and other substrates and metabolites across biological membranes. The pmf powers the rotation of flagellae in motile bacteria. In newly born children and in hibernating animals, it is converted directly into heat by uncoupling the mitochondria in brown adipose tissue. Some bacteria that live in saline conditions generate a sodium-motive force to act as an equivalent intermediate in their

energy conversion processes.^[2] The general notion of creating a proton- (or sodium-) motive force and then using it as a source of energy for other biochemical functions is known as chemiosmosis.

Today, the general outlines of chemiosmosis are well established. It is accepted that during electron transport in mitochondria, redox energy derived from NADH is used by three proton-pumping enzymes called complex I (NADH: ubiquinone oxidoreductase), complex III (ubiquinone:cytochrome c oxidoreductase), and complex IV (cytochrome c oxidase). They act consecutively and produce the pmf by ejecting protons from the matrix (the inside) of the organelle (Figure 1). Until recently, the workings of these chemiosmotic proton pumps were obscure, but currently our understanding is being transformed by the application of modern methods of molecular biology for the analysis of their structures and functions. For example, two independent atomic-resolution

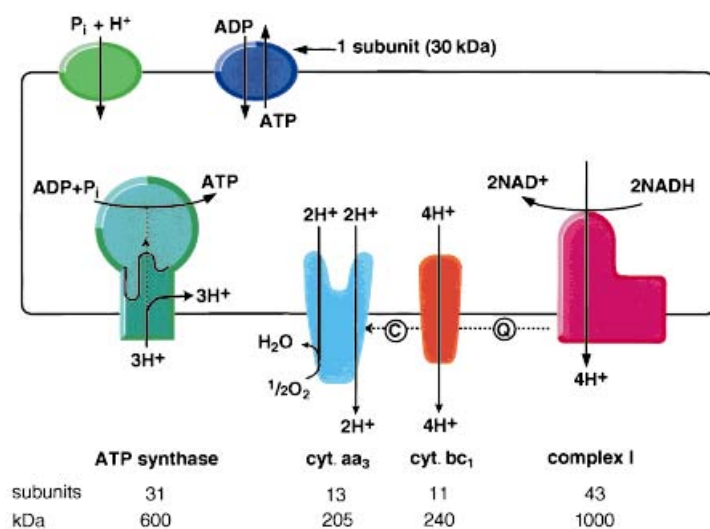


Figure 1. The enzyme complexes involved in oxidative phosphorylation in the inner membranes of mammalian mitochondria. Three proton pumps—complex I, complex III (cytochrome bc₁), and complex IV (cytochrome aa₃)—convert redox energy in NADH into the proton-motive force (pmf) by ejecting protons from the matrix of the mitochondrion. The ATP synthase uses the energy of the pmf to produce ATP from ADP and phosphate. ADP and phosphate are brought into the mitochondrion by related protein carriers. External ADP is exchanged for internal ATP, making the newly synthesized ATP available for many biological functions. The dotted lines between complexes I, III, and IV indicate electron pathways; Q and C are the mobile electron carriers ubiquinone and cytochrome c, respectively.

[*] Prof. Dr. J. E. Walker
The Medical Research Council
Laboratory of Molecular Biology
Hills Road, Cambridge CB2 2QH (UK)
Fax: (+44) 1-223-213-556
E-mail: walker@mrc-lmb.cam.ac.uk

[**] Copyright© The Nobel Foundation 1998. We thank the Nobel Foundation, Stockholm, for permission to print this lecture.

structures of cytochrome c oxidase isolated from bovine mitochondria^[3, 4] and from the bacterium *Paracoccus denitrificans*^[5, 6] are guiding mutational and spectroscopic experiments that are providing new insights into its mechanism. Partial structures of mitochondrial complex III from two different species^[7] will have a similar impact soon on our understanding of that enzyme. Complex I, the third proton pump in mitochondria, is an assembly of at least 43 different polypeptides in mammals, with a combined molecular mass in excess of 900 000.^[8] In addition, it has a noncovalently bound flavin mononucleotide, and at least five iron–sulfur clusters that act as redox centers. A consequence of this extreme complexity is that the structural analysis of complex I is less advanced than those of complexes III and IV, although the general outline of the complex has been established by electron microscopy.^[9, 10]

The ATP Synthase

Since 1978 my colleagues and I have concentrated on analyzing the structure of the ATP synthase, another multi-subunit complex from mitochondria, which is found in the inner membrane alongside the three proton-pumping enzymes (Figure 1). Similar complexes are found in chloroplast and eubacterial membranes. Throughout our endeavours, we have been motivated by the expectation that detailed knowledge of its structure would lead to a deeper understanding of how ATP is made. A substantial part of our efforts has been directed at establishing the subunit compositions of the ATP-synthesizing enzymes from various sources, and with determining the primary sequences of the subunits.^[11–31] These rather extensive analyses helped to show that the overall structure of the ATP synthase, and hence the general principles governing its operation, is very similar in mitochondria, chloroplasts, and eubacteria, although the enzymes from the various sources differ in the details of both their sequences and subunit compositions (Table 1). It is also known that the ATPases from various sources differ in the mechanisms that regulate their catalytic activities.^[32]

In 1962 the inside surface of the inner membranes of bovine heart mitochondria was found by electron microscopic examination to be lined with mushroom-shaped knobs about 100 Å in diameter (Figure 2A).^[33] Later on, similar structures

Table 1. Equivalent subunits in ATP synthases in bacteria, chloroplasts, and bovine mitochondria.

Type	Bacteria	Chloroplasts	Mitochondria ^[a]
F ₁	<i>α</i>	<i>α</i>	<i>α</i>
	<i>β</i>	<i>β</i>	<i>β</i>
	<i>γ</i>	<i>γ</i>	<i>γ</i>
	<i>δ</i>	<i>δ</i>	OSCP
	<i>ε</i>	<i>ε</i>	<i>δ</i>
F _o	—	—	<i>ε</i>
	<i>a</i>	<i>a</i> (or <i>x</i>)	<i>a</i> (or ATPase 6)
	<i>b</i> ^[b]	<i>b</i> and <i>b'</i> (or I and II)	<i>b</i>
	<i>c</i>	<i>c</i> (or III)	<i>c</i>

[a] The ATP synthase in mitochondria also contains the F₆, inhibitor, A6L, *d*, *e*, *f*, and *g* subunits, which have no equivalents in the enzymes in bacteria or chloroplasts. [b] ATP synthases in *E. coli* and bacterium PS 3 (both eight-subunit enzymes) have two identical copies of subunit *b* per complex. Purple non-sulfur bacteria and cyanobacteria appear to have nine different subunits, the extra subunits (known as *b'*) being a homologue of *b*. Similarly, chloroplast enzymes are made of nine nonidentical subunits, and the chloroplast subunits known as I and II are the homologues of *b* and *b'*.

were found to be associated with the thylakoid membranes of chloroplasts (Figure 2B),^[34] and with the inner membranes of eubacteria (Figure 2C). At the time of their discovery, the function of these membrane-bound knobs was not known, but they were thought to be probably important in biological energy conversion, and hence they were named „the fundamental particles of biology“.^[35] In a brilliant series of biochemical reconstitution experiments conducted in the 1960s. Efraim Racker established that they were the ATP-synthesizing enzyme complex (for example see references [36–38]) and hence that these early micrographs were the first glimpses of its structure.

We now know that the head of the mushroom is a globular protein complex (known as the F₁ domain), where the catalytic sites of the ATP synthase lie. The F₁ part is attached to the membrane sector by a slender stalk about 45 Å long. The hydrophobic membrane domain (known as F_o) transports protons back through the energized membrane into the matrix, somehow releasing energy in this process and making it available to drive ATP synthesis in the catalytic F₁ domain. For some years, it has been accepted that three protons are transported back through the F_o membrane sector for each ATP molecule that is formed in F₁.^[1] However, recent experiments suggest that the chloroplast enzyme transports



John E. Walker was born in 1941 in Halifax, UK. He obtained his M. A. degree at Oxford University, where he also finished his D. Phil. degree. Since 1982 he has been working as a Senior Scientist in the Laboratory of Molecular Biology at The Medical Research Council in Cambridge. He was named a Fellow of the Royal Society in 1995, and received the Nobel Prize in Chemistry in 1997.

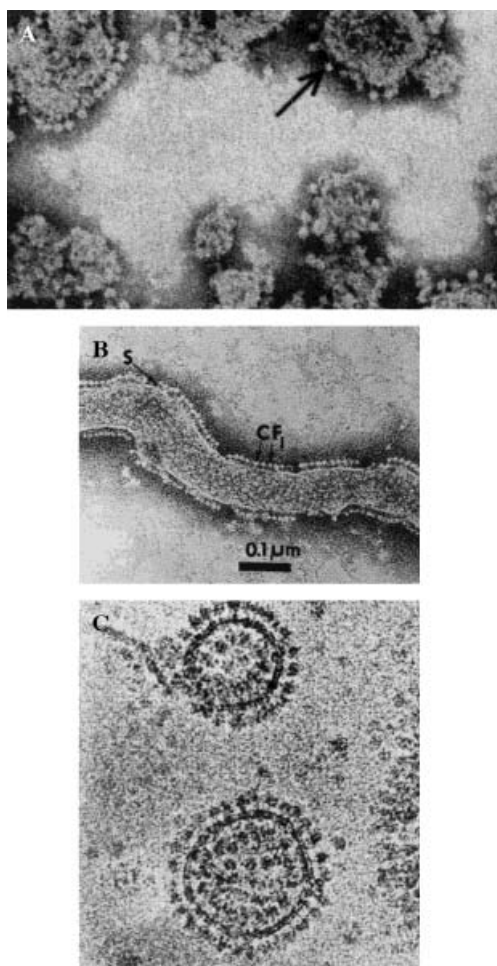


Figure 2. Knobs associated with biological membranes as detected by electron microscopy in negative stain. A) Inside-out vesicles from bovine heart mitochondria; B) thylakoid membranes from pea chloroplasts; C) inside-out vesicles from *E. coli*. Different magnifications have been used for the three images, and the knobs are all about 100 Å in diameter. Reproduced with permission from references [88, 89].

four protons through the membrane for each ATP that is made.^[39] Therefore, it appears that either one or, less likely, both of these values of the H^+ :ATP ratio are incorrect, or that the mechanisms and structures of the mitochondrial and chloroplast enzymes differ significantly in their F_o domains. This point will be elaborated later in a consideration of the possible structure and mechanism of F_o .

The general model of the mechanism of the ATP synthase that will be developed below is that the F_o membrane domain

contains a rotating molecular motor fuelled by the proton-motive force. It is proposed that this motor is mechanically coupled to the stalk region of the enzyme, and that the rotation of the stalk affects the catalytic domain and makes the three catalytic sites pass through a cycle of conformational states in which first substrates are bound and sequestered, then second ATP is formed from the sequestered substrates, and finally the newly synthesized ATP is released from the enzyme. This cycle of interconversion of the three catalytic sites is part of a binding change mechanism of ATP synthesis developed by Paul Boyer (Figure 3).^[40, 90] One of its basic tenets is that the energy-requiring steps in this cycle of ATP synthesis are in the binding of substrates and in the release of products. This mechanism also implies that the ATP synthase must have an asymmetrical structure, and structural asymmetry is also implicit in the molar ratios of the subunits of F_1 -ATPase. Indeed, it is now clear from the asymmetrical features that are inherent in the enzyme's structure that there can be no structurally symmetrical states in the catalytic cycle.

The Structure of F_1 -ATPase

An important practical point about the ATP synthase complex that has influenced the strategy for analyzing its structure is that, as Racker had shown in the 1960s, the globular catalytic domain F_1 -ATPase can be detached from the membrane domain and studied separately in aqueous solution. Subsequently, Alan Senior and Harvey Penefsky purified the bovine F_1 complex^[41, 42] and Penefsky demonstrated that it is an assembly of five different kinds of polypeptides, which he called α , β , γ , δ , and ϵ .^[42] Eventually, it was accepted that they were assembled in the complex in the molar ratios $3\alpha:3\beta:1\gamma:1\delta:1\epsilon$. Hence, each F_1 particle is an assembly of nine polypeptides, and in the bovine heart enzyme their combined molecular mass is about 371 000 (Table 2).

Table 2. The subunits of bovine F_1 -ATPase.

Subunit	M_r [a]	Function
α	55 247	nucleotide binding
β	51 705	nucleotides, catalysis
γ	30 141	link to F_o
δ	15 065	stalk
ϵ	5 632	stalk

[a] The relative molecular mass of the total complex $\alpha_3\beta_3\gamma\delta\epsilon$ is 371 694.

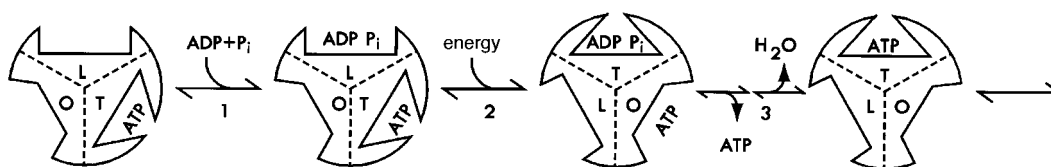


Figure 3. An energy-dependent binding change mechanism of ATP synthesis. The catalytic sites in the β subunits interact and interconvert between three forms: O = open, site with very low affinity for substrates and catalytically inactive; L = loose site, loosely binding substrates and catalytically inactive; T = tight site, tightly binding substrates and catalytically active. The proton-induced conformational changes convert a T-site with bound ATP into an O-site, releasing the bound nucleotide. Concomitantly, an L-site with loosely bound ADP and phosphate is converted into a T-site in which substrates are bound and ATP forms. Fresh substrates bind to an O-site, converting it into an L-site, and so on. One-third of the catalytic cycle is illustrated. Reproduced with permission from reference [40].

Both the α and β subunits bind nucleotides, and we now know that the catalytic nucleotide binding sites lie almost entirely within the β subunits (Figure 4). The nucleotides bound to α subunits remain associated during the catalytic cycle and do not participate directly in ATP synthesis. What they are doing remains mysterious, although both structural and regulatory functions have been suggested.

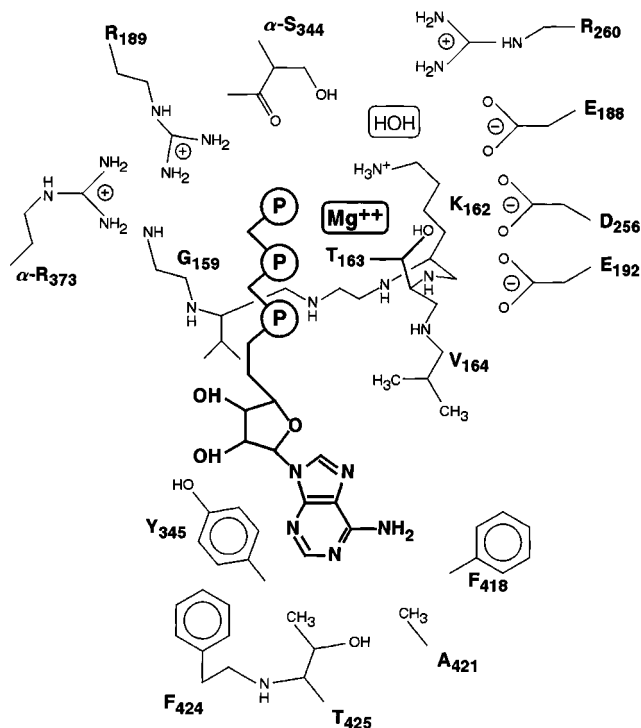


Figure 4. The nucleotide binding site in the β_{TP} subunit of bovine F_1 -ATPase. Except for Arg373 of the α_{TP} subunit and the main-chain carbonyl groups and the side chain of Ser344 of the α_{TP} subunit, all of the amino acids are in β_{TP} . Residues 159–164 are part of the P-loop sequence. The ordered water molecule is poised for nucleophilic attack on the terminal phosphate group and is activated by Glu188. As an incipient negative charge develops on the terminal phosphate group in a pentacoordinated transition state of ATP hydrolysis, it will be stabilized by the guanidinium group of Arg373 of the α subunit. Reproduced with permission from reference [50].

In 1981 we found that the sequences of the α and β subunits were related weakly through most of their length,^[12, 13] and Matti Saraste and I wondered which regions of the sequences were contributing to the nucleotide binding sites. By examination of the known primary and atomic structures of adenylate kinase,^[43] and of the sequence of myosin from *Caenorhabditis elegans* (at the time unpublished information, made available to me by Jonathan Karn), we were able to propose that two short degenerate sequence motifs common to adenylate kinase, myosin and the α and β subunits, of F_1 -ATPase were involved in helping to form their nucleotide binding pockets.^[44]

This proposal has had far greater consequences than we ever imagined at the time of its publication in 1982. Over the years, one of the two motifs has become established as a reliable indicator of the presence of purine nucleotide binding sites in proteins of known sequence, but of unknown biochemical function. One spectacular demonstration of its

predictive value has been in the identification of members of the widely dispersed family of ABC (adenosine binding cassette) transport proteins,^[45] which includes the cystic fibrosis protein and multidrug resistance proteins. Another early success was its help in the identification of the oncogene protein p21 as a GTPase.^[46] The atomic structure of F_1 -ATPase described below has shown that, as in other proteins, the two sequence motifs describe amino acids that are involved in forming the phosphate binding region of its nucleotide binding sites. For this reason, one of the sequences is often referred to as the P-loop (phosphate binding loop) sequence (Figure 5).^[47]

consensus		G	X	X	X	X	G	K	T
α 169–176		G	D	R	Q	T	G	K	T
β 159–163		G	G	A	G	V	G	K	T

Figure 5. The sequence motif of the phosphate binding loop in the α and β subunits of bovine F_1 -ATPase. In some purine binding sites, the final threonine is replaced by a serine residue.

In the determination of the atomic structure of F_1 -ATPase from bovine heart mitochondria, the key problem that had to be solved was how to grow crystals of the protein complex that would diffract X-rays to appropriately high resolution. Crystals were obtained at the beginning of our efforts, but, as often happens, they diffracted X-rays rather poorly. Therefore, over a period of seven years, factors influencing crystal formation were studied systematically, and the diffraction properties of the crystals were improved gradually. Eventually, suitable crystals were obtained in 1990. In retrospect, the important factors for obtaining these crystals were to use highly pure preparations of enzyme, from which trace impurities had been eliminated; to remove endogenous bound nucleotides and to replace them with a non-hydrolyzable chemical analogue of ATP—namely, 5'-adenylylimidodiphosphate (AMP-PNP)—which has the effect of locking the complex in a unique conformation; and to grow the crystals in the presence of deuterium oxide instead of water. By exposing the crystals to X-rays at a synchrotron source, it was demonstrated that crystals of bovine F_1 -ATPase grown under these conditions diffracted to at least 2.8 Å resolution.^[48, 49] Dr. René Lutter and Dr. Rose Todd were key collaborators during this critical period. At this point, for the first time the structural analysis of F_1 -ATPase appeared to be a realistic possibility. Our chances of success with such a large protein complex were increased significantly by collaborating with Dr. Andrew Leslie, who is a professional protein crystallographer. Together with him and a post-doctoral visitor, Dr. J. P. Abrahams, we were able to arrive at an atomic-resolution structure^[50] surprisingly rapidly, given the size of the complex and the associated problems of collecting and processing the X-ray diffraction data.

The structural model of bovine F_1 -ATPase contains 2983 amino acids. Except for short disordered stretches at their N terminals, the sequences of the α - and β subunits were traced in their entirety. Three α -helical segments of the γ subunit corresponding to residues 1–45, 73–90, and 209–272 were also built into the model. The segments linking these

three segments are also disordered, as are the entire δ and ϵ subunits 8150 and 50 amino acids, respectively). These disordered regions of the γ , δ , and ϵ subunits, comprising in total about 300 amino acids, probably lie beneath the $\alpha_3\beta_3$ subcomplex, where the γ subunit protrudes from the structure (the γ subunit is blue in Figures 6 and 7). The protrusion is probably a vestige of the 45 Å stalk that links the F_1 and F_0 domains in the complete ATP synthase complex.

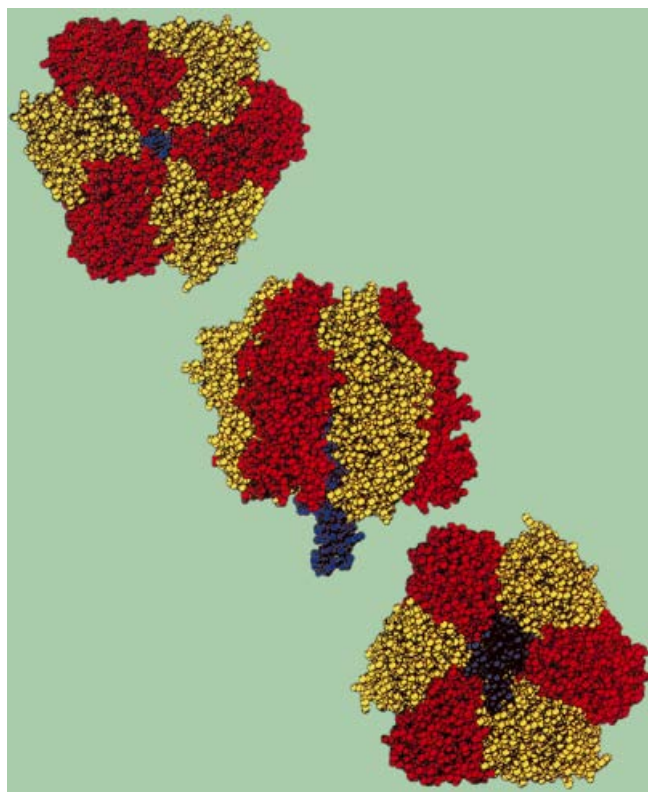


Figure 6. The three-dimensional structure of bovine F_1 -ATPase shown in a space-filling representation. The red, yellow, and blue parts correspond to α , β , and γ subunits, respectively. From top to bottom the complex is viewed from above (towards the membrane in the intact ATP synthase), from the side, and from beneath.

The structural model shows that the three α subunits and the three β subunits are arranged in alternation around a sixfold axis of pseudo-symmetry provided by an α -helical structure in the single γ subunit (Figures 6 and 7). Despite the large excesses of AMP-PNP and ADP in the mother liquor surrounding the crystals, five, and not six, nucleotides are bound to each enzyme complex. An AMP-PNP molecule is found in each α subunit and a fourth one in one β subunit. An ADP molecule is bound to the second β subunit, and the third β subunit has no bound nucleotide at all. A comparison of the structures of the three chemically identical β subunits in the F_1 complex provides an explanation. The two catalytic β subunits that have AMP-PNP and ADP bound to them (known as β_{TP} and β_{DP} , respectively. Figures 7b and 7c) have different but rather similar conformations, whereas the structure of the third β subunit, to which no nucleotide has bound (known as

β_E ; Figure 7d), differs substantially from the other two, particularly in the central domain where the nucleotides are bound in β_{TP} and β_{DP} . In β_E , the C-terminal half of this central domain, together with the bundle of six α helices that form the C-terminal domain, have rotated away from the sixfold axis of pseudo-symmetry. This disruption of the central domain removes the capacity of the β_E subunit to bind nucleotides. Therefore, the crystal structure of F_1 -ATPase contains the asymmetry required by the binding change mechanism, and the three different conformations of the subunits β_E , β_{TP} , and β_{DP} could be interpreted as representing the “open”, “loose”, and “tight” states, respectively.

More recent extensive crystallographic analyses of F_1 -ATPase with bound antibiotic inhibitors,^[51, 52] of enzyme occupied with ADP and ATP,^[91] of enzyme inhibited by ADP and aluminium fluoride,^[92] and of enzyme covalently inhibited with 7-chloro-4-nitrobenzofurazan^[93] leave little room for any doubt that the high-resolution structure described above represents a state in the active cycle of the enzyme.

The most exciting aspect of the structure is that it suggests a mechanism for interconverting the three catalytic subunits through the cycle of conformations required by the binding change mechanism. It appears from the structure (Figure 7) that the nucleotide binding properties of the three catalytic β subunits are modulated by the central α -helical structure in the γ subunit. This structure is curved, and its coiled-coil region is likely to have rigidity. In the crystal structure, its curvature appears to be imposing the “open state” on the β_E subunit by pushing against the C-terminal domain of the protein, forcing the nucleotide binding domain to split and hinge outwards, thereby removing its nucleotide-binding capacity. Therefore, by inspection of the model, the simplest way of interconverting the three conformations of β subunits would be to rotate this central α -helical structure. As it is rotated, the curvature of the γ subunit moves away from the β_E conformation, allowing that subunit to close, progressively entrapping substrates, and allowing ATP to form spontaneously. At the same time, the next β subunit will be progressively opened by the effect of the curvature of the γ subunit, allowing the ATP that has already formed in its nucleotide binding site to be released.

Evidence for a Rotary Mechanism in ATP Synthase

The suggestion that ATP synthesis involves the cyclic modulation of nucleotide-binding properties of the three catalytic β subunits by rotation of the γ subunit was attractive because it provided a reasonable structural basis for the binding change mechanism. However, the proposal was based upon the interpretation of a static atomic model, and there was no proof that the enzyme operated in this way in reality. Therefore, in the laboratories of Richard Cross, Rod Capaldi, and Wolfgang Junge, various experiments were carried out to test the rotary hypothesis.^[53–55] These experiments were all consistent with the rotary model, and they provided convincing evidence of the movement of the γ subunit through

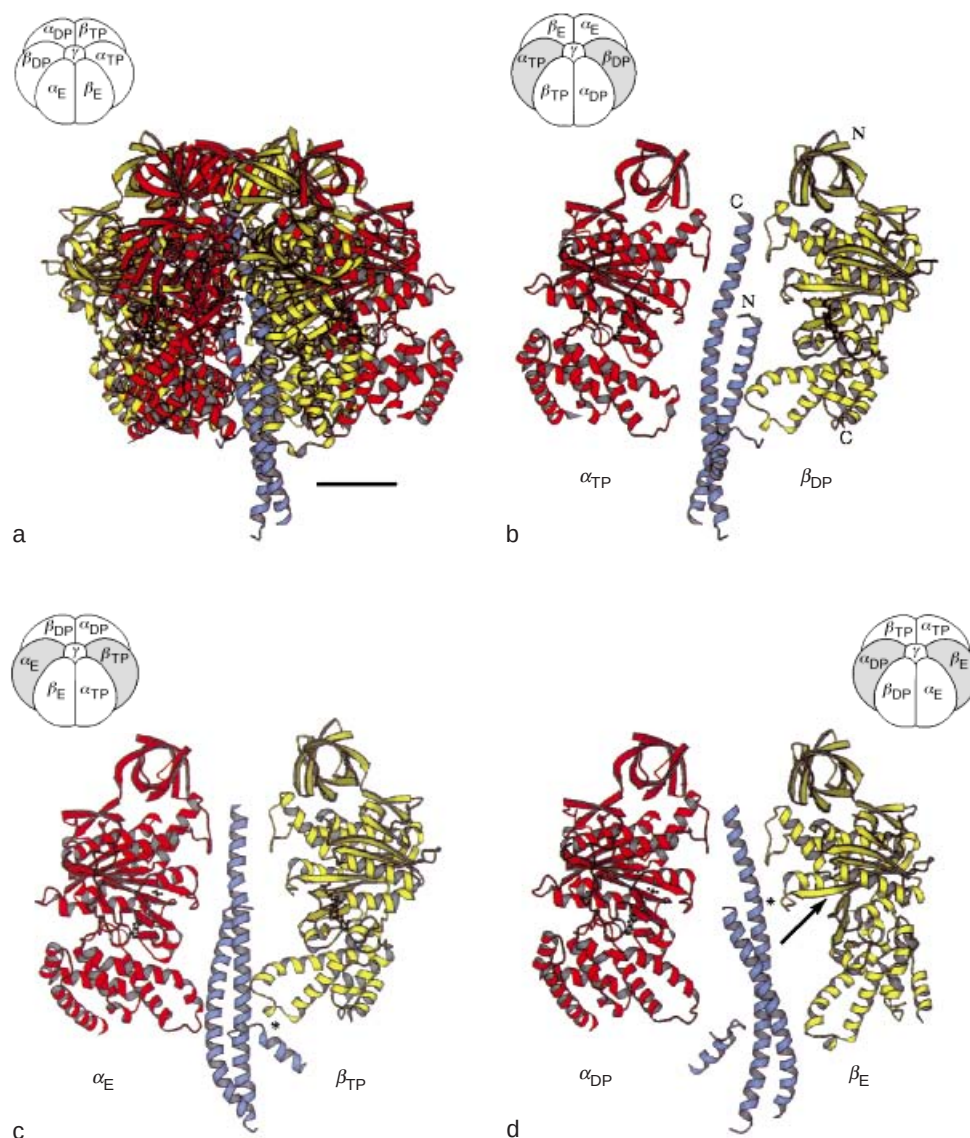


Figure 7. The three-dimensional structure of bovine F_1 -ATPase shown in a ribbon representation. The color code for subunits is the same as in Figure 6, and nucleotides are black in a ball-and-stick representation. The axis of pseudo-symmetry is vertical. AMP-PNP is bound to the three α subunits and to the β subunit defined as β_{TP} . Subunit β_{DP} has bound ADP, and subunit β_E has no associated nucleotide. Subunits α_{TP} , α_E , and α_{DP} occupy the same relative positions as the corresponding β subunits, but are rotated by -60° . The relationships of the various α and β subunits to each other is summarized in the drawing in the top left or right corner of a)–d). In c) and d), the shaded part of the drawing shows which subunits are depicted. Subunit α_{TP} contributes to the nucleotide binding site of β_{TP} , and the similar is true for α_{DP} and α_E . Subunits α and γ are numbered from 1–510 and 1–272, respectively. By convention, the fifth amino acid (serine) in subunit β is residue 1, and the first four amino acids (Ala-Ala-Gln-Ala) are referred to as residues –1 to –4. The C-terminal amino acid is residue 478. a) A view of the entire F_1 particle in which subunits α_E and β_E point towards the viewer, revealing the anti-parallel coiled-coil of the N- and C-terminal helices of the γ subunit through the open interface between them. The bar is 20 Å long. b) Subunits α_{TP} , γ , and β_{DP} from a similar viewpoint as in a), but rotated by 180° about the axis of pseudo-symmetry. The N and C termini of the β and γ subunits are shown. c) Subunits α_E , γ , and β_{TP} from a similar viewpoint as in a), but rotated by -60° . The asterisk indicates an interaction of the loop containing the DELSEED sequence and the γ subunit. d) Subunits α_{DP} , γ , and β_E from a similar viewpoint as in a), but rotated by 60° . The arrow indicates the disruption of the β sheet in the nucleotide binding domain. Residues Asp 316, Thr 318, and Asp 323 in a loop of the nucleotide binding domain of the β_E subunit make hydrogen bonds with residues Arg 254 and Gln 255 from the C-terminal helix of the γ subunit 6 Å below the hydrophobic sleeve. The asterisk indicates a loop that makes an interaction with the C-terminal part of the γ subunit. Reproduced with permission from reference [50].

90 – 240° , but conclusive proof of repeated net rotations through 360° was lacking.

Early in 1997 clear evidence of continuous rotation of the γ subunit relative to the surrounding $\alpha_3\beta_3$ subcomplex was

able to assume that the γ subunit rotates in the opposite direction, and that the order of conformational changes in the β subunits is the reverse of those occurring during ATP hydrolysis.

provided by a spectacular experiment conducted at the Tokyo Institute of Technology by Masasuke Yoshida and colleagues.^[56] The essence of this experiment (Figure 8) was to bind the $\alpha_3\beta_3\gamma_1$ subcomplex to a nickel-coated glass surface in a unique orientation, by introducing the nickel binding sequence (histidine)₁₀ at the N terminals of the β subunits. A cysteine residue, introduced by mutagenesis into the exposed tip of the γ subunit, distal from the nickel surface, was biotinylated, thereby allowing a fluorescently labelled biotinylated actin filament to be attached through an intermediate streptavidin molecule which has four biotin binding sites. The actin filaments were 1–3 μm long, and their ATP dependent anticlockwise rotation could be seen in a fluorescence microscope. The rate of rotation was approximately once per second, about one-fiftieth of the rate anticipated from the turnover number of the fully active enzyme. The reduced activity can be attributed to the load of the actin filament and to the absence of the δ and ϵ subunits.

In addition to its impact in providing direct visual proof of the rotation of the γ subunit, one crucially important aspect of this experiment is that it establishes the order of interconversion of the three conformations of β subunits observed in the crystal structure. During ATP hydrolysis, the β_{DP} subunit converts into the β_E state, β_E changes to β_{TP} , and β_{TP} changes to β_{DP} . During ATP synthesis, it is reason-

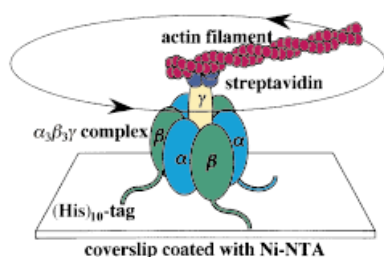


Figure 8. Experimental observation of the ATP-dependent rotation of the γ subunit of the $\alpha_3\beta_3\gamma_1$ subcomplex. For an explanation, see the text. Reproduced with permission from reference [56]. NTA = nitrilotriacetate.

Generation of Rotation by Proton Transport through the F_o Membrane Domain

Once convincing evidence of rotation of the γ subunit had been obtained, among the next questions for consideration were: how is rotation generated by proton transport through F_o , and what is the nature of the connections between the F_1 and the F_o domains? A high-resolution structure is likely to be crucial in providing clear answers to both questions, but as yet there is no such structure for either the F_o domain or the central stalk between F_1 and F_o , except for the ordered protrusion of the γ subunit. Structures of the isolated ϵ subunit^[57, 58] and of a fragment of subunit δ of the *E. coli* enzyme^[59] have been established. The bacterial ϵ subunit (equivalent to the bovine δ subunit)^[60] probably interacts with the protruding γ subunit, and the bacterial δ subunit (equivalent of the bovine OSCP subunit)^[60] appears to interact with the N-terminal region of the α subunits (see below), but the precise locations and functions of these proteins in ATP synthase are unclear.

Despite the lack of a detailed structure of the F_o domain, evidence about the arrangement of the membrane subunits is accumulating. The simplest F_o domain characterized so far is the one found in eubacterial enzymes exemplified by *E. coli*. It has three constituent subunits named *a*, *b*, and *c* assembled in the molar ratios $a_1b_2c_{9-12}$.^[61, 62] The uncertainty in the number of *c* subunits per complex is a consequence of the experimental difficulties associated with making appropriate measurements. Secondary structural models for all three subunits have been advanced by interpretation of the sequences of the bacterial F_o subunits.^[63] The sequence of subunit *a* has been interpreted variously as indicating the presence of five, six, or seven hydrophobic membrane-spanning subunits in the protein, but recent experimental evidence indicates that the correct value is five.^[64] In its C terminus and in penultimate α helices are found positively charged amino acids that are essential for a functional F_o . Subunit *b* is anchored in the membrane by a single N-terminal α helix.^[65] The remainder of this protein is highly charged and may form a homo-dimer by making a parallel α -helical coiled-coil. This polar extramembrane region interacts with subunits in F_1 .^[66] The model of subunit *c* has two antiparallel transmembrane α helices linked by an extra-membranous loop, and this has been shown by NMR spectroscopy to be the structure of the protein in a chloroform/methanol solvent mixture.^[64] Cysteine residues introduced by mutation into the

loop region and into the tip of the γ subunit form a disulfide link under oxidizing conditions, showing that in the intact enzyme these regions are either in contact (possibly transiently) or close to each other.^[67] Similar kinds of experiment provide evidence of interactions between subunits ϵ and *c*.^[68] The most important feature of subunit *c* is the side-chain carboxyl group of an aspartate residue, which is buried in the membrane in the C-terminal α helix. This carboxyl group is conserved throughout all known sequences of *c* subunits, and it is required for transmembrane proton transport.^[61, 63] Depending on the exact number of *c* subunits per complex, there are 9–12 such buried carboxyl groups in each ATP synthase complex.

The mitochondrial ATP synthase complex contains subunits that are equivalent to subunits *a* and *c* (Table 1). Mitochondrial subunit *b* is probably the equivalent of its bacterial homonym, although it appears to have two antiparallel transmembrane α helices at its N terminus rather than one, and there is only one *b* subunit per enzyme complex. Presumably the role of the second *b* subunit in the bacterial complex is performed by other subunits that are unique to the mitochondrial complex (for example subunits *d* and F_6), but such matters will only become clear when more detailed structural evidence becomes available for both bacterial and mitochondrial enzymes. Nonetheless, the bacterial and mitochondrial F_o domains have many features in common, and it is highly probable that they operate by very similar mechanisms.

Models have also been advanced about the association of the F_o subunits in the membrane domain. One such model suggests that the *c* subunits form a ring by interactions of their C-terminal α helices with the N-terminal α helices outside the ring,^[69] and annular structures of *c* subunits have been visualized by atomic force microscopy.^[70, 71] Some preliminary experimental evidence of this arrangement has also been obtained by formation of disulphide cross-links after introduction of cysteine residues at appropriate sites.^[94] In addition, the atomic force microscopy images indicate that the *b* subunits are placed peripheral to a ring of *c* subunits.^[71] Currently, there is no experimental evidence that shows whether the *a* subunit lies outside or within the *c* annulus.

Wolfgang Junge has proposed a model of how proton transport through F_o might generate a rotary motion^[72] (Figure 9). The essence of this hypothetical rotary motor is that the essential carboxyl groups in the *c* subunits are arranged around the external circumference of the *c* annulus. Part of the external surface of the annulus interacts with subunit *a*, and in this region the carboxyl groups are negatively charged. It is envisaged that subunit *a* has an inlet port on the external surface of the membrane which allows a proton to neutralize one of the negatively charged carboxylate group. The resulting un-ionized carboxyl group will find its way by thermal vibrations to its preferred environment in contact with the phospholipid bilayer. The neutralization of this carboxylate group at one point of the circumference is accompanied by reionization of another group further around the circumference of the *c* annulus, release of the proton on the opposite side of the membrane through an exit port in subunit *a*, and regeneration of a negative charge in the *c* annulus – subunit *a* interface. These protonation/deprotona-

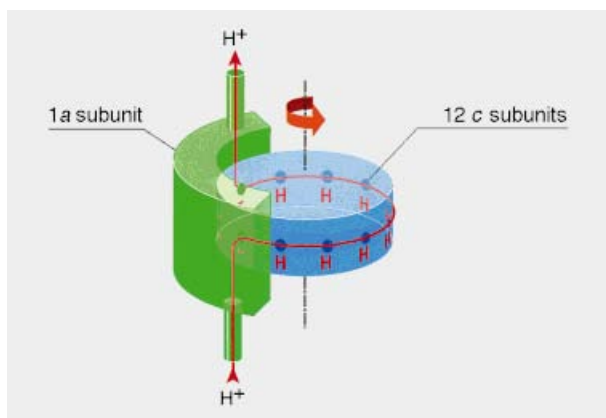


Figure 9. A hypothetical model for generation of rotation by proton transport through the F_0 domain of ATP synthase (according to W. Junge). The central cylindrical part is made up of c subunits, and the external curved structure is the single a subunit. The heavy red line indicates the path of the protons. For further explanation, see the text.

tion events result in a rotary movement of the c annulus. The rotation brings the next negatively charged carboxyl group to the inlet port, where in turn it is neutralized by another proton. The accompanying release of another proton through the exit port generates further rotation. It is envisaged that this rotary device is directly coupled to the γ subunit.

The synthesis of each ATP molecule requires a rotation of the γ subunit by 120° ; thus, each complete rotation of the γ subunit in F_1 produces three ATP molecules. In a hypothetical proton motor with a c annulus consisting of twelve c subunits, this corresponds to the sequential neutralization of four carboxylate groups by proton binding (and accompanying sequential proton release from four other groups). In other words, a H^+ :ATP ratio of four is compatible with a molar ratio of c subunits in F_0 of twelve. Likewise, a H^+ :ATP ratio of three requires nine c subunits in each F_0 .

Connections between the F_1 and F_0 Domains of ATP Synthase

The evidence for the interaction of the central γ subunit and the associated ε subunit in bacterial F_1 with the loop region of a c subunit in F_0 has been described above. It is likely that these proteins are the principal components making the central interaction between F_1 and F_0 , which is visualized as the central 45 Å long stalk. There is accumulating evidence for a second link between F_1 and F_0 . It is known that the bacterial δ subunit and the equivalent bovine OSCP subunit interact with the N-terminal part of the α subunits,^[73, 74] which are now known to be on top of F_1 distal from the membrane domain. Since the 1960s, it has been known that bovine OSCP is required for binding F_1 to F_0 , implying that it interacts with subunits in the membrane domain. Therefore, the inescapable conclusion is that OSCP (and possibly also subunit δ in the bacterial and chloroplast enzymes) extends from the top of F_1 , down its external surface, to a region associated with the membrane domain. In the bovine enzyme, the N-terminal part of OSCP interacts with the N-terminal part of the α subunits.^[75, 76] Additionally, the interactions of bovine

OSCP with various F_0 components have been studied by in vitro reconstitution experiments.^[77] They indicate that OSCP binds mainly to the polar extramembranous part of subunit b (referred to as b'), and not with subunits d and F_6 . However, subunits d and F_6 bind to the b' –OSCP complex to forming a stoichiometric complex containing one copy of each of the four proteins. This complex (unfortunately named as “stalk”) makes no strong interactions with a complex of bovine subunits δ and ε ,^[78] consistent with the bovine “stalk” complex being separate from the central 45 Å long stalk.

By single-particle analysis of negatively stained samples of monodisperse bovine ATP synthase,^[79–82] Simone Karrasch has obtained electron microscopic evidence for a second peripheral stalk (Figure 10). A similar feature has been observed

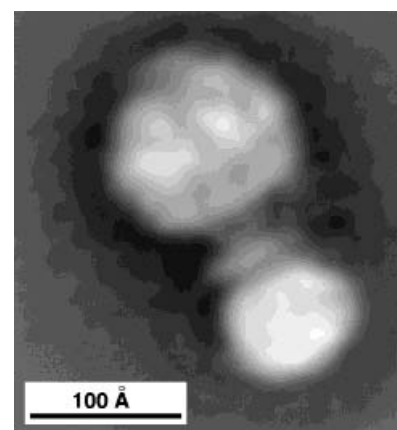


Figure 10. Electron microscope image of bovine ATP synthase obtained by averaging 4940 single negatively stained particles of the enzyme. The plane of the membrane with which the assembly is associated in mitochondria runs upwards, from left to right, at an angle of 45° . The larger sphere is the F_1 catalytic domain, and the smaller sphere beneath it is F_0 (or part of F_0). The new features are the collar apparently surrounding the central stalk and, on the right, the faint peripheral connection between the collar and F_1 , which may serve as a “stator”. There may also be extra material on top of the F_1 domain that is not present in isolated F_1 -ATPase (for more detailed discussion, see the text).

independently in the *E. coli* enzyme^[95] and in a V-type ATPase (a relative of ATP synthase) from *Clostridium fervidus*.^[83] The image of the bovine enzyme also contains another novel feature, seen as a disc-shaped structure or collar evidently sitting between the central stalk and F_0 domains; a similar collar was observed in the Clostridial enzyme. It remains to be established which subunits of the bovine enzyme are responsible for the peripheral stalk and the collar. The OSCP and subunit b are likely candidates for being components of the former, and the collar may be composed of parts of the c subunits.

At present, we can only speculate about the role of the peripheral stalk, but it may be acting as a stator to counter the tendency of the $\alpha_3\beta_3$ subcomplex to follow the rotation of the central γ subunit. However, it is unlikely that this peripheral stalk remains bound in a unique position, because the nature of the surface of the $\alpha_3\beta_3$ subcomplex must change cyclically in response to the rotating γ subunit. Hence, the preferred binding site of the peripheral structure must also move in the same way. The role of the collar is an even bigger mystery.

Evolution of ATP Synthase and its Relationship to Other Enzymes

In bacterial operons coding for the subunits of ATP synthase, the genes for F_1 and F_0 subunits are often clustered separately. This arrangement suggested the possibility that the two domains have evolved separately as structural modules,^[84] similar to the “modular evolution” of heads and tails of bacteriophages.^[85, 86] If this suggestion were correct, it might be expected that the F_1 and F_0 modules would be found to fulfill other biochemical functions elsewhere in biology.

It is too early to know whether there is any significant structural and mechanistic relationship between F_0 and the motors that drive the flagellae of bacteria, although this remains a distinct possibility. However, there is emerging evidence of significant similarities, both functional and structural, between the F_1 domain of ATP synthase and DNA and RNA helicases that employ energy released by hydrolysis of ATP or GTP to separate the strands of nucleic acid duplexes (for example, see reference [87]). Therefore, the rotary mechanism of ATP synthase may turn out to be the first example of a more general principle in enzyme catalysis.

Concluding Remarks

The high-resolution structure of the catalytic domain of the ATP-synthesizing enzyme has provided new insights into our understanding of how ATP is made in biology. Nevertheless, challenging structural experiments lie ahead in the quest to understand the generation of rotation by transmembrane proton transport through its membrane sector. A short poem written by Robert Frost^[96] provides an appropriate summary of the current state of affairs.

*We dance round in a ring and suppose
The secret sits in the middle and knows*

I am glad to have played a role in arriving at our present level of understanding of ATP synthesis, and in the future I hope to contribute to the revelation of the secret sitting in the middle.

From what I have written, it is obvious that the work summarized is the outcome of the joint efforts of many extremely able and highly valued colleagues and collaborators, including Ph. D. students and post-doctoral visitors, whom I have been privileged to lead. To all of them, I offer my thanks for their contributions. I am particularly grateful to The Medical Research Council, which has supported my work unstintingly for more than 20 years. Many post-doctoral visitors were supported by fellowships from The European Molecular Biology Organization, and others by fellowships from the European Community and the Human Frontiers of Science Project. I thank these organizations also for their support.

Received: April 27, 1998 [A 280 IE]

German version: *Angew. Chem.* **1998**, *110*, 2438–2450

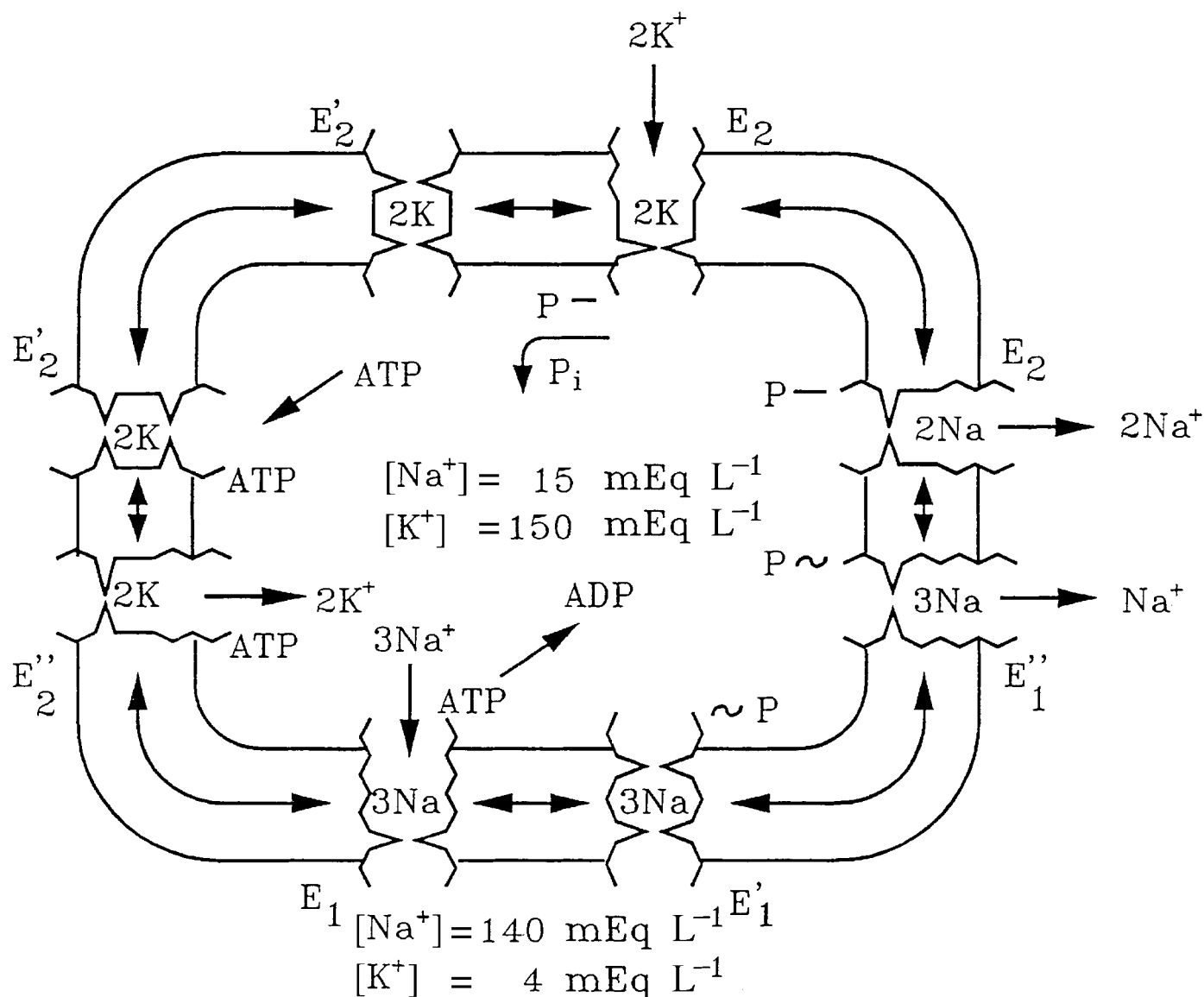
Keywords: ATP • bioenergetics • enzyme catalysis • Nobel lecture • protein structures

- [1] D. G. Nicholls, S. J. Ferguson in *Bioenergetics* 2, Academic Press, London, **1992**.
- [2] “ Na^+ -coupled alternative to H^+ -coupled primary transport system in bacteria”: P. Dimroth, *Bioessays* **1991**, *13*, 463–468.
- [3] “Structures of the metal sites of oxidized cytochrome c oxidase at 2.8 Å resolution”: T. Tsukihara, H. Aoyama, E. Yamashita, T. Tomizaki, H. Yamaguchi, K. Shinzawa-Itoh, R. Nakashima, D. Yaono, S. Yoshikawa, *Science* **1995**, *269*, 1069–1074.
- [4] “The whole structure of the 13-subunit oxidized cytochrome c oxidase at 2.8 Å”: T. Tsukihara, H. Aoyama, E. Yamashita, T. Tomizaki, H. Yamaguchi, K. Shinzawa-Itoh, R. Nakashima, D. Yaono, S. Yoshikawa, *Science* **1996**, *272*, 1136–1144.
- [5] “Structure at 2.8 Å resolution of cytochrome c oxidase from *Paracoccus denitrificans*”: S. Iwata, C. Ostermeier, B. Ludwig, H. Michel, *Nature* **1995**, *376*, 660–669.
- [6] “Structure at 2.7 Å of the *Paracoccus denitrificans* two-subunit cytochrome c oxidase with an antibody F_v fragment”: C. Ostermeier, A. Harrenga, U. Ermler, H. Michel, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 10547–10553.
- [7] “Crystal structure of the cytochrome bc_1 complex from bovine heart mitochondria”: D. Xia, C. A. Yu, H. Kih, J. Z. Xia, A. M. Kachurin, L. Zhang, L. Yu, J. Deisenhofer, *Science* **1997**, *277*, 60–66.
- [8] “The NADH:ubiquinone oxidoreductase (complex I) of respiratory chains”: J. E. Walker, *Q. Rev. Biophys.* **1992**, *25*, 253–324.
- [9] “Three-dimensional structure of NADH-dehydrogenase from *Neurospora crassa* by electron microscopy and conical tilt reconstruction”: V. Guénbaut, R. Vincentelli, D. Mills, H. Weiss, K. Leonard, *J. Mol. Biol.* **1997**, *265*, 409–418.
- [10] “Three-dimensional structure of bovine NADH:ubiquinone oxidoreductase (complex I) at 22 Å in ice”: N. Grigorieff, *J. Mol. Biol.* **1998**, *277*, 1033–1046.
- [11] “The *atp* operon: nucleotide sequence of the promoter and the genes for the membrane proteins and the δ subunit of *Escherichia coli* ATP synthase”: N. J. Gay, J. E. Walker, *Nucleic Acids Res.* **1981**, *9*, 3919–3926.
- [12] “The *atp* operon: nucleotide sequence of the region encoding the α subunit of *Escherichia coli* ATP synthase”: N. J. Gay, J. E. Walker, *Nucleic Acids Res.* **1981**, *9*, 2187–2194.
- [13] “The *atp* operon: nucleotide sequence of the genes for the γ , β and ϵ subunits of *Escherichia coli* ATP synthase”: M. Saraste, N. J. Gay, A. Eberle, M. J. Runswick, J. E. Walker, *Nucleic Acids Res.* **1981**, *9*, 5287–5296.
- [14] “The amino acid sequence of the β subunit of ATP synthase from bovine heart mitochondria”: M. J. Runswick, J. E. Walker, *J. Biol. Chem.* **1983**, *258*, 3081–3089.
- [15] “*Rhodospseudomonas blastica atp* operon: Nucleotide sequence and transcription”: V. L. J. Tybulewicz, G. Falk, J. E. Walker, *J. Mol. Biol.* **1984**, *179*, 185–214.
- [16] “The *unc* operon: nucleotide sequence, regulation and structure of ATP synthase”: J. E. Walker, M. Saraste, N. J. Gay, *Biochim. Biophys. Acta* **1984**, *768*, 164–200.
- [17] “Nucleotide sequence of the *Rhodospirillum rubrum atp* operon”: G. Falk, A. Hampe, J. E. Walker, *Biochem. J.* **1985**, *228*, 391–407.
- [18] “Primary structure and subunit stoichiometry of F_1 -ATPase from bovine mitochondria”: J. E. Walker, I. M. Fearnley, N. J. Gay, B. W. Gibson, F. D. Northrop, S. J. Powell, M. J. Runswick, M. Saraste, V. L. J. Tybulewicz, *J. Mol. Biol.* **1985**, *184*, 677–701.
- [19] “A sixth subunit of ATP synthase, an F_0 component, is encoded in the pea chloroplast genome”: A. L. Cozens, J. E. Walker, A. L. Phillips, A. K. Huttly, J. C. Gray, *EMBO J.* **1986**, *5*, 217–222.
- [20] “Two overlapping genes in bovine mitochondrial DNA encode membrane components of ATP synthase”: I. M. Fearnley, J. E. Walker, *EMBO J.* **1986**, *5*, 2003–2008.
- [21] “The organization and sequence of the genes for ATP synthase subunits in the cyanobacterium *Synechococcus* 6301: support for an endosymbiotic origin of chloroplasts”: A. L. Cozens, J. E. Walker, *J. Mol. Biol.* **1987**, *194*, 359–383.

- [22] "ATP synthase from bovine mitochondria: sequences of imported precursors of oligomycin sensitivity conferral protein, factor 6 and adenosine triphosphatase inhibitor protein": J. E. Walker, N. J. Gay, S. J. Powell, M. Kostina, M. R. Dyer, *Biochemistry* **1987**, 26, 8613–8619.
- [23] "ATP synthase from bovine mitochondria: characterization and sequence analysis of two membrane associated subunits and of their corresponding c-DNAs": J. E. Walker, M. J. Runswick, L. Poulter, *J. Mol. Biol.* **1987**, 197, 89–100.
- [24] "DNA sequence of a gene cluster coding for subunits of the F_0 membrane sector of ATP synthase in *Rhodospirillum rubrum*": G. Falk, J. E. Walker, *Biochem. J.* **1988**, 254, 109–122.
- [25] "ATP synthase from bovine mitochondria: complementary DNA sequence of the import precursor of a heart isoform of the alpha subunit": J. E. Walker, S. J. Powell, O. Vinas, M. J. Runswick, *Biochemistry* **1989**, 28, 4702–4708.
- [26] "The δ subunit of ATP synthase from bovine heart mitochondria. Complementary DNA sequence of its import precursor cloned with the aid of the polymerase chain reaction": M. J. Runswick, S. M. Medd, J. E. Walker, *Biochem. J.* **1990**, 266, 421–426.
- [27] "The epsilon subunit of ATP synthase from bovine heart mitochondria: complementary DNA, expression in bovine tissues and evidence of homologous sequences in man and rat": O. Viñas, S. J. Powell, M. J. Runswick, V. Iacobazzi, J. E. Walker, *Biochem. J.* **1990**, 265, 321–326.
- [28] "Identification of the subunits of F_1F_0 -ATPase from bovine heart mitochondria": J. E. Walker, R. Lutter, A. Dupuis, M. J. Runswick, *Biochemistry* **1991**, 30, 5369–5378.
- [29] "Organization and sequence of genes for subunits of ATP synthase in the thermophilic cyanobacterium *Synechococcus* 6716": H. S. van Walraven, R. Lutter, J. E. Walker, *Biochem. J.* **1993**, 294, 239–251.
- [30] "The F_0 membrane domain of ATP synthase from bovine heart mitochondria: purification, subunit composition and reconstitution with F_1 -ATPase": I. R. Collinson, M. J. Runswick, S. K. Buchanan, I. M. Fearnley, J. M. Skehel, M. J. van Raaij, D. E. Griffiths, J. E. Walker, *Biochemistry* **1994**, 33, 7971–7978.
- [31] "The F_1F_0 -ATPase complex from bovine heart mitochondria: the molar ratio of the subunits in the stalk region linking the F_1 and F_0 domains": I. R. Collinson, J. M. Skehel, I. M. Fearnley, M. J. Runswick, J. E. Walker, *Biochemistry* **1996**, 35, 12 640–12 646.
- [32] "The regulation of catalysis in ATP synthase": J. E. Walker, *Curr. Opin. Struct. Biol.* **1994**, 4, 912–918.
- [33] "Cell-membrane ultrastructure. Low-temperature electron microscopy and x-ray diffraction studies of lipoprotein components in lamellar systems": H. Fernández-Morán, *Circulation* **1962**, 26, 1039–1065.
- [34] "Partial resolution of the enzymes catalyzing photophosphorylation. Stimulation of photophosphorylation by a preparation of a latent, Ca^{++} -dependent adenosine triphosphatase from chloroplasts": V. K. Vambutas, E. Racker, *J. Biol. Chem.* **1965**, 240, 2660–2667.
- [35] "The Mitochondrion": D. E. Green, *Sci. Am.* **1964**, 210, 63–74.
- [36] "Partial resolution of the enzymes catalyzing oxidative phosphorylation. Correlation of morphology and function in submitochondrial particles": Y. Kagawa, E. Racker, *J. Biol. Chem.* **1966**, 241, 2475–2482.
- [37] "Partial resolution of the enzymes catalyzing oxidative phosphorylation. Properties of a factor conferring oligomycin sensitivity on mitochondrial adenosine triphosphatase": Y. Kagawa, E. Racker, *J. Biol. Chem.* **1966**, 241, 2462–2466.
- [38] "Partial resolution of the enzymes catalyzing oxidative phosphorylation. Reconstruction of oligomycin-sensitive adenosine triphosphatase": Y. Kagawa, E. Racker, *J. Biol. Chem.* **1966**, 241, 2467–2474.
- [39] "The H^+ /ATP ratio of the ATP synthase from the thiol modulated chloroplasts and two cyanobacterial strains is four": H. van Walraven, H. Strotmann, O. Schwartz, B. Rumberg, *FEBS Lett.* **1996**, 379, 309–313.
- [40] "The binding change mechanism for ATP synthase – some probabilities and possibilities": P. D. Boyer, *Biochim. Biophys. Acta* **1993**, 1140, 215–250.
- [41] "Methods for the purification of each subunit of the mitochondrial oligomycin-insensitive adenosine triphosphatase": J. C. Brooks, A. E. Senior, *Biochemistry* **1972**, 11, 4675–4678.
- [42] "The subunit structure of beef heart mitochondrial adenosine triphosphatase": A. F. Knowles, H. S. Penefsky, *J. Biol. Chem.* **1972**, 247, 6616–6623.
- [43] "Substrate positions and induced-fit in crystalline adenylate kinase": E. F. Pai, W. Sachsenheimer, R. H. Schirmer, G. E. Schulz, *J. Mol. Biol.* **1977**, 114, 37–45.
- [44] "Distantly related sequences in the α and β subunits of ATP synthase, myosin, kinases and other ATP requiring enzymes and a common nucleotide binding fold": J. E. Walker, M. Saraste, M. J. Runswick, N. J. Gay, *EMBO J.* **1982**, 1, 945–951.
- [45] "ABC transporters: from microorganisms to man": C. F. Higgins, *Annu. Rev. Cell Biol.* **1992**, 8, 67–113.
- [46] "Homology between human bladder carcinoma oncogene product and mitochondrial ATP synthase": N. J. Gay, J. E. Walker, *Nature* **1983**, 301, 262–264.
- [47] "A superfamily of ATPases with diverse functions containing either classical or deviant ATP-binding motif": E. V. Koonin, *J. Mol. Biol.* **1993**, 229, 1165–1174.
- [48] "Structural aspects of proton pumping ATPases": J. E. Walker, I. M. Fearnley, R. Lutter, R. J. Todd, M. J. Runswick, *Philos. Trans. R. Soc.* **1990**, 326, 367–378.
- [49] "Crystallization of F_1 -ATPase from bovine heart mitochondria": R. Lutter, J. P. Abrahams, M. J. van Raaij, R. J. Todd, T. Lundqvist, S. K. Buchanan, A. G. W. Leslie, J. E. Walker, *J. Mol. Biol.* **1993**, 229, 787–790.
- [50] "Structure at 2.8 Å resolution of F_1 -ATPase from bovine heart mitochondria": J. P. Abrahams, A. G. W. Leslie, R. Lutter, J. E. Walker, *Nature* **1994**, 370, 621–628.
- [51] "The structure of bovine F_1 -ATPase complexed with the antibiotic inhibitor aurovertin": M. J. van Raaij, J. P. Abrahams, A. G. W. Leslie, J. E. Walker, *Proc. Natl. Acad. Sci. USA* **1996**, 93, 6913–6917.
- [52] "The structure of bovine F_1 -ATPase complexed with the peptide antibiotic efrapeptin": J. P. Abrahams, S. K. Buchanan, M. J. van Raaij, I. M. Fearnley, A. G. W. Leslie, J. E. Walker, *Proc. Natl. Acad. Sci. USA* **1996**, 93, 9420–9424.
- [53] "Rotation of subunits during catalysis by *Escherichia coli* F_1 -ATPase": T. M. Duncan, V. V. Bulygin, Y. Zhou, M. L. Hutcheon, R. L. Cross, *Proc. Natl. Acad. Sci. USA* **1995**, 92, 10964–10968.
- [54] "Structural changes in the γ and ϵ subunits of the *Escherichia coli* F_1F_0 -type ATPase during energy coupling": R. A. Capaldi, R. Aggeler, S. Wilkens, G. Grüber, *J. Bioenerg. Biomembr.* **1996**, 28, 397–401.
- [55] "Intersubunit rotation in active F -ATPase": D. Sabbert, S. Engelbrecht, W. Junge, *Nature* **1996**, 381, 623–625.
- [56] "Direct observation of the rotation of F_1 -ATPase": H. Noji, R. Yasuda, M. Yoshida, K. Kinosita, Jr., *Nature* **1997**, 386, 299–302.
- [57] "Structural features of the ϵ subunit of the *Escherichia coli* ATP synthase determined by NMR spectroscopy": S. Wilkens, F. W. Dahlquist, L. P. McIntosh, L. W. Donaldson, R. A. Capaldi, *Nature Struct. Biol.* **1995**, 2, 961–967.
- [58] "Crystal structure of the ϵ -subunit of the proton-translocating ATP synthase from *Escherichia coli*": U. Uhlin, G. B. Cox, J. M. Guss, *Structure* **1997**, 5, 1219–1230.
- [59] "Solution structure of the N-terminal domain of the δ -subunit of the *E. coli* ATP synthase": S. Wilkens, S. D. Dunn, J. Chandler, F. W. Dahlquist, R. A. Capaldi, *Nature Struct. Biol.* **1997**, 4, 198–201.
- [60] "Subunit equivalence in *Escherichia coli* and bovine heart mitochondrial F_1F_0 ATPases": J. E. Walker, M. J. Runswick, M. Saraste, *FEBS Lett.* **1982**, 146, 393–396.
- [61] "Membrane sectors of F - and V -type H^+ -transporting ATPases": R. H. Fillingame, *Curr. Opin. Struct. Biol.* **1996**, 6, 491–498.
- [62] "Stoichiometry of subunits in the H^+ -ATPase complex of *Escherichia coli*": D. L. Foster, R. H. Fillingame, *J. Biol. Chem.* **1982**, 257, 2009–2015.
- [63] "Molecular mechanics of ATP synthesis by F_1F_0 -type H^+ -transporting ATPases": R. H. Fillingame, *Bacteria* **1990**, 12, 345–391.
- [64] "Subunit interactions coupling H^+ transport and ATP synthesis in F_1F_0 ATP synthase": R. H. Fillingame, M. E. Girvin, W. Jiang, F. Valiyaveetil, J. Hermolin, *Acta Physiol. Scand.*, in press.
- [65] "*E. coli* F_1 -ATPase interacts with a membrane protein component of a proton channel": J. E. Walker, M. Saraste, N. J. Gay, *Nature* **1982**, 298, 867–869.
- [66] "The polar domain of the b subunit of *Escherichia coli* F_1F_0 -ATPase forms an elongated dimer that interacts with the F_1 sector": S. D. Dunn, *J. Biol. Chem.* **1992**, 267, 7630–7636.

- [67] “The gamma subunit in the *Escherichia coli* ATP synthase complex (ECF₁F₀) extends through the stalk and contacts the *c* subunits of the F₀ part”: S. D. Watts, Y. Zhang, R. H. Fillingame, R. A. Capaldi, *FEBS Lett.* **1995**, 368, 235–238.
- [68] “Subunits coupling H⁺ transport and ATP synthesis in the *Escherichia coli* ATP synthase: Cys-Cys crosslinking of F₁ subunit ϵ to the polar loop of F₀ subunit *c*”: Y. Zhang, R. H. Fillingame, *J. Biol. Chem.* **1995**, 270, 24609–24614.
- [69] “Model of the *c*-subunit oligomer in the membrane domain of F-ATPases”: G. Groth, J. E. Walker, *FEBS Lett.* **1997**, 410, 117–123.
- [70] “Topographical structure of membrane-bound *Escherichia coli* F₁F₀ ATP synthase in aqueous buffer”: S. Singh, P. Turina, C. J. Bustamante, D. J. Keller, R. A. Capaldi, *FEBS Lett.* **1996**, 397, 30–34.
- [71] “Molecular imaging of *Escherichia coli* F₀F₁-ATPase in reconstituted membranes by atomic force microscopy”: K. Takeyasu, H. Omote, S. Nettikadan, F. Tokumasu, A. Iwamoto-Kihara, Futai, M., *FEBS Lett.* **1996**, 392, 110–113.
- [72] “Rotary catalysis by F-ATPase: real-time recording of intersubunit rotation”: W. Junge, D. Sabbert, S. Engelbrecht, *Ber. Bunsen-Ges. Phys. Chem.* **1996**, 100, 2014–2019.
- [73] “The NH₂-terminal proton of the α -subunit of the *Escherichia coli* F₁-ATPase is required for binding the δ -subunit”: S. D. Dunn, L. A. Heppel, C. S. Fullmer, *J. Biol. Chem.* **1980**, 255, 6891–6896.
- [74] “Lack of ability of trypsin-treated mitochondrial F₁-ATPase to bind to the oligomycin sensitivity conferring protein (OSCP)”: T. Hundal, B. Norling, L. Ernster, *FEBS Lett.* **1983**, 162, 5–10.
- [75] “Oligomycin sensitivity-conferring protein (OSCP) of mitochondrial ATP synthase. The carboxy terminal region of OSCP is essential for the reconstitution of oligomycin-sensitive H⁺-ATPase”: S. Joshi, A. A. Javed, L. C. Gibbs, *J. Biol. Chem.* **1992**, 267, 12860–12867.
- [76] “Topology and function of “stalk” proteins in the bovine mitochondrial H⁺-ATPase”: S. Joshi, M. J. Pringle, R. Siber, *J. Biol. Chem.* **1986**, 261, 10653–10658.
- [77] “ATP synthase from bovine heart mitochondria: *in vitro* assembly of a stalk complex in the presence of F₁-ATPase and in its absence”: I. R. Collinson, M. J. van Raaij, M. J. Runswick, I. M. Fearnley, J. M. Skehel, G. L. Orriss, B. Miroux, J. E. Walker, *J. Mol. Biol.* **1994**, 242, 408–421.
- [78] “The δ - and ϵ -subunits of bovine F₁-ATPase interact to form a heterodimeric subcomplex”: G. L. Orriss, M. J. Runswick, I. R. Collinson, B. Miroux, I. M. Fearnley, J. M. Skehel, J. E. Walker, *Biochem. J.* **1996**, 314, 695–700.
- [79] “F₁F₀-ATPase from bovine heart mitochondria: development of the purification of a monodisperse oligomycin sensitive ATPase”: R. Lutter, M. Saraste, H. S. van Walraven, M. J. Runswick, M. Finel, J. F. Deatherage, J. E. Walker, *Biochem. J.* **1993**, 295, 799–806.
- [80] “Structural analysis of ATP synthase (F₁F₀-ATPase) from bovine heart mitochondria”: J. E. Walker, I. R. Collinson, M. J. van Raaij, M. J. Runswick, *Methods Enzymol.* **1995**, 163–190.
- [81] “Large scale chromatographic purification of F₁F₀-ATPase and complex I from bovine heart mitochondria”: S. K. Buchanan, J. E. Walker, *Biochem. J.* **1996**, 318, 343–349.
- [82] “ATP synthase from bovine heart mitochondria: reconstitution into unilamellar phospholipid vesicles of the pure enzyme in a functional state”: G. Groth, J. E. Walker, *Biochem. J.* **1996**, 318, 351–357.
- [83] “Visualization of a peripheral stalk V-type ATPase: evidence for the stator structure essential to rotational catalysis”: E. Boekema, T. Ubbink-Kok, J. S. Lolkema, A. Brisson, W. N. Konings, *Proc. Natl. Acad. Sci. USA*, in press.
- [84] “Evolution of ATP synthase”: J. E. Walker, A. L. Cozens, *Chem. Scr.* **1986**, 26B, 263–272.
- [85] “A theory for molecular evolution of bacteriophages”: D. Botstein, *Ann. N. Y. Acad. Sci.* **1980**, 354, 484–491.
- [86] “Comments on the arrangement of the morphogenetic genes of bacteriophage lambda”: S. Casjens, R. Hendrix, *J. Mol. Biol.* **1974**, 90, 20–23.
- [87] “The RecA hexamer is a structural homologue of ring helicases”: X. Yu, E. H. Egelman, *Nature Struct. Biol.* **1997**, 4, 101–104.
- [88] “Cryoelectron microscopy of *Escherichia coli* F₁ adenosine triphosphatase decorated with monoclonal antibodies to individual subunits of the complex”: E. P. Gogol, R. Aggeler, M. Sagerman, R. A. Capaldi, *Biochemistry* **1989**, 28, 4717–4724.
- [89] G. Weissman, R. Claibourne *Cell Membranes: Biochemistry, Cell Biology and Pathology*, **1975**.
- [90] P. D. Boyer, *Angew. Chem.* **1998**, 110, 2424–2436; *Angew. Chem. Int. Ed.* **1998**, 37, 2296–2307.
- [91] K. Braig, M. Montgomery, A. G. W. Leslie, J. E. Walker, unpublished results.
- [92] K. Braig, I. Menz, M. Montgomery, A. G. W. Leslie, J. E. Walker, unpublished results.
- [93] “Bovine F₁-ATPase covalently inhibited with 4-chloro-7-nitrobenzofuran: the structure provides further support for a rotary catalytic mechanism”: G. L. Orriss, A. G. W. Leslie, K. Braig, J. E. Walker, *Structure* **1998**, 6, 831–837.
- [94] N. J. Glavas, J. E. Walker, unpublished results.
- [95] S. Wilkens, R. A. Capaldi, personal communication.
- [96] *The Poetry of Robert Frost—The Complete Poems, Complete and Unabridged* (Ed.: E. C. Latham), **1975**, Holt, Rinehart, and Winston, New York, p. 362.

The $\text{Na}^+\text{--K}^+$ transport system of the cell, the $\text{Na}^+\text{--K}^+$ pump, consists of a carrier part located in the interior of the membrane and the ATP-binding part on the cytoplasmic side of the membrane. The carrier exists in two conformations: E_1 is the high-affinity Na^+ form, and E_2 is the high-affinity K^+ form.



The carrier part has two gates, energy barriers, which can open or close access to the channel side and to the cytoplasmic side. For each ATP that is hydrolyzed to ADP and inorganic phosphate P_i , three Na^+ ions are pumped out of and two K^+ ions into the cell; 70–85% of the free energy of the ATP hydrolysis is used.

The Identification of the Sodium–Potassium Pump (Nobel Lecture)**

Jens C. Skou

Looking for the answer

*You hunt it,
you catch it,
you fool yourself;
the answer,
is always,
a step ahead.*

J. C. S.

Introduction

The cell membrane separates the cell from the surrounding medium. In 1925 Gorter and Grendel^[1] extracted the lipids from red blood cells, spread them in a monomolecular layer on a water phase, and measured the compressed area. It was about twice the surface area of the extracted red blood cells. They suggested that the cell membrane is a bilayer of lipids with the charged head groups of the phospholipids facing the water phase on the two sides of the membrane, and with the hydrocarbon chains meeting in the middle of the membrane. The thickness of the membrane is about 40 Å, much too small to be seen under a microscope.

The surface tension of invertebrate eggs and other cells is, however, much lower than for a water–lipid interphase. To explain this, Danielli and Davson in 1935^[2] suggested that there is an adsorbed layer of proteins on each side of the lipid bilayer. They also introduced a layer of nonoriented lipids in the middle of the bilayer.

In the cytoplasm there are proteins for which the cell membrane is impermeable. At the cell pH level they carry negative charges, neutralized by potassium, which in the cell is at a concentration of about 150 milligram equivalents per liter (mEq L⁻¹), while outside the cell the K⁺ concentration is 4 mEq L⁻¹. The difference in K⁺ concentration was explained as being due to a Donnan effect of the proteins, and the fact that the membrane is permeable to K⁺. The Donnan effect gives an osmotic pressure which is higher inside the cell than outside; since the membrane is permeable to water, water will

flow in, and as the lipid bilayer cannot resist a hydrostatic pressure the cell will swell and finally burst.

The higher osmotic pressure inside the cell is opposed by a high concentration of sodium outside (140 mEq L⁻¹), while the concentration inside is low (about 10–20 mEq L⁻¹). It is a problem to explain how this difference in the Na⁺ concentration on the two sides of the membrane can be maintained. There are two possible explanations:

One is that the membrane is impermeable to Na⁺, that it is an equilibrium situation. This view was advocated by Conway, an Irish biochemist from Dublin. Boyle and Conway published in 1941 a paper in which they showed that for muscle fibers soaked in solutions with varying K⁺ concentrations, the calculated intracellular K⁺ concentrations based on this assumption agreed with the measured.^[3] There were, however, two problems. One was that this agreement did not hold at the normal physiological concentrations of K⁺, only at higher concentrations. The other was the requirement of Na⁺ impermeability. But how then to explain that there is sodium in the cell, even if it is at a low concentration. Conway gave no answers to these problems.

The other possibility is that the membrane is permeable to Na⁺, and that there are secretory, energy-dependent processes in the cell which compensate for the steady influx of Na⁺, a steady-state distribution. This view was advocated by R. B. Dean in a paper also published in 1941 entitled “Theories of Electrolyte Equilibrium in Muscle”.^[4] Referring to investigations by L. A. Heppel (1939, 1940), by L. A. Heppel and C. L. A. Schmidt (1938), and by H. B. Steinbach (1940)^[4] on muscle fibers, which had shown that the muscle membrane, contrary to the view held by Conway, is permeable to Na⁺, Dean concluded: “the muscle can actively move potassium and sodium against concentration gradients [...] this requires work. Therefore there must be some sort of a pump possibly located in the fiber membrane, which can pump out sodium or, what is equivalent, pump in potassium.”

In the following decade, helped by the introduction of radioactive isotopes of Na⁺ and K⁺,^[5] it was shown not only from experiments on muscle fibers, but on red blood cells, on nerves, and on frog skin that the membrane is permeable to Na⁺ as well as to K⁺ (for references see an extensive review by Ussing^[6]). An energy-dependent efflux of Na⁺ is therefore necessary.

However, Conway strongly defended his view about the impermeability to sodium, and only reluctantly gave way. He

[*] Prof. Dr. J. C. Skou
Department of Biophysics
University of Århus
Ole Worms Allé 185, DK-8000 Aarhus C (Denmark)
Fax: (+45) 8612-9599

[**] Copyright© The Nobel Foundation 1998. We thank the Nobel Foundation, Stockholm, for permission to print this lecture.

admitted that there may be a certain permeability for Na^+ and thereby a need for a pump, but maintained that low permeability for Na^+ is the main explanation of the concentration gradient. Conway's concern was that it is a waste of energy to have a membrane permeable to Na^+ and then spend energy to pump Na^+ out. Krogh^[7] had in a Croonian lecture in 1946 entitled "The active and passive exchange of inorganic ions through the surfaces of living cells and through living membranes generally" criticized Conway's view about impermeability to sodium. Krogh concluded: "The power of active transport of ions is of a common occurrence both in the vegetable and the animal kingdom and is possibly a general characteristic of the protoplasmic surface membrane". Conway replied the same year in a paper in *Nature*:^[8] "Krogh [...] considers the apparent impermeability to sodium as due to an active extrusion, sodium ions entering the (muscle) fibers as fast, if indeed not faster, than potassium. The following may then be considered: the minimal energy required for extrusion of sodium ions from the normal frog's sartorius if sodium enters as fast as potassium". A calculation showed that the energy requirement was about twice the resting metabolism of the muscle. Ussing^[9] came to the same result, but the explained what the apparent problem was. Only a part of the measured Na^+ flux is due to active transport of Na^+ , the other part is due to an exchange across the membrane of Na^+ from the one side for Na^+ from the other side, a $\text{Na}-\text{Na}$ exchange which is energetically neutral and which gives no net flux of Na^+ across the membrane. Taking this into account, the energy available is more than sufficient. However, Conway's concern was relevant in the sense that with the knowledge at that time about membrane function, an active transport seemed energetically an expensive way to solve the osmotic problem of the cell.

In the 1940s and first half of the 1950s the concept of active transport developed.^[6] It was defined as a transport against an electrochemical gradient.^[10] It was shown that the active efflux of sodium was coupled to an influx of potassium, a pump, and that the substrate for the transport was energy-rich phosphate esters.^[11]

But what was the nature of the pump? With the information available in the beginning of the 1950s it was possible to foresee that the pump is a membrane-bound protein with enzymatic activity, which has ATP as substrate and is activated by Na^+ on the cytoplasmic side and by K^+ on the

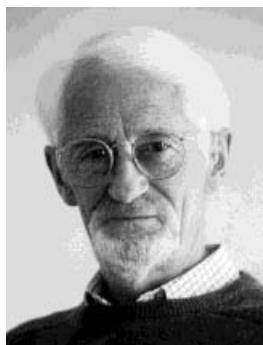
extracellular side. But nobody apparently thought that way. A reason may be that the membrane according to the model by Danielli and Davson is a bilayer of lipids with no room for proteins inside the bilayer spanning the bilayer. On the contrary, it was assumed that protein in the bilayer would destabilize the cell membrane. It was assumed that the protein was in the interphase between the lipids and the water on the two sides of the membrane.

The Way to the Sodium Pump^[12, 13]

My scientific interest was the mechanism of action of local anaesthetics. I held a position at the Institute of Physiology at the University of Århus, and was using this problem as subject for a thesis. In 1953 I had finished a series of experiments on the problem, which was published in 1954 as a book in Danish, and accepted by the faculty to be defended for the medical doctors degree.^[14] It was also published as six papers in English.^[15]

I had received my medical degree in the summer of 1944, and started my internship at a hospital in Hjørring in the northern part of the country, six months in the medical ward followed by six months in the surgical ward. I became interested in surgery, and after my internship I continued for another year in the surgical ward. We had no anaesthetists and, to avoid the unpleasant ether narcosis, we used whenever possible spinal and local anaesthesia. From the teaching of pharmacology I knew the Meyer–Overton theory,^[16, 17] which states that there is a correlation between solubility of general anaesthetics in lipids and the anaesthetic potency. General anaesthetics are nonpolar substances, while local anaesthetics are weak bases, which at the physiological pH exist as a mixture of charged and uncharged molecules. I wondered which of the two components is the anaesthetic component, and whether a correlation, similar to that for the general anaesthetics, existed for the local anaesthetics. I decided to use this problem as a subject for a thesis. After the two years at the hospital in Hjørring, I took up a position for a year at the Orthopaedic Hospital in Århus, and after this in 1947 I applied for and received a position at the Institute of Medical Physiology at Århus University.

Århus University was young, founded 19 years earlier. There were Institutes for Anatomy, Biochemistry, and Phys-



Jens C. Skou was born in 1918 in Lemvig, Denmark. He received his medical degree at Copenhagen University in 1944. He got his doctor of medical sciences degree in 1954 at Århus University, where he became Professor of Physiology as well as Chairman of the Institute of Physiology in 1963. In 1977 he was appointed Professor of Biophysics at the same university. He is a member of the Danish Academy of Sciences, and has received numerous awards, among them the 1997 Nobel Prize in Chemistry.

iology as a beginning of a Medical Faculty, which was not completed until 1957. These were the only biological Institutes at the Campus, and the scientific biology milieu was poor, with little or no contact with the outside scientific world. We were three young doctors besides the Professor, Søren L. Ørskov, in the department, each working on our thesis. None of us had any scientific background, but Ørskov was very helpful and patient and let us take the necessary time. We had an intake of 140 medical students a year so the teaching load was heavy. After having passed physiology the students had to continue at the Medical Faculty in Copenhagen for their medical degree.

I used the intact sciatic nerve of frog legs as a test object for measuring the blocking potency of five different local anaesthetics, which are weak bases, and of butanol as a representative of a nonpolar blocking agent. After removing the sheath around the nerve to get easier access to the single nerve fibers, I measured the blocking concentration as a function of time, and from this the minimum blocking concentration at infinite time of exposure could be determined. The concentrations necessary varied from the weakest to the strongest of the local anaesthetics by a factor of 1:920 (with butanol included, 1:13 500). The order of anaesthetic potency and solubility in lipids were the same, but the quantitative correlation was poor, that is, local anaesthetics did not follow the Meyer–Overton rule for general anaesthetics.

I was looking for another test object. As the cell membrane is a bilayer of lipids, I decided to use a monomolecular layer of lipids on a Krebs–Ringer water phase as a model for a water–cell membrane interphase. The inspiration came from reading about Langmuir's work on monomolecular layers of lipids on a water phase in "The Physics and Chemistry of Surfaces" by N. K. Adam, and that Schulmann had applied capillary active drugs in the waterphase beneath the monolayer and observed that they penetrated up into the monolayer.^[18]

In a Langmuir trough the area of the monolayer can be measured as a function of the pressure that the monolayer exerts on a floating barrier which separates the monolayer from the pure water phase without the monolayer. My first experiments were with a monolayer of stearic acid. At a given area per molecule, which also means at a given surface pressure, application of the local anaesthetics to the water phase gave an increase in pressure, indicating that the local anaesthetics penetrated up into the monolayer, and the pressure increased with the concentration. There was a certain correlation between anaesthetic potency and pressure increase, but quantitatively not clear enough. However, with a monolayer of lipids extracted from the sciatic frog nerves there was a reasonably good correlation. The order of the concentrations necessary to increase the pressure followed the order of anaesthetic potency. And the minimum blocking concentration of the five local anaesthetics, which as mentioned varied by a factor of 1:920, gave a pressure increase in the monolayer at a certain area which was of the same order; they varied by a factor of 1:3.2. Also the effect of a change in pH on the local anaesthetic potency correlated reasonably well to the effect of pH on the pressure increase at a given area.

The rising phase of the nerve impulse, the depolarization, is due to a transient increase in permeability of the membrane for Na^+ .^[19] The molecular basis for this was unknown, but it seemed unlikely that it was connected to the lipids. I assumed that the permeability increase was on proteins in the membrane. The monolayer results suggested to me that the effect of the penetration of local anaesthetics into the lipid part of the nerve membrane was a blocking of the conformational change in proteins in the membrane, which gave the increase in permeability to Na^+ .

To test this I wanted to see if pressure in a monolayer could influence the enzymatic activity of a protein in the monolayer, and take this as indication of an effect of pressure on conformation. And if there was an effect, I then wanted to form a monolayer of a mixture of lipids and the enzyme, and test if penetration of local anaesthetics into the monolayer had an effect on the enzymatic activity. For this I needed an enzyme with high activity, and which was related to membrane function. A candidate was acetylcholinesterase, which was then being prepared from electric eel by Professor Nachmansohn at Columbia University in New York. It had the further advantage that it involved a visit New York.

The Professor of Physiology in Copenhagen, Einar Lunds-gaard, was a close friend of David Nachmansohn and introduced me. I had planned to spend August in New York, take a break at the end of August and beginning of September to attend the 19th International Congress of Physiology in Montreal, and then return to New York in September (and not, as mentioned in ref. [12, 13], in July or August). This would fit with my teaching schedule. Nachmansohn would not be in New York until September, as he spent the summer at the Marine Biological Station in Woods Hole; he therefore suggested I should join him there in August. In September he would return to New York. I agreed, although I did not know what to do in Woods Hole; there was no access to electric eel.

Scientists interested in the function of the nervous system came from all over the world to Woods Hole during the summer to use the giant axons from squids as test objects. Coming from a young University with a poor scientific milieu, this was like coming to another planet. The place was bubbling with scientific activity. I realized that science is a serious affair and not just a temporary hobby for young doctors writing a thesis in order to qualify for a clinical career. And also that it is competitive. I listened to lectures, met people whose names I knew from the textbooks and from the literature, and spent time in the laboratories looking on and learning from the experiments.

In between I did some reading, and in a paper written by Nachmansohn it was mentioned that B. Libet^[20] in 1948 had shown that there is an ATP hydrolyzing enzyme in the sheath part of the giant axon from squid: an ATPase. As ATP is the energy source in cells I wondered what the function could be of an ATPase in the membrane of a nerve. As it is situated in the membrane, I assumed that it was a lipoprotein, and this was what I needed for the monolayer experiments. I decided to look for the enzyme when I came home.

I prepared acetylcholinesterase at Columbia University in September from the electric eel. Back in Århus I continued the monolayer experiments. I had no access to giant axons in

Århus, but decided to look for the putative nerve membrane ATPase in crab nerves because the crab nerve, like the giant axon, has no myelin sheath. In 1954 I arranged with a fisherman south of Århus to send me some crabs and started to isolate the sciatic nerve from the legs. The nerves were homogenized, and the membrane pieces isolated by a differential centrifugation.

The experiments showed that the membrane fractions had a low Mg^{2+} -activated ATP hydrolyzing enzyme activity. Addition of Na^+ besides Mg^{2+} gave a slight increase in activity. K^+ had no effect in the presence of Mg^{2+} (Figure 1). However, the activity varied from experiment to experiment.

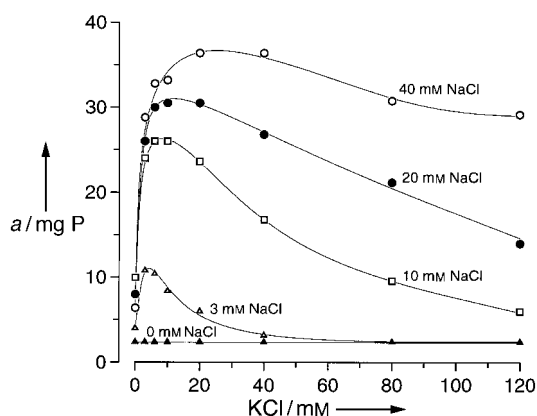


Figure 1. Effect of Na^+ and K^+ in the presence of Mg^{2+} on the hydrolysis of ATP by membrane fractions isolated from nerves of the shore crab *Carcinus maenas*. The test solution contained 30 mM histidine HCl as buffer (pH 7.2), 3 mM ATP, 6 mM Mg^{2+} , Na^+ (0 $\blacktriangle$, 3 $\triangle$, 10 $\square$, 20 $\bullet$, 40 mM $\circ$), and K^+ in concentrations shown. The activity a is given as the amount [mg] of inorganic phosphate (P) hydrolyzed from ATP in 30 min at 36 °C (reprinted with permission from ref. [27]).

Calcium was excluded as the reason for the variations. After having spent November and December trying to find a solution, I gave up and went on my Christmas holidays. I resumed the experiments in June of the following year, but still unable to get reproducible results, went on summer holidays. Returning in August, I made a Na^+ salt and a K^+ salt of ATP and found to my surprise that the activity with the K^+ salt was higher than with the Na^+ salt. This could not be due to a difference in ATP, but to an effect of K^+ which differed from that of Na^+ . But why in this experiment and not in the previous experiments, where K^+ had no effects in the presence of Mg^{2+} ? The answer was that in the experiments with the K^+ salt of ATP there was Na^+ in the medium. In other words the enzyme needed a combined effect of Na^+ and K^+ for activation. I then started a systematic investigation of the combined effect of the two cations.

As seen from Figure 1, K^+ has two effects in the presence of Na^+ . It activates with increasing concentration of Na^+ . The K^+ affinity for the activating effect is high. At higher concentrations the activating effect of K^+ decreases, and the apparent affinity for K^+ for this effect decreases with an increase in the Na^+ concentration. With 3 mM Na^+ it is seen that K^+ not only inhibits its own activation, but also the small activation due to Na^+ . The results suggest that there are two sites on the enzyme, one where Na^+ is necessary for activation and

another where K^+ activates when Na^+ is bound to the former. When present in higher concentrations K^+ competes with Na^+ at the Na^+ site, and by displacing Na^+ from the site decreases the activity.

I now understood the reason for the varying results. With little effect of Na^+ on the activity, and of no effect of K^+ , I had not bothered whether or not there was Na^+ or K^+ in the medium. I got ATP as an insoluble barium salt, which was converted into a soluble Na^+ or K^+ salt, sometimes the one sometimes the other, and in between instead of homogenizing the nerves in glucose I used a 0.58 M KCl solution. It never occurred to me that there could be a combined effect of Na^+ and of K^+ .

The problem then was, what was the physiological function of the enzyme? I was interested in the effect of local anaesthetics on nerve conduction, and my first reaction was that this was the Na^+ channel which opens for the influx of Na^+ leading to the nerve impulse. I soon rejected the idea because the opening of the channel is dependent on voltage, and not on ATP. The other possibility was that it was part of or the sodium pump. As I had little knowledge about the active transport of Na^+ and of K^+ , I started to look into the literature to see what the substrate was for the active transport in nerves. I had limited access to the literature, so there were few papers I read about active transport. The closest I could come was that A. L. Hodgkin and R. D. Keynes^[21] had shown that poisoning giant axons with dinitrophenol, cyanide, or azide decreased the active transport of sodium, suggesting that high-energy phosphate esters are the substrate. And as ATP is a high-energy phosphate ester, I thought it likely that it could be the substrate.

There were two papers I did not read: One was by G. Gardos^[22] from Budapest published in 1954 in a Hungarian journal, which I did not have access to and which was not cited in the paper by Hodgkin and Keynes. In this Gardos showed that ATP supported the active uptake of K^+ in red blood cells. The other was a paper published in 1956 by Hodgkin and Keynes,^[23] in which they reported that injecting ATP in a giant axon poisoned with cyanide gave no dramatic recovery of the active extrusion of sodium. Fortunately, I did not see this last paper until I had sent my paper on the crab nerve enzyme for publication. In 1957 the experiment was repeated by Caldwell and Keynes,^[24] with the result that ATP was the substrate for the active transport.

In a discussion after a paper by R. D. Keynes on „Electrolytes and Nerve Activity“^[25] at an international symposium on Neurochemistry in Århus in 1956, I showed the results with the crab nerve ATPase.^[26] The same year I wrote the paper, and suggested, from the characteristics of the effect of the cations and the fact that ATP was a substrate, that the enzyme was involved in the active transport of Na^+ across the cell membrane. I considered putting the word pump in the title, but found it too provocative, so it became “The Influence of Some Cations on an Adenosine Triphosphatase from Peripheral Nerves”. No wonder that few people noticed that this enzyme had to do with active transport of Na^+ . It was published in 1957.^[27]

With my little knowledge about active transport, I was unaware of the importance of the observation on the crab

nerves. Parallel with the crab nerve experiments I continued the experiments on the monolayer with the acetylcholinesterase. In 1958 I presented a paper at the 4th International Congress of Biochemistry in Vienna on “The Influence of the Degree of Unfolding and the Orientation of the Side Chains on the Activity of a Surface Spread Enzyme”.

There was one important experiment I had not done. I realized this when I met Robert Post at the conference. I knew Robert from Woods Hole. We had spend time in the same laboratory, and I had driven with him and his wife Elizabeth in their car from Woods Hole to the International Congress for Physiology in Montreal. He told me that he had since worked with active transport of Na^+ and K^+ in red blood cells, and had shown that the stoichiometry between the Na^+ transport out of and of K^+ into the cell was 3:2.^[28]

I told him about the $\text{Na}^+ + \text{K}^+$ -activated crab nerve enzyme, and that it seemed to be part of or the sodium pump. His reaction suggested to me that this was more important than surface spread enzymes. “Is it inhibited by ouabain?” he asked. “What is ouabain?” was my reply. He then told me that Schatzmann in Switzerland in 1954 had shown that cardiac glycosides, of which ouabain is the most water-soluble, specifically inhibits the active transport in red blood cells.^[29] When Robert Post came to Århus after the conference I had the answer. The enzyme was inhibited by ouabain, even if the sensitivity of the crab nerve enzyme is much lower than the sensitivity of the transport in red blood cells. It convinced Robert that the enzyme had to do with active transport. I had learned that red blood cells were a classical test object for experiments on active transport, and had started to look for the enzyme in these cells. Robert asked if he could go on with these experiments when he returned to U.S. I had no experience with this test object, and as he had the experience, I agreed and continued the experiments with the crab nerve enzyme^[30] and looked for the enzyme in other tissues.^[31]

In 1959, after I had given my first paper on the crab nerve enzyme at the 21th International Congress for Physiology in Buenos Aires, Professor Hodgkin, who was the great name in neurophysiology and came from the famous Cambridge University, invited me for lunch to hear more about the enzyme. His interest suggested to me that the observation was of a certain importance.

Looking back, it was a very simple experiment to identify the pump. Just break the membrane and thus gain access to the Na^+ site on the inside and the K^+ site on the outside, add some ATP, and test for the combined effect of Na^+ and K^+ . It ought to have been done by someone who worked in the transport field and knew about active transport. I felt like an intruder in a field that was not mine.

There was, however, much luck involved. First, that Nachmansohn had invited me to Woods Hole, where I learned about the giant axons and read about the observation by Libet. Next that from the monolayer experiments I became interested in membrane proteins, especially lipoproteins, and therefore took notice of Libet’s observation. Finally, that I chose crab nerves as a test object. I learned later that after homogenization of most other tissues in order to break the membrane, the membrane pieces form vesicles, which must be opened by treatment with detergent in order to get access to

both sides of the membrane and thereby to see the combined effect of Na^+ and K^+ . This is not the case with the crab nerve membranes.

From then on the Na^+/K^+ -ATPase took me away from the monolayer experiments. I never did the planned experiments on the effect of the local anaesthetics on a monolayer of a mixture of lipids and proteins; and I never used the Na^+/K^+ -ATPase for monolayer experiments. First of all because it was not until 1980 that it became possible to extract the enzyme from a membrane in a pure stable watersoluble form, and secondly, because that was only possible with the use of detergent.^[32] A problem would have been the detergent, but I had lost interest in monolayers.

In 1960 Robert Post published the paper on the red blood cell experiments “Membrane adenosine triphosphatase as a participant in the active transport of sodium and potassium in the human erythrocytes”.^[33] In this he convincingly showed that in the red blood cells there is a $\text{Na}^+ + \text{K}^+$ -activated ATPase also, and that the effect of the cations on the activity correlated with the effect on transport. Robert Post was known in the transport field, and his paper had a better title than mine, so it attracted more attention.

In the following few years many papers were published which showed that the enzyme could be found in many different tissues, and evidence was given for its involvement in active transport.^[34] In 1965 so much evidence was at hand, that in a review paper I could conclude that the enzyme system fulfilled the following requirements for a system responsible for the active transport across the cell membrane:

- 1) It is located in the cell membrane.
- 2) On the cytoplasmic side, it has a higher affinity for Na^+ than for K^+ .
- 3) It has an affinity for K^+ on the extracellular side which is higher than that for Na^+ .
- 4) It has enzymatic activity and catalyzes ATP hydrolysis.
- 5) The rate of ATP hydrolysis depends on cytoplasmic Na^+ as well as on extracellular K^+ .
- 6) It is found in all cells that have coupled active transport of Na^+ and K^+ .
- 7) The effect of Na^+ and of K^+ on transport in intact cells, and on the activity of the isolated enzyme, correlates quantitatively.
- 8) The enzyme is inhibited by cardiac glycosides, and the inhibitory effect on the active fluxes of the cations correlates with the inhibitory effect on the isolated enzyme system.^[34]

The enzyme was named the Na^+ - and K^+ -activated ATPase, or Na^+/K^+ -ATPase.

The Na^+/K^+ -ATPase as an Energy Transducer

Let us return to Conway’s concern about the waste of energy. Conway was right in the sense that even if the cell membrane is permeable to sodium, and therefore an energy-requiring pump is needed, the ground permeability to sodium of the cell membrane must be low, so that the maintenance of the gradient for sodium does not become energetically too costly for the cell. But what is the meaning of having a membrane permeable to sodium and then spend energy, 10–

60% of the cell metabolism, to keep Na^+ out of the cell and K^+ within the cell?

1) As mentioned above it solves the osmotic problem due to the presence of impermeable protein anions in the cytoplasm.

2) Furthermore, the gradients for Na^+ into and K^+ out of the cell sustained by the pump represent an energy source, which is used for the creation of a membrane potential. The cell membrane is more permeable to K^+ than to Na^+ , which means that K^+ flows out of the cell faster than Na^+ into the cell. This leads to a diffusion potential across the membrane, negative on the inside, which slows the K^+ outflux and increases the Na^+ influx until the potential reaches a value of about -70 mV , at which point the rates of the two fluxes are equal; a steady-state situation. The membrane potential is the basis for the function of all excitable tissue. The nerve impulse is a depolarization of the membrane potential due to a transient increase in permeability to Na^+ , with influx of Na^+ followed by a repolarization due to an outflux of K^+ .^[35] This leads to an increase in intracellular Na^+ and a decrease in K^+ , which subsequently must be compensated for by the pump.

3) The energy from the concentration gradient is used for transport of other substances in and out of the cell (Figure 2). In the cell membrane there are a number of protein molecules which act as co- or countertransporters, or sym- and antiporters.^[36] There are cotransporters which use the gradient for Na^+ into the cell to transport glucose^[37] or amino acids^[38] into cells so that they have a higher concentration inside than outside, and a Na^+/Cl^- , a $\text{Na}^+/\text{K}^+/2\text{Cl}^-$, and a K^+/Cl^- cotransporter, which may be involved in volume regulation.^[39] There is a $3\text{Na}^+/\text{Ca}^{2+}$ countertransporter of importance for regulation of the intracellular Ca^{2+} concentration^[40] and a Na^+/H^+ countertransport for regulation of internal pH. In addition, there are other examples.

4) The energy from the concentration gradient is used for transepithelial transport in intestine, kidney, and secretory glands.

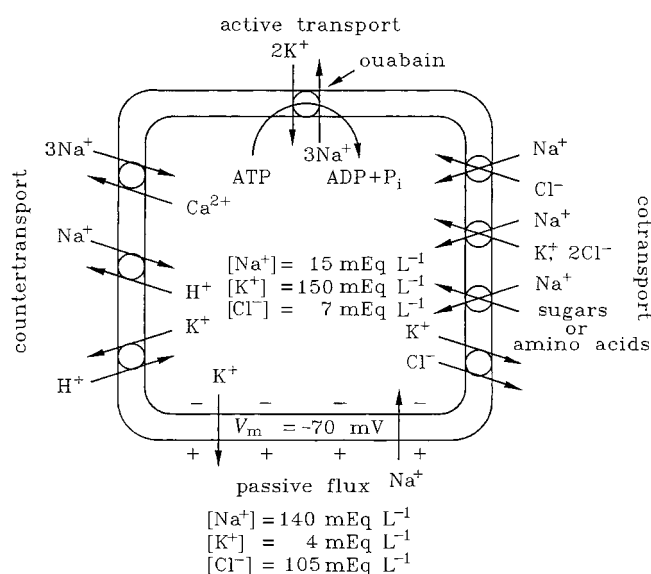


Figure 2. Transport across the cell membrane. For an explanation see text (reproduced with permission from ref. [73]).

The $\text{Na}^+ - \text{K}^+$ pump thus acts as an energy transducer that converts the chemical energy from the hydrolysis of ATP into another form of energy, a concentration gradient, which is used for exchange of substances across the cell membrane. This is named a secondary active transport, while the transport which is directly dependent on the energy from a chemical reaction, the active Na^+/K^+ transport, is named a primary active transport. The Na^+/K^+ -ATPase has thus a key function in the exchange of substances across the cell membrane.

A problem was where to place the Na^+/K^+ -ATPase in the membrane. The transport system, which is a protein, must have access to both sides of the membrane. As mentioned previously there is no room for proteins in the bilayer of the Danielli–Davson membrane model. Neither is there in Robertson's unit membrane model from 1959^[41] which replaced it. The unit membrane was a bilayer of lipids with proteins arranged asymmetrically on the two sides of the membrane, but still with no proteins spanning the membrane. It was not until 1972 that a suitable model was introduced by Singer and Nicolson.^[42] In their fluid mosaic membrane model there are globular proteins embedded with their nonpolar parts in the bilayer, and with the polar parts facing the two sides of the bilayer. They can move laterally in the membrane, but do not flip-flop. They form pathways for the transport of hydrophilic substances across the membrane.

Other mammalian ion-transporting pumps were identified in the following years: a Ca^{2+} -ATPase in sarcoplasmic reticulum in muscle responsible for the transport of Ca^{2+} out of the muscle fiber,^[43] a Ca^{2+} -ATPase isolated from red blood cells which transports Ca^{2+} out of the cell,^[44] and a H^+/K^+ -ATPase in the stomach which transports H^+ out of the cells in exchange for K^+ , producing the stomach acid.^[45] They all have in common with the Na^+/K^+ -ATPase that the reaction with ATP involves a phosphorylation, and they are therefore named P-type ATPases. A number of other P-type ATPases have been identified in bacteria and fungi.^[46]

In the years that followed the identification of the sodium–potassium pump, many scientists from many countries took part in the elucidation of the structure of the system and of the reaction steps in the transport process. This cannot be covered in the present lecture, but for those interested I shall refer to an extensive review by I. Glynn in 1985,^[11] to the proceedings from the international conferences on the Na^+/K^+ -ATPase held every third year of (the latest is from 1996),^[47] to recent reviews,^[48–50] and to the recently published book by J. D. Robinson: “Moving Questions. A History of Membrane Transport and Bioenergetics”.^[46]

There is, however, one question I would like to touch on shortly without going into details, namely this: What is our present view on the way the system transports the cations?

A Model for the Transport Reaction

The model in Figure 3 is based on the Albers–Post scheme, a reaction scheme in which the system reacts consecutively with the cations, and in which the reaction with ATP in the

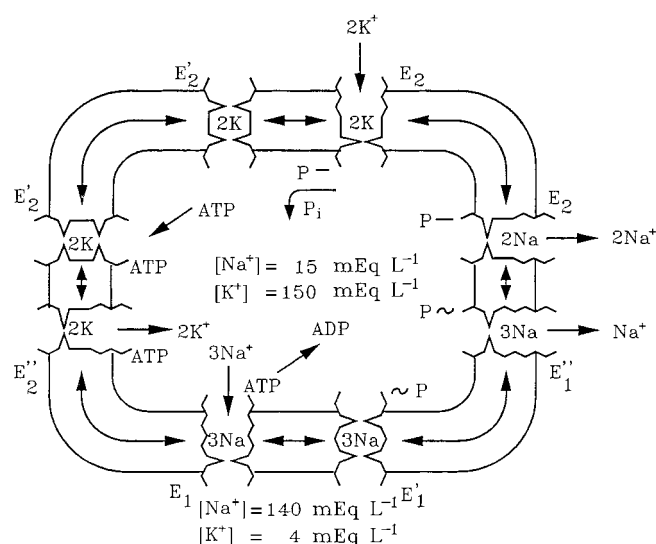


Figure 3. The active transport reaction. For an explanation see text (reproduced with permission from ref. [73]).

presence of Na^+ leads to a phosphorylation and the following reaction with K^+ to a dephosphorylation.^[51–56]

The transport system consists of a carrier part located in the innermost part of the membrane with the ATP-binding part on the cytoplasmic side of the membrane (Figure 3). The carrier is in series with a narrow channel which spans half to two-thirds of the membrane and opens to the extracellular side of the membrane^[57, 58] (in Figure 3 the channel part is shown only as the opening to the outside). The carrier exists in two major different conformations:^[51–56, 59–65] E_1 , which is the high-affinity sodium form, and E_2 , which is the high-affinity potassium form. Each of the two conformations can exist in a phosphorylated^[51–56] and a nonphosphorylated form,^[59–65] and each of the two major conformations have subconformations marked with primes in Figure 3. The carrier part has two gates, energy barriers, which can open and close access to the channel side and to the cytoplasmic side, respectively.

Referring to the model, with the system in the E_1 conformation with the gate to the cytoplasmic side open but that to the channel side closed, three Na^+ ions are bound, two of them as a neutral complex and the third one as an ion. The system is catalytically active. The affinity for ATP is high (apparent K_D is about $0.1 \mu\text{M}$ ^[59, 60]), and with ATP bound the enzyme is phosphorylated^[51–56, 66, 67] to an ADP sensitive form. This means that a high-energy phosphate bond is formed ($\text{E}_1 \sim \text{P}$), which closes the gate to the cytoplasmic side. The three Na^+ ions are occluded inside the carrier part.^[68] The following two steps involve conformational changes and rearrangements of the phosphate bond from a high-energy to a low-energy bond ($\text{E}_1' \sim \text{P}$ to $\text{E}_2 - \text{P}$);^[51–56, 66, 67] deocclusion and release of one Na^+ from the $\text{E}_1' \sim \text{P}$ form^[67] to the extracellular side of the membrane takes place. The transition to the $\text{E}_2 - \text{P}$ form deoccludes, opens the gate for the remaining two Na^+ ions, and the affinity decreases for Na^+ and increases for K^+ . By this, the two Na^+ are exchanged for two K^+ ions from the extracellular medium ($\text{E}_2 - \text{PNa}_2$ to $\text{E}_2 - \text{PK}_2$). With two K^+ ions bound the system is dephosphorylated; the extracellular gate closes and the two K^+ ions are

occluded ($\text{E}_2' \cdot (2\text{K})$).^[69, 70] ATP bound to $\text{E}_2' \cdot (2\text{K})$ on the cytoplasmic side, with an affinity which is low (apparent K_D is about 0.1 mM), increases the rate at which the cytoplasmic gate opens and decreases the affinity for K^+ ($\text{E}_2' \cdot (2\text{K}) \cdot \text{ATP}$ to $\text{E}_2' \cdot (2\text{K}) \cdot \text{ATP}$).^[69] The two K^+ ions are exchanged for three Na^+ ions from the cytoplasmic medium, and this closes the cycle.

The transport system is a very efficient pump. It pumps three Na^+ ions out of and two K^+ ions into the cell for each ATP hydrolyzed to ADP and P_i , and for this it uses 70–85% of the free energy of the hydrolysis of ATP.^[50] With the normal intra- and extracellular concentrations of Na^+ and K^+ , the activity of the pump is 10–15% of maximum; that is, the pump has a considerable reserve power. At 37°C and pH 7.4 the enzyme turns over at a rate of about 160 per second.

In the transport reaction one net positive charge is carried to the outside. The transport is therefore electrogenic, but due to a high permeability of the membrane to Cl^- it only adds a few millivolts to the membrane potential. Each of the two conformations E_1 and E_2 seem to have two negatively charged binding sites on which the positive charge of the cations are neutralized; in addition, the E_1 conformation, as mentioned above, binds a third Na^+ ion in ionic form.^[71, 72]

To obtain transport of the cations against an electrochemical gradient coupled to a chemical reaction, the hydrolysis of ATP, it is necessary that there is a tight coupling between each of the steps in the catalytic reaction and each of the corresponding steps in the translocation reaction, as suggested in the model. The shift in affinities, and the opening and closing of the gates, are coupled to the stepwise degradation of ATP from phosphorylation with a high-energy $\text{E}_1 \sim \text{P}$ bond to a low-energy $\text{E}_2 \sim \text{P}$ bond, and finally to dephosphorylation. This divides the translocation into steps in which local gradients are created along which the ions can flow, and thereby they are transported against their overall gradient.

The model is a working hypothesis which explain a good deal of the experimental observations. There are, however, observations which do not fit with the model. And even though we have much information about the structure, there are many unanswered questions, especially at the molecular level: What is the nature of the gates, where are the binding sites for the cations, and of what nature, and how does the system discriminate between Na^+ and K^+ , etc.

Conclusion

It may seem disappointing that 30 years of work, since the conclusion that the membrane-bound Na^+/K^+ -ATPase is identical with the $\text{Na}^+ - \text{K}^+$ pump, has not given us an understanding of the basic molecular events behind the transport. However, considering that the problem is to reveal how 1320 amino acids inside a volume of $60 \times 60 \times 100 \text{ \AA}^3$ can be assembled to a very efficient machine which can convert the chemical energy from the hydrolysis of ATP into work, namely the transport of cations against their electrochemical gradient, and which can distinguish between so closely related cations as Na^+ and K^+ , it can be of no surprise that progress is slow.

Thirty years ago it seemed impossible to find a way to purify the enzyme, not to speak of getting it into solution and reconstituting it into liposomes. Nobody dared to dream about knowing the sequence, and yet this and much more has been accomplished.

Received: April 17, 1998 [A278IE]

German version: *Angew. Chem.* **1988**, *110*, 2452–2461

Keywords: ATP • ion transport • membranes • Nobel lecture • sodium–potassium pump

- [1] E. Gorter, F. Grendel, *J. Exp. Med.* **1925**, *41*, 439.
- [2] J. F. Danielli, H. Davson, *J. Cell. Comp. Physiol.* **1935**, *5*, 495.
- [3] P. J. Boyle, E. F. Conway, *J. Physiol.* **1941**, *100*, 1.
- [4] R. B. Dean, *Biol. Symp.* **1941**, *3*, 331.
- [5] G. Hevesy, *Enzymologia* **1938**, *5*, 138.
- [6] H. H. Ussing, *Physiol. Rev.* **1949**, *29*, 129.
- [7] A. Krogh, *Proc. R. Soc. London B* **1946**, *133*, 140.
- [8] E. J. Conway, *Nature* **1946**, *157*, 715.
- [9] H. H. Ussing, *Nature* **1947**, *160*, 262.
- [10] T. Rosenberg, *Acta Chem. Scand.* **1948**, *2*, 14.
- [11] I. M. Glynn in *The Enzymes of Biological Membranes*, Vol. 3 (Ed.: A. N. Martonosi), New York, Plenum **1985**, p. 28.
- [12] J. C. Skou, *Biochim. Biophys. Acta* **1989**, *1000*, 435.
- [13] J. C. Skou in *Membrane Transport: People and Ideas* (Ed.: D. Tosteson), American Physiological Society **1989**, p. 155.
- [14] „Lokalanestetika“: J. C. Skou, Dissertation, Universitetsforlaget Aarhus, **1954**.
- [15] J. C. Skou, *J. Pharm. Pharmacol.* **1961**, *13*, 204.
- [16] H. H. Meyer, *Arch. Exp. Pathol. Pharmacol.* **1899**, *42*, 109.
- [17] E. Overton, *Studien über die Narkose zugleich ein Beitrag zur allgemeinen Pharmakologie*, Jena, Fischer, **1901**.
- [18] N. K. Adam, *The Physics and Chemistry of Surfaces*, London, Oxford University Press, **1941**.
- [19] A. L. Hodgkin, B. Katz, *J. Physiol. (London)* **1949**, *108*, 37.
- [20] B. Libet, *Fed. Proc.* **1948**, *7*, 72.
- [21] A. L. Hodgkin, R. D. Keynes, *J. Physiol. (London)* **1955**, *128*, 28.
- [22] G. Gardos, *Acta Physiol. Acad. Sci. Hung.* **1954**, *6*, 191.
- [23] A. L. Hodgkin, R. D. Keynes, *J. Physiol. (London)* **1956**, *131*, 592.
- [24] P. C. Caldwell, R. D. Keynes, *J. Physiol. (London)* **1957**, *137*, 12P.
- [25] R. D. Keynes, in *Metabolism of the Nervous System* (Ed.: D. Richter), Pergamon, London, **1957**, p. 159.
- [26] J. C. Skou, in *Metabolism of the Nervous System* (Ed.: D. Richter), Pergamon, London, **1957**, p. 173.
- [27] J. C. Skou, *Biochim. Biophys. Acta* **1957**, *23*, 394.
- [28] R. L. Post, P. Jolly, *Biochim. Biophys. Acta* **1957**, *25*, 118.
- [29] H. J. Schatzmann, *Helv. Physiol. Pharmacol. Acta* **1953**, *11*, 346.
- [30] J. C. Skou, *Biochim. Biophys. Acta* **1960**, *42*, 6.
- [31] J. C. Skou, *Biochim. Biophys. Acta* **1962**, *58*, 314.
- [32] M. Esmann, J. C. Skou, C. Christiansen, *Biochim. Biophys. Acta* **1979**, *567*, 410.
- [33] R. L. Post, C. R. Merritt, C. R. Kinsolving, C. D. Albright, *J. Biol. Chem.* **1960**, *235*, 1796.
- [34] J. C. Skou, *Physiol. Rev.* **1965**, *45*, 596.
- [35] A. L. Hodgkin, A. F. Huxley, *J. Physiol. (London)* **1952**, *116*, 449.
- [36] P. Mitchell, *Biochem. Soc. Symp.* **1963**, *22*, 142.
- [37] R. K. Crane, *Comp. Biochem.* **1983**, *35*, 43.
- [38] H. Kromphardt, H. Grobecker, K. Ring, E. Heinz, *Biochim. Biophys. Acta* **1963**, *74*, 549.
- [39] E. K. Hoffmann, L. O. Simonsen, *Physiol. Rev.* **1989**, *69*, 315.
- [40] B. J. R. Pitts, *J. Biol. Chem.* **1979**, *254*, 6232.
- [41] J. D. Robertson, *Biochem. Soc. Symp.* **1959**, *16*, 3.
- [42] S. J. Singer, G. L. Nicolson, *Science* **1972**, *175*, 720.
- [43] W. Hasselbach, M. Makinose, *Biochem. Z.* **1961**, *333*, 518.
- [44] H. J. Schatzmann, *Experientia* **1966**, *22*, 364.
- [45] B. Stewart, B. Wallmark, G. Sachs, *J. Biol. Chem.* **1981**, *256*, 2682.
- [46] J. D. Robinson, *Moving Questions. A History of Membrane Transport and Bioenergetics*, American Physiological Society, NY **1997**.
- [47] *Na/K-ATPase and Related Transport ATPases: Structure, Mechanism and Regulation*, Vol. 834 (Eds.: L. A. Beaugé, D. C. Gadsby, P. J. Garrahan), Annals New York Academy Science, New York, **1997**.
- [48] P. L. Jørgensen, in *Molecular Aspects of Transport Proteins* (Ed.: J. H. M. M. De Pont), Elsevier Service Publisher, **1992**, p. 1.
- [49] I. M. Glynn, *J. Physiol. (London)* **1993**, *462*, 1.
- [50] F. Cornelius, *Biomembranes* **1996**, *5*, 133.
- [51] R. W. Albers, *Annu. Rev. Biochem.* **1967**, *36*, 727.
- [52] R. W. Albers, S. Fahn, G. J. Koval, *Proc. Natl. Acad. Sci. USA* **1963**, *50*, 474.
- [53] S. Fahn, G. J. Koval, R. W. Albers, *J. Biol. Chem.* **1968**, *243*, 1993.
- [54] R. L. Post, S. Kume, *J. Biol. Chem.* **1973**, *248*, 6993.
- [55] R. L. Post, S. Kume, T. Tobin, B. Orcutt, A. K. Sen, *J. Gen. Physiol.* **1969**, *54*, 306S.
- [56] R. L. Post, A. K. Sen, A. S. Rosenthal, *J. Biol. Chem.* **1965**, *240*, 1437.
- [57] P. Läuger, *Biochim. Biophys. Acta* **1979**, *552*, 143.
- [58] D. C. Gadsby, R. F. Rakowsky, P. De Weer, *Science* **1993**, *260*, 100.
- [59] J. G. Nørby, J. Jensen, *Biochim. Biophys. Acta* **1971**, *233*, 104.
- [60] C. Hegyvary, R. L. Post, *J. Biol. Chem.* **1971**, *246*, 5234.
- [61] P. L. Jørgensen, *Biochim. Biophys. Acta* **1975**, *401*, 399.
- [62] S. J. D. Karlsh, D. W. Yates, *Biochim. Biophys. Acta* **1978**, *527*, 115.
- [63] S. J. D. Karlsh, D. W. Yates, I. M. Glynn, *Biochim. Biophys. Acta* **1978**, *525*, 252.
- [64] J. C. Skou, M. Esmann, *Biochim. Biophys. Acta* **1981**, *647*, 232.
- [65] S. J. D. Karlsh, *J. Bioenerg. Biomembr.* **1980**, *12*, 111.
- [66] J. G. Nørby, I. Klodos, N. O. Christiansen, *J. Gen. Physiol.* **1983**, *82*, 725.
- [67] S. Yoda, A. Yoda, *J. Biol. Chem.* **1986**, *26*, 1147.
- [68] I. M. Glynn, Y. Hara, D. E. Richards, *J. Physiol. (London)* **1984**, *351*, 531.
- [69] R. L. Post, C. Hegyvary, S. Kume, *J. Biol. Chem.* **1972**, *247*, 6530.
- [70] L. A. Beaugé, I. M. Glynn, *Nature* **1979**, *280*, 510.
- [71] M. Nakao, D. C. Gadsby, *Nature* **1986**, *323*, 628.
- [72] R. Goldschleger, S. J. D. Karlsh, A. Raphaeli, W. D. Stein, *J. Physiol. (London)* **1987**, *387*, 331.
- [73] J. C. Skou, *News Physiol. Sci.* **1992**, *7*, 95.

The Crystal Structure of a Potassium Channel— A New Era in the Chemistry of Biological Signaling

Dennis A. Dougherty* and Henry A. Lester

Some of the most impressive chemistry of living systems is performed by the integral membrane proteins of the nervous system—ion channels, neuroreceptors, and neurotransmitter transporters. These are the molecules of thought, memory, and sensory perception, and in one sense, we know a great deal about them. For example, the exquisite sensitivity of the patch-clamp technique enables the characterization of an ion channel if it opens for only 0.1 ms every 20 min—a dynamic range of 10^7 s. Furthermore, site-directed mutagenesis has been applied in hundreds of studies showing interesting functional changes that point to the roles of individual side chains in ion channels. Yet, from a chemist's perspective, we know little about the structural details that underlie ion channel function. The reason for this ignorance is simple: High-resolution structural tools such as X-ray crystallography and NMR spectroscopy are at best marginally applicable to integral membrane proteins. In this light, the recent report^[1] of a 3.2 Å resolution crystal structure of a K^+ channel from Rod MacKinnon and a group from the Rockefeller University represents a landmark achievement, and perhaps a turning point for molecular neurobiology.

Potassium channels play a central role in the function of nearly every living cell. In the nervous system they regulate the action potential and set the resting membrane potential, thereby governing the frequency of nerve impulses. In the cardiovascular system, K^+ channels regulate the duration and frequency of the heartbeat. Elsewhere, they control the passage of water and salts across the membranes of the kidney, windpipe, and intestine. They also accomplish a remarkable feat of chemistry. The K^+ channels are highly selective—perhaps as much as 10000:1 for K^+ over Na^+ ,

despite the minimal structural difference between the two (ionic radii of 1.33 and 0.95 Å, respectively). At the same time, K^+ channels promote tremendous ion flux; in some cases on the order of 10^8 ions per second pass through a single open channel. Chemists typically equate high selectivity with tight binding, but clearly nature has found a way to achieve the former without the latter.

In little more than a decade, we have come from almost complete ignorance about the molecular nature of K^+ channels to a high-resolution structure. The first breakthrough was the cloning by three labs of the Shaker channel (named after a *Drosophila* mutant that shakes its legs on exposure to ether).^[2] This was followed by a flurry of activity to define crucial structural determinants, rendering 1990 the “annus mirabilis of K^+ channels”.^[3] The next crucial step was the discovery^[4] that K^+ channels fall into two distinct families: the voltage-gated channels, K_v (which includes the Shaker channel), and the inward rectifier channel, K_{ir} (Figure 1). As the names imply, the first family “gates” (that is, opens or closes) in response to changes in the cell's membrane potential, while the second allows K^+ flow only in the inward

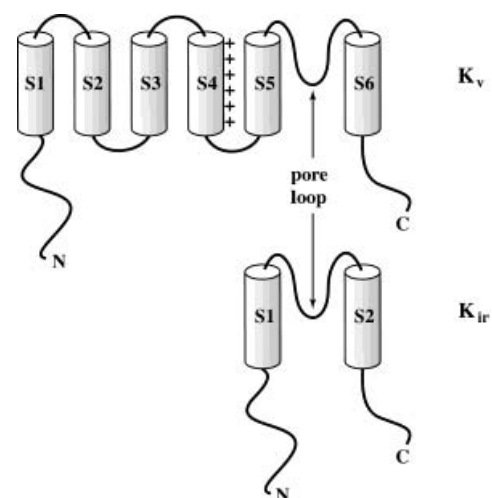


Figure 1. Predicted topologies of the two families of K^+ channels, based on sequence analysis and biochemical studies. The voltage-gated (K_v) channels such as Shaker have six transmembrane domains, while the inward-rectifier (K_{ir}) channels have only two. For both families, the N and C termini are intracellular. Both families feature a pore (P) loop—a conserved sequence that was proposed to line much of the channel and to contain the selectivity filter. The KcsA channel discussed here has the topology of a K_{ir} channel.

[*] Prof. D. A. Dougherty
Division of Chemistry and Chemical Engineering
California Institute of Technology
Pasadena, CA 91125 (USA)
Fax: (+1) 626-564-9297
E-mail: dad@igor.caltech.edu

Prof. H. A. Lester
Division of Biology
California Institute of Technology
Pasadena, CA 91125 (USA)

[**] We thank Professors Doug Rees (California Institute of Technology), Chris Miller (Brandeis), and Rod MacKinnon (Rockefeller) for helpful discussions. Our own work on K^+ channels and related structures is supported by the NIH (NS-34407 and GM 29836).

direction, against the natural concentration gradient—another remarkable bit of chemistry. Structurally, the K_{ir} channels are smaller, consisting of two transmembrane domains with an intervening pore (P) region. The K_v channels have an additional four transmembrane domains, including one (S4) that has a positive charge every third residue and plays the role of the voltage sensor. In each case the functional channel is a tetramer of the protein shown in Figure 1.

The path to a high-resolution structure began with another advance in cloning. In 1995 Schempf et al. reported^[5] the identification, cloning, and characterization of a K^+ channel from the bacterium *Streptomyces lividans*, a result that was made possible by the intense activity on the sequencing of small genomes. Although bacteria are not neurons, all workers recognized that this bacterial channel resembled the K^+ channels of eukaryotic cells closely enough to share key structural elements. Furthermore, this bacterial channel was quite robust, easily reconstituting in artificial membranes. The fact that it is a bacterial channel suggested a solution to one of the biggest hurdles to determining a structure: obtaining large quantities of material. Indeed, the *S. lividans* K^+ channel, now known as KcsA, could be overexpressed in *E. coli*. The race was on to obtain a structure!

Even with adequate quantities of protein, obtaining the structure was a challenge. The crystals are radiation-sensitive, they diffract anisotropically, and a number of site-directed mutants were necessary to obtain heavy-atom derivatives. In the end, by use of the Cornell High Energy Synchrotron Source, a viable structure was obtained. It should be appreciated from the start that 3.2 Å is not high resolution by today's standards of macromolecular crystallography. A backbone trace is clearly visible, but individual carbonyl groups, for example, cannot be seen. Side chains can be seen, but with minimal detail. Still, much can be learned at this level.

Topologically, KcsA falls into the K_{ir} family, with two transmembrane domains. The structure reveals that these domains are highly α -helical in appearance (Figure 2). The eight helices (two from each subunit) wrap around the central pore, and tilt and kink a bit to open up like a flower or an inverted teepee toward the extracellular surface of the channel. With so few high-resolution structures of integral membrane proteins available,^[6] every new structure greatly expands our knowledge of the manners in which proteins assemble and pack within a membrane. Transmembrane helices are becoming common, although sheet structures are also known. Like other membrane proteins, KcsA shows two belts of aromatic amino acids near the membrane–water interface. Gratifyingly, the structure is consistent with a number of inferences from biochemical and mutagenesis studies. For example, residues that influence channel blockade by internally applied reagents face the inside of the cell; those that influence external blockade face the outside and include a number of well-characterized sites in the “turret” region that interact with toxins such as agitoxin2 or charybdotoxin. Still, the critical issue is the pore: how is ion selectivity achieved?

The answer is clear from the structure. In the P loop of all K^+ channels there is a highly conserved “signature sequence”

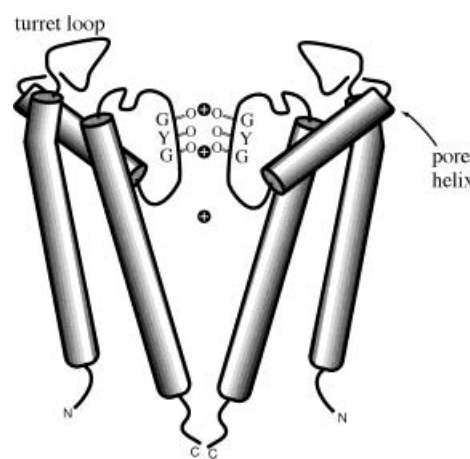


Figure 2. Schematic representation of the K^+ channel structure. Two of four subunits are shown, the other two lie above and below the plane of the page. Beginning at the intracellular N terminus, each subunit contains: an α helix, with a slight kink at the top; the “turret” loop, which contains binding sites for toxins; the pore helix; the Gly-Tyr-Gly (GYG) loop; and a large C-terminal helix. Also shown are three positive ions that correspond roughly to positions in the structure where ions were located. Two lie in the GYG selectivity filter, while the bottom ion lies in the aqueous “pool” that lies near the middle of the transmembrane region. Note that a number of intracellular residues (22 on the N terminus and 39 on the C terminus) are not seen, either because of disorder or, in the case of 32 C terminus residues, because they had been removed by proteolysis. This picture is adapted from figures presented by Doyle et al.^[1]

Thr-Xxx-Thr-Thr-Xxx-Gly-Tyr-Gly.^[7] This region, and especially the Gly-Tyr-Gly sequence, plays a key role in ion selectivity. Two models for ion selectivity had been proposed. One, first proposed by MacKinnon^[8] and supported by work from one of us,^[9] invokes cation– π interactions between the permeant ions and the conserved aromatic ring of the Tyr residue of the Gly-Tyr-Gly unit. The other, more traditional mechanism invokes carbonyl oxygen atoms from the peptide backbone as forming the selectivity filter.^[7] In K^+ channels, tradition has won out.

The P region forms a loop involving first a small helix, the “pore helix”, and then a turn that contains the crucial Gly-Tyr-Gly sequence (Figure 2). It is clear that the Tyr side chain points back away from the channel, and is unable to contribute any cation– π interactions to ion binding. Although individual atoms of the backbone cannot be resolved, the authors make the reasonable assumption that the carbonyl oxygen atoms point in toward the pore. Apparently, three consecutive carbonyl groups from each subunit point inward, establishing rings of oxygen atoms that define cation binding sites. The analogy to crown ethers is immediately apparent, with the caveat that these are amide carbonyl groups, which contain a more potent negative electrostatic potential than ether oxygen atoms. Soaking the crystals with Rb^+ ions (whose permeation through most K^+ channels can be measured) and evaluating electron density differences allows explicit ions in the P region to be identified.

How does such an arrangement produce a selective pore? The authors propose that the rest of the protein structure maintains the Gly-Tyr-Gly carbonyl groups in precisely the correct position for binding K^+ , but prevents the structure from adjusting to allow favorable interactions with Na^+ —an

impressive feat for a tetrameric protein embedded in a membrane. The highly conserved Tyr residue plays a key role in defining the molecular scaffolding. It hydrogen bonds to a Trp in the pore helix and experiences a favorable van der Waals interaction (perhaps an edge-to-face interaction between two aromatic rings?) with another Trp in the pore helix of an adjacent subunit. When propagated by the fourfold symmetry of the structure, this arrangement produces a “massive sheet of aromatic amino acids” that produces a “layer of springs” to hold the carbonyl oxygen atoms in precisely the correct position. These crucial Trp residues are conserved in all members of the K_v family. An interesting aspect of KcsA is that, while it has only two transmembrane domains like a K_{ir} channel (Figure 1), its P-region sequence much more closely resembles a K_v sequence, so the structure in the pore region is presumably more relevant to this family of channels. It should be remembered that, at 3.2 Å resolution, a model for precise positioning must be considered speculative. Nevertheless, this is the first attempt to put chemical-scale flesh on the channel's skeleton, and it will certainly inspire many experiments.

Interestingly, the narrowest part of the channel, the selectivity filter, is toward the extracellular face of the channel. Many had anticipated an hourglass shape for the pore, with the narrowest portion in the middle of the channel. A K^+ ion in the very middle of the channel, the most hydrophobic part of the membrane, experiences a very low dielectric constant, an uncomfortable situation for an ion. Again, nature has found a clever solution to this problem. Right below the selectivity filter the channel opens up, creating a cavity with quite hydrophobic walls that holds a “pool” of water. An ion in this region (Figure 2) is solvated by all the water in the cavity. In addition, the four pore helices point right at this pool. Each helix is aligned such that its C terminus, which has a substantial negative electrostatic potential (“the helix dipole”), points toward the aqueous pool. This alignment is proposed to provide extra stabilization to an ion located in the pool.

We have a selective binding site, but how do we achieve high flux? As mentioned above, the selectivity filter contains more than one ion. This supports the generally held view, based on decades of measurements with ionic currents and with radiolabeled tracer fluxes, that K^+ channels are multi-ion pores.^[10] The model for flux is that one ion binds, followed by a second at an adjacent site. The binding of the second ion destabilizes the first electrostatically—like charges repel! This pushes the first ion out of the selectivity filter, the second ion takes its place, and a new ion moves in. The entire process is driven by the high concentration of K^+ in physiological solutions. The presence of several ions in the channel simultaneously in the crystal structure nicely confirms a crucial conclusion derived from functional studies.

So what is next for K^+ channels? Certainly, a higher resolution structure would be reassuring and informative, and it seems likely that one will appear soon. It will also be interesting and important to evaluate the extent to which the motifs of the KcsA structure carry over to other ion channels, including both the K_v family and more distant relatives such as Na^+ , Ca^{2+} , and ligand-gated ion channels. A very recent

crystal structure from Choe and co-workers^[11] should provide further information on the K_v family. These workers determined a 1.55 Å resolution structure of a *soluble fragment* of the Shaker channel known as the tetramerization (T1) domain. This region lies on the N-terminal end of the protein within the intracellular stretch that precedes S1 (Figure 1). An 87 amino acid segment of the protein was studied, and remarkably, in the crystal, it formed a perfectly fourfold symmetric, tetrameric structure with a large pore down the middle! This broad pore is presumably the intracellular vestibule of the channel. No doubt modelers will be racing to merge the tetramerization domain with the KcsA structure, in hopes that the likely positions of S1–S4 will become apparent.

Another interesting issue that will require further attention is the mechanism by which the crucial positioning of the carbonyl groups in the selectivity filter is achieved. As mentioned, the key Trp residues are conserved in all of the K_v channels (remember the pore sequence of KcsA is K_v -like). However, these Trps are universally replaced by Leu and Phe in K_{ir} channels. This requires different contacts with the Tyr of the Gly-Tyr-Gly, especially since the proposed Trp...Tyr hydrogen bond is no longer possible. Apparently, nature has found two ways to attain the requisite positioning of the Gly-Tyr-Gly carbonyl groups. Finally, there are the dynamic aspects of channel function, especially the gating phenomena induced by voltage or ligand binding, issues that will be difficult to address with static crystallography. Nevertheless, it is clear that MacKinnon's accomplishment represents a giant leap for the ion channel field, one that will influence all further work to come.^[12]

German version: *Angew. Chem.* 1998, 110, 2463–2466

Keywords: ion channels • membrane proteins • protein structures • signal transduction • structure elucidation

- [1] D. Doyle, J. M. Cabral, R. A. Pfueter, A. Kuo, J. M. Gulbis, S. L. Cohen, B. T. Chait, R. MacKinnon, *Science* **1998**, 280, 69–77.
- [2] A. Baumann, I. Krah-Jentgens, R. Müller, F. Müller-Holtkamp, R. Seidel, N. Kecskemethy, J. Casal, A. Ferrus, O. Pongs, *EMBO J.* **1987**, 6, 3419–3429; A. Kamb, L. E. Iverson, M. A. Tanouye, *Cell* **1987**, 50, 405–413; D. M. Papazian, T. L. Schwarz, B. L. Tempel, Y. N. Jan, L. Y. Jan, *Science* **1987**, 237, 749–753.
- [3] C. Miller, *Science* **1991**, 252, 1092–1096.
- [4] K. Ho, C. Nichols, G. Lederer, J. Lytton, P. M. Vassilev, M. V. Kanazirska, S. C. Hebert, *Nature* **1993**, 362, 31–38; Y. Kubo, T. J. Baldwin, Y. N. Jan, L. Y. Jan, *Nature* **1993**, 362, 127–133.
- [5] H. Schrempf, O. Schmidt, R. Kümmerlen, S. Hinnah, D. Müller, M. Betzler, T. Steinkamp, R. Wagner, *EMBO J.* **1995**, 14, 5170–5178.
- [6] D. Rees, A. J. Chirino, K.-H. Kim, H. Komiya in *Membrane Protein Structure* (Ed.: S. H. White), Oxford University Press, New York, **1994**, pp. 1–26.
- [7] L. Heginbotham, Z. Lu, T. Abramson, R. MacKinnon, *Biophys. J.* **1994**, 66, 1061–1067.
- [8] L. Heginbotham, R. MacKinnon, *Neuron* **1992**, 8, 483–491.
- [9] R. A. Kumpf, D. A. Dougherty, *Science* **1993**, 261, 1708–1710.
- [10] H. A. Lester, D. A. Dougherty, *J. Gen. Physiol.* **1998**, 111, 181–183.
- [11] A. Kreusch, P. J. Pfaffinger, C. F. Stevens, S. Choe, *Nature* **1998**, 392, 945–948.
- [12] Note added in proof (July 22, 1998): A computational model for KcsA and the Shaker K_v channel has appeared, and it is in excellent agreement with the crystal structure: S. R. Durell, Y. Hao, H. R. Guy, *J. Struct. Biol.* **1998**, 121, 263–284.

Combinatorial Chemistry in Heterogeneous Catalysis: A New Scientific Approach or “the King’s New Clothes”?**

Robert Schlögl*

When considering the future of chemistry one immediately finds that heterogeneous catalysis plays an important role. Biocatalysis and homogeneous catalysis are fields of ever increasing importance, but heterogeneous catalysis remains the workhorse for many industrial syntheses and treatment processes for environmental emissions.^[1] Therefore, an enormous interest exists in the development of new, and the optimization of currently implemented, heterogeneously catalyzed processes.

The “empirical approach” is currently the only proven successful industrial approach for developing novel catalysts. However, it often proves to be very labor-intensive and uneconomical, since the potential for optimization is limited by the relatively small body of knowledge available from previous work. The “rational approach” is taken when a more detailed understanding of the fundamental reaction steps in a given catalytic process is desired. This approach is also used in industry as it provides fundamental information important to process optimization. The success of the “single-crystal approach”^[2a] has provided a wealth of information about qualitative and quantitative properties of elementary steps which form a complex sequence of events in every ever so simple catalytic reaction.^[2b] Further advances in the theoretical understanding of catalytic processes have been provided by microkinetic modeling studies.^[3] Novel analytical tools including various in situ techniques and surface imaging by

scanning probe microscopies are constantly being developed. Well thought out application of these techniques can significantly decrease the time required for process optimization.

A rational approach to catalyst development involves a series of steps, which should ideally be carried out in parallel. In the end, however, further optimization based on a fundamental understanding of the chemistry is necessary. It is also critical to assess the technical aspects of a process under study as early as possible in the development scheme. Table 1 shows the steps which are most critical when carrying out a rational approach to catalysis development. The interdisciplinary nature of this approach is also outlined with the various fields of expertise necessary for carrying out each step.

It is immediately clear that this approach is labor-intensive and requires excellent coordination. Industrial researchers typically invest most effort in the empirical component of catalyst research and very little in the rational approach. The implementation of a combinatorial chemistry^[4, 5] approach interests, therefore, both those with the purely pragmatic desire to develop new catalysts^[6] as well as those interested in obtaining a better understanding of fundamental catalytic processes.^[7]

The combinatorial chemistry approach^[8] distinguishes itself from the empirical approach in that the parallel investigation of a large number of catalysts allows statistically well-founded empirical rules to be derived for optimization strategies. In

Table 1. Important steps in the “rational approach” for the development of heterogeneous catalysts along with related disciplines.

Research step	Related discipline
catalyst screening with intuition of chemistry	chemistry
mini-reactor tests with the goal of optimizing the material and/or reaction conditions	chemistry, chemical engineering
technical relevance	chemical engineering
identification of the active phase(s)	physical chemistry
synthesis of model substances exhibiting the pure active phase(s)	solid-state chemistry
qualitative and quantitative analysis of the important elementary steps	surface science, physical chemistry, physics
development of a microkinetic model	chemical engineering, physical chemistry

[*] Prof. Dr. R. Schlögl
Fritz-Haber-Institut der Max-Planck Gesellschaft
Faradayweg 4–6, D-14195 Berlin (Germany)
Fax: (+49) 30-8413-4401
E-mail: schloegl@fhi-berlin.mpg.de

[**] This project was supported by the Fonds der Chemischen Industrie. The experiment described in Figure 1 was conducted by R. Gottschall, N. Pfänder, and G. Mestl.

addition, the multidimensional parameter space is dramatically more precisely explored, which adds greatly to the chance of finding a global reaction optimum. Realizing such a combined approach requires the use of the most modern laboratory equipment available such as microreactors and automated microanalytical equipment^[9] such as micro-gas chromatography. Accurate process control as well as data

interpretation is only made possible with the help of substantial computer support. Statistical analysis of data minimizes the number of measurements needed by basing the course of future experimentation on previously obtained results. Combining statistical design strategies with good quality control results in precise and reproducible data and minimizes the likelihood of systematic errors occurring.

The huge success of the combinatorial chemistry approach in various areas of molecular chemistry has resulted in the development of a number of novel pioneering applications.^[10] However, several difficulties that arise for its use in the field of heterogeneous catalysis^[11] are presented below.

The combinatorial approach requires a sound hypothesis describing the structure–activity relationship for a given process. Such hypothesis are, in the case of heterogeneous catalysis, usually wide open to question. There are a number of exceptions, such as the idea of “selective lattice oxygen” in the catalysis of partial oxidations. The determination of the structure–activity relationship is one of the most sought after goals in modern catalysis research. Solution of this problem requires the combined knowledge of experimental and theoretical chemistry as well as that of the surface physics of a given reaction. Although, huge strides have been made in this area in the recent past, a complete understanding of such systems is a far removed.

A further problem is establishing clearly defined synthetic building blocks as well as determining a strategy for the reproducible preparation of the catalyst. The elementary steps involved in most solid-state synthesis are, at best, poorly understood. This is due to the enormous complexity of the heterogeneous interface reactions which form the foundation of most catalyst syntheses (precipitation, oxidation, reduction, calcination).

Identification of a well-defined “active site” as a target of optimization is a challenging problem in heterogeneous catalysis. For small molecules the structure and dynamics can be theoretically modeled with a great degree of accuracy. A large ensemble of small molecules is characterized by the individual molecular properties and/or their sphere of solvation. A material is therefore defined by the additive contribution of properties of all molecules present. The structure and reactivity of solids are, however, poorly understood in comparison, and the exact nature of the catalytically active material is often not known. This arises, in part, from the fact that solids contain a variety of defects which effect the reactivity. A correlation between the properties of the macroscopic material and its molecular building blocks is, therefore, difficult to establish for most solid materials. This naturally complicates the synthesis of the catalyst.

It is generally accepted that surface and volume defect sites function as the catalytically active sites in many reactions.^[12] Typical examples of this are the phenomena of structure sensitivity, metal–support interactions, and the effect of surface deposits on catalytic activity. The development of the active phase is, in many catalyst systems, only achieved after significant structural reorientation (reconstruction)^[13] of the catalyst surface and/or volume^[14] under the reaction conditions. This activation period can range from minutes to many hundreds of hours,^[15] and directly reflects the influence

of the reaction conditions on the solid-state dynamics away from thermodynamic equilibrium. Most modern analytical tools only enable a relatively poor determination of both the type and quantity of solid-state defects. The direct synthesis of the catalytically active phase (defect structure) for relevant materials is, therefore, not possible. Close attention must be paid, when applying the combinatorial approach, to the solid-state dynamics of the test substance. An understanding of the synthesis steps involved is usually not available and a rational synthesis strategy is therefore not known beforehand. These would, however, be necessary prerequisites for performing a combinatorial chemical approach.

The micro and mesoporous materials may be considered as an exception to this rule. Here, one often has the possibility of determining the exact structure. A quantification of qualitatively well-defined active sites in the catalyst is therefore possible.^[16]

Figure 1 shows an example of the complexity of the structure–activity relationship often encountered in heterogeneous catalysis. A slight variation of the long-range order of an X-ray amorphous, mixed oxide Mo_5O_{14} catalyst^[17] leads to a new catalyst which exhibits greatly different catalytic activity for the oxi-dehydrogenation of methanol to form-

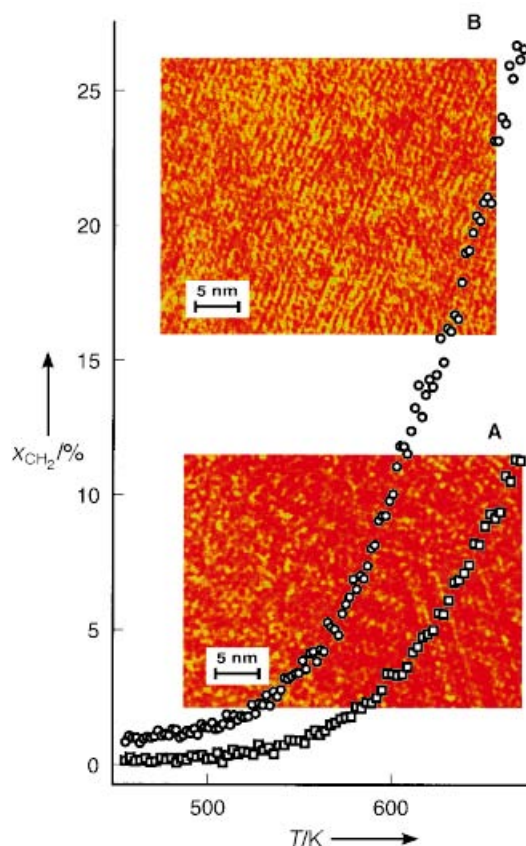


Figure 1. Yield x of formaldehyde for the catalytic oxi-dehydrogenation of methanol with a stoichiometric feed amount and 25 mg of catalyst. A) The precursor catalyst was used. B) The catalyst was heated at 573 K under argon with a slow heating rate prior to reaction. The HR-TEM micrographs (Phillips CM 200 FEG, 200kV, powder on carbon foil) emphasize differences in the long-range order. This is not observable with X-ray diffraction, but is clearly seen with differential scanning calorimetry. The catalytically active material is a metastable intermediate in the crystallization of the amorphous precursor.

aldehyde (based on product selectivity for formaldehyde). The identical precursor was used for both runs, but was first tempered in argon before the second run (Figure 1 B). A slight variation in the oxygen stoichiometry, which was not measurable with standard analytical tools, was observed after close inspection of high-resolution transmission electron microscopy (HR-TEM) micrographs. A variation in the connectivity of the octahedral building blocks resulted in a dramatic change in catalytic activity. Thermal analysis was used to define the optimum conditions for activation of the precursor: gas composition, heating rate, holding temperature, and total time of activation were the parameters which had to be optimized.

A problem is encountered in automated catalyst synthesis when going from microreactor-sized tests to industrial-sized syntheses. The catalytic activity found during screening tests is usually not reproducible after scaling-up to larger processes. This last problem involves the parameter space required for the test experiments. The test conditions for life science systems or for the search for light-emitting materials^[18] are set within well-defined limits. A platform for a comparison of experimental results is, therefore, guaranteed. The a priori definition of the necessary conditions for determination of the optimum performance of a heterogeneous catalyst is, in contrast, not possible. Different catalysts exhibiting nearly identical compositions often require dramatically different reaction conditions in order to obtain optimal performance. An efficient test protocol involving an automatic variation of controllable parameters such as reactant composition, temperature, pressure, space velocity, and reactor dwell time is therefore necessary. Past experience has shown that results obtained when testing catalysts under conditions where low conversions are desired for the sake of analysis are of limited practical use for the prediction of high conversion performance used in industry.

This arises, in part, from the fact that the performance of a catalyst depends on the conditions under which it is tested.^[19] Not only the reaction conditions, but also the parameters of the reactor (reactor type, energy and mass transport, catalyst rheology) play a critical role. This dependence results in the well known "scale-up" problem encountered when attempting to use a laboratory-tested catalyst on an industrial scale. Implementation of microreactors and automated synthesis techniques without a reproducible catalyst ultimately leads to complications in the scale-up of the process at a very early stage. This will likely lead to serious delays in catalyst implementation.

One can therefore answer the question posed in the title very clearly. The implementation of the combinatorial chemistry approach is a novel scientific development in the field of molecular chemistry. Its application in heterogeneous catalysis is, however, very reminiscent of the strategy described 50 years ago by A. Mittasch.^[20] This finding substantiates the doubts expressed in the title. Combinatorial chemistry is at best a modern variation of the Mittasch method which can never replace the efforts necessary for the rational approach. However, it provides another powerful tool for efficient catalyst screening. If one could understand all of the fundamental processes occurring at the heterogeneous interface, one could develop a device which would automatically

select the best candidates as catalysts for particular chemical reactions, thus guaranteeing an efficient development process.

The results provided by such a presently still imaginary process would still not be immediately applicable to the synthesis of large amounts of catalysts. In no case is the development of a general "recipe" for catalyst preparation based solely on combinatorial chemistry experiments to be expected. Various approaches to synthesis of the target compound identified by combinatorial chemistry followed by thorough characterization will be necessary for efficient catalyst development. This essentially leads back to the rational implementation scheme outlined in Table 1. It is also not realistic to expect that one can determine a global minimum for a selected heterogeneously catalyzed reaction using combinatorial chemistry alone, since, in the overwhelming majority of cases, one cannot predict the exact material properties prior to their synthesis.

Proof that the scientific community is aware of such problems can be found in the materials science literature.^[18a] Here, the development of a new material within a very well defined parameter space is carried out with the acceptance of the previously mentioned limitations.^[18b] This is done using parallel synthesis routes which are contained in an inorganic "library".^[18c] Despite the obviously positive results of such studies there is no novel scientific knowledge produced in comparison to a typical empirical design method. Although it is potentially useful, the combinatorial chemistry approach earns the title of this article with regard to its application in parallel synthesis and testing of new materials.

The combinatorial chemistry method provides, therefore, no new alternative to the rational method. It is rather a new tool to be used along with those currently available, such as the single-crystal approach. The combinatorial chemistry method differs greatly from the single-crystal approach in that it delivers no new fundamental understanding of the catalytic system under investigation. The latter should not be considered as a tool for developing a catalyst, but rather as an excellent means^[21] for gaining fundamental insight into a catalytic reaction. Use of the combinatorial chemistry approach does, however, enable a substantially larger body of possible materials to be examined than the conventional synthesis making use of chemical intuition. This can result in a significant reduction in development time, provided the scale-up problems specifically associated with functional inorganic solids can be efficiently solved. Such an achievement may be reason enough to implement this technique in heterogeneous catalysis research. The chemist's intuition is then necessary for the optimal programming of the method as well as for the demanding analysis of the obtained data and materials.

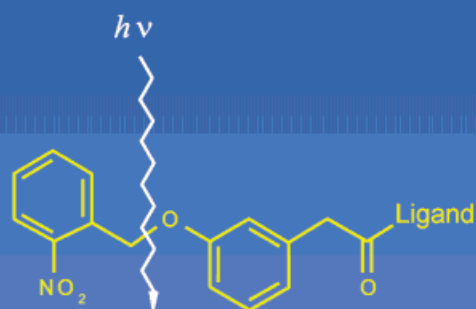
German version: *Angew. Chem.* **1998**, *110*, 2467–2470

Keywords: combinatorial chemistry • correspondence • heterogeneous catalysis • solid-state chemistry • structure–activity relationships • surface chemistry

[1] *Handbook of Heterogeneous Catalysis* (Eds.: G. Ertl, H. Knözinger, J. Weitkamp), WILEY-VCH, Weinheim, **1997**.

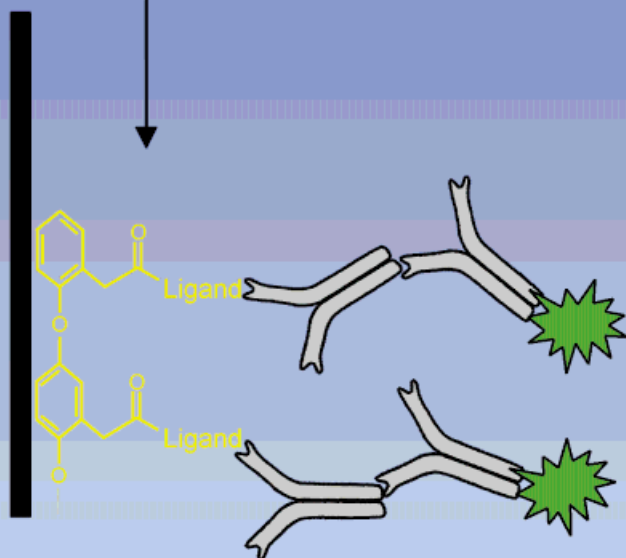
[2] a) G. Ertl in *Catalysis, Science and Technology*, Vol. 4 (Eds.: J. R. Anderson, M. Boudart), Springer, Berlin, **1983**, p. 209; b) *Surface*

- Reactions*, Vol. 34 (Ed: R.J. Madix), Springer Series in Surface Sciences, Springer, Berlin, **1994**.
- [3] J. A. Dumesic, D. F. Rudd, L. M. Aparicio, J. E. Reksoke, A. A. Trevino, *The Microkinetics of Heterogeneous Catalysis*, ACS Professional Reference Book, ACS, Washington, **1993**.
- [4] J. A. Niemantsverdriet, *Spectroscopy in Catalysis*, VCH, Weinheim, **1993**.
- [5] S. Bormann, *Chem. Eng. News* **1996**, 74(45), 37.
- [6] O. Reiser, *Nachr. Chem. Tech. Lab.* **1996**, 44, 1182.
- [7] "Kombinatorische Chemie und ihre Anwendungsperspektiven": DE-CHEMA, commissioned by the BMBF, Frankfurt, **1997**.
- [8] A. W. Czarnik, *Acc. Chem. Res.* **1996**, 29, 112; K. Burgess, H. J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem.* **1996**, 108, 192; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 220; G. Quinkert, H. Bang, D. Reichert, *Helv. Chim. Acta* **1996**, 79, 1260; C. von dem Bussche-Hünnefeld, F. Balkenhohl, A. Landsky, C. Zechel, *Fresenius J. Anal. Chem.* **1997**, 359, 3; C. Gennari, H. P. Nestler, U. Piarulli, B. Salom, *Liebigs Ann.* **1997**, 637.
- [9] R. C. Wilson, *Ind. Eng. Chem. Res.* **1996**, 35, 4803.
- [10] C. L. Hill, R. D. Gall, *J. Mol. Catal. A* **1996**, 114, 103.
- [11] E. K. Wilson, *Chem. Eng. News* **1997**, 75(49), 24.
- [12] J. M. Thomas, W. J. Thomas, *Principles and Practice of Heterogeneous Catalysis*, WILEY-VCH, Weinheim, **1997**, p. 328.
- [13] G. A. Somorjai, *Introduction to Surface Chemistry and Catalysis*, Wiley, New York, **1994**, p. 55.
- [14] a) X. Bao, G. Lehmppfuhl, G. Weinberg, R. Schlögl, G. Ertl, *J. Chem. Soc. Faraday Trans.* **1992**, 88, 865; b) T. Ilkenhans, B. Herzog, T. Braun, R. Schlögl, *J. Catal.* **1995**, 153, 275.
- [15] M. Muhler, R. Schlögl, G. Ertl, *J. Catal.* **1995**, 138, 413.
- [16] J. M. Thomas, *Chem. Eur. J.* **1997**, 3, 1557.
- [17] H. Werner, O. Timpe, D. Herein, Y. Uchida, N. Pfänder, U. Wild, R. Schlögl, *Catal. Lett.* **1997**, 44, 153.
- [18] a) G. Briceno, H. Chang, X. Sun, P. G. Schultz, X. D. Xiang, *Science* **1995**, 270, 273; b) E. Danielson, J. H. Golden, E. W. McFarland, C. M. Reaves, W. H. Weinberg, X. D. Wu, *Nature* **1997**, 389, 944; c) X. D. Sun, C. Gao, J. Wang, X. D. Xiang, *Appl. Phys. Lett.* **1997**, 70, 3353.
- [19] J. N. Armor, *Catal. Today* **1995**, 25, 197.
- [20] A. Mittasch, *Adv. Catal.* **1950**, 2, 81.
- [21] *Surface Science of Catalysis*, Vol. 482 (Eds.: D.J. Dwyer, F.M. Hoffmann), ACS Symposium Series, ACS, Washington, **1992**.

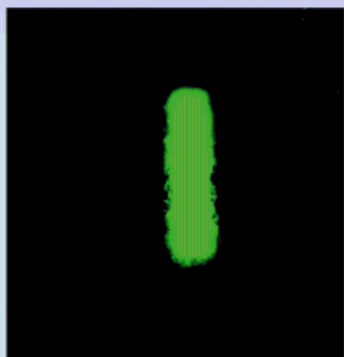


A novel method for spatially resolved immobilization is provided by electrochemical polymerization after photolytic cleavage of a protecting group.

+ 1.0 V



Fluorescein-labeled antibodies allow detection of the layer. See the following pages.



Spatially Resolved Immobilization of Peptides by Electrochemical Polymerization after Photolytic Cleavage of a Protecting Group**

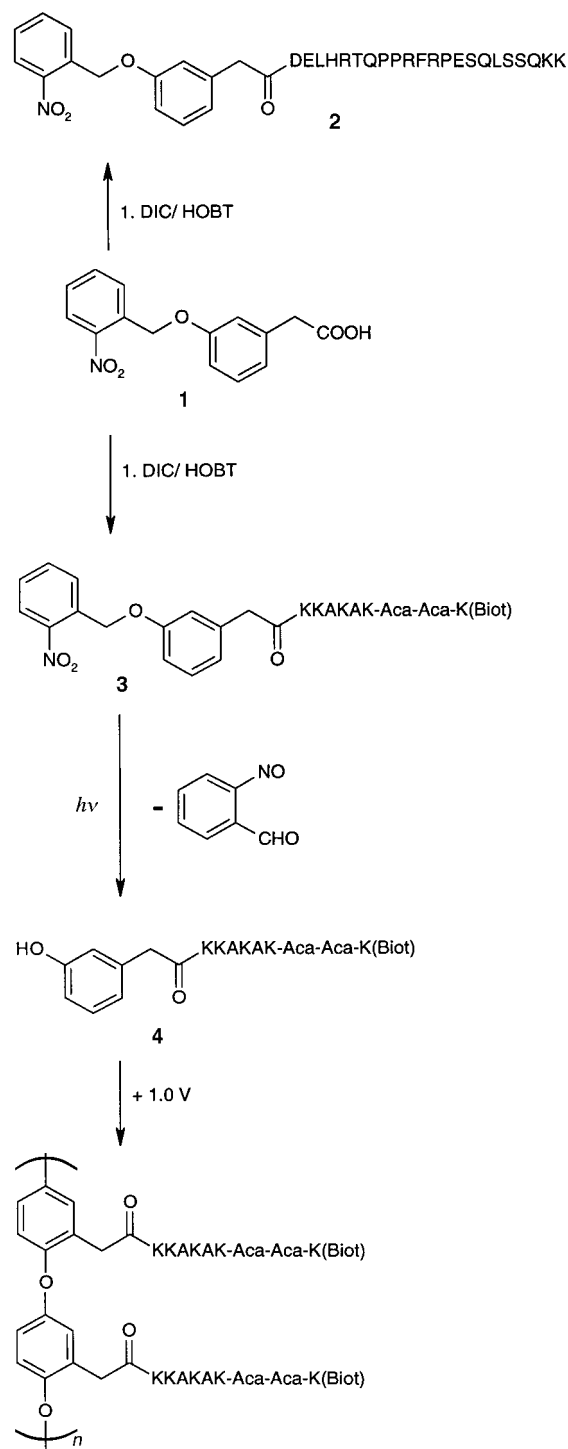
Dietmar Leipert, Peter Heiduschka, Jürgen Mack, Hans-Joachim Egelhaaf, Dieter Oelkrug, and Günther Jung*

Biopolymer-modified surfaces are used in biosensing, diagnostics, cell adhesion, and nanotechnology.^[1, 2] Microstructured immobilization of macromolecules on solid supports is accomplished by photolithography of photoactive groups. For example, peptides and nucleotides have been synthesized with spatial resolution on a glass surface by the mask technique.^[3] Proteins have been bound selectively to surfaces with photoactive benzophenones, diazines,^[4] and phenyl azide derivatives,^[5] and photoactive groups have been immobilized on gold with self-assembled monolayers of alkanethiols.^[6] Caged biotin, a biotin derivative that does not bind avidin, can be bound covalently to a substrate and induced photochemically to bind to avidin with the mask technique.^[7] Morgan et al.^[2] immobilized avidin on a gold substrate coated with thiol groups and incubated it with photobiotin (a nitroaryl azide derivative of biotin). The photobiotin was activated to bind covalently to antibodies by photolithography. The same principle underlies the direct binding of photobiotin to a carbon substrate.^[1]

We report here a new and generally applicable method for the immobilization of antibodies, receptors, macromolecules, and compounds of low molecular weight on light-addressable sites of a conducting substrate. We have combined photolithographical techniques with the electropolymerization of a biopolymer on a conducting surface. In previous work we demonstrated that peptides with N-terminal 3-hydroxyphenylacetic acid (HPA) can be polymerized anodically through the phenol groups and then bound firmly to the surface.^[8] Peptide functionalization of surfaces of glassy carbon electrodes (GCEs) and platinum electrodes was confirmed with fluorescein-labeled antibodies.^[8] A particular advantage of this method is that further reagents are unnecessary, and the polymerization is dependent only upon the applied potential and the electrolytes.

The novel feature of the new method is that the phenolic hydroxyl group of HPA is protected from oxidative polymerization by temporary protection with the 2-nitrobenzyl (Nbz) group (Scheme 1), and polymerizable monomer is released only after irradiation. The Nbz group can be cleaved selectively by photolysis, is chemically inert, fulfills the conditions for solid-phase synthesis, and has been used to mask tyrosine.^[9, 10] The peptide sequences were prepared by automated multiple synthesis on a solid phase and coupled at the N terminus with the photolabile protected 3-hydroxyphenylacetic acid (Nbz-HPA, **1**)^[11] in the final step.

group (Scheme 1), and polymerizable monomer is released only after irradiation. The Nbz group can be cleaved selectively by photolysis, is chemically inert, fulfills the conditions for solid-phase synthesis, and has been used to mask tyrosine.^[9, 10] The peptide sequences were prepared by automated multiple synthesis on a solid phase and coupled at the N terminus with the photolabile protected 3-hydroxyphenylacetic acid (Nbz-HPA, **1**)^[11] in the final step.



Scheme 1. Synthesis of the Nbz-HPA-peptides **2** and **3** as well as the photolytic deprotection of **3** to **4**, and its electrooxidative polymerization. Aca = 6-aminocaproic acid.

[*] Prof. Dr. G. Jung, Dipl.-Chem. D. Leipert, Dipl.-Chem. J. Mack
Institut für Organische Chemie der Universität
Auf der Morgenstelle 18, D-72076 Tübingen (Germany)
Fax: (+49) 7071-29-6925
E-mail: guenther.jung@uni-tuebingen.de

Dr. P. Heiduschka
Augenkl. der Universität
Abt. für Experimentelle Ophthalmologie
Domagkstrasse 15, D-48149 Münster (Germany)
Dr. H.-J. Egelhaaf, Prof. Dr. D. Oelkrug
Institut für Physikalische Chemie der Universität
Auf der Morgenstelle 8, D-72076 Tübingen (Germany)

[**] This work was supported by the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (project 0310853). We thank E. Braun for the preparation of the flow cell.

An electrochemical flow cell was constructed to achieve spatially resolved electrochemical polymerization (Figure 1). Flushing with a solution of the Nbz-protected peptides **2** and **3** fills the chambers of a plastic mask, and thus diffusion of the deprotected monomer into neighboring regions is prevented.

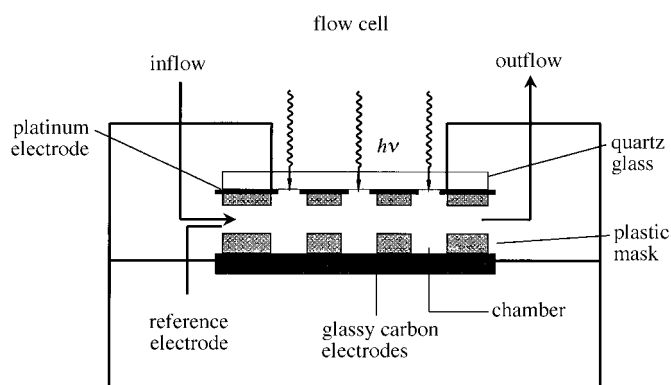


Figure 1. Flow cell for spatially resolved electropolymerization after photolytic cleavage of the Nbz protecting group. The individual chambers have a width of 250 μm .

Gaps in the platinum counterelectrode determine which chambers are irradiated. A potential of 1.0 V is applied to the GCEs. The process is illustrated in Figure 2: The Nbz-HPA-peptide **2** with a photolabile protecting group is situated between the two electrodes. Gaps in the platinum electrode allow the chambers to be irradiated individually to cleave the protecting group. If a constant potential of 1.0 V is applied, the deprotected HPA-peptide can be polymerized electrochemically at the GCE through the HPA groups.

The spatially resolved immobilization of **2** was visualized in the fluorescence microscope by sequential incubation with

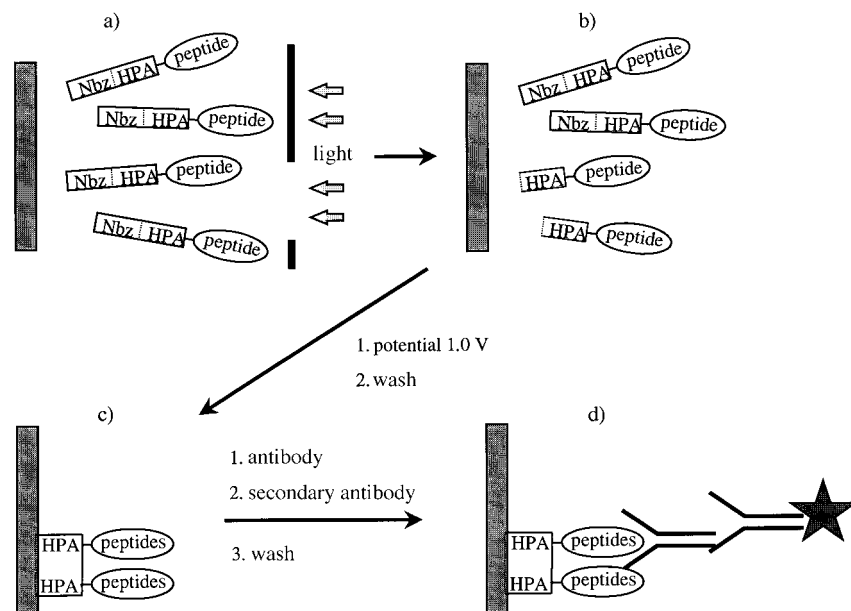


Figure 2. Spatially resolved immobilization of antibodies by electropolymerization. a, b) The photolabile Nbz group is specifically removed; c) application of a potential of 1.0 V leads to electropolymerization of the HPA-peptide; d) recognition of the immobilized peptides by means of antipeptide antibodies and fluorescein-labeled secondary antibodies.

antipeptide antibodies and fluorescein-labeled secondary antibodies (Figure 3). In the case of biotinylated Nbz-HPA-peptide **3** spatially resolved coating was confirmed with

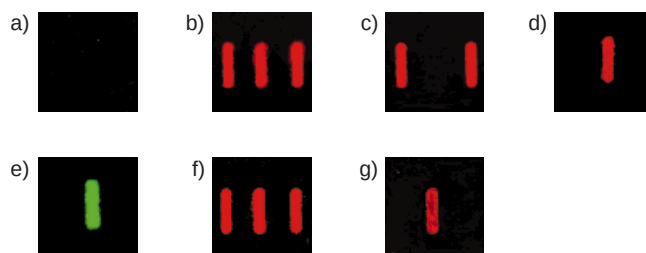


Figure 3. Spatially resolved immobilization of peptides on a GCE by electropolymerization. The chambers of the flow cell were filled with solutions of the Nbz-HPA-peptides **2** and **3**, a potential of 1.0 V was applied for 5 min, and the individual chambers (250 $\mu\text{m} \times 1200 \mu\text{m}$) were irradiated with UV light (280 nm, 13 W cm^{-2}) for 1 min according to the desired pattern. The electropolymerized layer was detected under a fluorescence microscope by fluorescein-labeled antibodies or streptavidin. No immobilization on the electrodes is detected without irradiation (a). Photolytic cleavage of the Nbz protecting group and electropolymerization of peptide **4** with different patterns. Detection with rhodamine-labeled streptavidin (b, c, d) and with fluorescein-labeled streptavidin (e). Solution of **2** with irradiation of all three chambers or the middle chamber, detection with antibodies and rhodamine-labeled secondary antibodies (f, g).

fluorescein-labeled streptavidin. To confirm spatially resolved electropolymerization, the three chambers of the flow cell were filled with solutions of **2** or **3**, a potential of 1.0 V was applied for 5 min, and the respective chambers were irradiated with UV light for 1 min according to the desired pattern. The GCEs were treated with fluorescein-labeled streptavidin or antibodies, rinsed after 90 min, and dried. As a negative control, product **3** in phosphate-buffered saline (PBS) was filled into the flow cell, and a potential was applied (1.0 V, 5 min). To demonstrate that the Nbz-protected HPA-peptide **3** was not polymerized electrochemically, the nonirradiated chambers were incubated directly with fluorescein-labeled streptavidin. No coating was observed by fluorescence microscopy (Figure 3a). In contrast, spatial resolution with the HPA-peptide **4** was clearly visible in the regions where light had initiated the cleavage of the protecting group of the Nbz-HPA-peptide and electropolymerization had been facilitated. Product **2** was similarly bound to the GCE in a spatially resolved manner. In one instance all three chambers were irradiated (Figure 3 f), in another the middle chamber only (Figure 3 g).

We were thus able to apply locally addressed peptides to conducting substrates by electropolymerization following photolytic cleavage of the Nbz protecting group (Figure 3). The chambers with their current width of 250 μm will be miniaturized in further refinements of the method. Immobilization of macromolecules or

chemoreceptors can lead to integration in routine analytical procedures. In addition, an application as a multianalytical sensor with a flow injection system is planned. When associated with highly diverse cyclopeptide libraries^[12] that may also be immobilized electrochemically, the method offers particular possibilities in chemosensing for rapid analysis by pattern recognition. The spatially resolved adhesion of nerve cells and the growth of axons are possible with peptides derived from laminin that may also be polymerized electrochemically with retention of their biological function.^[13]

Experimental Section

2, 3: Multiple parallel peptide syntheses (each 15 μmol) on Wang resin with 9-fluorenylmethoxycarbonyl (Fmoc) amino acids and activation with N,N' -diisopropylcarbodiimide (DIC). Product **1**^[11] (8.6 mg, 0.03 mmol) and 1-hydroxybenzotriazole (HOBt; 4.6 mg, 0.03 mmol) in DMF (200 μL) were coupled with 1.5 M DIC in DMF (20 μL , 0.03 mmol) for 4 h.

Cleavage from the resin: trifluoroacetic acid/water/triisopropylsilane (95/2.5/2.5; 500 μL ; 3 h), Nbz-HPA-peptide precipitated with diethyl ether, centrifuged, dissolved in *tert*-butyl alcohol/water (4/1), and lyophilized. **2:** ESI-MS: $m/z = 1467.7$ [$M+2H$]²⁺; **3:** ESI-MS: $m/z = 1523.6$ [$M+H$].

The photochemical cleavage of **3** was investigated by UV spectroscopy and HPLC. At the start of the reaction an absorption maximum for the peptide is present at 214 nm, and for the protecting group at 275 nm. During photolysis a further maximum for the cleaved protecting group appears at 315 nm. Within 1 min 70% of protected peptide **3** is cleaved, and after 5 min complete conversion into the free phenolic end group had occurred. These results indicate a stoichiometric formation of **4** (Scheme 1). A homogeneous product was also obtained with **2**; that is, the amino acids do not participate in detectable side reactions. However, Trp, Tyr, and His residues are partially oxidized during electropolymerization, but this does not have consequences for the practical use of peptide-functionalized surfaces, for example, for ELISA. To ensure that the Nbz-HPA-peptides **2** and **3** and the by-products released during photolysis cannot be oxidized, peptides **2–4** were measured by differential pulse voltammetry. This showed that electrochemical oxidation occurred with the photochemically deprotected HPA-peptide **4** at 0.6 V, whereas **2** and **3** were electrochemically inert at this potential.

After electrochemical polymerization by photolytic cleavage of the protecting group of the Nbz-HPA-peptide (1.0 V, 5 min), the GCE is rinsed with water. To block nonspecific binding sites 1% BSA/PBS (BSA = bovine serum albumine) is applied (500 μL per electrode). After 2 h a solution of streptavidin (rhodamine- or fluorescein-labeled) in 0.1 mg mL⁻¹ PBS is applied. After 2 h incubation the electrode is washed. The antibody-coated electrode is treated with a secondary antibody (rhodamine-labeled) in 0.1 mg mL⁻¹ PBS and washed after 2 h.

Received: April 8, 1998 [Z11707IE]

German version: *Angew. Chem.* **1998**, *110*, 2472–2474

Keywords: biosensors • electrochemistry • peptides • photochemistry • surfaces

- [1] N. Dontha, W. B. Nowall, W. G. Kuhr, *Anal. Chem.* **1997**, *69*, 2619–2625.
- [2] H. Morgan, D. J. Pritchard, J. M. Cooper, *Biosens. Bioelectron.* **1995**, *10*, 841–846.
- [3] S. P. A. Fodor, J. L. Read, M. C. Pirrung, L. Stryer, A. L. Lu, D. Solas, *Science* **1991**, *251*, 767–773.
- [4] a) L. Rozsnay, D. Benson, S. Fodor, P. Schultz, *Angew. Chem.* **1992**, *104*, 801–802; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 759–761; b) H. Sigrist, A. Collioud, J. F. Clemence, H. Gao, R. Luginbühl, G. Sunderababu, *Opt. Eng.* **1995**, *34*, 2339–2348; c) G. Sunderababu, H. Gao, H. Sigrist, *Photochem. Photobiol.* **1995**, *61*, 540.
- [5] T. Matsuda, T. Sugawara, *Langmuir* **1995**, *11*, 2272.

- [6] a) L. F. Rozsnay, M. S. Wrighton, *Langmuir* **1995**, *11*, 3913–3920; b) E. Delamarche, G. Sunderababu, H. Biebuyck, B. Michel, C. Gerber, H. Sigrist, H. Wolf, H. Ringsdorf, N. Xanthopoulos, H. J. Mathieu, *Langmuir* **1996**, *12*, 1997–2006.
- [7] S. A. Sundberg, R. W. Barrett, M. Pirrung, A. L. Lu, B. Kiangsoontra, C. P. Holmes, *J. Am. Chem. Soc.* **1995**, *117*, 12050–12057.
- [8] P. Heiduschka, W. Göpel, W. Kraas, S. Kienle, G. Jung, *Chem. Eur. J.* **1996**, *2*, 667–672.
- [9] B. Amit, E. Hazum, M. Fridkin, A. Patchornik, *Int. J. Pept. Protein Res.* **1977**, *9*, 91–96.
- [10] V. N. R. Pillai, *Synthesis* **1980**, *1*, 1–26.
- [11] Obtainable from ECHAZ microcollections EMC, Sindelfingerstrasse 3, D-72070 Tübingen (Germany).
- [12] a) *Combinatorial Peptide and Nonpeptide Libraries* (Ed.: G. Jung), VCH, Weinheim, **1996**; b) G. Jung, H. Hofstetter, S. Feiertag, D. Stoll, O. Hofstetter, K.-H. Wiesmüller, V. Schurig, *Angew. Chem.* **1996**, *108*, 2261–2263; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2148–2150.
- [13] M. Huber, P. Heiduschka, S. Kienle, C. Pavlidis, J. Mack, T. Walk, G. Jung, S. Thanos, *J. Biomed. Mater. Res.* **1998**, *41*, 278–288.

Solution of the Crystal and Molecular Structure of Complex Low-Symmetry Organic Compounds with Powder Diffraction Techniques: Fluorescein Diacetate**

Kenneth D. Knudsen,* Philip Pattison, Andrew N. Fitch, and Robert J. Cernik

Data from modern X-ray and neutron diffractometers and improvements in computational techniques have allowed increasingly complex crystal structures to be solved from powders. The use of synchrotron radiation has had a marked impact, and provides very narrow and accurately positioned diffraction peaks. The largest structures solved are of inorganic compounds, and sequential radiation with X-rays and neutrons was exploited to locate heavier and then lighter atoms. Example include $\text{Ga}_2(\text{HPO}_3)_3 \cdot 4\text{H}_2\text{O}$ ^[1] and $\text{La}_3\text{Ti}_5\text{Al}_{15}\text{O}_{37}$ ^[2] with 29 and 60 atoms, respectively, in the asymmetric unit. For organic compounds, the structures solved to date are simpler; for example, the structure of chlorothiazide^[3] with 17 atoms was determined by direct methods. Various algorithms have also been developed to locate the positions of known molecular fragments within the unit cell.^[4–9] Here we report on the structure solution of fluorescein diacetate ($\text{C}_{24}\text{H}_{16}\text{O}_7$). All 31 carbon and oxygen atoms were accurately located, without employing any prior knowledge of the molecular

[*] Dr. K. D. Knudsen, Dr. P. Pattison
Swiss–Norwegian beamline
European Synchrotron Radiation Facility (ESRF)
BP 220, F-38043 Grenoble Cedex (France)
Fax: (+33)4-76882694
E-mail: knudsen@esrf.fr
Dr. A. N. Fitch, Dr. R. J. Cernik
CCLRC Daresbury Laboratory, Warrington WA44AD (UK)

[**] The authors would like to thank Henrik Birkedal and Angela Altomare for useful discussions, Hermann Emerich for technical assistance during the experiment, and Giuseppe Cruciani for suggestions regarding the Rietveld procedure. K.D.K. acknowledges support from the Research Council of Norway (project no. 100822/431).

structure, using direct methods and Fourier recycling. This represents a considerable advance in the size of an organic molecule solved *ab initio* from powder diffraction data. The data were collected at a third-generation synchrotron radiation source, and we believe that quite large organic structures can be solved routinely from powders using such facilities.

The determination of the crystal structure of any material or compound can usually be achieved if a single crystal, even a very small one, can be grown. Many compounds do not form single crystals, however, and exist only in the form of microcrystalline powders. Powder diffraction techniques must then be used to obtain information about the structure. However, owing to the projection of the data onto a single angular scale of 2θ , coincidence or overlap of peaks will occur, making determination of the individual integrated intensities impossible or much more difficult. When overlap becomes severe, even the 2θ positions of the individual peaks may be hard to measure with certainty. These problems make the solution of crystal structures from powders much less certain than from single crystals.

The solution of structures from powders requires data of the highest quality. Modern diffractometers, and especially those exploiting synchrotron radiation, can yield diffraction patterns from which structures can be solved without any prior knowledge. The keys to success are high angular resolution and hence narrow peak widths, accurate determination of peak positions, and good counting statistics throughout the diffraction pattern. Improved resolution reduces the overlap between adjacent reflections, so that individual peak intensities can be extracted with the highest level of reliability. With narrow peak widths, small peak splittings may also be resolved, perhaps revealing a lower symmetry than would be apparent with data measured at lower angular resolution. Accurate peak positions are required for indexing the unit cell, that is, recovering the three-dimensional crystal lattice from the one-dimensional powder pattern. Good counting statistics are essential for accurately fitting diffraction peaks during the extraction of the integrated intensities, which occurs prior to structure determination by traditional single-crystal techniques such as direct methods or Patterson synthesis. Synchrotron radiation offers all these attributes owing to the abundant photon flux, the low beam divergence, and the small source size. The combination of the low beam divergence and high flux also makes it feasible to incorporate an analyzer crystal in the diffracted beam in order to further enhance the angular resolution of the powder diffractometer. A sample of good crystallinity, free from strain and particle-size broadening, is also advantageous to exploit the capabilities of synchrotron radiation fully.

An early example of the power of high-resolution powder diffraction for structure solution was provided by McCusker^[10] in 1988, when the structure of a clathrasil (Sigma-2, 17 non-hydrogen atoms in the asymmetric unit) was solved using data collected at NSLS in Brookhaven. This publication also gives a general overview of the procedures involved in structure solution. More recently, synchrotron radiation has been increasingly employed for powder diffraction studies. Most of the studies have been carried out on inorganic compounds, and there are fewer examples of organic struc-

tures solved from powder data. One reason for this scarcity, apart from the increased molecular complexity, is the poorer scattering at high angle due to the fall-off in the form factor of the light atoms which make up the organic structure. In addition, larger thermal displacement parameters in organic molecules lead to a stronger exponential decay of the scattered intensities with $\sin \theta/\lambda$.

Here we report the complete solution of the crystal and molecular structure of fluorescein diacetate ($C_{24}H_{16}O_7$), a molecule with 31 carbon and oxygen atoms, without any prior structural knowledge. Some organic structures of comparable complexity have been solved before from synchrotron radiation data, though these have required the input of the known molecular structure, or at least part of it. For example, for the red form of fluorescein, a molecule closely related to fluorescein diacetate, the complete molecule was moved around the unit cell using a Monte Carlo approach that seeks to minimize the differences between observed and calculated diffraction patterns.^[9] Genetic algorithms,^[4] simulated annealing,^[5] or a grid search^[6–8] (for structures with few degrees of freedom) are alternative approaches to the solution of crystal structures; in this case the position, orientation, and conformation of known molecular fragments, or whole molecules, are adjusted.

Fluorescein diacetate powder (Sigma, 98% purity) was loaded into a thin-walled borosilicate glass capillary with a diameter of 1.5 mm. A powder diffraction pattern was measured at room temperature with a wavelength of 1.0 Å at the Swiss–Norwegian beam line (BM1) at the European Synchrotron Radiation Facility (ESRF) in Grenoble. This diffractometer is equipped with a Si111 analyzer stage, yielding intrinsic peak widths of about 0.012° . The diffraction pattern could be indexed with a triclinic lattice with the program ITO^[11] from the position of 20 low-angle reflections with a figure of merit M_{20} of 118. The volume of the unit cell indicates that there are two molecules per cell, and hence a possible space group is $P\bar{1}$. However the structure could not be solved, possibly because of the low intensities of the reflections at high angle, a region of vital importance if direct methods are to be successful. A new diffraction pattern was measured on the powder diffraction beam line BM16 at the ESRF at a wavelength of 0.6006 Å while the sample was cooled to 100 K with a stream of cold nitrogen gas. The high-angle part of the diffraction pattern ($2\theta = 20–50^\circ$) was scanned twice as often as the low-angle part to improve the statistical quality of this region. The beam line BM16 is equipped with nine detectors that are spaced at intervals of approximately 2° behind a Ge111 analyzer crystal. In effect, nine diffraction patterns offset from one another by 2° are collected simultaneously. Following data collection, the counts from the nine channels are combined and normalized, taking into account the exact angular separation between channels, their different efficiencies, and the fall-off in the incident intensity as the electron current in the storage ring gradually decays with time. This provides an efficient method for measuring a high-resolution powder diffraction pattern.

A total of 2905 individual values of F_{hkl}^2 were extracted from the normalized data with the program EXTRA;^[12] this is equivalent to 511 statistically independent observations.^[13]

The program EXTRA performs a fit to the observed diffraction profile, using as input the unit-cell parameters to calculate peak positions, but without any structural model. A pseudo-Voigt function was used to fit the profiles. The low-temperature data confirmed the presence of a $P\bar{1}$ cell. In EXTRA, intensities are obtained following the method initially described by Le Bail.^[14] The extracted intensities, together with refined lattice parameters, wavelength, space group, and information on the cell contents were input to the associated direct-methods program SIRPOW.^[15] The distribution of normalized E values was compatible with the assumption of a centrosymmetric structure. In the phasing section, 32 permutations were performed to produce 10 possible sets, which were ranked according to their combined figure of merit. These were then used for the Fourier transform and generation of the E map. With the default settings, the structure was not successfully solved with SIRPOW. However, after the parameter that controls whether SIRPOW considers neighboring reflections as overlapped was changed from the default value of 0.1 to 0.2, the E map revealed a fragment of the molecule comprising 14 atoms (part of the xanthenone group). The combined figure of merit at this stage was 0.988. In subsequent cycles of Fourier synthesis and least-squares refinement, the rest of the structure was located with SIRPOW. The complete molecule was found, with carbon and oxygen atoms correctly assigned, and all bond distances were within about 0.1 Å of what would be expected.

The structure was refined by the Rietveld method, using the PC version of the program GSAS.^[16] This program incorporates the correction described by Finger et al.^[17] for peak asymmetry caused by axial divergence. This tends to be quite pronounced with BM16 data because of the narrow peak widths and because the short wavelength used pushes more peaks to lower diffraction angles, where the asymmetry is most marked. First the background, overall scale factor, zero point, and lattice parameters were refined, and then the profile parameters. The atomic positions were refined with the

bond lengths restrained to the values found in a single-crystal diffraction study of a related system.^[18] Hydrogen atoms were included in the model at their expected positions making use of the XP utility in the SHELXTL program.^[19] At the end of the refinement, assuming an overall isotropic temperature factor, the resulting R values were $R_p = 7.1\%$ and $R_{wp} = 9.7\%$ ($\chi^2 = 4.1$). One molecule of fluorescein diacetate placed in the unit cell is shown in Figure 1.^[21] The final atomic coordinates are given in Table 1, and the fit between the observed and calculated powder diffraction patterns is shown in Figure 2. In contrast to the case of fluorescein^[9] or the 1:1 complex of acetone with the lactoid form of fluorescein,^[18] where a network of intermolecular $C=O \cdots H-O$ hydrogen bonds is present, fluorescein diacetate forms weaker $C-H \cdots O$ bonds

Table 1. Final atomic coordinates for fluorescein diacetate at 100 K after refinement in the triclinic spacegroup $P\bar{1}$ by the Rietveld method. The atom numbering scheme is shown in Figure 1. $U_{iso} = 0.013 \text{ Å}^2$; $a = 11.044$, $b = 11.730$, $c = 7.371 \text{ Å}$, $\alpha = 95.759$, $\beta = 97.429$, $\gamma = 94.830^\circ$, $V = 938 \text{ Å}^3$; $\rho_{calcd} = 1.48 \text{ g cm}^{-3}$; $Z = 2$.

O(1)	0.4604(6)	0.4752(6)	0.2509(9)
O(2)	0.8007(5)	0.8828(5)	0.7038(8)
O(3)	0.2246(5)	0.1647(5)	−0.1026(9)
O(4)	0.9035(5)	0.2219(5)	0.4728(8)
O(5)	0.6440(6)	0.8359(5)	0.4809(9)
O(6)	0.7331(6)	0.3090(5)	0.3879(9)
O(7)	0.2458(5)	−0.0303(5)	−0.0977(9)
C(1)	0.0548(6)	0.0382(11)	−0.2296(17)
C(2)	0.7863(8)	0.5715(9)	0.3815(16)
C(3)	0.3445(7)	0.3089(8)	0.0794(15)
C(4)	0.6694(8)	0.7252(6)	0.4429(15)
C(5)	0.4566(9)	0.3648(6)	0.1638(14)
C(6)	0.6837(9)	0.4972(7)	0.3050(14)
C(7)	0.6837(12)	1.0387(6)	0.6179(19)
C(8)	0.8945(9)	0.3843(9)	−0.1474(13)
C(9)	0.5612(8)	0.2014(8)	0.0495(16)
C(10)	0.3407(6)	0.2025(8)	−0.0210(13)
C(11)	0.7164(8)	0.9170(6)	0.6117(12)
C(12)	0.5620(8)	0.3113(7)	0.1401(13)
C(13)	0.5637(7)	0.6538(8)	0.3775(17)
C(14)	0.8775(8)	0.3082(9)	0.1919(12)
C(15)	0.7850(7)	0.6864(9)	0.4428(15)
C(16)	0.9772(8)	0.2837(8)	0.1023(14)
C(17)	0.1844(6)	0.0471(5)	−0.1347(15)
C(18)	0.5708(8)	0.5410(7)	0.3091(14)
C(19)	0.7823(9)	0.3639(9)	0.1125(12)
C(20)	0.4478(8)	0.1484(6)	−0.0246(15)
C(21)	0.7931(9)	0.4006(8)	−0.0574(12)
C(22)	0.8487(7)	0.2813(8)	0.3718(12)
C(23)	0.6824(7)	0.3730(7)	0.2316(12)
C(24)	0.9884(9)	0.3281(10)	−0.0619(15)
H(1)	0.0331(62)	−0.0448(15)	−0.233(12)
H(2)	−0.0018(54)	0.0600(62)	−0.143(7)
H(3)	0.0147(68)	0.0075(68)	−0.354(4)
H(4)	0.8723(23)	0.5644(61)	0.366(10)
H(5)	0.2718(32)	0.3386(48)	0.123(8)
H(6)	0.7209(64)	1.0999(50)	0.714(8)
H(7)	0.6998(63)	1.0927(56)	0.529(8)
H(8)	0.6064(33)	1.0478(64)	0.667(10)
H(9)	0.9032(61)	0.4282(52)	−0.252(6)
H(10)	0.6397(26)	0.1774(50)	0.019(9)
H(11)	0.4837(24)	0.6815(47)	0.391(9)
H(12)	0.8684(27)	0.7162(56)	0.428(10)
H(13)	1.0646(19)	0.2983(55)	0.151(9)
H(14)	0.4607(63)	0.0683(20)	−0.062(9)
H(15)	0.7802(58)	0.4773(21)	−0.001(8)
H(16)	1.0689(32)	0.3221(60)	−0.102(10)

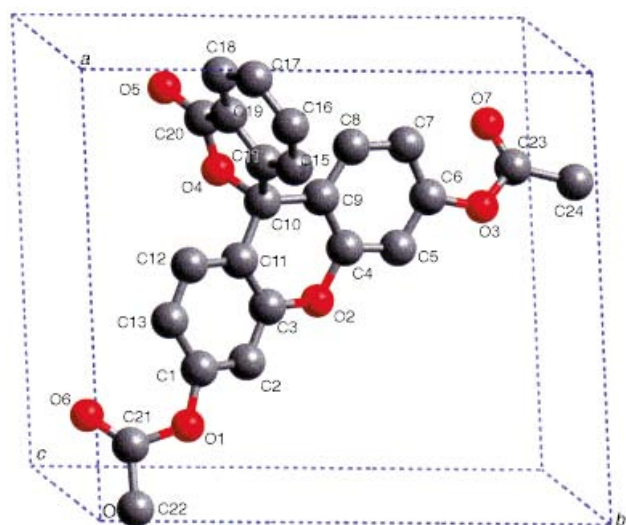


Figure 1. One molecule of fluorescein diacetate in the unit cell. Hydrogen atoms are not shown.

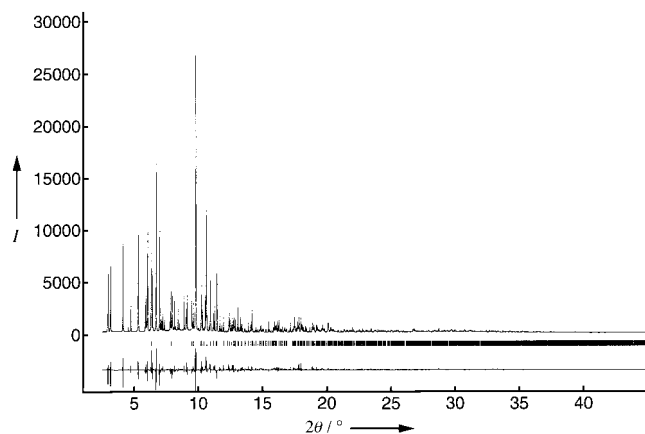


Figure 2. Results from the data collection on polycrystalline fluorescein diacetate at the beam line BM16 at the ESRF: experimental (dots) and calculated powder diffraction data (solid line, final result from the Rietveld refinement) together with the difference curve (bottom, observed minus computed intensities).

between the molecules. There is general consensus that C–H...O bonds influence crystal packing, especially when stronger hydrogen bonding is absent.^[20] A summary of potential hydrogen bonds is given in Table 2 along with

Table 2. Analysis of the C–H...O hydrogen bonds in fluorescein diacetate.^[a]

D–H...A	Distance D–A [Å]	Angle D–H–A [°]
C(22)–H(1)...O(7)	3.189	127.7
C(12)–H(10)...O(6)	3.053	152.3
C(7)–H(12)...O(5)	3.484	151.4
C(18)–H(13)...O(7)	3.510	179.7
C(15)–H(15)...O(2)	3.475	173.1

[a] D = donor, A = acceptor.

donor–H...acceptor distances and bond angles. The acetate groups on both sides of the xanthenone moiety play an important role in the formation of hydrogen bonds in this system. The three rings in the xanthenone group each have a high degree of planarity, and the end rings are inclined to each other at an angle of about 10°, which is in agreement with the results of the single-crystal study of the lactoid form of fluorescein.^[18]

The collection of data combining high resolution, accurate peak positions, and good statistics by use of the powder diffractometers at the ESRF—the world's first third-generation synchrotron radiation source—has led to the solution of a complex organic structure without any prior structural knowledge. Only the chemical formula was used as input information in the procedure, as is usually the case for single-crystal studies. The collection of data at 100 K and additional scanning of the high-angle region to improve the statistics has without doubt improved the quality of the data, but apart from that no special procedures were followed. The structure was obtained from direct methods with only one parameter in SIRPOW being changed from its default value. It seems probable that by using more optimized methods of data

collection, such as those advised by David and co-workers,^[3] and by exploiting the many options available in program packages for carrying out direct methods, structures of significantly greater complexity may be obtainable solely from high-quality powder diffraction data. This is of clear importance for characterizing the large number of compounds that do not easily form single crystals, and leads us to believe that the goal of solving the structures of complex polymorphs of organic compounds, perhaps with specific pharmacological activity, is now attainable.

Received: February 25, 1998 [Z11517IE]
German version: *Angew. Chem.* **1998**, *110*, 2474–2478

Keywords: ab initio calculations • fluorescein • structure elucidation • synchrotron radiation • X-ray scattering

- [1] R. E. Morris, W. T. A. Harrison, J. M. Nicol, A. P. Wilkinson, A. K. Cheetham, *Nature* **1992**, 359, 519.
- [2] R. E. Morris, J. J. Owen, J. K. Stalick, A. K. Cheetham, *J. Solid State Chem.* **1994**, 111, 52.
- [3] K. Shankland, W. I. F. David, D. S. Sivia, *J. Mater. Chem.* **1997**, 7, 569.
- [4] K. Shankland, W. I. F. David, T. Csoka, *Z. Kristallogr.* **1997**, 212, 550.
- [5] Y. G. Andreev, G. S. MacGlashan, P. G. Bruce, *Phys. Rev. B* **1997**, 55, 12011.
- [6] R. E. Dinnebier, P. W. Stephens, J. K. Carter, A. N. Lommen, P. A. Heiney, A. R. McGhie, L. Brard, A. B. Smith III, *J. Appl. Crystallogr.* **1995**, 28, 327.
- [7] G. Reck, R.-G. Kretschmer, L. Kutschabsky, W. Pritzkow, *Acta Crystallogr. Sect. A* **1988**, 44, 417.
- [8] J. Cirujeda, L. E. Ochando, J. M. Amigó, C. Rovira, J. Rius, J. Veciana, *Angew. Chem.* **1995**, 107, 99; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 55.
- [9] M. Tremayne, B. M. Kariuki, K. D. M. Harris, *Angew. Chem.* **1997**, 109, 788; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 770.
- [10] L. McCusker, *J. Appl. Crystallogr.* **1988**, 21, 305.
- [11] J. W. Visser, *J. Appl. Crystallogr.* **1969**, 2, 89.
- [12] A. Altomare, M. C. Burla, G. Cascarano, A. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, *J. Appl. Crystallogr.* **1995**, 28, 842.
- [13] C. Giacovazzo, *Acta Crystallogr. Sect. A* **1996**, 52, 331.
- [14] A. Le Bail, H. Duroy, J. L. Forquet, *Math. Res. Bull.* **1988**, 23, 447.
- [15] A. Altomare, G. Cascarano, A. Giacovazzo, A. Guagliardi, *J. Appl. Crystallogr.* **1994**, 27, 435.
- [16] A. C. Larson, R. B. von Dreele, *Los Alamos Natl. Lab. Rep.* **1987**, LA-UR-86-784.
- [17] L. W. Finger, D. E. Cox, A. P. Jephcoat, *J. Appl. Crystallogr.* **1994**, 27, 892.
- [18] R. S. Osborn, D. Rogers, *Acta Crystallogr. Sect. B* **1975**, 31, 359.
- [19] Siemens Analytical X-ray Instruments, Inc., SHELXTL PC, Release 4.1, **1990**.
- [20] G. R. Desiraju, *Acc. Chem. Res.* **1996**, 29, 441.
- [21] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101114. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Porphyrin Tessellation by Design: Metal-Mediated Self-Assembly of Large Arrays and Tapes**

Charles Michael Drain,* Fotis Nifiatis,
Alexander Vasenko, and James D. Batteas

In light of the tremendous versatility of porphyrins and metalloporphyrins in mediating electron and energy transfer, their utility as redox catalysts, and their dynamic photo-physical properties, there have been considerable efforts made in the design and synthesis of oligoporphyrins. These covalent compounds yield information on the mechanisms of electron and energy transfer, and demonstrate the possibility to use these chromophores in photonic devices.^[1] In the synthesis of discrete ordered arrays of covalently linked porphyrins, there now seems to be a practical limit of about ten macrocycles.^[2] To create ever larger arrays in reasonable yields, a supramolecular approach has been employed to design a variety of discrete porphyrin arrays;^[3–6] self-assembly makes use of molecular recognition through hydrogen bonds,^[3] coordination of transition metal ions,^[4] electrostatic interactions,^[5] and self-coordination of metallo derivatives.^[6] Notably, the largest designed discrete assemblies containing six or more components have been squares made up of four porphyrins assembled by four transition metal ions,^[4] and a rosette containing six porphyrins assembled by hydrogen bonding.^[3b]

Herein we push the methodology into the next level of complexity and present the design of a discrete supramolecular array of nine porphyrins (Figure 1). Self-assembly is accomplished by coordination of exocyclic pyridyl groups on three different porphyrin derivatives to 12 palladium(II) dichloride units: Four different types of molecules self-assemble to a 21-membered, array that is 25 nm² large.^[7]

These types of systems are expected to further our understanding of photonic communication between chromophores mediated by noncovalent interactions, serve as a guide for the formation of molecular channels or receptors, and be a foundation for the development of molecular photonic materials such for use in nonlinear optics.^[1, 2] The well-characterized photophysical behavior of these macrocycles provides a tool for the examination of the kinetics, mecha-

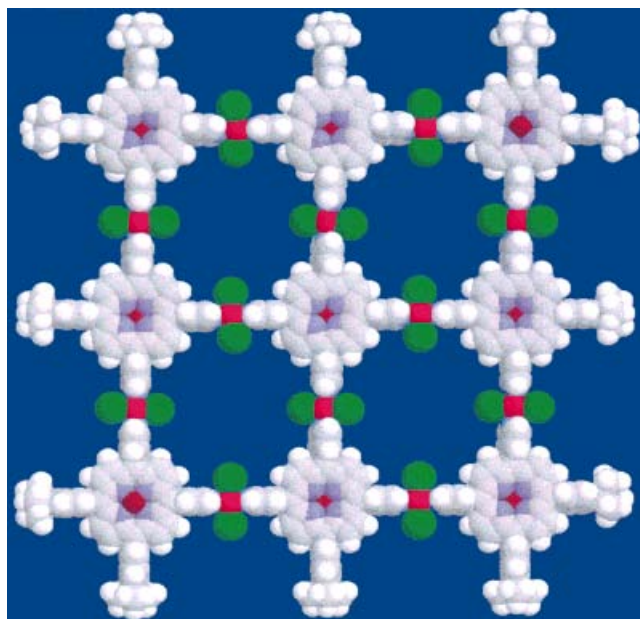


Figure 1. Space-filling model of the tessellated porphyrin **6b**.

nism, and thermodynamics of self-assembly. The formation and characterization of porphyrin squares, whose self-assembly is mediated by one or two different transition metals, have been well documented.^[4]

We designed the nonameric arrays **5** and **6** by appropriate choice of *trans* coordination by the relatively labile square-planar bis(benzonitrile)palladium(II) dichloride (**4**), the correct stoichiometries of the components, and the correct substitution patterns of three different porphyrins: one central X-shaped unit (porphyrin **1**), four T-shaped units on the sides (porphyrin **2**), and four L-shaped units in the corners (porphyrin **3**; Scheme 1). The “molecular information” inherent in the individual molecules and the stoichiometry (12Pd, 1“X”, 4“L”, and 4“T”) favors the formation of the desired arrays, but the reversibility of pyridyl–palladium bond formation is also crucial for reaching what appears to be the thermodynamic product. Thus, the desired arrays are formed in approximately 90 % yield at room temperature in less than 30 minutes when **4** is added to the correct mixture of porphyrins (total concentration < 10 μM) in chloroform, mineral oil, or toluene. At concentrations of about 20 μM the yield is reduced to less than 70 %. One key feature of this system is that there are three different porphyrins, so any combination of free base and metallo compounds may be used to make the supramolecular arrays. This results in arrays with metallo derivatives in predictable positions. In the present study only the all-free base or all-zinc complexes are presented to avoid the kinetic and spectroscopic complications that arise from axial coordination by the pyridyl groups to other metalloporphyrins (homocoordination).

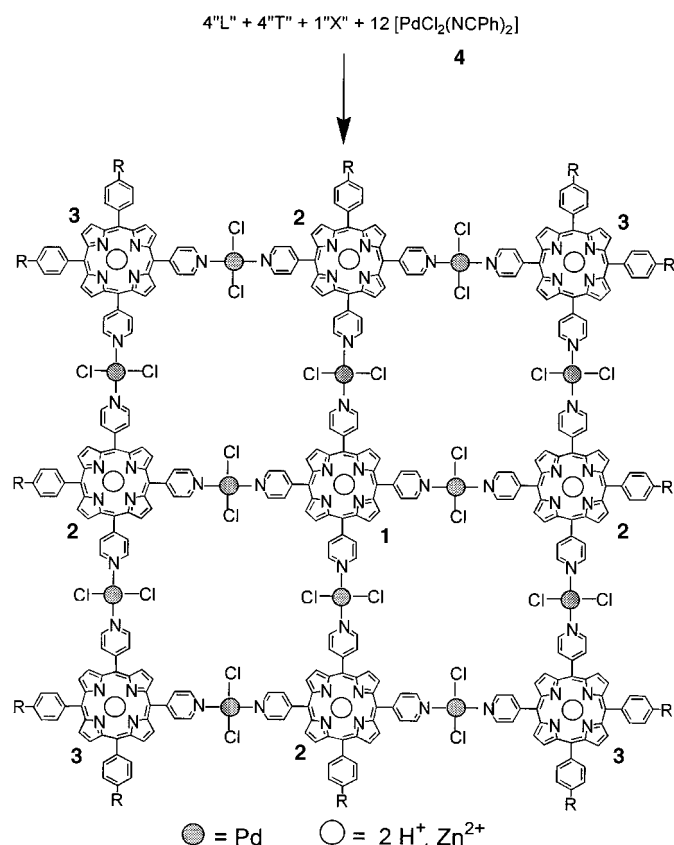
Porphyrin tapes (Scheme 2) are made in a manner similar to that of the nonamers. For example, addition of two porphyrins **7b** (“O”) to two “T”-shaped porphyrins **8b** and two equivalents of **4** results in the palladium-based tape **9b** as a mixture of the dimer, the trimer, and the tetramer in a ratio of about 3:8:2. For tape **10a**, which is made by mixing porphyrins

[*] Prof. Dr. C. M. Drain, F. Nifiatis, A. Vasenko
Department of Chemistry at Hunter College
The City University of New York
New York, NY 10021 (USA)
Fax: (+1) 212-772-5332
E-mail: cdrain@shiva.hunter.cuny.edu

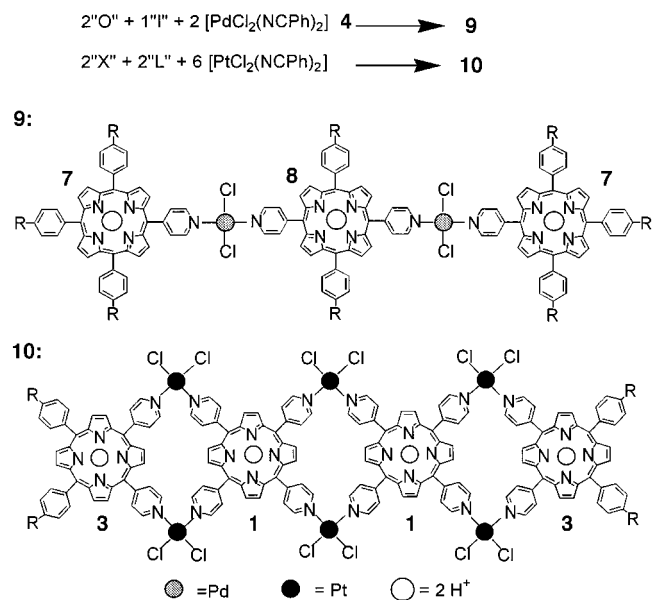
Prof. Dr. J. D. Batteas
Department of Chemistry at the College of Staten Island
The City University of New York (USA)

[**] Financial support from RCMI from the National Institutes of Health (RR-03037), New York State GRI grants to Hunter College, a Hunter College Presidential Scholar Fellowship to A.V., the NSF (Career CHE-9732950), and a CUNY Collaborative Research Grant to C.M.D. are gratefully acknowledged. We thank Vinita Tiwari and Suhel Ahmed for help in preparing some of the porphyrins.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 1. Self-assembled planar nonameric arrays of porphyrins. Porphyrins: "T": **2a**, R = methyl; **2b**, R = *tert*-butyl; "L": **3a**, R = methyl; **3b**, R = *tert*-butyl; "X": **1**. Arrays: **5a**, R = methyl, $\circ = 2\text{H}^+$; **5b**, R = *tert*-butyl; $\circ = 2\text{H}^+$; **6a**, R = methyl, $\circ = \text{Zn}^{2+}$; **6b**, R = *tert*-butyl, $\circ = \text{Zn}^{2+}$.



Scheme 2. Self-assembled tapes of porphyrins. Porphyrins: "L": **3a**, R = methyl; **3b**, R = *tert*-butyl; "O": **7a**, R = methyl; **7b**, R = *tert*-butyl; "I": **8a**, R = methyl; **8b**, R = *tert*-butyl. Tapes: **9a**, R = methyl, $\circ = 2\text{H}^+$; **9b**, R = *tert*-butyl, $\circ = 2\text{H}^+$; **10a**, R = methyl, $\circ = \text{Zn}^{2+}$; **10b**, R = *tert*-butyl, $\circ = \text{Zn}^{2+}$.

1 and **3** (2 "X" and 2 "L") for 4–5 days at 40 °C, a mixture of the trimer, the tetramer, and the pentamer in a ratio of about 2:4:1 is obtained, as determined by electrospray (ES) mass

spectrometry. The asymmetric distribution of the subunits probably arises for reasons of entropy and solubility.

Titration of **4** into a solution of the porphyrins in toluene, mineral oil, or chloroform results in clear isosbestic points for the Q and B (Soret) bands in the UV/Vis spectra of the porphyrins, indicating the formation of only one species in solution.^[8] The substantial broadening, concomitant decrease in intensity, and red shift of the Soret band is typical for electronically coupled porphyrins. It is observed to a lesser extent for the Pd-mediated dimer and tetramer arrays and other squares.^[4] There is a consistent red shift of about 2 nm (and broadening) per porphyrin in going from the linear Pt-linked dimer to tetramer of **10a** and **10b**. This is also observed for the Pd-linked tapes **9a** and **9b**. This and previous UV/Vis data^[4a] suggest that the number of porphyrins in the array and their relative geometry are of great importance.

The fluorescence emission of a stoichiometric mixture of porphyrins is quenched to greater than 90 % as **4** is titrated into the solution to form the tessellated nonamer **5b**. This is confirmed by the measurements of the excited state lifetime; the average lifetime for a mixture of porphyrins in toluene at room temperature is 12 ns, and that of the array is less than 1 ns.^[9] There is a quadratic decrease in the intensity of the fluorescence emission of tetrapyrrolylporphyrin (**1**) with each successive binding of a palladium complex $[\text{Pd}_2\text{Cl}_4(\text{Ph}_3\text{P})_2]$, which is capable of binding only one pyridyl moiety (confirmed by the fluorescence lifetime studies) and arises due to the heavy-atom effect. From the latter data, one would expect that the nonamer fluorescence should be quenched by about 57 % due to the heavy-atom effect. The substantial additional quenching for the arrays is likely due to energy transfer from one porphyrin moiety to another, and to some π stacking of the nonamers.^[9]

The ^1H NMR titrations exhibit similar trends as those observed for other porphyrin squares,^[4] namely, there is a highly characteristic shift in the pyridyl protons upon coordination of a metal ion. In the starting stoichiometric mixture of the porphyrins (1 "X", 4 "T", and 4 "L") there are four sets of protons α to the pyridyl nitrogen atom; each signal should be a doublet, but a complex multiplet at $\delta = 9.05$ is observed in the ^1H NMR spectrum. As **4** is titrated into a 10 μM mixture of **2b**, **3b**, and **4**, the peaks at $\delta = 9.05$ decrease in intensity as new resonances at $\delta = 9.45$ grow. Significantly, the signals for the *tert*-butyl protons shift (from one peak at $\delta = 1.621$ to two peaks at $\delta = 1.627$ and 1.634 with the expected 2:1 ratio) and broaden slightly, and indicate a greater than 70 % yield for **5b**. Although these new resonances are broader, consistent with the large increase in molecular size and slower tumbling, the line width indicates that the material in solution is of the size expected for **5b**. Similar to previous studies,^[4a] the zinc porphyrin array **6b** can be titrated with 4.5 equivalents of 4,4'-bipyridine (bpy) to form a sandwich of nine bpy molecules between two nonamer zinc–porphyrin arrays, that is, 18 porphyrins in one system. This is clearly indicated by the new resonances for the α protons on bpy at $\delta = 2.2$ and 5.2 with a broadening of about 80 %, which again is consistent with the formation of a much larger species and not a collection of polymeric materials.

Light-scattering results suggest that clusters with a radius of 5–7 nm are present in solution. Depending on solution conditions, deposition of nonameric arrays on polished glass substrates results in the formation of nanoparticle clusters. Characterization of the three-dimensional arrangement of these clusters by atomic force microscopy (AFM) suggests that the nonameric arrays deposit as columnar structures on the glass surface, potentially as nanocrystals. The clusters range in height from 1.3 to 39 nm with over 75% between 4.5–6.5 nm, which is consistent with the light-scattering data. Widths of 5 nm for single nonameric arrays on the surface were not observed. However, as the images of the clusters so closely match that of the expected AFM tip profile, the nonamers likely stack as columns on the surface with widths less than that of the nominal radius of curvature of the AFM probe tip (ca. 20 nm). Therefore, such sharp, clear images of the tip structure (Figure 2) strongly suggest the nonamers deposit as stacks on the order of $5 \times 5 \times 5 \text{ nm}^3$. These

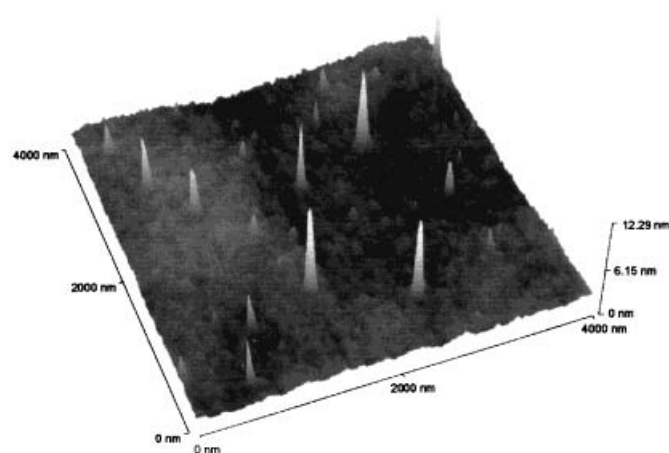


Figure 2. Typical atomic force microscope image of **5b** on a glass surface showing the sharp AFM probe tip structure produced from scanning the columnar stacks of nonameric arrays.

arrangements are induced by a significant intermolecular π -stacking energy per porphyrin face (ca. 5 kcal mol⁻¹) depending on solvent and concentration. These nanocrystalline materials are expected to have interesting photo- and electrochemical properties,^[1, 7] and are currently under investigation.

Other evidence for the formation of the arrays and tapes comes from a variety of methods: dynamic light scattering and size-exclusion chromatography of **5a**, **5b**, **10b**, and **10b**; ES-MS of **10a** and **10b**; and vapor phase osmometry on **5a** and **5b**. Electrospray mass spectra of the four nonameric arrays (in CHCl₃ with 0.3% trifluoroacetic acid or acetic acid) shows the expected signals for molecular ions with charges of 3+ and 4+, consistent with the arrays.^[8] The highly characteristic envelope due to the various isotopes (especially of Cl and Pd) greatly assist in the identification of the tri- and tetra-protonated nonamer. Peaks consistent with the loss of three and four chloride ions are also observed.^[8]

The data taken together indicate formation of nonamer arrays that are about 25 nm² large, objects that are between discrete chemical species and polymeric materials. This work demonstrates that it is possible to design and self-assemble large, complex arrays of ridged dye molecules such as

porphyrins by choosing the appropriate geometry of the building blocks and metal ions. The properties of these arrays and materials may be readily fine-tuned by the choice of metal ion linker, the metalloporphyrins used, and further substituents on the macrocycle (such as bromo, nitro, and amino groups) at one or more β -pyrrole positions.

Experimental Section

Porphyrins **1**, **2a**, **3a**, **7a**, and **8a** are prepared by either the Adler^[10a] or high-temperature methods^[10b] from a mixture of 4-methylbenzaldehyde, pyridine-4-carbaldehyde, and pyrrole (2:2:4). The six possible compounds were separated on two flash chromatography columns with hexane/toluene/chloroform gradients. Porphyrins **2b**, **3b**, **7b**, and **8b** are made similarly. Although these are new derivatives, the parent pyridyl compounds have been described in the literature. All starting porphyrins gave satisfactory UV/Vis and ¹H NMR spectra, as did all the arrays and tapes. Satisfactory fast atom bombardment (FAB) mass spectra for the starting porphyrins and ES mass spectra for the arrays and tape were also obtained.

Preparation of arrays and tapes (for example, **5b**): To a solution of **1** (0.222 μM), **2b** (0.888 μM), and **3b** (0.888 μM ; 1:4:4, 2 μM in porphyrins) is added **4** in four aliquots at intervals of at least five minute to reach a concentration of 2.66 μM . Typically this is done in a 3-mL cuvette, and the reaction is monitored by UV/Vis spectroscopy (see Figure 1 of the Supporting Information). The arrays with the zinc complex are formed in a similar procedure. The nonameric array is more soluble when the methyl group on the phenyl rings is replaced by *tert*-butyl (< 1 μM concentrations of **1a**, **2a**, and **3a** are used to form **5a** and **6a**). When a Pd complex with only one binding site coordinates to a monopyridylporphyrin there is a red shift of about 1 nm and a slight broadening of the Soret band; when **1a** or **1b** coordinate four of these Pd complexes, there is a net red shift of about 4 nm and the broadening is less than 10%. When the solvent is evaporated very small amounts of **5a** and **5b** can be resolubilized, which is most likely due to π -stacking interactions. Thus, the arrays are stored in solution in the dark under an inert atmosphere, where they are stable for months. Tapes **9a** and **9b** are formed by similar procedures (see above), but formation of tapes **10a** and **10b** require vigorous stirring at about 40 °C for 5–6 days under nitrogen in the dark.

AFM data were obtained with a Topometrix Explorer stand-alone microscope in an environmental chamber under dry air with a relative humidity of less than 2%. Data were collected in the attractive noncontact mode to avoid altering the surface features. Imaging in the constant-force DC contact mode was observed to damage the nanoparticles. The glass slides were cleaned, dipped into a 0.5 μM solution of **5a** for 3 h, and dried under vacuum. Control experiments with individual porphyrins, mixtures of porphyrins, and the Pd starting material yield no discernible structures. Many different samples and tips yield the same results. Additionally, these readily prepared structures provide a remarkably consistent way to obtain high-quality probe tip images.

Received: November 25, 1997

Revised version: May 22, 1998 [Z11194IE]

German version: *Angew. Chem.* **1998**, *110*, 2478–2481

Keywords: atomic force microscopy • coordination chemistry • nanostructures • porphyrinoids • supramolecular chemistry

- [1] a) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VHC, Weinheim, **1995**; b) J. S. Lindsey, *New J. Chem.* **1991**, *15*, 153–180.
- [2] a) S. Anderson, H. L. Andersen, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2247–2254; b) D. L. Officer, A. K. Burrell, D. C. W. Reid, *Chem. Commun.* **1996**, 1657–1658; c) D. Fenyo, B. T. Chait, T. E. Johnson, J. S. Lindsey, *J. Porphyrins Phthalocyanines* **1997**, *1*, 93–99.
- [3] a) C. M. Drain, R. Fischer, E. Nolen, J.-M. Lehn, *J. Chem. Soc. Chem. Commun.* **1993**, 243–245; b) C. M. Drain, K. C. Russell, J.-M. Lehn, *Chem. Commun.* **1996**, 337–338.

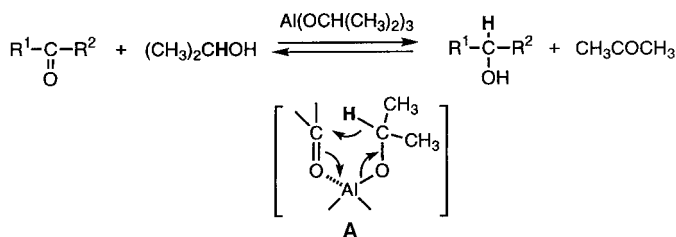
- [4] a) C. M. Drain, J.-M. Lehn, *J. Chem. Soc. Chem. Commun.* **1994**, 2313–2315; b) H. Yuan, L. Thomas, L. K. Woo, *Inorg. Chem.* **1996**, *35*, 2808–2817; c) P. J. Stang, J. Fan, B. Olenyuk, *Chem. Commun.* **1997**, 1453–1454; d) R. V. Slone, J. T. Hupp, *Inorg. Chem.* **1997**, *36*, 5422–5437.
- [5] a) C. M. Drain, D. Mauzerall, *Biophys. J.* **1992**, *63*, 1556–1563; b) K. Araki, M. J. Wagner, M. S. Wrighton, *Langmuir* **1996**, 5393–5398.
- [6] K. Funatsu, A. Kimura, T. Imamura, Y. Sasaki, *Chem. Lett.* **1995**, 765–766.
- [7] While coordination polymers have been known for many decades, the formation of discrete ordered coordination arrays is enjoying a renaissance: a) J.-M. Lehn, *Angew. Chem.* **1990**, *102*, 1347–1362; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304–1319; b) M. Fujita, Y. J. Kwon, S. Washizu, K. Ogura, *J. Am. Chem. Soc.* **1994**, *116*, 1151–1152; c) R. V. Slone, J. T. Hupp, C. L. Stern, T. E. Albrecht-Schmitt, *Inorg. Chem.* **1996**, *35*, 4096–4097; d) B. Linton, A. D. Hamilton, *Chem. Rev.* **1997**, *97*, 1669–1680; e) P. J. Stang, B. Olenyuk, *Acc. Chem. Res.* **1997**, *30*, 507–518.
- [8] a) The UV/Vis spectra (see Figure 1 of the Supporting Information) were measured with a 0.5 μM solution in toluene (formation of nonamer **5b** from the porphyrin mixture **1** + **2b** + **3b**); Soret bands (half-width) in nm (porphyrin mixture $\rightarrow$ **5b**): 418.9 (15.3)–408.4 (23.2), 425.9 (18.2), 439.6 (20.4). b) The ES mass spectrum (HP-1100 LC/MS, direct injection at 0.1 mL min⁻¹, N₂ carrier gas at 1 mL min⁻¹, ionization potential 150 kV, positive-ion mode) of **5a** in CHCl₃ with 0.3 % acetic acid (see Figure 3 of the Supporting Information) shows the tri- and tetra-protonated nonamer at m/z = 2619 and 1965, respectively. Additionally, it shows the loss of three and four chloride ions at m/z = 2583 and 1928, respectively. Vapor-phase osmometry studies used toluene as solvent and were standardized with polystyrene of a known average molecular weight. c) ¹H NMR (300 MHz, CDCl₃; see Figure 4 of the Supporting Information) for nonamer **5b** formed from **1** + **2b** + **3b**: α -pyridyl (δ = 9.051 $\rightarrow$ 9.454), β -pyridyl (δ = 8.13 $\rightarrow$ 8.32), *tert*-butyl (δ = 1.621 $\rightarrow$ 1.627 and 1.634), pyrrole NH (δ = -2.816, -2.866, -2.906 $\rightarrow$ -2.786, -2.811, -2.840). The width at half-height of the methyl peaks broadens from about 2 Hz to 4.2 Hz.
- [9] Fluorescence quenching (supramolecular array/porphyrin mixture at the same optical density): **5a** (ca. 87 % in toluene, ca. 93 % in CCl₄), **5b** (>90 % in CHCl₃ or mineral oil), **9a** (14 % in toluene), **10a** (18 % in toluene). The complete photophysical characterization of these systems will be reported elsewhere.
- [10] a) A. D. Adler, F. R. Longo, W. Shergalis, *J. Am. Chem. Soc.* **1964**, *86*, 3145–3148; b) C. M. Drain, X. Gong, *Chem. Commun.* **1997**, 2117–2118.

Highly Efficient, Catalytic Meerwein–Ponndorf–Verley Reduction with a Novel Bidentate Aluminum Catalyst**

Takashi Ooi, Tomoya Miura, and Keiji Maruoka*

The Meerwein–Ponndorf–Verley (MPV) reaction, named after the independent originators, involves the chemoselective reduction of carbonyl substrates with aluminum alkoxides, generally Al(O*i*Pr)₃, as catalyst and *i*PrOH as hydride source.^[1–3] In the MPV reduction, a reversible hydride transfer from the alcoholate to a carbonyl acceptor via a six-

membered transition state **[A]** is initiated by the activation of the carbonyl group by coordination to the Lewis acidic aluminum center (Scheme 1).^[4] Acetone is formed as a



Scheme 1. MPV reduction of carbonyl compounds with Al(O*i*Pr)₃ in *i*PrOH, which proceeds via transition state **A**.

volatile side product, which is easily removed during the reaction. Advantages of the MPV reduction include chemoselectivity, mild reaction conditions, operational simplicity, safe handling, and ready adaptation both in the laboratory and on a large scale.^[5]

Nonetheless, there are several practical problems with the MPV reduction such as the need for an excess of alcohol as hydride source, low reaction rate, formation of condensation products, and need for higher reaction temperatures so that the concurrent removal of acetone shifts the equilibrium towards the formation of alcohol. The most important side reactions are the aldol condensation and the Tishchenko reaction; the latter leads to the formation of carboxylic esters, especially in the case of the more reactive aldehydes.^[6] Accordingly, various modifications of the MPV reduction have been developed in order to overcome these disadvantages. The more recent improvements are the use of catalytically active lanthanide alkoxides,^[7] microwave irradiation,^[8] and the addition of CF₃CO₂H to Al(O*i*Pr)₃ to accelerate the reduction.^[9] Herein we report the highly accelerated MPV reduction of carbonyl substrates with a bidentate aluminum catalyst. The realization of this modern MPV reduction is crucially dependent on the effective use of our recently developed bidentate Lewis acid chemistry.^[10]

The typical MPV reduction of carbonyl substrates proceeds quite reluctantly. For example, reduction of benzaldehyde in CH₂Cl₂ with Al(O*i*Pr)₃ (1 equiv) at room temperature for 1 h gave rise to benzyl alcohol in 34 % yield.^[11] When the reaction was carried out in CH₂Cl₂ with *i*PrOH (1 equiv) and a catalytic amount of Al(O*i*Pr)₃ (10 mol %) at room temperature for 2 h, benzyl alcohol was obtained in only 10 % yield (Table 1). Under similar reduction conditions, ketone substrates (e.g., 4-phenylcyclohexanone and 2-undecanone) were totally unreactive, and most of the starting material was recovered. In marked contrast, however, use of the bidentate aluminum catalyst **1** in the reduction of benzaldehyde produced the benzyl alcohol at room temperature instantaneously and almost quantitatively (Scheme 2). Catalyst **1** is generated in situ from 2,7-dimethyl-1,8-biphenylenediol, Me₃Al (2 equiv), and *i*PrOH (4 equiv). Moreover, even with 5 mol % of **1** the reduction proceeds quite smoothly at room temperature to furnish benzyl alcohol in 81 % yield after 1 h. This remarkable efficiency can be ascribed to the double

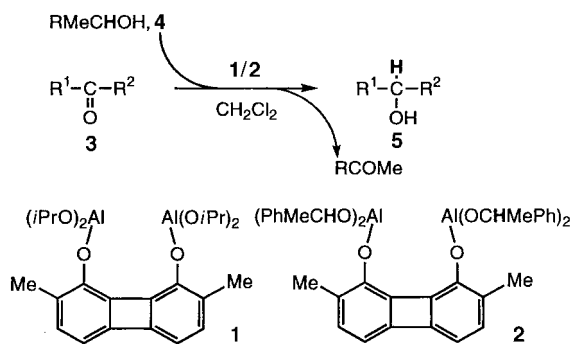
[*] Prof. K. Maruoka, Dr. T. Ooi, T. Miura
Department of Chemistry, Graduate School of Science
Hokkaido University
Sapporo, 060–0810 (Japan)
Fax: (+81) 11-746-2557
E-mail: maruoka@sci.hokudai.ac.jp

[**] This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

Table 1. Catalytic MPV reduction of carbonyl substrates with **1** or **2**.

Substrate	Al reagent (mol %)	Hydride source (equiv)	<i>t</i> [h]	Yield [%] ^[a]
PhCHO	Al(O <i>i</i> Pr) ₃ (100)	–	1	34
PhCHO	Al(O <i>i</i> Pr) ₃ (10)	<i>i</i> PrOH (1)	2	10
PhCHO	1 (100)	–	(5 min)	99
PhCHO	1 (5)	<i>i</i> PrOH (1)	1	81
PhCHO	1 (5)	<i>i</i> PrOH (3)	1	96
PhCH(CH ₂) ₄ C=O	Al(O <i>i</i> Pr) ₃ (100)	–	1	(trace)
PhCH(CH ₂) ₄ C=O	1 (5)	<i>i</i> PrOH (1)	1	91
PhCH(CH ₂) ₄ C=O	1 (5)	<i>i</i> PrOH (1)	2	99
PhC(O)CH ₂ Cl	Al(O <i>i</i> Pr) ₃ (100)	–	2	– ^[b]
PhC(O)CH ₂ Cl	1 (5)	<i>i</i> PrOH (1)	2	75
PhC(O)CH ₂ Cl	1 (5)	<i>i</i> PrOH (1)	10	89
PhC(O)CH ₂ Cl	2 (5)	PhMeCHOH (1)	2	99
CH ₃ (CH ₂) ₈ COCH ₃	Al(O <i>i</i> Pr) ₃ (100)	–	5	– ^[b]
CH ₃ (CH ₂) ₈ COCH ₃	1 (5)	<i>i</i> PrOH (3)	5	50
CH ₃ (CH ₂) ₈ COCH ₃	2 (5)	PhMeCHOH (1)	5	73
CH ₃ (CH ₂) ₈ COCH ₃	2 (5)	PhMeCHOH (3)	5	89
CH ₃ (CH ₂) ₈ COCH ₃	2 (5)	PhMeCHOH (6)	5	99
PhCH=CHCOCH ₃	1 (5)	<i>i</i> PrOH (1)	5	31 ^[c]
PhCH=CHCOCH ₃	2 (5)	PhMeCHOH (6)	5	70 ^[c]

[a] Yield of isolated product. [b] No reaction. [c] Yield of 1,2-reduction product.

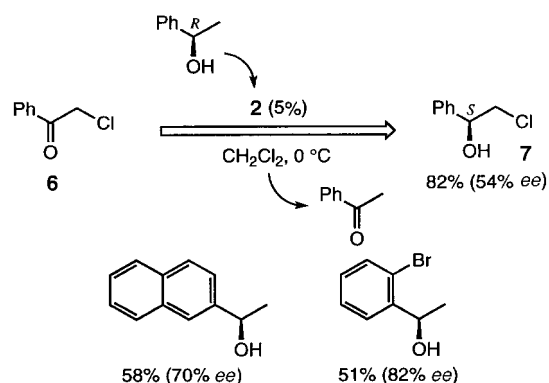


Scheme 2. Catalytic MPV reduction of aldehydes and ketones with **1** or **2**.

electrophilic activation of carbonyl groups by the bidentate aluminum catalyst.^[12]

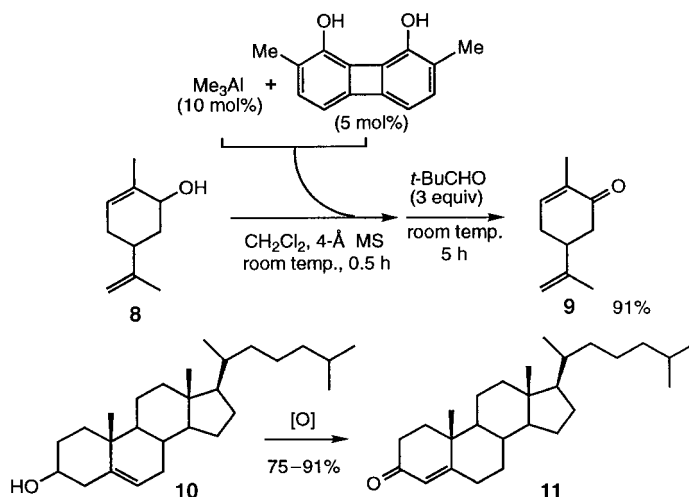
Other selected examples are listed in Table 1. In addition to aldehydes, both cyclic and acyclic ketones can be reduced equally well. *sec*-Phenethyl alcohol (**4**, $\text{R} = \text{Ph}$) is a more effective hydride source than *i*PrOH. This finding prompted us to examine the enantioselective MPV reduction of unsymmetrical ketones with chiral alcohols in the presence of catalyst **2** (Scheme 3).^[13] Indeed, treatment of 2-chloroacetophenone (**6**) with optically pure (*R*)-(+)-*sec*-phenethyl alcohol (1 equiv) under the influence of **2** at 0 °C for 10 h afforded (*S*)-(+)-2-chloro-1-phenylethanol (**7**) with moderate asymmetric induction (82% yield, 54% *ee*).^[14] Switching chiral alcohols from (*R*)-(+)-*sec*-phenethyl alcohol to (*R*)-(+)- α -methyl-2-naphthylmethanol and (*R*)-(+)-*sec*-*o*-bromophenethyl alcohol further enhanced the optical yields of **7** to 70 and 82% *ee*, respectively.^[14, 15]

The present approach is applicable to the reverse reaction of the MPV reduction, that is, the Oppenauer oxidation.^[16, 17] We have successfully developed a highly accelerated Oppenauer oxidation system using a bidentate aluminum catalyst of type **1** and **2**. This modified, catalytic system effectively oxidizes a variety of secondary alcohols to the corresponding



Scheme 3. Enantioselective MPV reduction with chiral secondary alcohols as hydride source.

ketones. For example, sequential addition of a 1M solution in hexane of Me_3Al (10 mol %) and carveol (**8**) to 2,7-dimethyl-1,8-biphenylenediol (5 mol %) in CH_2Cl_2 at room temperature in the presence of 4-Å molecular sieves and subsequent treatment with pivalaldehyde (3 equiv) at room temperature for 5 h provided carvone (**9**) in 91% yield. Under similar oxidation conditions, cholesterol (**10**)^[18] was converted into 4-cholesten-3-one (**11**) in 75% yield (91% yield with 5 equiv of *t*BuCHO, Scheme 4).



Scheme 4. Catalytic Oppenauer oxidation of secondary alcohols with bidentate aluminum catalyst/pivalaldehyde system.

Experimental Section

MPV reduction of 4-phenylcyclohexanone: 2,7-Dimethyl-1,8-biphenylenediol (10.7 mg, 0.05 mmol) and predried, powdered 4-Å molecular sieves (ca. 60–70 mg) were placed in a dry two-neck flask with a stirring bar under argon, and freshly distilled CH_2Cl_2 (5 mL) was introduced. The suspension was carefully degassed and a 1M solution of Me_3Al (100 μL , 0.1 mmol) in hexane was added dropwise at room temperature. After the reaction mixture was stirred for 30 min, *i*PrOH (92 μL , 1.2 mmol) was added, and the stirring was continued for an additional 30 min. The resulting mixture was then treated with a solution of 4-phenylcyclohexanone (174 mg, 1.0 mmol) in CH_2Cl_2 and stirred at room temperature for 1 h. The reaction was quenched with 1N HCl, and the mixture was extracted with diethyl ether. The combined organic extracts were then dried over Na_2SO_4 . Evaporation of solvents and purification of the residual oil by column

chromatography on silica gel (CH_2Cl_2 as eluant) gave a *cis/trans* mixture of 4-phenyl-1-cyclohexanol (159 mg, 0.91 mmol, 91 % yield; *cis:trans* = 23:77).

Received: March 31, 1998 [Z11667IE]
German version: *Angew. Chem.* **1998**, *110*, 2524–2526

Keywords: aluminum • asymmetric synthesis • homogeneous catalysis • oxidations • reductions

- [1] H. Meerwein, R. Schmidt, *Justus Liebigs Ann. Chem.* **1925**, 444, 221.
- [2] a) A. Verley, *Bull. Soc. Chim. Fr.* **1925**, 37, 537; b) A. Verley, *Bull. Soc. Chim. Fr.* **1925**, 37, 1871; c) A. Verley, *Bull. Soc. Chim. Fr.* **1927**, 41, 788.
- [3] W. Ponnendorf, *Angew. Chem.* **1926**, 39, 138.
- [4] Reviews: a) A. L. Wilds, *Org. React.* **1944**, 2, 178; b) R. M. Kellogg in *Comprehensive Organic Synthesis*, Vol. 8 (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, p. 88.
- [5] C. De Graauw, J. Peters, H. Van Bekkum, J. Huskens, *Synthesis* **1994**, 1007.
- [6] W. Tischtschenko, *Chem. Zentralbl.* **1906**, 77, 1309.
- [7] a) H. Kagan, J. Namy, *Tetrahedron* **1986**, 42, 6573; b) J. Huskens, C. De Graauw, J. Peters, H. Van Bekkum, *Recl. Trav. Chim. Pays-Bas* **1994**, 1007.
- [8] D. Barbry, S. Torchy, *Tetrahedron Lett.* **1997**, 38, 2959.
- [9] a) K. G. Akamanchi, N. R. Varalakshmy, *Tetrahedron Lett.* **1995**, 36, 3571; b) K. G. Akamanchi, N. R. Varalakshmy, *Tetrahedron Lett.* **1995**, 36, 5085; c) K. G. Akamanchi, N. R. Varalakshmy, B. A. Chaudhari, *Synlett* **1997**, 371.
- [10] a) T. Ooi, M. Takahashi, K. Maruoka, *J. Am. Chem. Soc.* **1996**, 118, 11307; b) T. Ooi, E. Tayama, M. Takahashi, K. Maruoka, *Tetrahedron Lett.* **1997**, 38, 7403; c) T. Ooi, A. Saito, K. Maruoka, *Tetrahedron Lett.*, in press.
- [11] The reduction of benzaldehyde with $\text{Al}(\text{O}i\text{Pr})_3$ (1 equiv) in 2-propanol did not proceed at room temperature.
- [12] Our system surely takes advantage of the lower susceptibility of both acetone and acetophenone toward the MPV reduction with the reduction products as a hydride source. Indeed, attempted reaction of acetone with 4-phenylcyclohexanol (1 equiv) in the presence of **1** (5 mol %) in CH_2Cl_2 at room temperature for 1 h gave rise to 4-phenylcyclohexanone in only 8 % yield.
- [13] J. D. Morrison, H. S. Mosher, *Asymmetric Organic Reactions*, American Chemical Society, Washington, DC, **1976**, p. 160. Evans et al. reported the first catalytic and highly enantioselective MPV reduction with a chiral Sm complex: D. A. Evans, S. G. Nelson, M. R. Gagne, A. R. Muci, *J. Am. Chem. Soc.* **1993**, 115, 9800.
- [14] The enantiomeric excess of **7** was determined by comparison of the optical rotation with that of commercially available **7** (98 % *ee*). In the reaction with (*R*)-(+)-*sec*-o-bromophenethyl alcohol the *ee* value was measured after conversion into the corresponding styrene oxide: H. C. Kolb, K. B. Sharpless, *Tetrahedron* **1992**, 48, 10515.
- [15] Unfortunately, the asymmetric MPV reduction of dialkyl ketones gave unsatisfactory results in terms of reactivity and selectivity. For example, reaction of 2-undecanone under similar conditions with (*R*)-(+)-*sec*-o-bromophenethyl alcohol afforded 2-undecanol in 11 % yield with less than 25 % *ee*.
- [16] R. V. Oppenauer, *Recl. Trav. Chim.* **1937**, 56, 137.
- [17] For a recent modification, see K. G. Akamanchi, B. A. Chaudhari, *Tetrahedron Lett.* **1997**, 38, 6925.
- [18] Commercially available cholesterol was further dried according to the literature procedure: J. F. Eastham, R. Teranishi, *Org. Synth. Coll. Vol.* **1963**, 4, 192.

The Family Approach to the Resolution of Racemates **

Ton Vries,* Hans Wynberg,* Erik van Echten, Jan Koek, Wolter ten Hoeve, Richard M. Kellogg, Quirinus B. Broxterman,* Adri Minnaard, Bernard Kaptein, Sietse van der Sluis,* Lumbertus Hulshof, and Jaap Kooistra

A cornerstone of stereochemistry is the resolution of tartaric acid by Louis Pasteur.^[1,2] This conversion of a racemate with a chiral resolving agent and subsequent separation of the mixture of diastereomers formed is known as the “classical method of resolution”,^[3] and remains, 150 years after Pasteur, a paradigm of trial and error.^[4] Despite many attempts,^[3] neither computer-assisted modeling,^[5] detailed examination of the crystal structure data of diastereomeric salts,^[6] study of the energy differences of diastereomeric salts,^[7] nor empirical correlations^[8] have led to a hypothesis, let alone a theory, on which to base a predictable resolution technique.

All too aware of these problems on the basis of long experience and motivated by a need to develop fast and reliable protocols, we considered the combinatorial approach, a recent technique that has shown promise in the search for lead compounds in drug design.^[9] A rudimentary application of such methodology led to the remarkable results reported here.

The standard technique for the resolution of a racemate entails the addition of one chiral resolving agent to a racemate followed by a suitable waiting period in order to observe crystallization of one diastereomeric salt. We hoped that the simultaneous addition of several resolving agents might shorten the time required for the hit-and-miss method of finding a resolving agent. The addition of more than one resolving agent could result in the precipitation of the least soluble diastereomeric salt, thus obviating the need for repetition of the process of resolution with one resolving agent at a time. To our great surprise, the simultaneous addition of more than one member of a “family” of resolving agents (for a definition, see below) to a solution of a racemate usually causes very rapid precipitation of a crystalline diastereomeric salt in good to high enantiomeric purity and yield. The results from some of the more than two hundred successful experiments carried out during the past year^[10] are listed in Tables 1 and 2. In virtually all cases examined both the yields and enantiomeric excesses (*ee*) were superior to those obtained by the classical approach (compare entry 55 with entry 53).

[*] Dr. T. Vries, Prof. Dr. H. Wynberg, E. van Echten, J. Koek, Dr. W. ten Hoeve, Prof. Dr. R. M. Kellogg
Syncom BV
Nijenborgh 4, NL-9747 AG Groningen (The Netherlands)
Fax: (+31) 50-363-4875
E-mail: t.vries@chem.rug.nl

Dr. Q. B. Broxterman, Dr. A. J. Minnaard, Dr. B. Kaptein
Organic Chemistry & Biotechnology Section, DSM Research
P.O. Box 18, 6160 MO Geleen (The Netherlands)

Dr. S. van der Sluis, Prof. Dr. L. Hulshof, Dr. J. Kooistra
P.O. Box 81, 5900 AB Venlo (The Netherlands)

[**] Dr. Ton Vries is the discoverer of this new method.

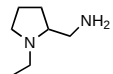
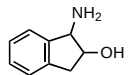
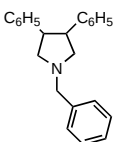
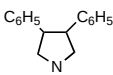
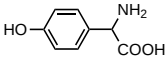
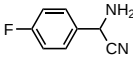
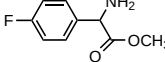
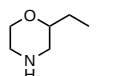
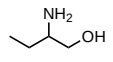
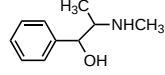
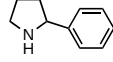
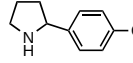
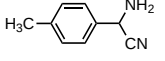
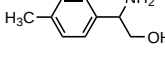
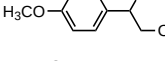
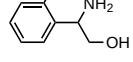
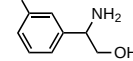
Table 1. Resolutions with mixtures of related reagents—the “family” approach.

Entry	Substrate	Reagent mix	Solvent ^[a]	Number of recryst. (solvent)	ee [%]	HPLC ^[b]	Reagent ratio ^[c]
1		M	A	1 (A)	96	1	1:5:0
2		P	A	1 (C)	98	1	— ^[e]
3		M	C	1 (D)	94	1	1:5:0
4		P	A	1 (A/B)	99	1	20:0:1
5		M	A/C	1 (C)	90	1	1:1 ^[d]
6		M	A/C	1 (A/C)	90	2 ^[g]	1:1 ^[d]
7		M	A/C	1 (A/C)	94	1	1:10 ^[d]
8		P	A/C	1 (C)	99	1	5:5:1
9		M	A/C	1 (C)	99	1	1:4 ^[d]
10		M	A/C	1 (C)	99	1	1:4 ^[d]
11	 <i>cis</i>	T	C	1 (C)	99		5:1:1
12		P	B	1 (C)	92	1	4:1:2
13		P	A	1 (A)	98	1	2:1:3
14	 <i>cis/trans</i>	P	A	1 (A/D)	98	1	4:1:0
15		P	A/D	1 (A/D)	66	2 ^[f]	1:1:2
16		T	D	1 (D/G)	98	2	1:10:4

The surprising discovery that the precipitate contained more than one component of the mixture of resolving agents was readily established and checked quantitatively by means of ¹H NMR spectroscopy, HPLC, or GC. Equally surprising was that the unusual nonstoichiometric compositions of the diastereomeric salts were retained even after several crystallizations. The ratio in the mixed salt of the two mandelic acid derivatives used for resolution (entry 25) was 1:3.7 after five recrystallizations (1:3.1 after a single recrystallization). Only on repeated recrystallization (sometimes more than ten times) did the composition of these salts begin to change to the standard 1:1 ratio of acid to base. Some salts retained their nonstoichiometric composition even after 20 recrystallizations. The ratio of the three phosphoric acids in the mixed salt of entry 26 was 1:14:55 after 20 recrystallizations.

Random combinations of resolving agents generally gave only moderate yields. The development of a principle of “families of resolving agents” was greatly aided by the fact that we had available in our laboratory an entire “family” of chiral phosphoric acids, based on the discovery of these acidic resolving agents 12 years ago.^[11] The members of a family in general bear a strong structural similarity and are stereochemically homogeneous (homochirality among family members and enantiomeric purity of the components). The combinations used for the current work were generally referred to in terms of coded “mixes”, the compositions of which are illustrated in Scheme 1 (page 2254). Usually, although not exclu-

Table 1. (Continued).

Entry	Substrate	Reagent mix	Solvent ^[a]	Number of recryst. (solvent)	ee [%]	HPLC ^[b]	Reagent ratio ^[c]
17		P	A	2 (A/C)	89	2 ^[f]	4:1:0
18	 <i>cis</i>	PGA	F	1 (F/A)	96	4	1:1.8:0.8
19	 <i>trans</i>	T	C	1 (C)	97	2	6:1:1
20		T	A	1 (A/D)	99	2 ^[g]	1:3:3
21		P	B/G	1 (B/G)	95	1	1:2:3
22		P	A	1 (A)	98	2	20:2:1
23		P	A	1 (B)	94	1	15:3:2
24		T	B	2 (B)	96	2 ^[g]	0:2:1
25		M	A	1 (A)	98	2 ^[g]	1:3.1 ^[d]
26	 <i>erythro</i>	P	C	1 (C)	98	1	1:1.2:1.1
27		P	C	1 (C)	93	1	– ^[e]
28		P	C	1 (C)	96	2 ^[g]	2:7:4
29		P	B/G	–	95	1	10:1:1
30		P	A	1 (B)	91	1	10:1:1
31		P	C	–	97	1	7:1:1
32		M	A	–	99	1	1:4:1
33		P	C	–	99	1	1:0:0 ^[h]

sively, the components of a family of resolving agents differ in the substitution pattern on an aromatic ring.^[12] An exception is the **PE-III** mix, whose members differ in the side chain.

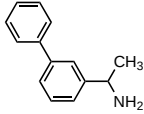
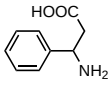
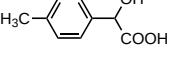
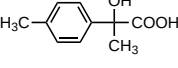
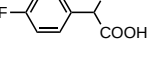
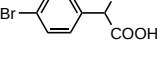
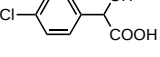
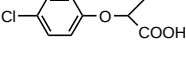
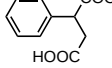
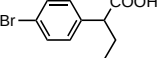
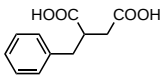
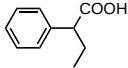
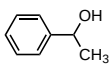
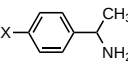
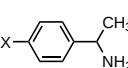
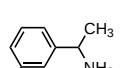
The current definition of a family is clearly not complete, and it is evident that many more families are possible. Eliel and Wilen^[13] list over 100 resolving agents, many of which could lend themselves to the preparation of a family. Note, for example, that tartaric acid does not belong to the family of benzoyltartaric acids.^[14]

Probably the most significant, as well as startling, feature of this new method for the resolution of racemates is the extremely high success rate, defined in terms of yield and enantiomeric excess in a first trial. We have resolved over 100 racemates, predominantly acids and bases, during the past year and have found only three that resisted resolution by the family approach. The failures appear to be due solely to lack of salt formation. This can occur in some cases when the racemate displays either steric hindrance or weak basicity or acidity, thus preventing salt formation with the relatively weak resolving acids or bases. This problem is being addressed by adding a family of stronger acids and bases to our list.

The most significant findings are as follows:

1) On addition of two or more resolving agents of a family to a racemate, rapid crystallization of a diastereomeric salt containing different family members takes place in good to excellent yield. The enantiomeric excess of the recovered enantiomer approaches 100% in many cases or is usually attained after one recrystalliza-

Table 1. (Continued).

Entry	Substrate	Reagent mix	Solvent ^[a]	Number of recryst. (solvent)	ee [%]	HPLC ^[b]	Reagent ratio ^[c]
34		P	A	1 (C)	86	3	— ^[e]
35		P	A	—	98	1	5:4:1
36		PE-II	A/D	1 (B/D)	99	2	1:4
37		PE-I	F	1 (F)	97	2	— ^[e]
38		PE-II	A	—	99	2	— ^[e]
39		PE-II	A	1 (A/D)	99	2	15:1:0
40		PE-II	A	1 (A/D)	95	2	35:1:0
41		PE-I	E	1 (E)	88	2	— ^[e]
42		PG	C	1 (B)	97	3	— ^[e]
43		PE-II	A	1 (C)	95	2	1:0:0
44		PE-II	A	1 (C)	88	3	2:2:1
45		PG	C	1 (C)	93	2	— ^[e]
46		TA	H	—	82	3	1:1
47	 X = Cl, Me, Br (1:1:1)	M2/M3	B	1 (B)	98	1	1:1:1 (amines), 1:1 (acids)
48	 X = Cl, Me, Br (1:1:1)	M2/PhCH₂CO₂H	B	1 (B/G)	98	1	1:1:1, contains both acids
49	 X = OMe, Cl, Br (1:1:1)	M2	B	—	98	1	2:4:4

[a] A: 2-butanone; B: ethanol; C: 2-propanol; D: methanol; E: ethyl acetate; F: toluene; G: water; H: hexane.
 [b] HPLC columns: 1: Crownpak Cr; 2: Chiralpak AD; 3: Chiralcel OD; 4: Chiralcel OB; 5: Chiralcel OJ; 6: R,R
 Whelk; 7: Ultron ESOVM. [c] The order given refers to the notation as indicated in the Experimental Section.
 [d] Only with **M1/M2**. [e] Could not be accurately determined by ¹H NMR spectroscopy, but three components
 were present. [f] HPLC analysis of the benzoate. [g] HPLC analysis of the tosylate. [h] **P2** and **P3** could not be
 detected by ¹H NMR spectroscopy (200 MHz).

tion (see Table 1). In this respect the work of Lahav and Addadi is highly pertinent to the phenomena observed here.^[15] The solubility behavior of the mixed salts warrants further study.

2) The high rate of success makes the method of commercial value. This new technique for the resolution of racemates, including the recovery of the resolving agent(s), is identical to that currently used in the laboratory and in industrial processes, except for the simultaneous use of multiple resolving agents. It proved most effective to carry out a resolution with a 1:1 or 1:1:1 mixture chosen from the family of resolving agents.

3) In illustration of the potential—and at the same time the complexity—of the method, it is possible to incorporate a racemic family member (Table 2, entries 51 and 52), a family member of the opposite absolute configuration (entry 54), and even an achiral family member (entry 56).

4) The method is applicable to resolutions through formation of molecular complexes using, for example, TADDOL derivatives (entry 46).^[16]

5) Mixtures of racemates can be resolved to enantiomerically pure mixtures either with a single resolving agent (entry 49) or with several resolving agents (entries 47 and 48).

The composition of the diastereomeric salts clearly deserves further study. The crystal structure of the mixed salt from (+)-(1*S*,2*R*)-ephedrine (100%), (–)-(*R*)-phencyphos (**P1**, 52.5%), and (–)-(*S*)-chlocyphos (**P2**, 47.5%) was determined. It was composed of a random distribution of the two resolving agents, which is seen as an average unit cell.

Furthermore, the unusual and unpredictable nonstoichiometric composition of the

Table 2. Resolutions with mixtures containing racemic reagents, achiral reagents, and reagents with opposite configuration.

Entry	Racemate	Acid	Acid	ee (acid) [%]	ee (amine) [%]	Ratio of acids
50		M1 (<i>S</i>)	M2 (<i>S</i>)	–	84	1:1
51		M1 (<i>S</i>)	M2 (rac.)	95 (<i>S</i>)- M2	90	4:3
52		M1 (rac.)	M2 (<i>S</i>)	95 (<i>S</i>)- M1	99	3:4
53 1:4		M1 (<i>S</i>)	M2 (<i>S</i>)	–	–	87
54		M1 (<i>R</i>)	M2 (<i>S</i>)	–	90	1:6
55		–	M2 (<i>S</i>)	–	57	–
56		–	M2 (<i>S</i>) (0.5 equiv.) PhCH ₂ CO ₂ H (0.5 equiv.)	–	90	contains both acids

diastereomeric salts appears to mirror to some extent findings in other fields.^[17] The recent use of “cocktails”, mixtures of drugs, to treat a disease bears interesting resemblance to our approach to resolutions. In an early and insightful comment^[6] Walkinshaw refers to the close analogy between the drug–receptor nonbonding interactions and those present during resolution phenomena.

The use of a family of agents for the resolution of racemates effectively changes the trial-and-error method of resolution into an acceptable and almost routine practice. The consequences of this novel approach for other fields of inquiry also need to be explored.

Experimental Section

General procedure for the small-scale resolution of amines or acids with reagent mixes: To a solution of a racemic substrate (3 mmol) in the appropriate solvent was added one equivalent of a mix (1 mmol of each component, e.g. **P1**–**P3**). The mixture was heated to reflux and allowed to cool to room temperature. The salt was collected and analyzed with ¹H NMR spectroscopy to determine the composition. HPLC analysis was used to determine the enantiomeric excess of the substrate. The salt obtained was recrystallized from the appropriate solvent(s) until a clear solution was obtained. The mixture was cooled to room temperature, and the salt again analyzed.

Preparation of the mixes: Unless otherwise stated all resolution mixes used were enantiopure.

P mix: Phencyphos (**P1**, 2-hydroxy-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane), chlocyphos (**P2**, 4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane), and anicyphos (**P3**, 2-hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane) were prepared and resolved according to standard procedures.

T mix: Dibenzoyltartaric acid (**T1**) and di-*p*-toluoyltartaric acid (**T2**) were obtained from Aldrich, and di-*p*-anisoyltartaric acid (**T3**) was prepared according to a standard procedure.

M mix: Mandelic acid (**M1**) was obtained from Aldrich, *p*-methylmandelic acid (**M2**) and *p*-bromomandelic acid (**M3**) were prepared from the corresponding acetophenones and resolved with phenylethylamine.

PE-I mix: 1-(*p*-Chlorophenyl)ethylamine (**PE2**), 1-(*p*-bromophenyl)ethylamine (**PE3**), and 1-(*p*-methylphenyl)ethylamine (**PE4**) were prepared by a Leuckart synthesis from the commercially available acetophenones. For resolution of the mix, see entries 47 and 48 in Table 1.

PE-II mix: Nitration of enantiomerically pure phenylethylamine with HNO₃ provided a mixture that contained phenylethylamine (**PE1**), 1-(*o*-nitrophenyl)ethylamine (**PE5**), and 1-(*p*-nitrophenyl)ethylamine (**PE6**) in equal amounts.

PG mix: Enantiomerically pure 2-amino-2-phenylethanol (**PG1**) was obtained by reduction of the phenylglycine methyl ester. Racemic 2-amino-2-(*p*-methylphenyl)ethanol (**PG2**) and 2-amino-2-(*p*-methoxyphenyl)ethanol (**PG3**) were obtained by reduction of the corresponding phenylglycines and resolved with phencyphos (**P1**).

PE-III mix: 1-Phenylethylamine (**PE1**) was obtained from Aldrich. α -Isopropylbenzylamine and α -ethylbenzylamine were prepared from the corresponding ketones by a Leuckart synthesis. The **PE-III** mix was obtained by resolution with phencyphos (**P1**).

PGA mix: The *N*-benzoylphenylglycines were obtained by Schotten–Baumann acylation of (*S*)-phenylglycine with benzoyl, *p*-toluoyl, and *p*-anisoyl chloride.

TA mix: (4*R*,5*R*)-2,2-Dimethyl- α,α,α' -tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL, **TA1**) and (4*R*,5*R*)- α,α,α' -tetra(*p*-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (**TA2**) were prepared according to standard procedures.

Received: April 21, 1998 [Z11763IE]

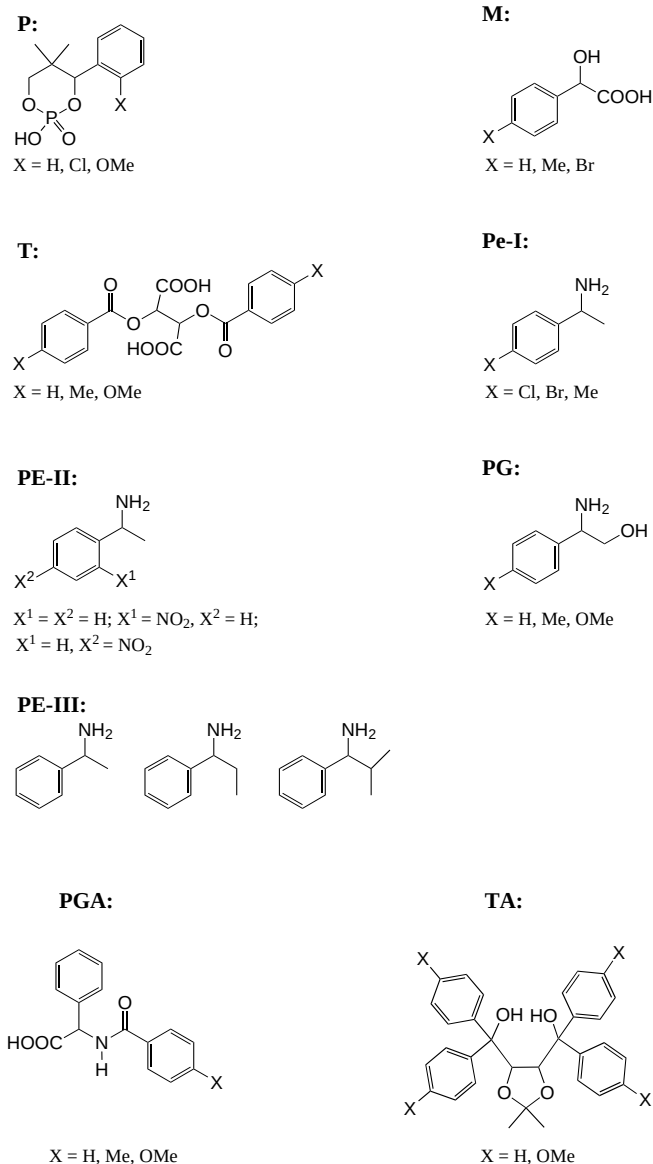
German version: *Angew. Chem.* **1998**, *110*, 2491–2496

Keywords: chirality • chiral resolution • enantiomeric resolution • combinatorial chemistry

[1] L. Pasteur, *Ann. Chim. Phys.* **1848**, *24*, 442–459.

[2] L. Pasteur, *C. R. Hebd. Seances Acad. Sci.* **1853**, *37*, 162–169.

[3] Comprehensive books on stereochemistry encompassing these 150 years: K. Freudenberg, *Stereochemie*, F. Deuticke, Leipzig, **1932**; E. L.



Scheme 1. Resolution of racemates with mixtures of reagents. Mixtures used: **P**: *ortho*-substituted phenylphosphoric acids; **M**: *para*-substituted mandelic acids; **T**: *para*-substituted benzoyltartrates; **PE-I**: *para*-substituted phenylethylamines; **PE-II**: nitrated phenylethylamines; **PG**: *para*-substituted 2-amino-2-phenylethanol; **PE-III**: α -alkylbenzylamines; **PGA**: *para*-substituted *N*-benzoylphenylglycines; **TA**: *para*-substituted bis(hydroxydiphenylmethyl)dioxalanes. For the preparation of the mixes, see the Experimental Section.

Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, **1962**; J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Wiley-Interscience, New York, **1981**; E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, **1994**; the most complete description of the resolution of racemates (167 pages of chapter 7) can be found in the latter book.

- [4] R. A. Sheldon, *Chirotechnology*, Marcel Dekker, New York, **1993**, chap. 6.
- [5] A. D. van der Haest, H. Wynberg, *Recl. Trav. Chim. Pays-Bas* **1992** *111*, 111–118; A. D. van der Haest, H. Wynberg, F. J. J. Leusen, H. J. Bruins, J. H. Noordik, A. Bruggink, *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 13–18.
- [6] R. O. Gould, M. D. Walkinshaw, *J. Am. Chem. Soc.* **1984**, *106*, 7840–7842; R. O. Gould, A. M. Gray, P. Taylor, M. D. Walkinshaw, *J. Am. Chem. Soc.* **1985**, *107*, 5921–5927. This paper specifically uses the term “a small family of related crystal structures” in discussing nonbonding

interactions. To our understanding the word “family” already implies a relationship. See also R. O. Gould, R. Kelly, M. D. Walkinshaw, *J. Chem. Soc. Perkin. Trans. 2* **1985**, 847–852.

- [7] S. P. Zingg, E. M. Arnett, A. T. McPhail, A. A. Bother-By, W. R. Gilkerson, *J. Am. Chem. Soc.* **1988**, *110*, 1565–1580; A. D. van der Haest, H. Wynberg, F. J. J. Leusen, A. Bruggink, *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 523–528.
- [8] E. Fogassi, F. Faigl, M. Acs, K. Simon, E. Kozsda, B. Podányi, M. Czugler, G. Reck, *J. Chem. Soc. Perkin Trans 2* **1988**, 1385–1392, and earlier papers.
- [9] *Acc. Chem. Res.* **1996**, *29* (special issue; Eds.: A. W. Czarnik, J. A. Ellman).
- [10] Because of the confidential nature of much of our work, less than half of the resolutions we have carried out during the past year are listed in Tables 1 and 2. Approximately half of all of the resolutions were performed on a 3-mmol scale, whereas the other half was carried out on a 5- to 500-g scale. The enantiomeric excesses was examined in all cases, but an accurate yield was determined for the larger scale resolutions only. In the latter cases this yield was consistently above 20% (50% maximum) and frequently in the range of 40–45%, even without complete optimization. The method has been patented: T. R. Vries, H. Wijnberg, E. van Echten, L. Hulshof and Q. B. Broxterman (DSMNV), NL 1004346, **1996**.
- [11] W. ten Hoeve, H. Wynberg, *J. Org. Chem.* **1985**, *50*, 4508–4514.
- [12] Exceptions to this generalization have already been found. Thus, when mixtures of amino acids are used as resolving agents, a single resolving agent was found in the diastereomeric salt. Substitution of the amino group of a single amino acid by various benzoyl chlorides led to formation of a “family” (**PGA** mix).
- [13] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, **1994**, pp. 329–343.
- [14] Tartaric acid, malic acid, and lactic acid also did not constitute a family.
- [15] L. Addadi, J. Van Mil, M. Lahav, *J. Am. Chem. Soc.* **1981**, *103*, 1249–1251.
- [16] See, for example, F. Toda, *Top. Curr. Chem.* **1987**, *140*, 43–51.
- [17] K. Mikami, S. Matsukawa, T. Volk, M. Terada, *Angew. Chem.* **1997**, *109*, 2936–2939; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2768–2771.

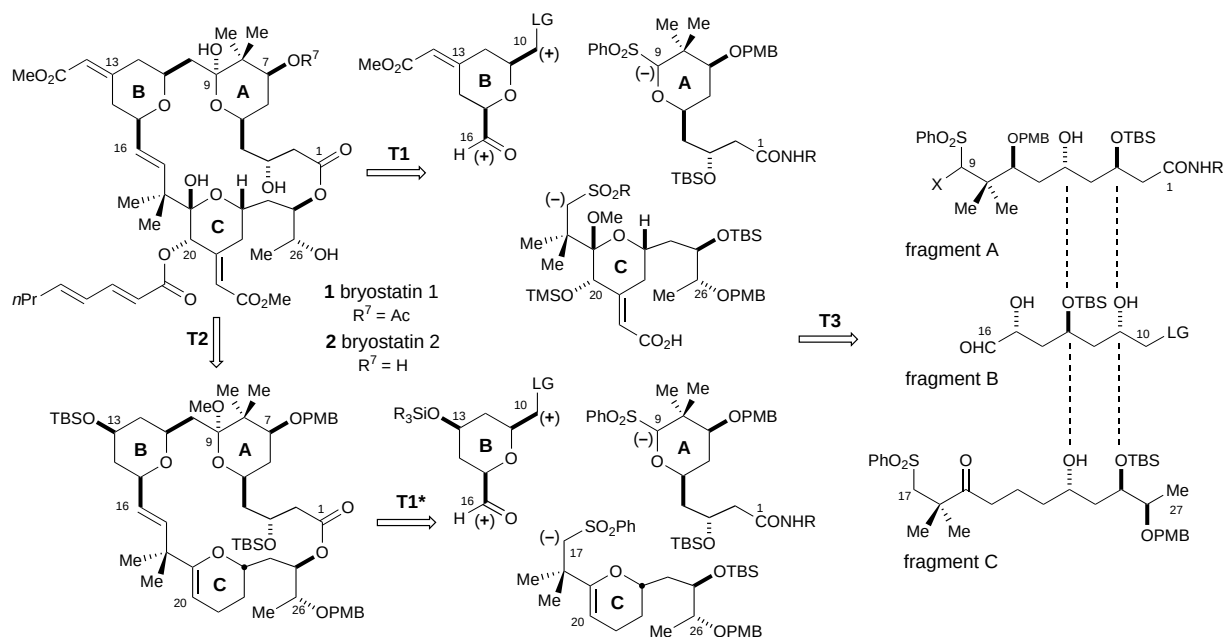
Asymmetric Synthesis of Bryostatin 2**

David A. Evans,* Percy H. Carter, Erick M. Carreira, Joëlle A. Prunet, André B. Charette, and Mark Lautens

Bryostatin 1 (**1**), a biologically active marine macrolide with clinical potential for the treatment of several forms of cancer,^[1] was isolated and structurally characterized by Pettit et al. in 1982.^[2] Since that time, Pettit and co-workers have reported the isolation of seventeen other bryostatin macrolides, most of which differ from **1** in their substitution at C7 or C20 (e.g. **2**).^[3] The biological and clinical importance of bryostatin 1 has prompted a major effort towards the syn-

[*] Prof. D. A. Evans, P. H. Carter, E. M. Carreira, J. A. Prunet, A. B. Charette, M. Lautens
Department of Chemistry & Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-1460
E-mail: evans@chemistry.harvard.edu

[**] Financial support has been provided by the National Institutes of Health. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities.

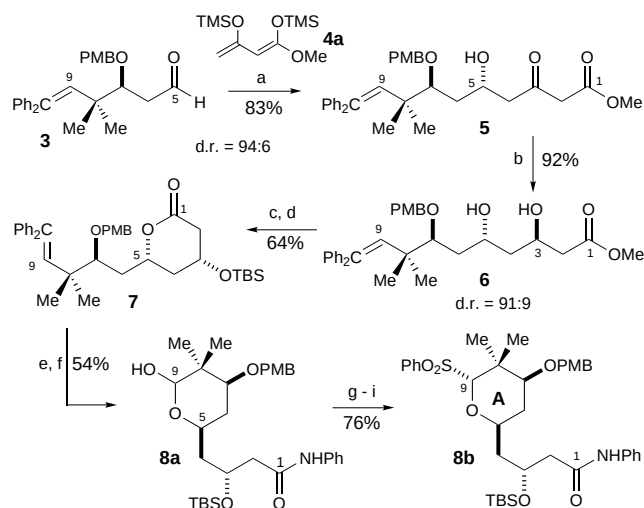


Scheme 1. Retrosynthetic analysis of bryostatins 1 and 2. See reference [7] for abbreviations.

thesis of this macrolide,^[4] including one total synthesis of bryostatin 7 (OAc at C7 and C20).^[5] Here we describe the first total synthesis of bryostatin 2 (**2**) by the general plan outlined in Scheme 1.^[6]

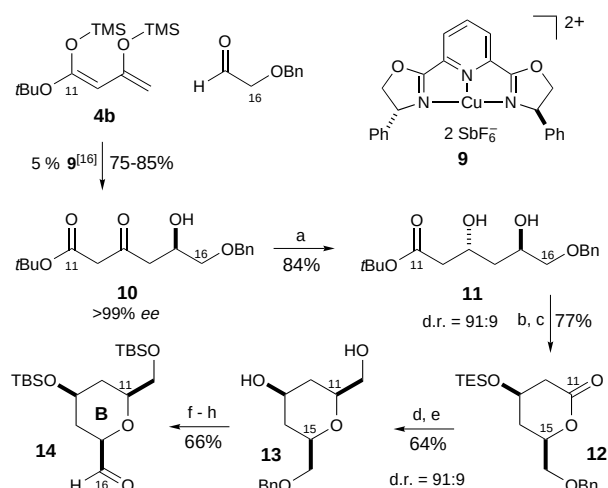
Following the retrosynthetic analysis shown, application of macrocyclization, olefination, and sulfone alkylation affords fragments **A**–**C** of comparable complexity (Scheme 1, T1). While each of the indicated subunits could be fully synthesized, sulfone-based fragment coupling could not be employed when the exocyclic enoate appendages at C13 and C21 were in place owing to unwanted proton transfer. Accordingly, the synthesis plan was modified to accommodate introduction of these moieties at a later stage (T2→T1*). Both the elaborated and simplified versions of rings **A**–**C** were derived from the same set of acyclic precursors, each of which contains a common *anti*-1,3-diol subunit (T3). In all instances, the synthesis of this stereochemical motif can be effectively addressed by sequential aldol and reduction reactions.

Our route to the ring **A** synthon (C1–C9) began with β -alkoxyaldehyde **3** (Scheme 2), which is available in greater than 98% *ee* via a chiral imide enolate.^[8] Addition of the bis(trimethylsilyl)dienol ether **4a**^[9] to **3** proceeded with good 1,3-*anti* diastereoselectivity (d.r. = 94:6)^[10] only when the alkoxytitanium Lewis acid $\text{TiCl}_2(\text{OiPr})_2$ was employed. Subsequent hydroxyl-directed 1,3-*anti* reduction^[11] afforded diol **6**, which was successively cyclized and monosylated to provide the diastereomerically pure lactone **7**. Lactone **7** was then transamidated^[12] to the open-chain anilide, which was cyclized to the lactol **8a** by oxidative cleavage of the C–C double bond.^[13] Acylation, thiol displacement,^[14] and thiol oxidation then served to convert **8a** (α : β = 1:1) into the analytically pure α -sulfone **8b** (76% yield for three steps).^[15] The carboxyl terminus of fragment **8b** was functionalized as an amide in order to accommodate the metalation of the C9 sulfone, an operation required for the union of rings **A** and **B**.



Scheme 2. Synthesis of the ring **A** synthon **8b** (C1–C9). a) $\text{TiCl}_2(\text{OiPr})_2$, PhCH_3 , -78°C ; then **4**, -78°C ; b) $\text{Me}_4\text{NHB}(\text{OAc})_3$, AcOH/MeCN , -35°C ; c) PPTS, C_6H_6 , 80°C ; d) TBSOTf , 2,6-lut, CH_2Cl_2 , -10°C ; e) Me_3Al , $\text{HCl}\cdot\text{H}_2\text{NPh}$, CH_2Cl_2 , 30°C ; then **7**, 0°C ; f) O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10/1), -78°C ; then Me_2S ; g) Ac_2O , pyr; h) PhTMS , ZnI_2 , $n\text{Bu}_4\text{NI}$, CH_2Cl_2 ; i) *m*CPBA, NaHCO_3 , EtOAc . See reference [7] for abbreviations.

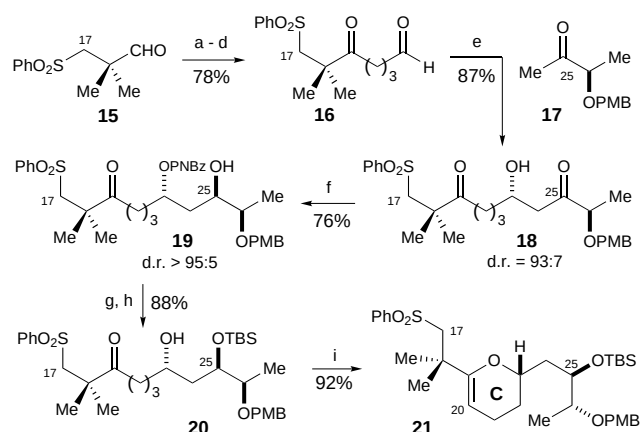
The synthesis of the ring **B** synthon (C10–C16) began with the enantioselective aldol reaction between enolsilane **4b** and α -benzyloxyacetaldehyde, catalyzed by the copper complex **9** (5 mol %), which afforded **10** in 75–85% yield and with greater than 99% *ee* (Scheme 3).^[16] Subsequent hydroxyl-directed 1,3-*anti* reduction^[11] provided synthon **11** in good yield.^[17] Sequential lactonization and protection with chlorotriethylsilane gave lactone **12**, which was homologated by treatment with *para*-methoxybenzyloxymethyl lithium.^[18] Reduction ($\text{BF}_3\cdot\text{OEt}_2$, Et_3SiH)^[19] of the derived lactols afforded the deprotected β -C-glycoside **13** in good yield and diastereoselectivity. Silylation of the hydroxyl groups, hydrogenol



Scheme 3. Synthesis of the ring **B** synthon **14** (C10–C16). (a) $\text{Me}_4\text{N}\cdot\text{HB}(\text{OAc})_3$, AcOH/MeCN , -35°C ; b) $\text{F}_3\text{CCO}_2\text{H}$, CH_2Cl_2 ; c) TESCl , im , CH_2Cl_2 , 0°C ; d) PMBOCH_2Li , THF , $-78 \rightarrow -50^\circ\text{C}$; e) $\text{BF}_3\cdot\text{OEt}_2$, Et_3SiH , CH_2Cl_2 , -20°C ; f) TBSCl , im , DMAP (cat.), CH_2Cl_2 ; g) H_2 (1 atm), 10% Pd/C , AcOH , EtOAc ; h) $(\text{COCl})_2$, DMSO , NEt_3 , CH_2Cl_2 , $-78 \rightarrow -50^\circ\text{C}$. See reference [7] for abbreviations.

ysis of the benzyl ether, and Swern oxidation of the resultant alcohol provided the target synthon **14**.

The synthesis of the ring **C** synthon (C17–C27) commenced with the homologation of aldehyde **15** (Scheme 4).^[20] Thus, addition of pent-1-en-5-ylmagnesium bromide was

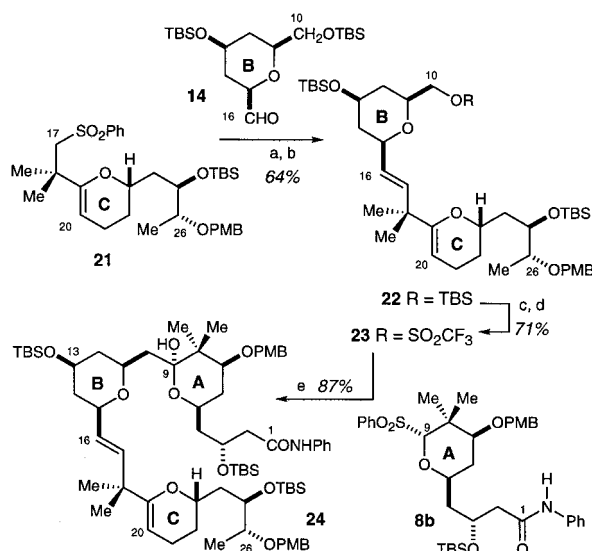


Scheme 4. Synthesis of the ring **C** synthon **21** (C17–C27). a) $\text{BrMg}(\text{CH}_2)_3\text{CH}=\text{CH}_2$, $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ (1/1), $0 \rightarrow -23^\circ\text{C}$; b) $(\text{COCl})_2$, DMSO , NEt_3 , CH_2Cl_2 , $-78 \rightarrow -50^\circ\text{C}$; c) $\text{K}_2\text{OsO}_4(\text{OH})_2$ (2 mol %), quinuclidine (2 mol %), $[\text{K}_3\text{Fe}(\text{CN})_6]$, K_2CO_3 , $t\text{BuOH}/\text{H}_2\text{O}$ (1/1); d) NaIO_4 , NaHCO_3 , $t\text{BuOH}/\text{H}_2\text{O}/\text{THF}$ (2/2/1); e) **17**, (–)- DIPCl , NEt_3 , CH_2Cl_2 , -78°C ; then **16**, -70°C ; f) SmI_2 (20 mol %), $p\text{-O}_2\text{NC}_6\text{H}_4\text{CHO}$, THF , 0°C ; g) TBSOTf , 2,6-lut, CH_2Cl_2 , -15°C ; h) LiOH , $\text{THF}/\text{MeOH}/\text{H}_2\text{O}$ (2/2/1); i) CSA (5 mol %), C_6H_6 , 80°C . See reference [7] for abbreviations.

followed by Swern oxidation, osmium-mediated dihydroxylation, and periodate cleavage to afford ketoaldehyde **16** in 78% overall yield. The aldol reaction of aldehyde **16** with ketone **17**^[21] was only moderately diastereoselective under a wide variety of enolization conditions.^[22] Accordingly, we used chiral boryl enolates, and found that the aldol addition could be carried out in good yield and diastereoselectivity with the isopinylboryl enolates of Paterson and Brown.^[23]

Subsequent samarium-promoted Tishchenko reduction^[24] afforded the *p*-nitrobenzoate **19**, which was readily converted into alcohol **20** in two steps. Acid-catalyzed cyclization and dehydration of **20** (CSA , C_6H_6 , 80°C) provided the target dihydropyran **21** in 92% yield.

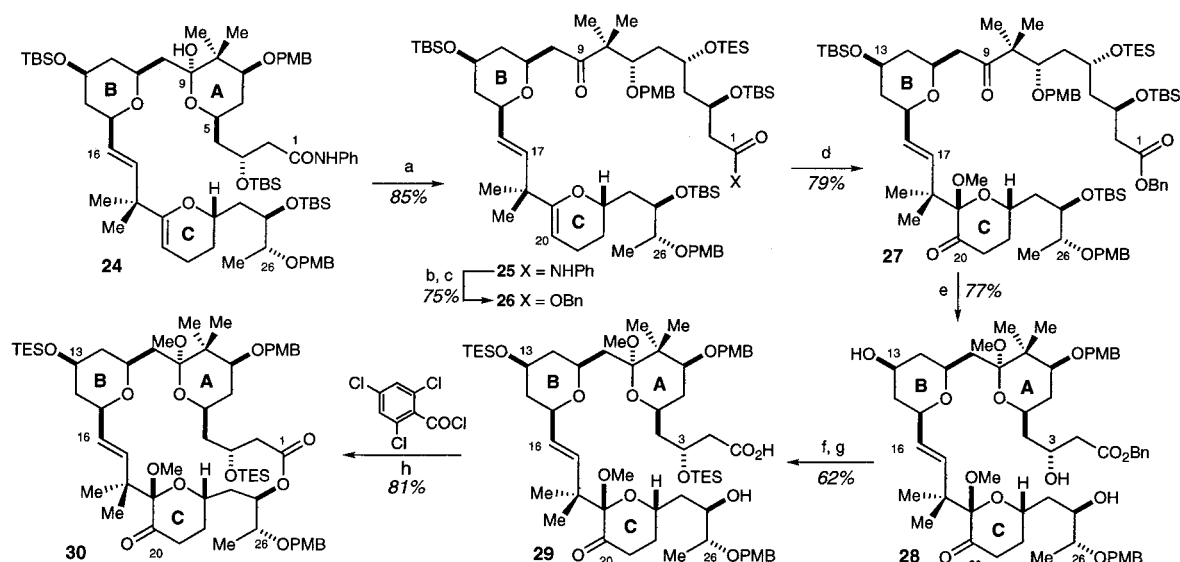
Exploratory experiments directed at defining the optimal sequence for fragment coupling revealed the preferred order to be **C** $\rightarrow$ **CB** $\rightarrow$ **CBA**. Accordingly, union of the metalated ring **C** sulfone **21** with one equivalent of aldehyde **14** afforded the hydroxysulfone adduct, which was transformed by a modified Julia procedure^[25] to *trans* olefin **22** (64% overall yield, *E*:*Z* > 95:5; Scheme 5). Selective removal of the TBS



Scheme 5. Fragment assemblage. a) 1. $n\text{BuLi}$, THF , -78°C ; then **14**, $-78 \rightarrow -50^\circ\text{C}$; 2. Ac_2O , DMAP , CH_2Cl_2 ; b) Mg , HgCl_2 (20 mol %), EtOH ; c) TBAF , THF , -15°C ; d) Ti_2O_3 , 2,6-lut, CH_2Cl_2 , -10°C ; e) **8b**, $n\text{BuLi}$ (2 equiv), THF , -78°C ; then HMPA ; then **23**, -78°C . See reference [7] for abbreviations.

group from the primary silyl ether (TBAF , -15°C) and treatment of the derived alcohol with buffered trifluoromethanesulfonic anhydride produced the unstable triflate **23**. The triflate was purified and then immediately coupled with bis-metalated **8b** (THF/HMPA , -78°C) in good yield (87%).^[26]

Refunctionalization of **24** to the optimal macrocyclization precursor **29** is shown in Scheme 6. While the overall transformations ideally could have been implemented in several different permutations, the indicated sequence of chemical events proved to be closely constrained by reactivity considerations. In preparation for the refunctionalization of the carboxyl terminus, the lactol (C9) was silylated to provide the open-chain silyl ether **25** (85%). Conversion of anilide **25** into the benzyl ester **26** was accomplished through the action of lithium benzyloxide on the *N*-Boc-amide (THF/DMF , -30°C , 75%).^[27] With the carboxyl terminus protected as its benzyl ester, the ring **C** glycal was elaborated by a three-step sequence: 1) epoxidation/methanolysis, 2) equilibration of the C19 ketal with monochloroacetic acid (d.r. > 95:5), and 3) Dess–Martin oxidation of the hydroxyl group at C20. These reactions were executed without purification of inter-



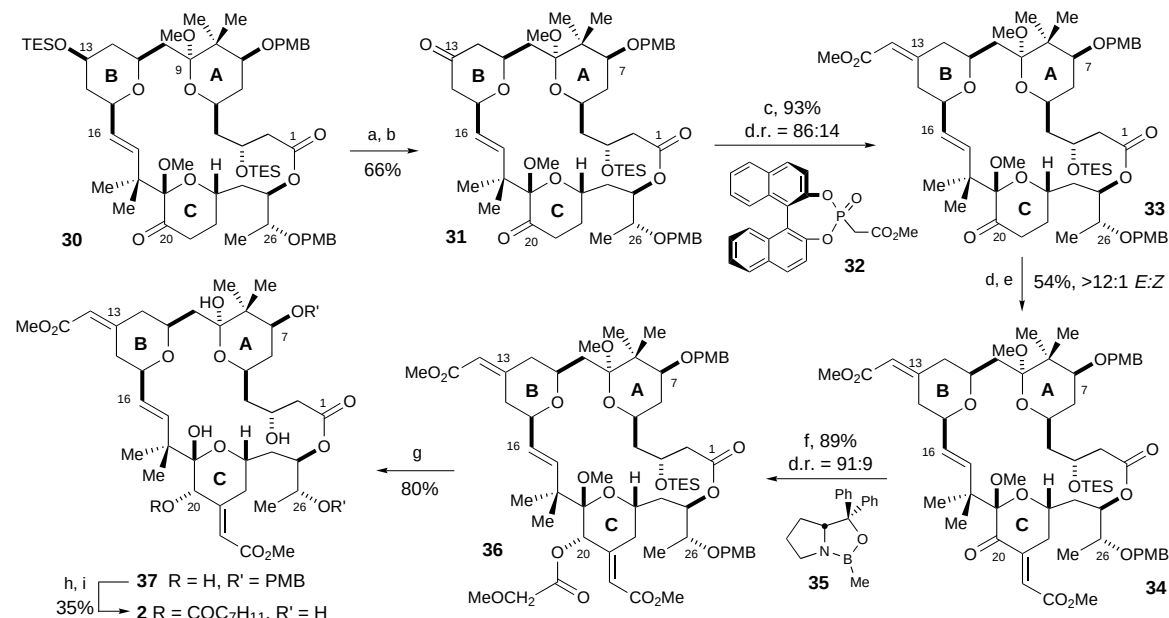
Scheme 6. Functionalization and macrocyclization of the tricycle. a) TESCl, im, MeCN; b) Boc₂O, DMAP, MeCN; c) BnOLi, THF/DMF (1/1), –30 °C; d) 1. *m*CPBA, MeOH, –20 °C; 2. ClCH₂CO₂H, MeOH, 0 °C; 3. Dess–Martin periodinane, pyr, CH₂Cl₂; e) HF·pyr, THF/MeOH/pyr (4/4/1); f) TESCl, DMAP, CH₂Cl₂, –10 °C (65% plus 15% each of the mono- and tris-silylether); g) 1,4-cyclohexadiene, 10% Pd/C (50 mol %), EtOAc; h) 2,4,6-trichlorobenzoyl chloride, *i*PrNEt₂, C₆H₆; then DMAP, C₆H₆ (1.0 mm). See reference [7] for abbreviations.

mediates to provide ketone **27** in 79% overall yield after chromatography on silica gel.

In preparation for macrocyclization, all silyl groups of ester **27** were removed with methanolic HF·pyridine to afford triol **28** (Scheme 6). Initial attempts to macrocyclize this triol-carboxylic acid were frustrated by the reactivity of the hydroxyl group at C3, and macrocyclization could only be accomplished in low yields (<35%) from the thiopyridyl ester. Consequently, the hydroxyl groups at C3 and C13 were selectively protected (TESCl, DMAP, –10 °C) before proceeding. Debenzylation of the ester (cyclohexadiene, 10%

Pd/C) provided the monohydroxy acid **29**, which was successfully lactonized in good yield (81%) according to a modified Yamaguchi procedure.^[28]

With macrocycle **30** in hand, elaboration of the ring **B** and **C** enoate moieties was undertaken. Selective deprotection of the silyl ether at C13 and Dess–Martin oxidation of the resultant hydroxyl group afforded C13,C20-diketone **31** (66%, Scheme 7). Condensation of **31** with two equivalents of Fuji's chiral phosphonate **32** as its derived sodium enolate^[29] selectively transformed the C13 ketone to the C13,C30-unsaturated enoate in 93% yield and diastereoselectivity of



Scheme 7. Synthesis of bryostatin 2 (**2**). a) PPTS (20 mol %), MeOH/(MeO)₂CH (2/1), CH₂Cl₂, –30 °C; b) Dess–Martin periodinane, pyr, CH₂Cl₂; c) **32**, NaHMS, THF, –78 °C; then **31**, –15 °C; d) KHMDS, THF, –78 °C; then OHCCO₂Me, –78 °C; e) Et₃NSO₂NCO₂Me, C₆H₆; f) **35**, BH₃·SMe₂, CH₂Cl₂; then MeOH; then (MAc)₂O, pyr, DMAP; g) 1. PPTS, THF/H₂O (3/1); 2. Na₂CO₃, MeOH; 3. TsOH, MeCN/H₂O (4/1); h) (E,E)-2,4-octadienoic acid, DIC, DMAP, CH₂Cl₂; i) DDQ, CH₂Cl₂/buffer (10/1, pH 7). See reference [7] for abbreviations.

Z:E = 86:14 (75 % yield of isolated **33**). Subsequent installation of the ring C enoate was best accomplished with a two-step protocol (KHMDS, OHCCO₂Me; then Burgess reagent). The ability of KHMDS to selectively enolize a ketone (C20) in the presence of an ester (C1) is precedented,^[30] and is favored in the present system by the conformation of macrolactone **33**.^[31] In contrast to its monocyclic analogue, reduction of the ring C enone in **34** was troublesome; however, it was eventually discovered that the CBS reagent^[32] **35** stereoselectively mediated this reduction when BH₃·Me₂S was utilized as the hydride source (89 %, d.r. = 10:1, 55–70 % yield of isolated **36**). In situ acylation of the hydroxyl group at C20 was required in order to isolate the product in good yield.

The deprotection of **36** required a careful ordering of the hydrolysis steps. A three-step sequence consisting of hydrolysis at C9 (and desilylation at C3), methanolysis of the methoxyacetate group, and hydrolysis at C19 could be reliably executed to afford **37** after only one chromatographic purification. The hydroxyl group at C20 could be selectively^[33] acylated using carbodiimide chemistry ((*E,E*)-2,4-octadienoic acid,^[34] DIC, DMAP, 23 °C, 1.5 d, 62 % yield). The subsequent oxidative removal of the PMB ethers was best effected under buffered conditions (DDQ, CH₂Cl₂, pH 7) to provide pure bryostatin 2 (**2**) in 57 % yield. The synthetic bryostatin 2 obtained by this procedure was identical to a natural sample^[35] by several criteria: [α]_D, R_f (TLC), reverse-phase HPLC, mass spectrometry, and ¹H NMR spectroscopy (500 MHz, CDCl₃ and C₆D₆, including COSY-90). Pettit et al. have previously documented the three-step conversion of bryostatin 2 (**2**) into bryostatin 1 (**1**).^[6]

Received: May 14, 1998 [Z11861IE]

German version: *Angew. Chem.* **1998**, *110*, 2526–2530

Keywords: aldol reactions • antitumor agents • bryostatin • total synthesis

- [1] a) A. S. Kraft, *J. Nat. Cancer Inst.* **1993**, *85*, 1790–1792; b) R. M. Stone, *Leukemia Res.* **1997**, *21*, 399–401.
- [2] G. R. Pettit, C. L. Herald, D. L. Doubek, D. L. Herald, E. Arnold, J. Clardy, *J. Am. Chem. Soc.* **1982**, *104*, 6846–6847.
- [3] See, for example, G. R. Pettit, F. Gao, P. M. Blumberg, C. L. Herald, J. C. Coll, Y. Kamano, N. E. Lewin, J. M. Schmidt, J.-C. Chapuis, *J. Nat. Prod.* **1996**, *59*, 286–289.
- [4] Review: a) R. D. Norcross, I. Paterson, *Chem. Rev.* **1995**, *95*, 2041–2114; recent work: b) S. Kiyooka, H. Maeda, *Tetrahedron: Asymmetry* **1997**, *8*, 3371–3374; c) J. M. Weiss, H. M. R. Hoffmann, *Tetrahedron: Asymmetry* **1997**, *8*, 3913–3920.
- [5] M. Kageyama, T. Tamura, M. H. Nantz, J. C. Roberts, P. Somfai, D. C. Whritenour, S. Masamune, *J. Am. Chem. Soc.* **1990**, *112*, 7407–7408.
- [6] For the conversion of bryostatin 2 (**2**) into bryostatin 1 (**1**), see G. R. Pettit, D. Sengupta, C. L. Herald, N. A. Sharkey, P. M. Blumberg, *Can. J. Chem.* **1991**, *69*, 856–860.
- [7] Abbreviations: Bn = benzyl; Boc = *tert*-butoxycarbonyl; CSA = camphorsulfonic acid; DDQ = 2,3-dichloro-5,6-dicyanoquinone; DIBALH = diisobutylaluminum hydride; DIC = diisopropylcarbodiimide; DIPCl = *B*-chlorodiisopinocampheylborane; DMAP = 4-dimethylaminopyridine; d.r. = diastereomer ratio; HMDs = bis(trimethylsilyl)amide; im = imidazole; LG = leaving group; 2,6-lut = 2,6-lutidine; MAc = methoxyacetate; mCPBA = *meta*-chloroperoxybenzoic acid; PMB = *para*-methoxybenzyl; PMP = *para*-methoxyphenyl; PNBz = *para*-nitrobenzoate; PPTS = pyridinium *p*-toluenesulfonate; pyr = pyridine; TBAF = tetrabutylammonium fluoride; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; Tf = trifluoromethanesulfonyl; TMS = trimethylsilyl; Ts = *p*-toluenesulfonyl.

- [8] Aldehyde **3** was prepared in six steps (58 % overall yield) from the known 2,2-dimethyl-4,4-diphenyl-3-butenal (H. E. Zimmerman, A. C. Pratt, *J. Am. Chem. Soc.* **1970**, *92*, 6259–6267): 1) (4S)-3-chloroacetyl-4-phenylmethyl-2-oxazolidinone, Bu₃BOTf, NEt₃, CH₂Cl₂, –78 → 0 °C (D. A. Evans, E. B. Sjogren, A. E. Weber, R. E. Conn, *Tetrahedron Lett.* **1987**, *28*, 39–42); 2) Zn, AcOH, THF; 3) LiBH₄, THF/MeOH, 0 °C; 4) PMPCH(OMe)₂, PPTS, CH₂Cl₂; 5) DIBALH, CH₂Cl₂, 0 °C; 6) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, –78 °C.
- [9] P. Brownbridge, T. H. Chan, M. A. Brook, G. J. Kang, *Can. J. Chem.* **1983**, *61*, 688–693.
- [10] D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.
- [11] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
- [12] J. I. Levin, E. Turos, S. M. Weinreb, *Synth. Comm.* **1982**, *12*, 989–993.
- [13] The epoxide was also isolated in about 20 % yield. This could be recycled by reduction with samarium diiodide (RT, THF, 50 % yield, unoptimized).
- [14] S. Hanessian, Y. Guindon, *Carbohydr. Res.* **1980**, *86*, C3.
- [15] Approximately 5 % of the (separable) C9 β-anomer was isolated from the thiol installation.
- [16] D. A. Evans, J. A. Murry, M. C. Kozlowski, *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815.
- [17] For an earlier approach to these synthons, see D. A. Evans, J. A. Gauchet-Prunet, E. M. Carreira, A. B. Charette, *J. Org. Chem.* **1991**, *56*, 741–750.
- [18] Prepared in analogous fashion to benzyloxymethylthium; see W. C. Still, *J. Am. Chem. Soc.* **1978**, *100*, 1481–1486.
- [19] M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.
- [20] Aldehyde **15** was prepared from 1,3-propanediol by the following four-step sequence in 76 % overall yield: 1) TsCl, pyr, 0 → 23 °C; 2) PhSnA, DMF, 80 °C; 3) mCPBA, CH₂Cl₂; 4) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, –78 → 0 °C.
- [21] Prepared in three steps from 3-methyl-4-phenyl-buten-2-ol: 1) L-(+)-DIPT (15 mol %), Ti(OiPr)₄ (10 mol %), *t*BuO₂H (0.7 equiv), CH₂Cl₂, –20 °C; 2) NaH, PMBBR, *n*Bu₄NI (cat.), THF; 3) O₃, CH₂Cl₂/MeOH, –78 °C; then Me₂S, –78 → 23 °C. This sequence was performed without purification of the intermediates to afford the resolved ketone **17** in 25–35 % overall yield and 96–99 % ee after flash chromatography.
- [22] a) For the synthesis of the undesired 1,4-*syn* diastereomer in the aldol reactions of lactate-derived methyl ketones, see: B. M. Trost, H. Urabe, *J. Org. Chem.* **1990**, *55*, 3982–3983; b) for the aldol reactions of lactate-derived ethyl ketones, see I. Paterson, D. J. Wallace, S. M. Velázquez, *Tetrahedron Lett.* **1994**, *35*, 9083–9086.
- [23] a) Fortuitously, this is an example of a “matched” double diastereodifferentiating reaction. b) P. V. Ramachandran, W.-C. Xu, H. C. Brown, *Tetrahedron Lett.* **1996**, *37*, 4911–4914; c) I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, R. D. Norcross, *Tetrahedron* **1990**, *46*, 4663–4684.
- [24] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
- [25] G. H. Lee, H. K. Lee, E. B. Choi, B. T. Kim, C. S. Pak, *Tetrahedron Lett.* **1995**, *36*, 5607–5610.
- [26] For a precedent for this transformation, see S. V. Ley, B. Lygo, F. Sternfeld, A. Wonnacott, *Tetrahedron* **1986**, *42*, 4333–4342, and references therein.
- [27] For amide deprotection, see D. A. Evans, P. H. Carter, C. J. Dinsmore, J. C. Barrow, J. L. Katz, D. W. Kung, *Tetrahedron Lett.* **1997**, *38*, 4535–4538.
- [28] a) D. A. Evans, A. S. Kim, *J. Am. Chem. Soc.* **1996**, *118*, 11323–11324; b) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
- [29] a) The use of trimethyl phosphonoacetate afforded a Z:E mixture (63:37) of **33** in 100 % yield. b) K. Tanaka, Y. Ohta, K. Fuji, T. Taga, *Tetrahedron Lett.* **1993**, *34*, 4071–4074; c) K. Tanaka, K. Otsubo, K. Fuji, *Tetrahedron Lett.* **1996**, *37*, 3735–3738.
- [30] a) R. E. Ireland, J. L. Gleason, L. D. Gegnas, T. K. Highsmith, *J. Org. Chem.* **1996**, *61*, 6856–6872; b) R. E. Ireland, P. Wipf, J. D. Armstrong, III, *J. Org. Chem.* **1991**, *56*, 650–657.

- [31] The conformation of **33** in solution was determined by NOESY analysis (500 MHz, $[D_6]$ acetone).
- [32] a) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926; b) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.
- [33] The hydroxyl groups at C20 and C26 of bryostatin 14 may be selectively acetylated (Ac_2O , pyr) in the presence of hydroxyl groups at C3, C9, and C19: G. R. Pettit, F. Gao, D. Sengupta, J. C. Coll, C. L. Herald, D. L. Doubek, J. M. Schmidt, J. R. Van Camp, J. J. Rudloe, R. A. Nieman, *Tetrahedron* **1991**, *47*, 3601–3610.
- [34] Prepared in good yield from 2-hexenal according to the method of Coutrot et al.: P. Coutrot, M. Snoussi, P. Savignac, *Synthesis* **1978**, 133–134.
- [35] We thank Prof. G. R. Pettit for providing us with a natural sample of bryostatin 2.

The Cluster Anion Si_9^{4-}

Hans Georg von Schnering,* Mehmet Somer, Martin Kaupp, Wilder Carrillo-Cabrera, Michael Baitinger, Andre Schmeding, and Yuri Grin

Dedicated to Professor Achim Müller on the occasion of his 60th birthday

The 40 valence electron cluster anions E_9^{4-} of the Group 14 (E14) elements Ge, Sn, and Pb have been known for many years. These anions form monocapped square antiprisms (SAPRS-9)—that is, the framework of a $22e$ *nido*- E_{10} Wade cluster—as shown by the investigations of Kummer et al.,^[1] Corbett et al.,^[2] and Fässler et al.^[3] Until recently, it appeared certain that these cluster anions are only formed by the reactions of intermetallic phases with suitable solvents.^[4] However, the existence of the isolated anions in these binary phases of the alkali metals $M=Na, K, Rb, Cs$ was then established.^[5, 6] Besides X-ray structure analyses, the successful stepwise thermal decomposition of the alkali metal tetrahydrides ME (M_4E_4), the quantitative analysis of the vibrational spectra, and the quantum chemical calculation of these spectra proved to be essential tools in our investigations.^[5] The binary compounds $M_{12}E_{17} = M_{12}[(E_4)_2E_9] = ME_{1,42}$ and $M_4E_9 = ME_{2,25}$, which contain the cluster anions E_4^{4-} and E_9^{4-} , were identified as well as clathrates of the types $M_6E_{25} = ME_{4,17}$,^[7] $M_8E_{44\Box_2} = ME_{5,50}$, and M_xE_{136} ($5 \leq x \leq 12$) $\approx ME_{11-27}$. These results also suggested a route to the elusive Si_9^{4-} , for which no evidence for its existence was available.

The thermal decomposition of the alkali metal monosilicides MSi (M_4Si_4) by Schäfer and Klemm^[8] 40 years ago only led to the clathrates $M_8Si_{44\Box_2}$ in steep thermogravimetric (TG)

steps, as was also observed for the germanides. We have now reinvestigated these reactions in a Knudsen cell under dynamic vacuum^[9] and found the following:

1. In the thermal decomposition of $NaSi$, a distinct step appears for $NaSi_{2.3}$ (Na_4Si_9 ?), followed very quickly by the steps for the clathrates Na_6Si_{25} and $Na_8Si_{44\Box_2}$, and then by that of Na_xSi_{136} .
2. According to DTG investigations, the thermal decomposition of KSi and $RbSi$ passes through two steps close to KSi_2 and $RbSi_2$. However, only the later formed clathrates M_6Si_{25} , $M_8Si_{44\Box_2}$, and M_xSi_{136} can be characterized unambiguously.
3. The thermal decomposition of $CsSi$ (Cs_4Si_4) starts at 500 K and passes through three distinct steps at 630, 690, and 850 K (Figure 1). These steps represent the formation and

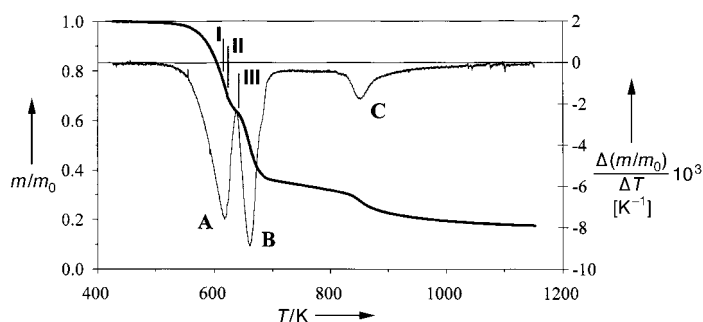


Figure 1. Thermal decomposition of Cs_4Si_4 in a Knudsen cell under dynamic vacuum (TG: bold lines; DTG: thin lines, m_0 = sample mass). See text for details of the analysis of the mass losses A–C and of products I–III.

decomposition of several phases, and these processes overlap over appreciable temperature intervals. The quantitative analysis of the DTG curves show that the mass loss at A corresponds to the formation and decomposition of the cluster phase $CsSi_{1.3}$ and the formation of the phase cluster $CsSi_{2.2}$. Before the formation of the latter is complete, its decomposition into the clathrate phases $CsSi_{4.2}$ and $CsSi_{5.5}$ commences (at B). The slightly declining TG plateau between 690 and 800 K indicates that the transformation into $CsSi_{5.5}$ needs a longer period of time. The mass loss at C corresponds to the formation of the clathrate phase Cs_xSi_{136} ($x \approx 10-12$, $CsSi_{11-14}$), which subsequently decomposes to silicon (ca. 1050 K). The phases identified here are direct analogues of the germanides and stannides of the types $M_{12}E_{17}$, M_4E_9 , M_6E_{25} , $M_8E_{44\Box_2}$, and M_xE_{136} .^[5]

We then tried to isolate individual phases during the decomposition. All attempts to characterize these phases by X-ray diffraction failed. Upon disappearance of the reflections of the M_4Si_4 phases, X-ray amorphous products were formed. After annealing for several weeks, these products gave sharp diagrams, but with many reflections of low intensity. We therefore applied Raman spectroscopy to the characterization of the phases close to $CsSi_2$.^[10] We used three samples from region A (Figure 1), which were obtained by stopping the decomposition reaction.

The vibrations of the tetrahydride anions E_4^{4-} ($E=Si, Ge, Sn$) have been described in detail by Kliche et al.^[11] These

[*] Prof. Dr. H. G. von Schnering, Priv. Doz. Dr. M. Kaupp, Dr. W. Carrillo-Cabrera, Dipl.-Chem. M. Baitinger, Dipl.-Ing. A. Schmeding, Dr. Yu. Grin
Max-Planck-Institut für Festkörperforschung
Heisenbergstrasse 1, D-70569 Stuttgart (Germany)
Fax: (+49) 711-689-1502
Prof. Dr. M. Somer
Koç Üniversitesi, Cayir Cad.5 İstinye
80860 Istanbul (Turkey)

anions are characterized by three intensive bands or groups of bands, which for Si_4^{4-} appear at 290, 355, and 480 cm^{-1} . The Raman spectra of the alkali metal compounds M_4E_9 and $\text{M}_{12}\text{E}_{17}$ showed that the cluster anions E_9^{4-} do also have simple characteristic vibrational patterns, the frequencies of which can be used for their identification.^[5] In particular, the almost constant ratio of the breathing frequencies is important: $\kappa = \tilde{\nu}(\text{E}_9)/\tilde{\nu}(\text{E}_4) = 220:274 = 0.81$ (Ge) and $152:185 = 0.82$ (Sn). With $\tilde{\nu}(\text{Si}_4) = 475\text{ cm}^{-1}$ for Cs_4Si_4 and $\kappa = 0.81$, we can thus expect $\tilde{\nu}(\text{Si}_9)$ at $385\text{--}390\text{ cm}^{-1}$.

The product **I** at $m/m_0 = 0.76$ exhibits, besides the typical bands of the Si_4^{4-} anion at 282, 355, and 475 cm^{-1} , a new strong band at 387 cm^{-1} (Figure 2), which gains intensity at $m/m_0 = 0.69$ (**II**) and with a wavenumber of 386 cm^{-1} is the most

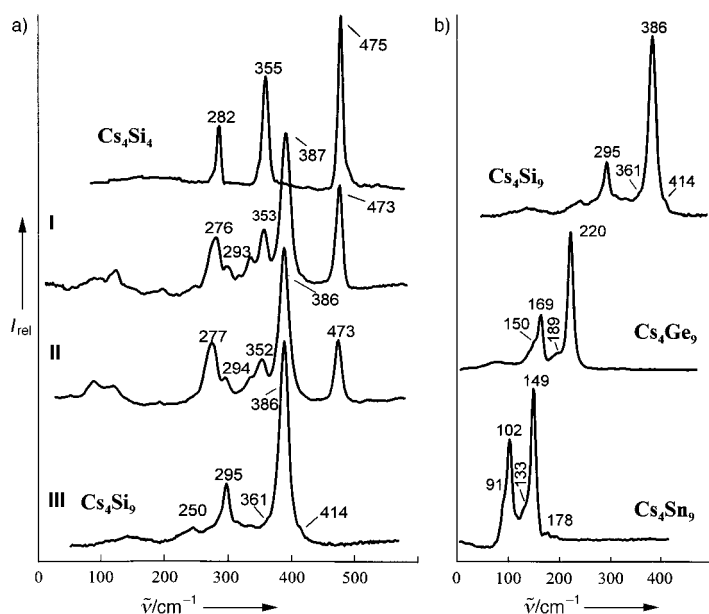


Figure 2. a) Raman spectra of Cs_4Si_4 and of the reaction products **I**–**III**. b) Comparison of the Raman spectrum of the decomposition product Cs_4Si_9 with those of Cs_4Ge_9 and Cs_4Sn_9 .^[5]

intense band in the spectrum of **III** at $m/m_0 = 0.58$. Simultaneously, the intensity of the Si_4 bands decreases, and they are absent from the spectrum of **III**. Besides the band at 386 cm^{-1} , the weaker bands at 295 and 250 cm^{-1} can now be clearly seen. For the homologues Ge and Sn, several compounds exist in the region $\text{M}:\text{E} \approx 1:2$. Among these, $\text{M}_{12}\text{E}_{17}$ ($\text{ME}_{1.42}$) and M_4E_9 ($\text{ME}_{2.25}$) are very well characterized.^[5, 6] Both phases contain isolated cluster anions E_9^{4-} , which in $\text{M}_{12}\text{E}_{17}$ exist together with the anions E_4^{4-} in the ratio $\text{E}_9:\text{E}_4 = 1:2$. The spectra of the decomposition products **I**–**III** of Cs_4Si_4 indicate a similar situation in the system Cs–Si. The spectrum of **III** characterizes a substance which contains only the anions Si_9^{4-} (Cs_4Si_9). In principle, the anion Si_3^{2-} might have formed at the composition $\text{CsSi}_{2.5}$. However, in this case $\kappa = \tilde{\nu}(\text{E}_5)/\tilde{\nu}(\text{E}_4) = 0.98$ ($\text{E} = \text{Ge}, \text{Sn}$) would lead to an expected breathing frequency of $\tilde{\nu}(\text{Si}_5) = 465\text{ cm}^{-1}$, which is clearly missing.

As in the case of the homologues Ge_9^{4-} and Sn_9^{4-} , the structure and the Raman spectrum of the anion Si_9^{4-} were calculated by quantum chemical methods.^[12] The optimization of the bare anion Si_9^{4-} indicated, as for Pb_9^{4-} ,^[14] that the

configuration with the symmetry $4mm$ (C_{4v}) is a minimum on the potential energy surface, but with very small energy differences to other arrangements. For example, a configuration with $\bar{6}m2$ (D_{3h}) symmetry is only 2.5 kJ mol^{-1} less stable. It is a degenerate transition state with an imaginary vibrational mode of E' symmetry. Figure 3a shows the optimized structure with $4mm$ (C_{4v}) symmetry. No experimental comparison was available for this structure (see below).

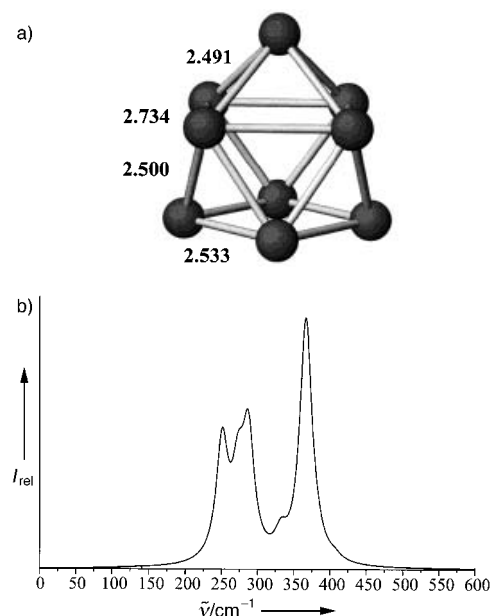


Figure 3. a) Quantum chemically optimized structure of the Si_9^{4-} anion (point symmetry $4mm$) with bond lengths [Å]. b) Calculated Raman spectrum of the Si_9^{4-} anion (see also Figure 2b).

However, an indirect comparison is possible by means of the ratios of the corresponding bond lengths $d_i(\text{E}–\text{E})$ in the known clusters Ge_9 and Sn_9 . These ratios agree well with those of the E14 diamond structures ($d(\text{Si}–\text{Si})/d(\text{Ge}–\text{Ge}) = 0.960$, $d(\text{Si}–\text{Si})/d(\text{Sn}–\text{Sn}) = 0.837$).

The calculated Raman frequencies and intensities agree well with the experimental data (Figures 2b and 3b). For the breathing mode, $\tilde{\nu}(\text{Si}_9) = 367\text{ cm}^{-1}$ (experimental: 386 cm^{-1}). Discrepancies in the intensities may be caused by systematic errors in the calculation on the isolated anion (large negative charge of the relatively small cluster anion; deviations from $4mm$ (C_{4v}) symmetry due to the influence of the surrounding cations or of packing effects in the crystal).

Together with the thermogravimetric measurements, the spectroscopic and quantum chemical results leave no doubt that binary compounds of the anion Si_9^{4-} are formed during the controlled thermal decomposition of cesium monosilicide.

We attempted to prepare silicides of the types $\text{M}_{12}\text{E}_{17}$ and M_4E_9 directly from the elements, in analogy to the corresponding germanides and stannides^[5, 6] (e.g., $\text{Cs}:\text{Si} = 4:9$; sealed Nb ampoules, reaction at 1000 K for 1 h ; annealing at 675 K for several days). The X-ray powder diagrams of products with the compositions $\text{Cs}_{12}\text{Si}_{17}$ and Cs_4Si_9 showed, in addition to reflections for Cs_4Si_4 and Si, numerous weak and diffuse reflections, which could not be indexed. Variations of

temperature (575–875 K) and annealing times did not give significant improvements. However, the diffraction pattern is in all cases reproducible. The Raman spectra are very similar to those of the decomposition products. The band at 386 cm^{-1} (Si_3^{4-}) is distinctly recognizable. The other bands found at 475 and/or 480 cm^{-1} , and at 353, 334, and 278 cm^{-1} and/or 519 cm^{-1} , may be assigned to the anion Si_4^{4-} and to elemental silicon. Even though no new products that exhibit only the spectrum of the anion Si_3^{4-} were obtained by this route, the synthesis from the elements Cs and Si does clearly produce compounds with this anion.

Meanwhile, our results have been confirmed by the investigations of Quéneau et al.^[16] who isolated the compound $\text{Rb}_{12}\text{Si}_{17}$ and elucidated its crystal structure. In full accordance with our predictions,^[5] this structure contains the clusters Si_4^{4-} and Si_3^{4-} . The bond lengths obtained from the structural analysis ($d(\text{Si}-\text{Si}) = 2.40, 2.64, 2.37, 2.38\text{ Å}$) largely agree with our values (Figure 3 a), but are generally somewhat smaller. This might be due to the quality of the experimental data ($R_F = 0.176$; $I > 2\sigma(I)$). In any case, it is clear that a combination of structural analyses, quantum chemical methods, and quantitative analyses of the vibrational spectra can prove,^[5] and allow more than to suggest,^[17] the existence of new cluster compounds.

Received: April 6, 1997 [Z11687IE]

German version: *Angew. Chem.* **1998**, *110*, 2507–2509

Keywords: ab initio calculations • clusters • Raman spectroscopy • silicon • thermogravimetry

- [1] D. Kummer, L. Diehl, *Angew. Chem.* **1970**, *82*, 881; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 895; L. Diehl, Dissertation, Universität Karlsruhe, **1971**; L. Diehl, K. Khodadadeh, D. Kummer, J. Strähle, *Z. Naturforsch. B* **1976**, *31*, 522.
- [2] J. D. Corbett, P. Edwards, *J. Am. Chem. Soc.* **1977**, *99*, 3313.
- [3] T. F. Fässler, M. Hunziker, *Inorg. Chem.* **1994**, *33*, 5380; T. Fässler, M. Hunziker, *Z. Anorg. Allg. Chem.* **1994**, *622*, 837.
- [4] J. D. Corbett, S. C. Crichtlow, R. C. Burns, *ACS Symp. Ser.* **1984**, *232*, 95; A. F. Hollemann, E. Wiberg, N. Wiberg, *Lehrbuch der Anorganischen Chemie*, 101st ed., de Gruyter, Berlin, **1995**, p. 956.
- [5] H. G. von Schnering, M. Baitinger, U. Bolle, W. Carrillo-Cabrera, J. Curda, Yu. Grin, F. Heinemann, J. Llanos, K. Peters, M. Somer, *Z. Anorg. Allg. Chem.* **1997**, *623*, 1037.
- [6] V. Quéneau, S. C. Sevov, *Angew. Chem.* **1997**, *109*, 1818; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1754.
- [7] R. Kröner, R. Nesper, H. G. von Schnering, *Z. Kristallogr.* **1988**, *182*, 164; H. G. von Schnering, R. Kröner, W. Carrillo-Cabrera, K. Peters, R. Nesper, *Z. Kristallogr. NCS* **1998**, *213*, 665.
- [8] R. Schäfer, W. Klemm, *Z. Anorg. Allg. Chem.* **1961**, *312*, 214.
- [9] The thermogravimetric (TG) and differential thermogravimetric (DTG) measurements were carried out with a Netzsch STA 429 apparatus with simultaneous mass spectrometer (Knudsen cell; heating rate 1 K min^{-1} ; vacuum 10^{-6} Pa).
- [10] Spectroscopic investigations have also been carried out in the systems with sodium, potassium, and rubidium. Only in the system $\text{Rb}-\text{Si}$ could characteristic bands of the Si_3^{4-} anion be observed.
- [11] G. Kliche, H. G. von Schnering, *Z. Anorg. Allg. Chem.* **1992**, *608*, 131.
- [12] The structure of Si_3^{4-} was optimized at the HF/6-31G(D) level in point symmetry $4mm$ (C_{4v}) with the Gaussian 94 program.^[13] The harmonic vibrational frequencies and Raman intensities were calculated analytically. It is not expected that Si_3^{4-} as a free anion in the gas phase will be stable with respect to electron loss. Nevertheless, sufficiently accurate structures and vibrational spectroscopic data

should be obtainable with the medium-sized 6-31G(D) basis set employed. It is known that a limited basis set disfavors the removal of electrons and thus approximately simulates a confining positive potential in the condensed phase (cf. P. Pykkö, Y. Zhao, *J. Phys. Chem.* **1990**, *94*, 7753). The Hartree–Fock method was preferred to the currently very popular density functional methods for two reasons: a) The usual density functionals in our experience give bonds that are too long and stretching frequencies that are too low for heavy p-block main group elements. This holds for the heavier E_3^{4-} ions and also for neutral molecules (M. Kaupp, *Chem. Ber.* **1996**, *129*, 535). b) For technical reasons, the calculation of Raman intensities with density functional methods is presently not possible in the Gaussian 94 program.

- [13] Gaussian 94, Revision E.2, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1995**.
- [14] The structures of Pb_3^{4-} and Pb_3^{3-} were optimized with density functional methods. The energetically most favorable configuration of Pb_3^{4-} has the symmetry $4mm$ (C_{4v}), and that of Pb_3^{3-} the symmetry $2mm$ (C_{2v}).^[15]
- [15] J. Campbell, D. A. Dixon, H. P. A. Mercier, G. J. Schrobilgen, *Inorg. Chem.* **1995**, *34*, 5798.
- [16] V. Quéneau, E. Todorov, S. C. Sevov, *J. Am. Chem. Soc.* **1998**, *120*, 3263.
- [17] V. Quéneau, S. C. Sevov, *Inorg. Chem.* **1998**, *37*, 1358.

Self-Organization of a Heteroditopic Molecule to Linear Polymolecular Arrays in Solution**

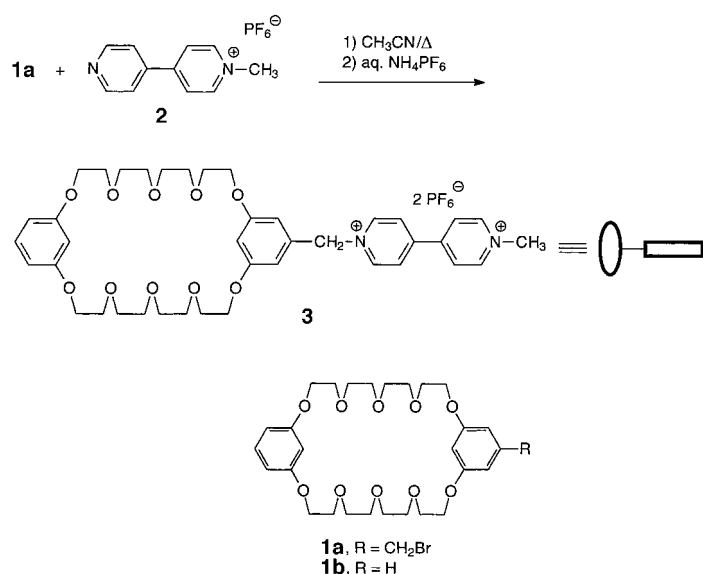
Nori Yamaguchi, Devdatt S. Nagvekar, and Harry W. Gibson*

Nature displays a variety of supramolecular structures within a scale of 1 to 100 nm, beautifully put together with relatively simple building blocks by means of self-organization.^[1] Over the last few decades chemists have elegantly adopted a variety of noncovalent bonding interactions to construct supramolecular architectures in the way that Nature does it.^[2] The versatility and efficiency of utilizing such noncovalent forces^[3] inspired us to design and to prepare a heteroditopic molecule to create linear oligo- and polymolecular arrays self-organized in solution by host–guest complexation.^[4]

The synthetic methodology employed for **3** from **1a**^[5] is depicted in Scheme 1. According to CPK models, the

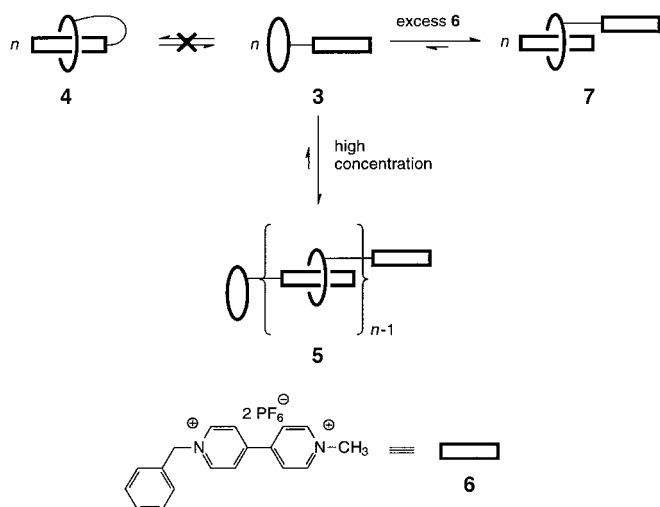
[*] Prof. H. W. Gibson, N. Yamaguchi, D. S. Nagvekar
Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, Virginia, 24061 (USA)
Fax: (540) 231-8517
E-mail: hwgibson@vt.edu

[**] This work was supported by the National Science Foundation (USA) through Individual Investigator Award CHE-95–21738. The authors thank Dr. Philip Mason for valuable discussions on the interpretation of the ^1H NMR data.



Scheme 1. The synthesis of the heteroditopic molecule **3**.

existence of the complex **4** was disregarded based on the stiffness of the molecule, which effectively prevents the paraquat unit from curling around to complex intramolecularly with the macrocyclic unit (Scheme 2). In contrast, intermolecular complexation of **3** can lead to the formation of linearly chained, pseudo-polymeric supramolecules **5**.



Scheme 2. Schematic illustration of the formation of the linear oligo- and polymolecular arrays **5** by self-organization of **3**.

The ^1H NMR spectra of **3** in $[\text{D}_6]$ acetone at 22°C (Figure 1) are concentration-dependent, which reflects the involvement of rapidly exchanging noncovalent bonding interaction(s) in solution. The chemical shift of a proton located in the cavity of the crown ether binding site H_g was monitored by ^1H NMR spectroscopy. The observed time-averaged chemical shifts δ_o can be defined according to Equation (1) by using the

$$\delta_o = \delta_c p + \delta_u (1 - p) \quad (1)$$

chemical shifts obtained for totally complexed and free crown ether. δ_c is the chemical shift in a solution in which the crown

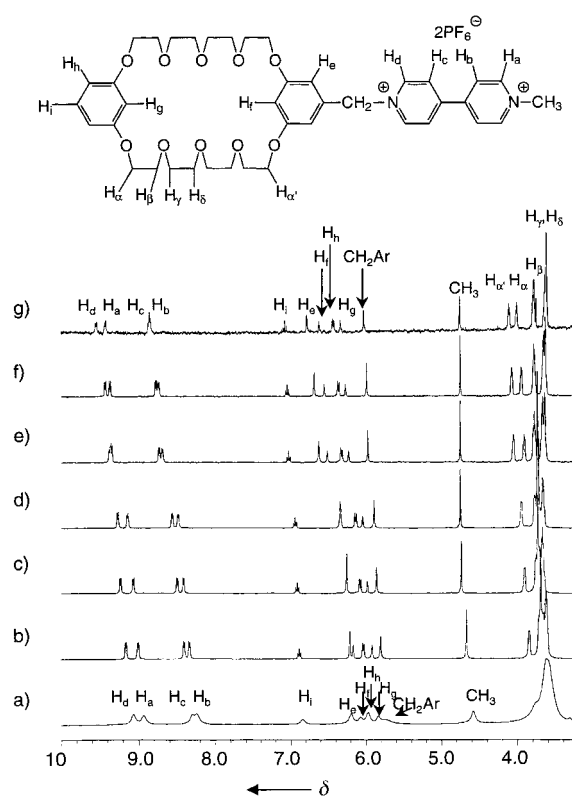


Figure 1. The ^1H NMR spectra (400 MHz, $[\text{D}_6]\text{acetone}$, 22°C) of **3** at different concentrations: a) 2.0 M, b) $5.0 \times 10^{-1}\text{M}$, c) $5.0 \times 10^{-2}\text{M}$, d) $1.0 \times 10^{-2}\text{M}$, e) $1.0 \times 10^{-3}\text{M}$, f) $5.0 \times 10^{-4}\text{M}$; g) $6.3 \times 10^{-5}\text{M}$.

ether is 100% complexed and δ_u is that of the free crown ether, and p is the fraction of the complexed crown ether.^[6, 7] From p the average number n of monomeric units in the aggregate **5** can be estimated according to Equation (2). The

$$n=1/(1-p) \quad (2)$$

n values calculated in this manner are given in Table 1.^[8] As concentration increases the size of the aggregates increases to truly large values and noncovalently bonded polymers are formed.^[9] Since the molecular weight of **3** is 1010 g mol⁻¹, for $n = 50$ the total molar mass is 50 500 g mol⁻¹.

The ^1H NMR spectrum of **3** at 2.0M (Figure 1a) clearly reveals signals substantially broadened with respect to the

Table 1. Dependence of the degree of aggregation n of **5** on the concentration of **3**, calculated from the chemical shift δ_0 of the NMR signal^[a] of H_g.

$c_0(\mathbf{3})[\text{M}]$	δ_0	p	n
2.0	5.839	0.98	50
1.4	5.862	0.93	14
1.0	5.881	0.89	9.1
5.0×10^{-1}	5.918	0.82	5.6
1.0×10^{-1}	5.964	0.73	3.7
6.7×10^{-2}	5.974	0.71	3.4
5.0×10^{-2}	5.977	0.70	3.3
1.0×10^{-2}	6.041	0.58	2.4
1.0×10^{-3}	6.227	0.21	1.3
5.0×10^{-4}	6.268	0.13	1.1

[a] 400 MHz, [D₆]acetone, 22 °C.

spectra recorded at lower concentrations. This can be understood in terms of the formation of larger pseudo-polymeric aggregates **5** at higher concentration; as a result the solution viscosity is increased (see below), and the mobility of the polymeric chain is restricted, thus causing the signal broadening in the NMR spectra. In contrast, the ^1H NMR spectrum of a 1:1 solution of monotopic components **1b** and **6** in acetone maintains sharp and well-resolved signals even at the highest concentration we investigated (2.0 M/2.0 M). This observation, therefore, rules out non-ideality of highly concentrated solutions per se as a cause for the signal broadening.

The 2D-NMR spectra (NOESY) were consistent with the pseudorotaxane geometry formed between the two complementary functionalities of adjacent units. As expected, the ethyleneoxy protons H_α , H_β , and H_γ strongly interact through space with the protons of the paraquat unit ($\text{H}_\text{a} - \text{H}_\text{d}$) and also with the benzylic methylene protons. Most importantly, the protons H_b and H_c of the paraquat moiety experience through-space interactions with the aromatic protons residing inside the crown ether cavity, H_f and H_g , but not with those outside the cavity, H_e , H_h , and H_i .

High solution viscosity is characteristic of linear polymeric structures.^[10] Indeed, the reduced viscosity of solutions of **3** in acetone increased in nonlinear fashion with concentration due to the formation of **5** (Figure 2a), while that of equimolar solutions of **1b** and **6** in acetone increased only slightly with concentration (Figure 2b), thus ruling out the polyelectrolyte effect as the major cause of the viscosity change observed with

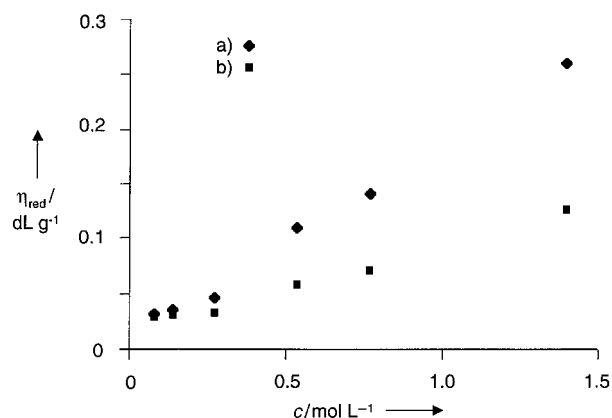


Figure 2. Reduced viscosity as a function of concentration (solutions in acetone at 22 °C): a) **3**, b) **1b** and **6** (1:1).

5. The high viscosity observed for **5** at 1.4 M ($n = 14$, Table 1), $\eta_{\text{red}} = 0.26$ vs. 0.13 dL g^{-1} for solutions of **1b** and **6** (1:1), and the fact that a 2.0 M solution of **3** in acetone was too viscous to flow through the viscometer^[11] argue against the presence of significant amounts of small cyclic species, since it is well known that cyclic molecules have smaller hydrodynamic volumes and hence lower viscosities than their linear counterparts.^[12]

Two red-orange samples of amorphous **5**, prepared by freeze-drying^[13] 0.1 and 1.0 M solutions of the heteroditopic molecule **3** in acetone, were studied by differential scanning calorimetry (DSC). The glass transitions (T_g) occurred at 42.1 and 58.3 °C, respectively. On the other hand, samples of **3**

recrystallized from water (in which self-organization does not occur) are crystalline, and display a melting transition at 80.3 °C. The amorphous nature of the samples prepared in acetone is indicative of linear polymers. Furthermore, the higher T_g value of **5**, which was obtained from the more concentrated solution, is consistent with a higher extent of self-organization n , as demonstrated by the ^1H NMR and viscosity experiments.

Mass spectrometric studies of **5** provided support for the existence of the self-organized linear arrays. The FAB mass spectrum^[14] (Figure 3) reveals peaks at $m/z = 3896$ and 3751,

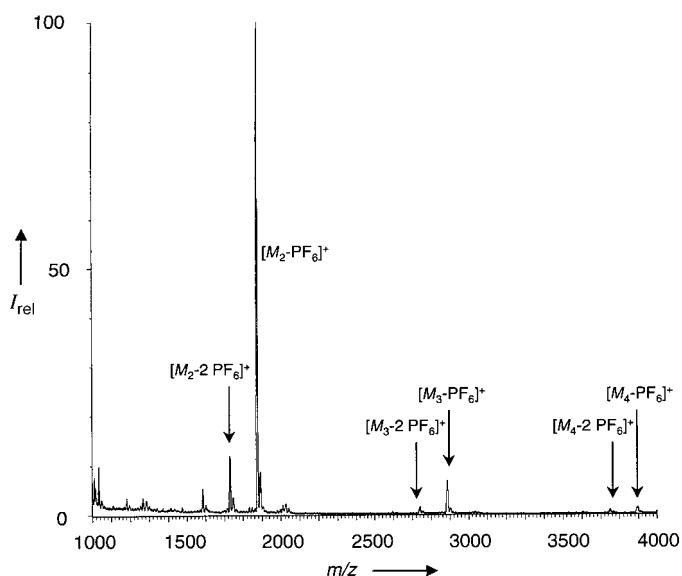


Figure 3. The FAB mass spectrum of the self-organized pseudo-oligomeric material **5**.

which can be attributed to the tetramer ($n = 4$, $[\text{M}_4 - \text{PF}_6]^+$ and $[\text{M}_4 - 2 \text{PF}_6]^+$). The peaks at $m/z = 2886$ and 2741 indicate the existence of trimeric oligomer ($n = 3$ $[\text{M}_3 - \text{PF}_6]^+$ and $[\text{M}_3 - 2 \text{PF}_6]^+$). In addition, we detected the $[\text{M}_2 - \text{PF}_6]^+$, $[\text{M}_2 - 2 \text{PF}_6]^+$, $[\text{M} - \text{PF}_6]^+$ and $[\text{M} - 2 \text{PF}_6]^+$ peaks, corresponding to the dimeric and monomeric species.

We have demonstrated that the heteroditopic molecule **3** instantaneously “self-associated” to form pseudo-oligomeric and pseudo-polymeric rotaxane types of linear arrays in solution. The trapping of the crown ether moieties in such linear arrays **5** by the use of blocking chemistry will lead to mechanically “locked-in” linear arrays which may ultimately be studied by using other characterization techniques available in polymer science. This exciting concept of utilizing noncovalent bonding interactions can potentially be expanded to achieve other novel self-organizing nanoscopic structures; we are pursuing such objectives.

Experimental Section

3: In a 50-mL round-bottomed flask equipped with a magnetic stirrer **1a**^[5] (0.35 g, 0.56 mmol), **2** (0.18 g, 0.57 mmol), and MeCN (20 mL) were refluxed for 24 h. The orange solution was precipitated in diethyl ether to afford a yellow solid, which was dissolved in H_2O , and aqueous NH_4PF_6 was added until no further precipitation was observed. The product was recrystallized from H_2O to give a yellow solid (0.50 g, 89 % yield), m.p. 79–

80 °C. ¹H NMR (400 MHz, [D₆]DMSO, 22 °C): δ = 3.55 (16 H, m), 3.70 (8 H, t, *J* = 3.2 Hz), 4.00 (4 H, t, *J* = 3.2 Hz), 4.07 (4 H, t, *J* = 3.2 Hz), 4.21 (3 H, s), 5.77 (2 H, s), 6.44–6.47 (3 H, m), 6.60 (1 H, s), 6.80 (2 H, s), 7.10 (1 H, t, *J* = 3.6 Hz), 8.69 (2 H, d, *J* = 6.4 Hz), 8.72 (2 H, d, *J* = 6.4 Hz), 9.25 (2 H, d, *J* = 6.4 Hz), 9.48 (2 H, d, *J* = 6.4 Hz); elemental analysis calcd for C₄₀H₅₂N₂O₁₀P₂F₁₂: C 47.63, H 5.00; found: C 47.35, H 5.02.

Received: October 7, 1997

Revised version: May 20, 1998 [Z11013IE]

German version: *Angew. Chem.* **1998**, *110*, 2518–2520

Keywords: crown compounds • noncovalent interactions • rotaxanes • self-organization • supramolecular chemistry

- [1] a) A. Klug, *Angew. Chem.* **1983**, *95*, 579–596; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 565–582; b) D. Philp, J. F. Stoddart, *ibid.* **1996**, *108*, 1242–1286 and **1996**, *35*, 1154–1196.
- [2] a) J.-M. Lehn, *Angew. Chem.* **1990**, *102*, 1347–1362; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304–1319; b) C. T. Seto, G. M. Whitesides, *J. Am. Chem. Soc.* **1990**, *112*, 6409–6411; c) C. T. Seto, G. M. Whitesides, *ibid.* **1991**, *113*, 712–713; d) J. A. Zeriowski, C. T. Seto, G. M. Whitesides, *ibid.* **1992**, *114*, 5473–5475; e) C. T. Seto, G. M. Whitesides, *ibid.* **1993**, *115*, 905–916; f) A. Harada, K. Li, M. Kamachi, *ibid.* **1994**, *116*, 3192–3196; g) A. Harada, K. Li, M. Kamachi, *Nature* **1994**, *370*, 126–128.
- [3] a) P. R. Ashton, J. Huff, S. Menzer, I. W. Parsons, J. A. Preece, J. F. Stoddart, M. S. Tolley, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1996**, *2*, 31–44; b) M. Asakawa, P. R. Ashton, S. Menzer, F. M. Raymo, J. F. Stoddart, A. J. P. White, D. J. Williams, *ibid.* **1996**, *2*, 877–893; c) D. P. Funeriu, J.-M. Lehn, G. Baum, D. Fenske, *ibid.* **1997**, *3*, 99–104; d) P. R. Ashton, S. E. Boyd, D. G. Claessens, R. E. Gillard, S. Menzer, J. F. Stoddart, M. S. Tolley, A. J. P. White, D. J. Williams, *ibid.* **1997**, *3*, 788–798; e) A. Mirzozian, A. E. Kaifer, *ibid.* **1997**, *3*, 1052–1058; f) P. R. Ashton, R. Ballardini, V. Balzani, S. E. Boyd, A. Credi, M. T. Gandolfi, M. Gómez-López, S. Iqbal, D. Philp, J. A. Preece, L. Prodi, H. G. Ricketts, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White, D. J. Williams, *ibid.* **1997**, *3*, 152–170.
- [4] For the self-organization of a monosubstituted β-cyclodextrin to a polymeric array in the solid state where the *tert*-butylsulfonyl group is intermolecularly included in the cavity of the cyclodextrin, see: K. Hirotsu, T. Higuchi, K. Fujita, T. Ueda, A. Shinoda, T. Imoto, I. Tabushi, *J. Org. Chem.* **1982**, *47*, 1143–1144. Indeed, as early as 1977 Cram et al. suggested the formation of polymeric species by complexation of bis(crown ethers) and α,ω-diammonium salts: R. C. Helgeson, T. L. Tarnowski, J. M. Timko, D. J. Cram, *J. Am. Chem. Soc.* **1977**, *99*, 6411–6418.
- [5] H. W. Gibson, D. S. Nagvekar, N. Yamaguchi, F. Wang, W. S. Bryant, *J. Org. Chem.* **1997**, *62*, 4798–4803.
- [6] The chemical shifts of H_g in the ¹H NMR spectra of the three most dilute solutions of **3** (6.5 × 10^{−5}, 3.1 × 10^{−5} and 1.6 × 10^{−5} M, [D₆]acetone) were unchanged at δ = 6.335. Thus, δ_a = 6.335. A dilute solution of **3** (5.0 × 10^{−4} M, [D₆]acetone) was gradually saturated with **6**, which closely resembles the paraquat component of **3**, to emulate the binding sites of **5** by forming the heterodimeric **7** (Scheme 2). The chemical shifts of H_g of **3** in the ¹H NMR spectra with the two most concentrated solutions of **6** (2.5 × 10^{−1} and 5.0 × 10^{−1} M, [D₆]acetone) were unchanged at δ = 5.825. This was taken as δ_c. Thus from δ_a, *p* was calculated.
- [7] The signal corresponding to the methyl group of the heteroditopic molecule in **5** is strongly shifted upfield (δ ≈ 0.2) at higher concentration (2.0 M in Figure 1). Similarly, a significant upfield chemical shift is observed for the methyl group of **6** in the ¹H NMR spectrum of a 1:1 solution of monotopic components **1b** and **6** ([D₆]acetone) at higher concentration (e.g., 2.0 M each). These observations can be explained by the increased concentration of PF₆[−] in solution. To demonstrate this experimentally, a solution of **6** in acetone (1.0 × 10^{−2} M) was mixed with various concentrations of tetrabutylammonium hexafluorophosphate solutions (from 0.1 to 2.0 M) and the ¹H NMR spectra were recorded. The higher the concentration of PF₆[−], the greater the upfield chemical shift of the methyl group. On the other hand, the chemical shift of the phenyl group of **6** is independent of the PF₆[−] concentration. Therefore, the chemical shifts of H_g (Figure 1) are influenced by complexation, not by the changes of PF₆[−] concentration, validating the calculation of *p* based on the ¹H NMR data.
- [8] Nearly identical results were obtained by analysis of the NMR signal for H_i.
- [9] The expression *n* = 1/(1 − *p*) assumes that the cyclic species do not contribute to consumption of host and guest sites. In covalent polymer chemistry it is well understood that the percentage of cyclic molecules of any size formed at high concentrations (e.g., 1.0 M) is very small indeed (< 3%) and that linear macromolecules are preferentially formed. For reviews on cyclization versus linear polymerization, see: a) G. Odian, *Principles of Polymerization*, 3rd ed., Wiley, New York, **1991**, p. 73; b) S. C. Hamilton, J. A. Semlyen, *Polymer*, **1997**, *38*, 1685–1691. Therefore, the assumption that the absence of cyclic complexes dramatically increases with concentration is validated.
- [10] S. Glasstone, D. Lewis, *Elements of Physical Chemistry*, 2nd ed., Van Nostrand, New York, **1960**, pp. 597–598.
- [11] Not surprisingly, fibers could be pulled from very concentrated solutions in acetone (> 2.0 M). This observation is indicative of significant linear array extension in the material, consequently giving rise to polymeric properties.
- [12] a) K. Dodgson, J. A. Semlyen, *Polymer*, **1977**, *18*, 1265–1268; b) G. Hild, C. Strazielle, P. Rempp, *Eur. Polym. J.*, **1983**, *19*, 721–727.
- [13] The solutions were slowly cooled to −95 °C and frozen with an acetone-ethanol/liquid nitrogen bath. The solvent was then removed under high vacuum to obtain red-orange solids. The ¹H NMR spectra of 0.1 and 1.0 M solutions in acetone at lower temperatures revealed that the chemical shifts of H_g observed at −20 °C down to slightly above the freezing temperature of the solvent (−94 °C) were unchanged at δ = 5.944 and 5.862, which correspond to *n* values of 4.3 and 14, respectively.
- [14] A 5.0 × 10^{−1} M solution of **3** in acetone (*n* = 5.6 Table 1) was mixed with the matrix (3-nitrobenzyl alcohol) on the probe. The spectrum was immediately recorded in the positive-ion mode. The relative intensities for the [M₁ − PF₆]⁺, [M₃ − PF₆]⁺, and [M₂ − PF₆]⁺ peaks were 0.29, 1.4, and 22% of the base peak [M − PF₆]⁺, respectively.

Toposelective and Chiroselective Self-Assembly of [2 × 2] Grid-Type Inorganic Arrays Containing Different Octahedral Metallic Centers

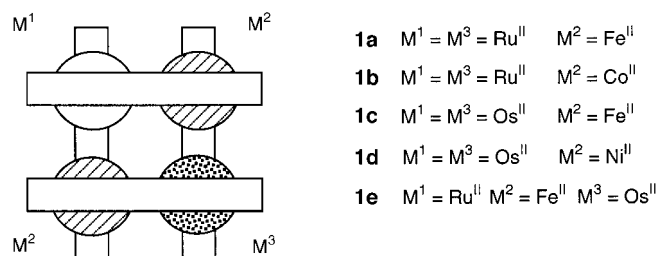
Dario M. Bassani, Jean-Marie Lehn,*
Katharina Fromm, and Dieter Fenske

The self-assembly of specific supramolecular architectures from a set of organic ligands and metal ions results from the processing of the structural information stored in the ligands by metal ions operating through the algorithm defined by their coordination geometry.^[1] It implies the design of ligands presenting suitable features (such as nature, number, and disposition of binding sites) and the choice of appropriate metal ions.

[*] Prof. Dr. J.-M. Lehn, Dr. D. M. Bassani
Laboratoire de Chimie Supramoléculaire, ISIS
Université Louis Pasteur, CNRS ESA-7006
4, rue Blaise Pascal, F-67000 Strasbourg (France)
Fax: (+33) 388-41-10-20
E-mail: lehn@chimie.u-strasbg.fr
Prof. Dr. D. Fenske, Dr. K. Fromm
Institut für Anorganische Chemie der Universität Karlsruhe
(Germany).

A great variety of complex inorganic architectures have been obtained that may be considered to follow this concept,^[1, 2] including, in our own laboratory, double- and triple-helical complexes^[1, 2b, 3, 4] as well as rack-^[5] and grid-type^[6, 7] arrays of metal ions. A higher level of complexity is reached with multicomponent self-assembly of several ligands and metal ions of different types, as in the formation of multicompartamental cylindrical cages.^[1, 2a, 8] Ligands made up of different coordination subunits may spontaneously generate species containing different metal ions at specific locations, as has been obtained, for instance, in helicates^[9] and in large multicomponent arrays.^[10]

On the other hand, there is a need for strategies providing toposelectivity, that is, strategies allowing the controlled introduction of given metal ions at specific sites and eventually in a given spatial and temporal sequence to form a complex architecture. They may involve sequential assembly procedures and/or protection/deprotection techniques. We now report such a strategy for the synthesis of the inorganic grid-type structures **1a–e**, which contain different metal ions



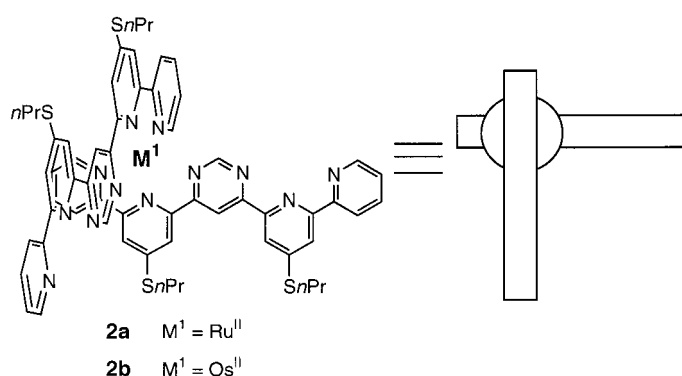
at specific locations. With four metal ions of two types, $[2 \times 2]$ grid-type structures may exist as either *anti* or *syn* topoisomers. The controlled generation of the *anti* structures **1a–d** represents an important step towards selecting and



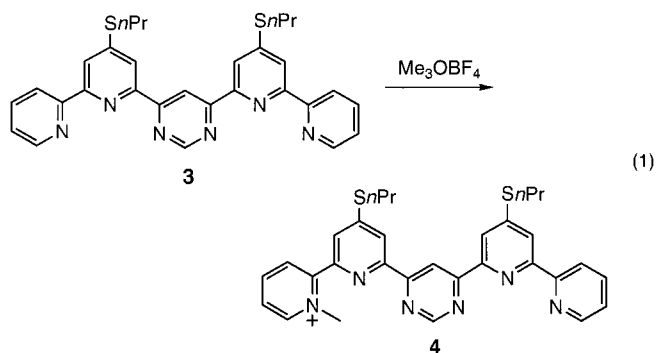
addressing individual positions in metallic arrays, and in the design of supramolecular species exhibiting tailored electrochemical, photochemical, and magnetic properties.

The self-assembly of $[2 \times 2]$ grids from ditopic ligands possessing terpyridine-like binding sites and four identical octahedral metal ions has been described.^[5] Complexes **1a–d**, which each contain two different pairs of octahedral metal ions located at opposite corners, were obtained by reaction of the corresponding ruthenium(II) or osmium(II) precursor **2a** or **2b** with a second metal ion (Fe^{II} , Co^{II} , Ni^{II}). To avoid scrambling of the metal centers, it is necessary to introduce the metal ions sequentially in order of increasing lability of the coordination center formed. For this reason, ruthenium(II) and osmium(II) were introduced first.

Different strategies were employed to obtain **2a** and **2b** from ligand **3**.^[11] In the case of **2a** it was necessary to proceed by protection of one of the two binding sites by monomethyl-



ation of **3** with trimethyloxonium tetrafluoroborate in refluxing 1,2-dichloroethane^[12] to give **4** [Eq. (1)]. Methylation of the terminal pyridine heterocycles in **3** was expected to



be favored since reaction at the internal pyridine rings is subject to steric hindrance and the pyrimidine nitrogen atoms are less nucleophilic. A small amount of ligand methylated at both terminal pyridine rings was also formed, but could be easily separated by chromatography. The reaction of **4** with $RuCl_3$ in ethanol/water followed by demethylation with excess diazabicyclo[2.2.2]octane (DABCO)^[11] in refluxing acetonitrile affords **2a** as a dark purple solid after purification by chromatography (alumina, acetonitrile/toluene 1/1).

In contrast, the reaction of ammonium hexachloroosmate with two equivalents of **3** in refluxing ethylene glycol proceeded smoothly to afford directly **2b** (40% yield after chromatography). The higher kinetic inertness of Os^{II} complexes relative to Ru^{II} complexes may allow the reaction to be stopped after complexation of one metal ion.

Addition of $Fe(BF_4)_2$ in acetonitrile to a solution of **2a** or **2b** resulted in a gradual color change from deep purple to dark green over a period of a few minutes. Isolation and purification of the complexes formed yielded **1a** and **1c** as dark green solids in 90 and 70% yield, respectively. The composition of the complexes was verified by fast atom bombardment mass spectrometry (FAB-MS), whereas the diagonal (*anti*) arrangement of the metal ions was confirmed by ^1H NMR spectroscopy, which showed different environments for the two binding sites of **3** in the complexes.^[13]

During the purification, it was noted that the complexes have an affinity for the chloride anion; the complete exchange of chloride by hexafluorophosphate counteranions required repeated precipitation from solutions of excess NH_4PF_6 . In the case of **1a**, FAB-MS analysis of the complex resulting

from incomplete anion exchange revealed the presence of at least one chloride ion which was not lost during sample ionization. The presence of chloride ions also affected the ^1H NMR spectrum, particularly the signals for H2 and H5 of the central pyrimidine ring which were considerably broadened and shifted downfield. Similar behavior was observed for **1c**. Strong binding of chloride to a pentanuclear circular helicate has been reported.^[4]

Crystals of **1a** suitable for crystallographic analysis were grown by slow diffusion of diethyl ether into a solution in acetonitrile. The resulting crystal structure^[14] (Figure 1) confirms the $[2 \times 2]$ grid structure of the complex as well as the

assembly process.^[15] The precursors **2a** and **2b** are themselves chiral and are obtained as a racemic mixture from achiral components. The formation of a grid structure in the presence of a second metal ion requires combination of two precursors of the same chirality ($R+R$ or $S+S$; Figure 2). The high

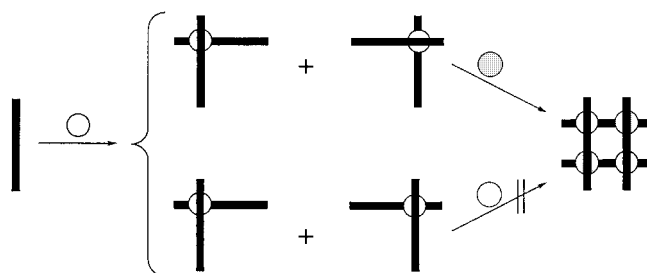


Figure 2. Generation of a $[2 \times 2]$ grid-type structure from two chiral precursors; only homochiral (top) but not heterochiral combination (bottom) leads to the grid array.

yields obtained indicate that chiral selection is efficient and that the self-assembly process is diastereoselective. The connection of an R and an S precursor into the corresponding *meso* diastereomer (R,S) is precluded for geometric reasons. It is interesting to note the analogy of the disconnection of a $[2 \times 2]$ grid structure into two substructures (of type **2**) of the same chirality to the “coupe du roi”,^[16] in which an achiral object is divided into two identical homochiral components.

Metallo-supramolecular structures combining different metal ions may be expected to display interesting optical and electrochemical behavior resulting from the predefined arrangement of the metal centers. This is the case for the grid complexes, where electronic communication between proximal metal centers is ensured by their vicinity and the presence of a bridging pyrimidine unit. Cyclic voltammetry (Table 1) of **2a** and **2b** shows a reversible oxidation wave at +1.12 and +0.92 V versus the standard calomel electrode (SCE), respectively. In the case of **2b**, complexation of Fe^{II} to form **1c** results in a second reversible oxidation wave at +1.52 V, which is assigned to the oxidation of Fe^{II} to Fe^{III} . The

Table 1. Electrochemical data for complexes **2a**, **2b**, **1a**, and **1c**.^[a]

Complex [V vs. SCE]	E^{ox} [mV]	ΔE^{ox} [V vs. SCE]	E^{red} [mV]	ΔE^{red}
2a	+1.12		−0.86 −1.03 ^[b]	
2b	+0.92		−0.82 −1.04 ^[b]	
1a	+1.32	170	−0.34 −0.40 −1.09 −1.22 −1.46 ^[b]	140
1c	+1.01 +1.52		−0.37 −0.57 −1.08 −1.19 −1.35 ^[b]	160

[a] Recorded in acetonitrile; scan rate 100 mVs^{−1}; 0.1M (*n*Bu₄N)PF₆.
[b] Stripping peak.

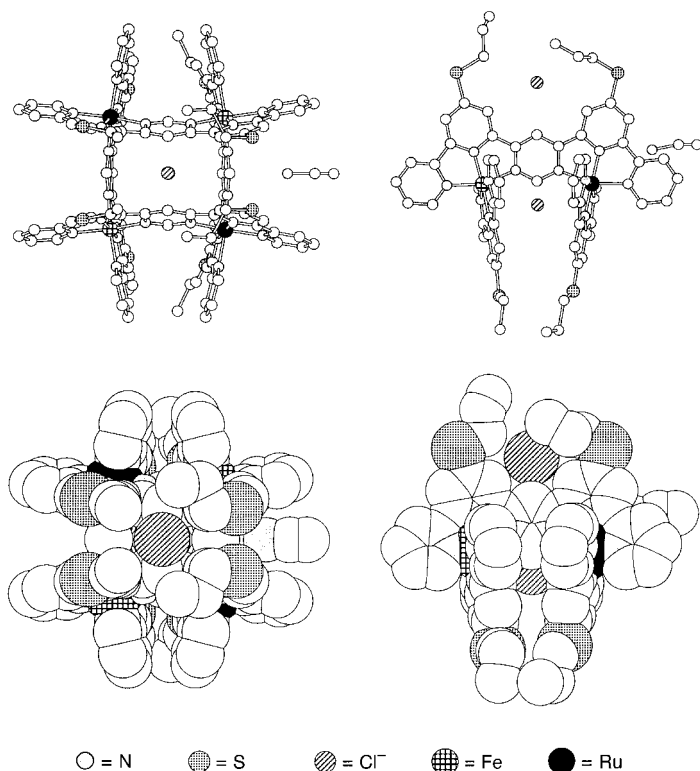


Figure 1. The molecular structure of **1a** as a ball-and-stick (top) and a space-filling representation (bottom) as viewed from the top (left) and from the side (right). Only one of the two enantiomeric forms is shown; hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Ru1–N1 1.991, Ru1–N2 1.958, Ru1–N3 2.036, Fe1–N4 2.008, Fe1–N5 1.923, Fe1–N6 2.020; N1–Ru1–N2 79.3, N2–Ru1–N3 79.2, N4–Fe1–N5 78.7, N5–Fe1–N6 80.2.

presence of two chloride anions and one acetonitrile molecule in close proximity. One of the chloride ions is situated 6.815 Å above the plane containing the four metal ions, whereas the other is buried deep within the central cavity of the structure (ca. 1.320 Å below the plane) and it is likely to be the more tightly bound of the two. Both the Ru and Fe ions are in a distorted octahedral environment in which the terminal pyridine rings are pulled in towards the metal center. Whereas $[2 \times 2]$ grid structures with four identical metal ions are achiral, **1a** is chiral and both enantiomers are present in the unit cell.

The generation of grid structures such as **1a–d** represents an interesting example of chiral selection during the self-

oxidation of the osmium centers in **1c** is shifted towards higher potentials with respect to that of $[\text{Os}^{\text{II}}(\text{terpy})_2]$ (+1.01 V; terpy = 2,2':6',2''-terpyridine) as a consequence of the presence of the Fe^{II} atoms. In contrast, only one broad oxidation wave at +1.32 V is observed for **1a**; the large separation between the forward and return sweep (170 mV) suggests that this feature consists of two closely spaced oxidation waves. In the negative potential region, ligand-based reductions are observed. A reversible wave (−0.86 and −0.82 V for **2a** and **2b**, respectively) corresponding to reduction of the pyrimidine rings is followed by a second reduction (−1.03 and −1.04 V for **2a** and **2b**, respectively) that leads to adsorption of the formally neutral complex on the electrode. Reduction of the pyrimidine groups in the grid assemblies is facilitated by the increased charge of the complex.

Recently, the $[2 \times 2]$ grids of four Co^{II} ions were shown to display molecular-based antiferromagnetic behavior.^[17] Mixed-metal grids containing Ru^{II} and Co^{II} (**1b**) and Os^{II} and Ni^{II} (**1d**) were prepared both to examine the versatility of the systems and to explore new materials possessing molecular-based magnetism. Compound **1b** was obtained as a green solid in 90 % yield from a solution of **2a** in nitromethane and $\text{Co}(\text{BF}_4)_2$. Likewise, the addition of $\text{Ni}(\text{ClO}_4)_2$ at room temperature to a solution of **2b** in acetonitrile led to the isolation of **1d** as a blue solid in 70 % yield.

The formation of multicomponent metal arrays was extended to systems containing three different metal ions arranged in a predefined order. Indeed, the addition of Fe^{II} ions to an equimolar solution of **2a** and **2b** led to the formation of **1e**, which contains one Ru^{II} and one Os^{II} ion separated by two Fe^{II} ions, as well as **1a** and **1c** in a 2:1:1 ratio. The presence of **1e** and the relative proportion of products was determined by FAB-MS and ^1H NMR spectroscopy.

The ability to introduce different metal ions at chosen positions in a metallosupramolecular array opens the way to the design of new materials possessing specific electrochemical, photochemical, and magnetic properties originating from the interaction of different metal ions held in a particular arrangement. Such systems are of much interest as inorganic supramolecular devices and components for nanotechnology. To this end, the spontaneous but directed assembly of topoisomers of different metal ions (of same or different coordination geometry) represents an important step forward. The additional binding of substrates, such as chloride anions in the central cavity, can be used to further modify their properties. Also of interest in the present self-assembly process is its diastereoselectivity, a form of chiral self-selection, which imposes the exclusive combination of homochiral components in order to form a grid structure. Extensions of the present work towards metallosupramolecular arrangements of higher order and complexity are in progress.

Received: March 30, 1998 [Z11659IE]

German version: *Angew. Chem.* **1998**, *110*, 2534–2537

Keywords: coordination chemistry • multinuclear complexes • N ligands • supramolecular chemistry • transition metals

- [1] J.-M. Lehn *Supramolecular Chemistry—Concepts and Perspectives*, VHC, Weinheim, **1995**.
- [2] a) *Comprehensive Supramolecular Chemistry*, Vol. 9 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, J.-M. Lehn), Pergamon, Oxford, **1996**; b) P. N. W. Baxter in ref. [2a], pp. 165–211; c) E. C. Constable in ref. [2a], pp. 213–252; d) M. Fujita in ref. [2a], pp. 253–282.
- [3] C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005.
- [4] a) B. Hasenknopf, J.-M. Lehn, B. O. Kneisel, G. Baum, D. Fenske, *Angew. Chem.* **1996**, *108*, 1987; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1838; b) B. Hasenknopf, J.-M. Lehn, N. Boumediene, A. Dupont-Gervais, A. Van Dorsselaer, B. Kneisel, D. Fenske, *J. Am. Chem. Soc.* **1997**, *119*, 10956.
- [5] G. S. Hanan, C. R. Arana, J.-M. Lehn, G. Baum, D. Fenske, *Chem. Eur. J.* **1996**, *2*, 1292; G. S. Hanan, C. R. Arana, J.-M. Lehn, D. Fenske, *Angew. Chem.* **1995**, *107*, 1191; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1122.
- [6] P. N. W. Baxter, J.-M. Lehn, J. Fischer, M.-T. Youinou, *Angew. Chem.* **1994**, *106*, 2432; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2284.
- [7] G. S. Hanan, D. Volkmer, U. S. Schubert, J.-M. Lehn, G. Baum, D. Fenske, *Angew. Chem.* **1997**, *109*, 1229; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1842.
- [8] P. N. W. Baxter, J.-M. Lehn, A. De Cian, J. Fischer, *Angew. Chem.* **1993**, *105*, 92; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 69; P. N. W. Baxter, J.-M. Lehn, unpublished results.
- [9] V. C. M. Smith, J.-M. Lehn, *Chem. Commun.* **1996**, 2733.
- [10] D. P. Funeriu, J.-M. Lehn, G. Baum, D. Fenske, *Chem. Eur. J.* **1997**, *3*, 99.
- [11] Synthesis of ligand **3**: D. M. Bassani, J.-M. Lehn, *Bull. Soc. Chim. Fr.* **1997**, *134*, 897.
- [12] S. Serroni, G. Denti, *Inorg. Chem.* **1992**, *31*, 4251.
- [13] Details of the synthesis and physical properties of the complexes will be published elsewhere. The analytical and spectral properties of the new compounds are in agreement with their structures.
- [14] Crystal data for **1a**: $\text{C}_{120}\text{H}_{112}\text{Fe}_2\text{Ru}_2\text{S}_8 \cdot 2\text{Cl} \cdot 6\text{PF}_6 \cdot 3\text{CH}_3\text{CN}$: data collection on a STOE IPDS diffractometer at 200 K, graphite-monochromated MoK_α radiation ($\lambda = 0.71073 \text{ \AA}$), monoclinic, space group $P2(1)/m$, $a = 17.127(3)$, $b = 29.381(6)$, $c = 18.348(4) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 105.08(3)^\circ$, $\gamma = 90^\circ$, $V = 8915(3) \text{ \AA}^3$, $Z = 2$, $\mu = 0.59 \text{ mm}^{-1}$, $F(000) = 3486$, $\rho_{\text{calc}} = 1.294 \text{ Mg m}^{-3}$, $2\theta_{\text{max}} = 52.16^\circ$, $-20 \leq h \leq 9$, $-35 \leq k \leq 30$, $-22 \leq l \leq 22$. Structure solution and refinement: A total of 23755 reflections were collected. Of 12527 independent reflections [$R(\text{int}) = 0.1231$], 12526 were used to fit 368 parameters. The structure was refined against F^2 (full-matrix least squares), GOF on $F^2 = S = 1.073$, $R1 = 0.1675$ [$R1 = 0.2250$ (all data)], $wR2 = 0.4523$ [$wR2 = 0.5358$ (all data)], max./min. residual density: $+1.556/-1.877 \text{ e \AA}^{-3}$. Owing to the presence of both enantiomers, the metal positions were calculated as a 1:1 mixture of Fe and Ru, which led to a centrosymmetric space group. The whole cationic structure was refined isotropically. All atoms in rings (except for central pyrimidines) are calculated as pertaining to a regular hexagon. The solvent and anionic parts of the structure show severe disorder and were refined isotropically on split positions except for the chlorine anions, which were refined anisotropically. All hydrogen positions are calculated. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101 633. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [15] W. Zarges, J. Hall, J.-M. Lehn, C. Bolm *Helv. Chim. Acta* **1991**, *74*, 1843.
- [16] R. Glaser, *Struct. Chem.* **1990**, *2*, 479; *Chirality* **1993**, *5*, 272.
- [17] O. Waldmann, J. Hassmann, P. Müller, G. S. Hanan, D. Volkmer, U. S. Schubert, J.-M. Lehn, *Phys. Rev. Lett.* **1997**, *78*, 3390.

A Tethered Porphyrin Dimer with π Overlap of a Single Pyrrole Ring

Spencer Knapp,* Jayasree Vasudevan, Thomas J. Emge, Byron H. Arison, Joseph A. Potenza,* and Harvey J. Schugar*

A “special pair” of π -interacting bacteriochlorophyll chromophores serves as the central electronic feature of the bacterial photosystem.^[1] It is unique among its accompanying antenna and accessory pigments in that full π overlap is limited to the pyrrole 1-rings.^[2] We report here the synthesis and spectroscopic characterization of **1**, a model system of the special pair (Figure 1). This amine-tethered zinc(II) porphyrin dimer exhibits mutual π overlap that is likewise limited to a single pyrrole ring.

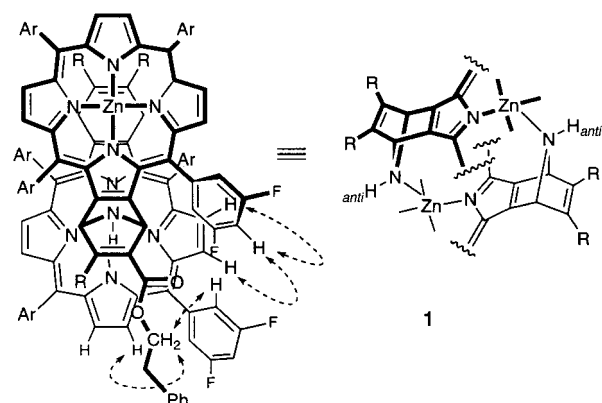


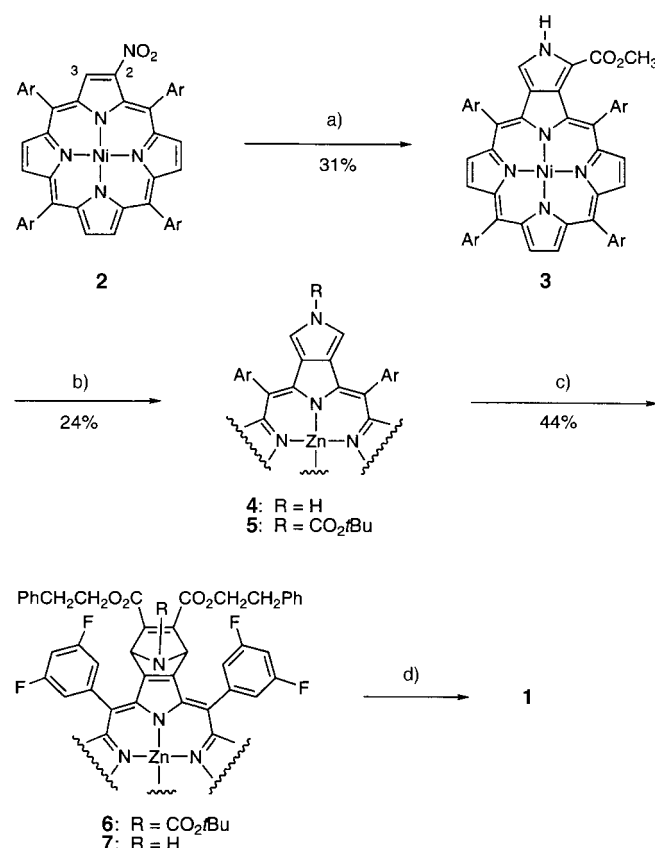
Figure 1. Top view of dimer **1** along with a side view of the partial structure. The inter-subunit contacts, as indicated by the 2D-ROESY NMR experiment for a solution of **1** in CDCl_3 , are marked with dashed arrows. Ar = 3,5-difluorophenyl, R = 2-phenylethoxycarbonyl.

Dimers of zinc(II) porphyrin^[3, 4] and bacteriochlorin^[5] have been assembled by attaching a zinc-ligating heterocyclic substituent such as 2-pyridyl or 2-imidazolyl to a peripheral carbon atom of the chromophore. The natural tendency of porphyrinoids to π stack in parallel planes about 3.2 Å apart,^[6] as well as the length, orientation, and point of attachment of the ligating tether, serve to position the π systems of the two rings in a stable dimeric arrangement that can be studied in solution. Overlapping component pigments in the bacterial photosystem possess spectroscopic and electronic characteristics critical for photosynthesis, such as red-shifted Q_y bands and perhaps unobserved features hidden by intense higher energy absorbances due to auxillary pigments.^[7] There is therefore an impetus to construct and evaluate model dimers with similar π overlap of a single pyrrole ring.

[*] Prof. Dr. S. Knapp, Prof. Dr. J. A. Potenza, Prof. Dr. H. J. Schugar, Dr. J. Vasudevan, Dr. T. J. Emge
Department of Chemistry
Rutgers—The State University of New Jersey
610 Taylor Road, Piscataway, NJ 08854-8087 (USA)
Fax: (+1) 732-445-5312
E-mail: knapp@rutchem.rutgers.edu
Dr. B. H. Arison
Merck Research Laboratories, Rahway, NJ (USA)

For the zinc(II) porphyrin/bacteriochlorin dimer system, this reduces to attaching a zinc-ligating atom along an axis through the midpoint of the C2–C3 bond (see **2**), with its lone pair of electrons positioned several angstroms outside of and above the π perimeter to interact with the zinc atom of the partner chromophore. These requirements are met by a 7-azabicyclo[2.2.1]heptadiene framework fused at C2–C3 of the porphyrin ring.

Nitration^[8] of [5,10,15,20-tetrakis(3,5-difluorophenyl)porphyrinato]nickel(II)^[3, 9] (81% yield, Scheme 1) gave the



Scheme 1. Synthesis of **1**. Ar = 3,5-difluorophenyl. a) $\text{CNCH}_2\text{CO}_2\text{CH}_3$, 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), THF, *t*BuOH, 15 min, reflux; b) 1.1% H_2SO_4 in TFA, room temperature (RT), 1 h; 2. $\text{Zn}(\text{OAc})_2$, MeOH, CH_2Cl_2 , RT, 10 min; 3. LiCl, DMSO, 3 h, reflux; 4. $(\text{BOC})_2\text{O}$, DMAP, CH_2Cl_2 , 5 min; c) 1. bis(2-phenylethyl) acetylenedicarboxylate, toluene, 15 min, reflux; 2. 10% TFA in CH_2Cl_2 , 0°C, 4 h; 3. $\text{Zn}(\text{OAc})_2$, MeOH, CH_2Cl_2 , RT, 15 min; d) spontaneous dimerization in solution.

mononitro derivative **2**, which was subjected to a Barton–Zard procedure^[10] to deliver the pyrroloporphyrin **3**. Replacement^[11] of Ni^{II} with Zn^{II} and subsequent decarboxylation^[12] led to **4**, which was further converted into the *N*-BOC derivative **5** (*N*-Boc = *tert*-butoxycarbonyl). Thereby activated,^[13] this diene reacted with bis(2-phenylethyl) acetylenedicarboxylate^[14] to give the Diels–Alder adduct **6** (the phenylethyl groups were chosen to improve the solubility of the dimer). Removal of the BOC group with trifluoroacetic acid (TFA) resulted in loss of Zn^{II} as well, but the metal was subsequently reintroduced to provide the required amino-tethered porphyrin **7**.

Several lines of evidence indicate that **7** dimerizes in solution to afford the overlapped structure **1**. Osmometric molecular weight determination of a solution in CHCl_3 (13.13 mg in 3 mL) gave $M_r = 2304$ (calcd for $\text{C}_{132}\text{H}_{78}\text{F}_{16}\text{N}_{10}\text{O}_8\text{Zn}_2$: 2367). The UV/Vis spectrum (5.1 mg mL^{-1} , Figure 2) shows a Q-band region that matches

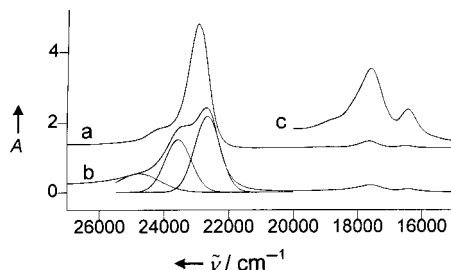


Figure 2. UV/Vis spectra (CHCl_3 , 25°C): a) **7**·DMAP (reference monomer; $[\mathbf{7}] = 5 \times 10^{-4} \text{ M}$, $[\text{DMAP}] = 5 \times 10^{-3} \text{ M}$, path length 0.016 cm, offset $A+1.3$); b) **1** ($4.3 \times 10^{-3} \text{ M}$, path length 0.0027 cm) from the dimerization of **7**; c) Q-band absorptions of **1** as in b), enlarged ten times.

that of typical five-coordinate zinc(II) porphyrins, but also a strongly split Soret band, which is indicative of close π interaction between porphyrin units.^[15] The 400-MHz ^1H NMR spectrum of a solution of **1** in CDCl_3 (2 mg in 0.5 mL) at 23°C shows signals for a single species. Included are several resonances for strongly shielded centers, which are assignable to protons in the vicinity of the amino nitrogen atom: The signal for the amino protons appears at $\delta = -2.01$, that for the bridgehead H atoms at -0.05 , and that for the ester α -methylene protons at 3.40. Upon addition of five equivalents of 4-(*N,N*-dimethylamino)pyridine (DMAP) to the solution in CDCl_3 (DMAP disrupts zinc(II) porphyrin/amino ligation^[3]), the corresponding resonances appear at positions expected for the DMAP-coordinated monomer (e.g., bridgehead protons at $\delta = 4.94$, α -methylene protons at $\delta = 4.22$).

A 2D-ROESY NMR experiment^[4, 16] performed at -10°C allowed the unambiguous assignment of all resonances. The nature of the overlap of the subunits in **1** is indicated by the pattern of shielding in which signals for protons closer to the coordinating amine appear at significantly higher field than those for otherwise similar protons. Most conclusively, inter-subunit crosspeaks (Figure 1) indicate the through-space proximity of the ester α -methylene protons of one subunit to the (otherwise) remote pyrrole protons and *endo-ortho*-protons of the aryl rings of the other subunit, and also the proximity in the dimer of the remaining pyrrole protons to the *para*-protons of the overlying aryl substituents of the partner subunit.

Gaussian deconvolution^[17] of the electronic spectrum for a solution of **1** in CHCl_3 (Figure 2) reveals that the prominent Soret absorption seen for the reference monomer **7**·DMAP at 22900 cm^{-1} is split (23600 , 22700 cm^{-1}). The observed splitting of about 900 cm^{-1} is comparable to the range (890 – 1040 cm^{-1}) previously observed for self-coordinating porphyrin dimers whose overlapped region comprises an entire edge (the β -carbon atoms of two pyrrole rings and their connecting *meso*-carbon atom).^[4]

In the region of the Q bands the spectra of **7**·DMAP and the dimer **1** are qualitatively similar.^[17, 18] More concentrated solutions of **1** (5.1 – 12.9 mg mL^{-1}) show increased intensities for all absorbances according to Beer's Law, whereas stepwise dilution of **1** to 0.026 mg mL^{-1} caused the emergence of blue-shifted Q bands at 19200 , 18200 , and 17200 cm^{-1} , which are diagnostic for the four-coordinate zinc(II) porphyrin monomer **7**.^[19]

Attempts to grow crystals of **1** with a wide variety of solvents and solvent mixtures were unsuccessful. However, the cyclic zinc(II) porphyrin hexamer **8** (Figure 3) was

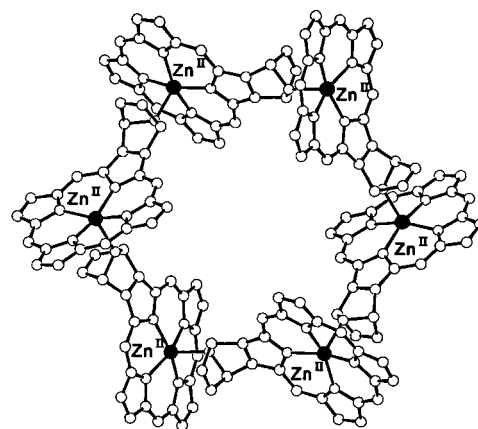


Figure 3. Ball-and-stick view of the hexameric units in crystals of **8** along the threefold inversion axis. Hydrogen atoms, ester groups, difluorophenyl groups, and solvate molecules have been omitted for clarity.

obtained as red rhomboids by slow evaporation of a solution of dimer **1** in *p*-xylene/ CHCl_3 (1/1).^[20] Each zinc atom of the hexamer is apically coordinated to the secondary amino nitrogen atom of an adjoining monomer unit **7** to afford a square-pyramidal geometry similar to that in self-coordinating zinc(II) porphyrin and bacteriochlorin dimers.^[4, 5] In contrast to the dimers, in which the porphyrin planes are approximately parallel and in π contact, the hexamer **8** features adjoining porphyrin ring π systems that are approximately orthogonal (Figure 4). This geometry is reminiscent of that in a polymeric oligomer of [10,15,20-triphenyl-5-(4-pyridyl)porphyrinato]zinc(II)^[22] and in other metalloporphyr-

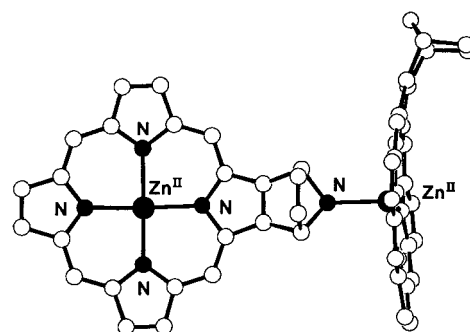


Figure 4. Ball-and-stick view of two adjoining porphyrin units in the hexameric crown in crystals of **8** approximately normal to one of the porphyrin planes.

ins.^[23] Such orthogonal porphyrin systems do not show splitting of the Soret absorptions.^[22, 23]

Dimer **1** and hexamer **8** also differ fundamentally in that the former features zinc coordination by the amino lone pair *syn* to the porphyrin ring (the N–H bond is *anti*), whereas the lone pair in the latter is coordinated in an *anti* position (the N–H bond is *syn*). As a consequence, hexamer **8** cannot arise directly from trimerization of dimer **1**, but instead both structures must come from monomer **7**. Crystals of **8** dissolve in CDCl₃ to reform **1**, according to the NMR spectrum. The degree of aggregation of **7** is thus phase-, concentration-, and additive-dependent.

Structural variations in partially π -overlapped porphyrin dimers now include the modes pyrrole-over-pyrrole (**1**), edge-over-edge,^[3, 4] and pyrrole-over-edge.^[4] The consequences for the electronic spectra for the first two modes are similar: split Soret absorptions and relatively unaffected Q bands. In contrast, the pyrrole-over-edge dimer^[4] exhibits unusually broad Soret absorptions and a slightly split low-energy Q band. A detailed understanding of the origin of these structure-dependent effects is needed, but lacking at present. The structural dependences of other photophysical properties (e.g., fluorescence polarization, resonance Raman effects) of these dimers and their radical cations also remain to be determined.

Received: January 5, 1998

Revised version: April 20, 1998 [Z 11327 IE]

German version: *Angew. Chem.* **1998**, *110*, 2537–2540

Keywords: N ligands • NMR spectroscopy • photosynthesis • porphyrinoids • UV/Vis spectroscopy

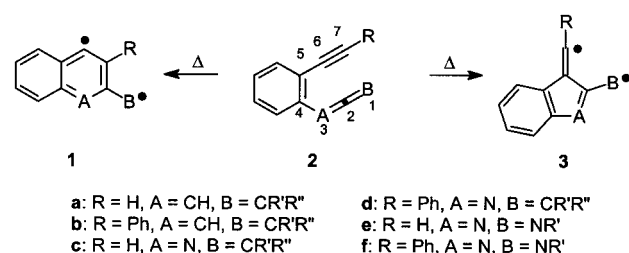
- [1] a) J. Deisenhofer, H. Michel, *Science* **1989**, *245*, 1463–1473; J. Deisenhofer, H. Michel, *Angew. Chem.* **1989**, *101*, 872–892; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 829–847; b) J. P. Allen, G. Feher, T. O. Yeates, H. Komiya, D. C. Rees, *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 8487–8491.
- [2] a) G. McDermott, S. M. Prince, A. A. Freer, A. M. Hawthornthwaite-Lawless, M. Z. Papiz, R. J. Cogdell, N. W. Isaacs, *Nature* **1995**, *374*, 517–521; b) J. Koepke, X. Hu, C. Muenke, K. Schulten, H. Michel, *Structure* **1996**, *4*, 581–597; c) H. Savage, M. Cyrklaff, G. Montoya, W. Kühlbrandt, I. Sinning, *Structure* **1996**, *4*, 243–252.
- [3] Y. Kobuke, H. Miyaji, *J. Am. Chem. Soc.* **1994**, *116*, 4111–4112.
- [4] R. T. Stibrany, J. Vasudevan, S. Knapp, J. A. Potenza, T. Emge, H. J. Schugar, *J. Am. Chem. Soc.* **1996**, *118*, 3980–3981.
- [5] J. Vasudevan, R. T. Stibrany, J. Bumby, S. Knapp, J. A. Potenza, T. J. Emge, H. J. Schugar, *J. Am. Chem. Soc.* **1996**, *118*, 11676–11677.
- [6] W. R. Scheidt, Y. J. Lee, *Struct. Bonding (Berlin)* **1987**, *64*, 1–70.
- [7] Possibilities of masked absorptions include higher energy Q bands, Soret bands, and predicted “charge-resonance” absorptions. For a discussion of the latter absorptions, see E. J. P. Lathrop, R. A. Freisner, *J. Phys. Chem.* **1994**, *98*, 3056–3066.
- [8] M. M. Catalano, M. J. Crossley, M. M. Harding, L. G. King, *J. Chem. Soc. Chem. Commun.* **1984**, 1535–1536.
- [9] A. D. Adler, F. R. Longo, F. Kampas, J. Kim, *J. Inorg. Nucl. Chem.* **1970**, *32*, 2443–2445.
- [10] a) D. H. R. Barton, J. Kervagoret, S. Z. Zard, *Tetrahedron* **1990**, *46*, 7587–7598; b) L. Jaquinod, C. Gros, M. M. Olmstead, M. Antolovich, K. M. Smith, *J. Chem. Soc. Chem. Commun.* **1996**, 1475–1476.
- [11] H. Callot, *Bull. Soc. Chim. Fr.* **1974**, *41*, 1492–1496.
- [12] J. Tang, J. G. Verkade, *J. Org. Chem.* **1994**, *59*, 7793–7802.
- [13] N. W. Gabel, *J. Org. Soc.* **1962**, *27*, 301–303.
- [14] L. Verbit, R. L. Tuggey, *Mol. Cryst. Liq. Cryst.* **1972**, *17*, 49–54.
- [15] a) M. A. Thompson, M. C. Zerner, J. Fajer, *J. Phys. Chem.* **1991**, *95*, 5693–5700; b) M. A. Thompson, G. K. Schenter, *J. Phys. Chem.* **1995**, *99*, 6374–6386.
- [16] H. Kessler, C. Griesinger, R. Kerssebaum, K. Wagner, R. Ernst, *J. Am. Chem. Soc.* **1987**, *109*, 607–609.
- [17] Gaussian-deconvoluted UV/Vis spectra: **7**·DMAP: λ_{max} [cm⁻¹] ($\epsilon \times 10^{-3}$ mol cm⁻¹) = 23 800 (60), 22 900 (400), 18 800 (3), 17 900 (22), 16 500 (7); **1** (ϵ calcd based on the concentration of Zn^{II}): 24 880 (46), 23 600 (130), 22 700 (180), 18 700 (5), 17 600 (17), 16 400 (7).
- [18] Less splitting of the relatively weak Q bands is predicted by the excitonic coupling model: M. Kasha, H. R. Rawls, M. A. El-Bayoumi, *Pure Appl. Chem.* **1965**, *11*, 371–392.
- [19] K. M. Kadish, L. R. Shiue, *Inorg. Chem.* **1982**, *21*, 3623–3630.
- [20] Crystals of **8** were fragile and unstable in the absence of mother liquor. A crystal (0.64 × 0.64 × 0.18 mm) was mounted in a glass capillary along with mother liquor (separated from the crystal). Data were collected at 297 K (CAD-4 diffractometer, rotating Cu anode, Cu α radiation, λ = 1.5418 Å). Attempts to collect data at low temperature were unsuccessful owing to crystal fracture. Crystal data: C₆₆H₃₉N₅O₄F₈Zn · 2.5 C₈H₁₀ · 0.2 CHCl₃; M_r = 1472.67, trigonal, space group $R\bar{3}$ (no. 148), a = 42.183(4), c = 21.849(2) Å, V = 33 670(5) Å³, Z = 18, ρ_{calcd} = 1.307 g cm⁻³; of 10 108 reflections ($2 < \theta < 42^\circ$), 5120 were unique and 3211 with $I > 2\sigma(I)$. Data were corrected for Lorentz, polarization, and absorption (numerical, SHELX-76^[21a]) effects. The structure was solved by the heavy-atom method SHELXS-86^[21b] and refined on F^2 with all unique data. Disorder in the difluorophenyl and ester groups and the presence of loosely bound solvates necessitated use of distance and displacement parameter restraints. The restraints used do not appear severe, and the central zinc(II) porphyrin portion of the structure does not appear to be disordered. Refinement (SHELXL-97^[21c]) 5120 data, 973 parameters, 820 restraints) gave R_F = 0.062 [$I > 2\sigma(I)$], wR_F = 0.150 (all data), GOF = 0.94. A final difference map showed excursions of –0.3 to 0.3 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-100 975. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [21] a) G. M. Sheldrick, *SHELX76 Program for Crystal Structure Determination*, University of Cambridge, UK, **1976**; b) G. M. Sheldrick, *SHELX86 Program for the Solution of Crystal Structures*, Universität Göttingen, Germany, **1986**; c) G. M. Sheldrick, *SHELXL97 Program for Crystal Structure Refinement*, Universität Göttingen, Germany, **1997**.
- [22] E. B. Fleischer, A. M. Shacter, *Inorg. Chem.* **1991**, *30*, 3763–3769.
- [23] Some recent examples: a) A. K. Burrell, D. L. Officer, D. C. W. Reid, K. Y. Wild, *Angew. Chem.* **1998**, *110*, 122–125; *Angew. Chem. Int. Ed.* **1998**, *37*, 114–117; b) R. K. Kumar, S. Balasubramanian, I. Goldberg, *Inorg. Chem.* **1998**, *37*, 541–552; c) N. Kariya, T. Imamura, Y. Sasaki, *Inorg. Chem.* **1997**, *36*, 833–839; d) K. Funatsu, A. Kimura, T. Imamura, A. Ichimura, Y. Sasaki, *Inorg. Chem.* **1997**, *36*, 1625–1635; e) X. Chi, A. J. Guerin, R. A. Haycock, C. A. Hunter, L. D. Sarson, *J. Chem. Soc. Chem. Commun.* **1995**, 2563–2565; f) X. Chi, A. J. Guerin, R. A. Haycock, C. A. Hunter, L. D. Sarson, *J. Chem. Soc. Chem. Commun.* **1995**, 2567–2569; g) S. Anderson, H. L. Anderson, A. Bashall, M. McPartlin, J. K. M. Sanders, *Angew. Chem.* **1995**, *107*, 1196–1200; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1096–1099; h) M. O. Senge, K. M. Smith, *J. Chem. Soc. Chem. Commun.* **1994**, 923–924; i) C. M. Drain, J.-M. Lehn, *J. Chem. Soc. Chem. Commun.* **1994**, 2313–2315.

Two Novel Thermal Biradical Cyclizations in Theory and Experiment: New Synthetic Routes to 6*H*-Indolo[2,3-*b*]quinolines and 2-Aminoquinolines from Enyne-Carbodiimides**

Michael Schmittel,* Jens-Peter Steffen, Bernd Engels,* Christian Lennartz, and Michael Hanrath

In memory of Reimund Stadler

We have recently become interested in controlling the regioselectivity of biradical cyclizations as a function of substituents. As a result, the novel thermal biradical C²–C⁶ cyclization^[1] of enyne-allenes **2b**→**3b** was established when aryl substituents (R = Ph) are attached at the alkyne terminus. This cyclization behavior contrasts the regiochemistry of the well-known Myers–Saito (C²–C⁷) cycloaromatization^[2] **2a**→**1a** (Scheme 1). The biradical intermediate **3b** has several



Scheme 1. Biradical intermediates of the thermal C²–C⁷ (**1**) and C²–C⁶ cyclization (**3**) of **2**.

options—depending on R' and R''—for efficient intramolecular follow-up reactions (to formal [4+2]^[3] and [2+2] cycloadducts^[4] and ene products^[5]), which makes it a versatile intermediate for the construction of various ring systems.^[6]

A similar switch in the regioselectivity of biradical cyclizations has been demonstrated with heteroanalogous enyne-allenes, such as enyne-ketenes^[7] and enyne-ketenimines **2c,d**,^[8] that undergo C²–C⁷ and C²–C⁶ cyclizations as a function of substituents at the alkyne terminus. Herein, we report that theoretical and experimental evidence points to the occurrence of equivalent biradical cyclizations in enyne-carbodiimides **2e,f**, which makes them versatile precursors to interesting heterocyclic systems.

To study the influence of substituents at the alkyne terminus on the cyclization behavior of the enyne-carbodi-

imides we have carried out quantum-chemical calculations. A correct description of biradical intermediates needs a multi-reference approach.^[9] However, because the biradical nature of the wavefunction develops only beyond the transition state (TS)—that is, in the density functional theory (DFT) calculations [S²] = 0 was found for all TSs—the influence of substituents on the activation energy (Δ*E*[‡]) of both processes can be obtained from DFT calculations.^[1b] Consequently, activation energies were determined with the density functional approach in combination with a 6-31G* AO basis set, while a multireference configuration interaction (MR-CI) approach was used for the computation of the reaction energies (Δ*E*[‡]).^[10, 11]

The theoretical results summarized in Table 1 suggest—as for enyne-allenes^[1b] and enyne-ketenimines^[8]—a switch in the

Table 1. Summary of the calculated data. While the energies of the reactants are given in Hartree, the energies computed for the other structures are presented relative to that of the reactants in kcal mol^{–1}. The energies of the TSs are in boldface. Distances *R* are given in Å.

Substituent	e: R = H	f: R = Ph
reactant 2 (R' = H) ^[a,b]	–455.976797	–687.047232
reactant 2 (R' = H) ^[a,c]	–454.538468	–
C ² –C ⁷ cyclization		
<i>R</i> _{C²–C⁷} = 2.0 ^[b]	26	30
<i>R</i> _{C²–C⁷} = 1.8 ^[b]	31	37
<i>R</i> _{C²–C⁷} = 1.66 ^[b]	26	32
<i>R</i> _{C²–C⁷} = 1.43 (1 , R' = H) ^[c,d]	24	22 ^[e]
C ² –C ⁶ cyclization		
<i>R</i> _{C²–C⁶} = 2.0 ^[b]	28	25
<i>R</i> _{C²–C⁶} = 1.8 ^[b]	39	32
<i>R</i> _{C²–C⁶} = 1.68 ^[b]	36	31
<i>R</i> _{C²–C⁶} = 1.53 (3 , R' = H) ^[c,d]	33	22 ^[e]

[a] *R*_{C²–C⁷} = 3.41 Å, *R*_{C²–C⁶} = 2.97 Å. [b] DFT(B3LYP) in combination with a 6-31G* basis set. [c] MR-CI+Q in combination with a double zeta polarization (DZP) basis set. [d] Biradical intermediate. [e] Reference [11].

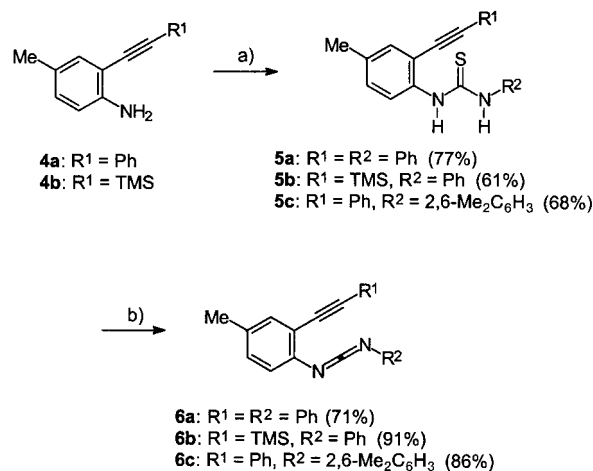
regioselectivity of the enyne-carbodiimide cyclization as a function of group R at the alkyne terminus. For R = R' = H our calculations predict an activation barrier (Δ*E*[‡]) of 31 kcal mol^{–1} for the C²–C⁷ cyclization of **2e** to **1e**, which is much lower than that for the C²–C⁶ cyclization to **3e** (Δ*E*[‡] = 39 kcal mol^{–1}). However, if R = H is replaced by R = Ph (R' = H) the activation barrier is increased to 37 kcal mol^{–1} for the C²–C⁷ cyclization **2f**→**1f**, whereas it is decisively lowered for the C²–C⁶ cyclization of **2f** to **3f** (Δ*E*[‡] = 32 kcal mol^{–1}). As such the calculations propose that the reaction switch is even more pronounced than with the corresponding enyne-allenes.^[1b]

However, the MR-CI calculations indicate that both biradical cyclizations of enyne-carbodiimides are strongly endothermic (Table 1), which is in contrast to the situation with enyne-allenes^[1b] and enyne-ketenimines.^[8] Since both intermediates **1e,f** and **3e,f** constitute (σ,π)-biradical intermediates such as **1a–d** and **3a–d**, the reason for the difference in reaction energies is not yet clear. Hence, from the above calculations it is not obvious whether the cyclization will be operating under kinetic control despite the fast follow-up reactions of **1e,f** and **3e,f** (*k* > 10⁶ s^{–1}).^[12]

[*] Prof. Dr. M. Schmittel, Dipl.-Chem. J.-P. Steffen
 Institut für Organische Chemie der Universität
 Am Hubland, D-97074 Würzburg (Germany)
 Telefax: (+49) 931-888-4606
 E-mail: mjls@chemie.uni-wuerzburg.de
 Priv.-Doz. Dr. B. Engels, Dipl.-Chem. C. Lennartz,
 Dipl.-Chem. M. Hanrath
 Institut für Physikalische und Theoretische Chemie der Universität
 Wegelerstrasse 12, D-53115 Bonn (Germany)
 Telefax: (+49) 228-73-9066
 E-mail: bernd@rs5.thch.uni-bonn.de

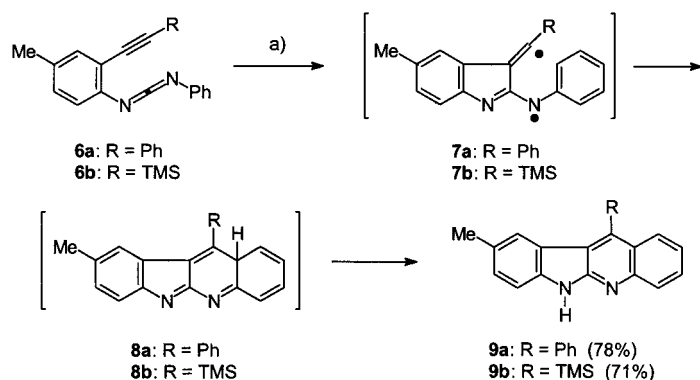
[**] Thermal and Electron Transfer Induced Reactions of Enediyne and Enyne-Allenenes, part 13. We gratefully acknowledge the financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 12: reference [8].

To probe the reaction switch experimentally enyne-carbodiimides **6a–c** were prepared from **4a,b** via thioureas **5a–c**^[13] by a procedure described by Fell and Coppola^[14] (Scheme 2). Compounds **6a–c**, which were fully characterized by standard spectroscopic means, constitute the first isolated members of this new class of heteroanalogues of enyne-allenes.^[15]



Scheme 2. Synthesis of enyne-carbodiimides **6a–c**. a) **5a**: R²NCS, EtOH, RT, 6 d, 35 °C, 10 min; **5b**: DMAP, acetone, 50 °C, 4.5 d; **5c**: acetone, reflux, 16 h; b) CH₃SO₂Cl, DMAP, NEt₃, CH₂Cl₂, 0 °C, 5 min.

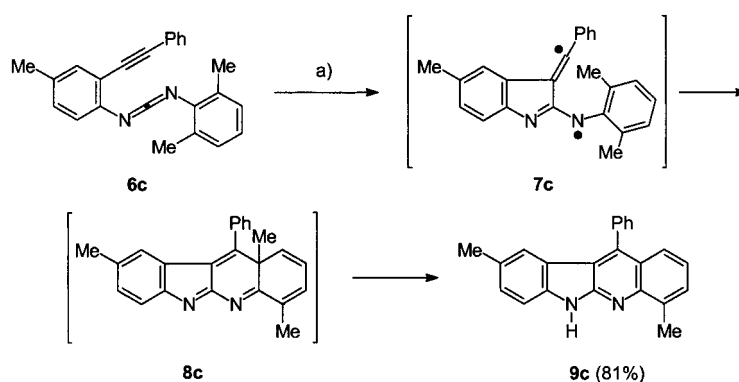
The thermal behavior of **6a,b** was investigated with differential scanning calorimetry (DSC). The enyne-carbodiimides exhibited an overall exothermic reaction, with the heat evolution starting at 97 °C (**6a**) and 166 °C (**6b**). Thermolysis of **6** (in toluene at reflux temperature) and **6b** (in mesitylene at reflux temperature) led to the formation of the 6*H*-indolo[2,3-*b*]quinolines **9a** and **9b** in 78 and 71 % yield, respectively (Scheme 3). Hence, the thermal reaction of **6a, b** proceeds analogously to the cyclization of phenyl- or trimethylsilyl-substituted enyne-allenes,^[4a, 6b, 12a] and it is tempting to rationalize the formation of **9a** and **9b** by an initial biradical cyclization via **7a, b** followed by intramolecular cyclization to **8a, b** and subsequent tautomerization.



Scheme 3. Synthesis of 6*H*-indolo[2,3-*b*]quinolines **9a, b**. a) **9a**: 1,4-cyclohexadiene, toluene, reflux, 6 h; **9b**: 1,4-cyclohexadiene, mesitylene, reflux, 18 h.

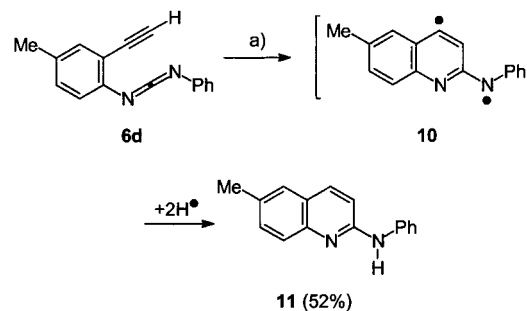
Nevertheless, formation of **9** cannot be regarded as a rigorous proof for the occurrence of a biradical cyclization via **7**, since it could have been formed in a concerted Diels–Alder reaction **6**→**8**.^[15, 16]

To rigorously test for a biradical intermediate the phenyl ring at the carbodiimide terminus in **6a** was replaced by a 2,6-dimethylphenyl group, because it is well established that in concerted Diels–Alder reactions *ortho*-alkyl substituents are prohibitive owing to steric hindrance.^[15b, 17] Despite the presence of the *ortho*-methylated phenyl group the thermal reaction of **6c** afforded as the only product the 6*H*-indolo[2,3-*b*]quinoline **9c** (81 %) at only slightly higher temperature (DSC: 118 °C for **6c**) than for the cyclization of **6a** (DSC: 97 °C). Certainly, such a behavior is in compliance with a rate-determining biradical cyclization to intermediate **7c** (Scheme 4), but not with a concerted Diels–Alder cycloaddition. Just as **7a, b**, biradical **7c** closes to the formal Diels–Alder cycloadduct **8c**, which subsequently loses a methyl group after protonation at the nitrogen atom in a S_N2-type reaction.^[8]



Scheme 4. Thermolysis of enyne-carbodiimide **6c**. a) 1,4-cyclohexadiene, toluene, reflux, 2 h.

After we had established a C²–C⁶ biradical cyclization in enyne-carbodiimides **6a–c**, we synthesized **6d** with a hydrogen atom at the alkyne terminus to experimentally check for the predicted C²–C⁷ biradical cyclization **2e**→**1e**. Compound **6d** was prepared along the same route as **6a–c** via the corresponding thiourea and fully characterized. Thermolysis of **6d** in toluene (1,4-cyclohexadiene as hydrogen donor) at 90–100 °C (DSC: 90 °C) afforded **11** in 52 % yield (Scheme 5),



Scheme 5. C²–C⁷ cycloaromatization of enyne-carbodiimide **6d**. a) 1,4-cyclohexadiene, toluene, 90–100 °C, 20 h.

but no C²–C⁶ cyclization product (detection limit 5%). The 2-aminoquinoline **11** is clearly derived from biradical **10** through hydrogen abstraction, which is indicative of a novel C²–C⁷ biradical cyclization in enyne-carbodiimides.

In conclusion, we have provided theoretical and experimental evidence for two novel biradical cyclizations triggered thermally from enyne-carbodiimides. The C²–C⁶ cyclization pathway via an azafulvene amine biradical is operative with aryl and trimethylsilyl groups at the alkyne terminus, and opens the way to a convenient synthesis of substituted 6H-indolo[2,3-*b*]quinolines with interesting pharmacological activity.^[18] Conversely, the presence of a hydrogen atom at the alkyne terminus leads to the C²–C⁷ cyclization. The fact that a clean switch between C²–C⁶ and C²–C⁷ cyclizations can now be effected in enyne-allenes, enyne-ketenes, enyne-ketenimines, and enyne-carbodiimides points to a rather general, hitherto little known motif to control the regioselectivity of biradical cyclizations.

Received: March 23, 1998 [Z11625IE]

German version: *Angew. Chem.* **1998**, *110*, 2531–2533

Keywords: carbodiimides • cycloaromatizations • diradicals • enynes • quantum chemical calculations

- [1] a) M. Schmittel, M. Strittmatter, S. Kiau, *Angew. Chem.* **1996**, *108*, 1952–1954; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1843–1845; b) B. Engels, C. Lennartz, M. Hanrath, M. Schmittel, M. Strittmatter, *Angew. Chem.* **1998**, *110*, 2067–2070; *Angew. Chem. Int. Ed.* **1998**, *37*, 1960–1963.
- [2] a) A. G. Myers, E. Y. Kuo, N. S. Finney, *J. Am. Chem. Soc.* **1989**, *111*, 8057–8059; b) R. Nagata, H. Yamanaka, E. Okazaki, I. Saito, *Tetrahedron Lett.* **1989**, *30*, 4995–4998; reviews: c) K. K. Wang, *Chem. Rev.* **1996**, *96*, 207–222; d) J. W. Grissom, G. U. Gunawardena, D. Klingberg, D. Huang, *Tetrahedron* **1996**, *52*, 6453–6518.
- [3] M. Schmittel, M. Strittmatter, K. Vollmann, S. Kiau, *Tetrahedron Lett.* **1996**, *37*, 999–1002.
- [4] a) T. Gillmann, T. Hülsen, W. Massa, S. Wocadlo, *Synlett* **1995**, 1257–1259; b) J. G. Garcia, B. Ramos, L. M. Pratt, A. Rodríguez, *Tetrahedron Lett.* **1995**, *36*, 7391–7394.
- [5] M. Schmittel, M. Strittmatter, S. Kiau, *Tetrahedron Lett.* **1995**, *36*, 4975–4978.
- [6] a) M. Schmittel, S. Kiau, *Liebigs Ann.* **1997**, 733–736; b) M. Schmittel, M. Maywald, M. Strittmatter, *Synlett* **1997**, 165–166; c) M. Schmittel, J.-P. Steffen, I. Bohn, *Heterocycl. Commun.* **1997**, *3*, 443–447; d) M. Schmittel, J.-P. Steffen, D. Auer, M. Maywald, *Tetrahedron Lett.* **1997**, *38*, 6177–6180; e) Ó. de Frutos, A. M. Echavarren, *Tetrahedron Lett.* **1997**, *38*, 7941–7942.
- [7] L. D. Foland, J. O. Karlsson, S. T. Perri, R. Schwabe, S. L. Xu, S. Patil, H. W. Moore, *J. Am. Chem. Soc.* **1989**, *111*, 975–989.
- [8] M. Schmittel, J.-P. Steffen, M. Á. Wencesla Ángel, B. Engels, C. Lennartz, M. Hanrath, *Angew. Chem.* **1998**, *110*, 1633–1635; *Angew. Chem. Int. Ed.* **1998**, *37*, 1562–1564.
- [9] A. Szabo, N. S. Ostlund, *Modern Quantum Chemistry*, Macmillan, New York, **1982**.
- [10] To compute the biradical intermediates an individually selecting MR-CI approach was used: a) M. Hanrath, B. Engels, *Chem. Phys.* **1997**, *225*, 197–202. The reference space consisted of up to 15 configurations. This led to total MR-CI configuration spaces of more than 500×10^6 configuration state functions (CSFs), whereby the secular equations actually solved were in the order of 5×10^6 – 8×10^6 CSFs. The influence of the neglected CSFs was estimated by the Buenker–Peyerimhoff extrapolation: b) R. J. Buenker, S. D. Peyerimhoff, *Theor. Chim. Acta* **1975**, *39*, 217–228; c) R. J. Buenker, S. D. Peyerimhoff, W. Butscher, *Mol. Phys.* **1978**, *35*, 771–791; d) R. J. Buenker, R. A. Phillips, *J. Mol. Struct.* **1985**, *123*, 291–300, and references therein. The influence of higher excitations was estimated by the normalized form of the usual Davidson correction: e) J. E. Del Bene, E. A. Stahlberg, I. Shaviatt, *Int. J. Quantum Chem. Symp.* **1990**, *24*, 455–466. In these calculations (in the following abbreviated as MR-CI+Q) all 34 valence electrons were correlated. The calculations were performed with the DIESEL-MR-CI program package: f) B. Engels, M. Hanrath: DIESEL-MR-CI (direct internal external separated individually selecting MR-CI) program package, Universität Bonn, Germany, **1997**. To determine the TSs the energy for fixed C²–C⁷ and C²–C⁶ distances, which represent the reaction coordinates for the C²–C⁷ and C²–C⁶ cyclizations, respectively, was computed. In these calculations all other geometrical parameters were optimized. These calculations were performed with the Gaussian94 program package^[10g] and the Turbo-Mol program:^[10h, i] g) M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Pittsburgh, PA, **1995**; h) R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165–169; i) O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, *102*, 346–354.
- [11] The MR-CI computations for **1f**, **3f** (R = Ph) were too demanding. Hence, we estimated $\Delta E^\ddagger$ for **2f** → **1f**, **3f** using an increment derived from the corresponding enyne-allene cyclization reaction energies.^[1b]
- [12] a) M. Schmittel, M. Keller, S. Kiau, M. Strittmatter, *Chem. Eur. J.* **1997**, *3*, 807–816; b) P. Chen, *Angew. Chem.* **1996**, *108*, 1584–1586; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1478–1480.
- [13] S. Kubota, K. Horie, H. K. Misra, K. Toyooka, M. Uda, M. Shibuya, H. Terada, *Chem. Pharm. Bull.* **1985**, *33*, 662–666.
- [14] J. B. Fell, G. M. Coppola, *Synth. Commun.* **1995**, *25*, 43–47.
- [15] Two examples for the pericyclic reactivity of in situ generated enyne-carbodiimides (starting with the corresponding iminophosphoranes) are known: a) M. Alajarin, P. Molina, A. Vidal, *J. Nat. Prod.* **1997**, *60*, 747–748; b) P. Molina, M. Alajarin, A. Vidal, P. Sánchez-Andrada, *J. Org. Chem.* **1992**, *57*, 929–939.
- [16] T. Saito, H. Ohmori, T. Ohkubo, S. Motoki, *J. Chem. Soc. Chem. Commun.* **1993**, 1802–1803.
- [17] R. Brückner, R. Huisgen, J. Schmid, *Tetrahedron Lett.* **1990**, *31*, 7129–7132.
- [18] W. Peczyńska-Czoch, F. Pognan, Ł. Kaszmarek, J. Boratyński, *J. Med. Chem.* **1994**, *37*, 3503–3510.

Synthesis of Hyperbranched Aminopolysaccharides

Jun-ichi Kadokawa,* Mitsuru Sato, Masa Karasu, Hideyuki Tagaya, and Koji Chiba

Dendritic polymers such as dendrimers and hyperbranched polymers have a highly branched backbone and exhibit very different properties compared to their linear analogues. Dendrimers, which have a perfect branched and exact monodisperse structure, are prepared by either divergent or convergent methods.^[1] However, their preparation normally

[*] Dr. J. Kadokawa, M. Sato, M. Karasu, Prof. Dr. H. Tagaya, Prof. Dr. K. Chiba
Department of Materials Science and Engineering
Faculty of Engineering, Yamagata University
Yonezawa, Yamagata 992-0038 (Japan)
Fax: (+81) 238-26-3413
E-mail: tj321@dip.yz.yamagata-u.ac.jp

involves numerous protection, deprotection, and purification procedures.

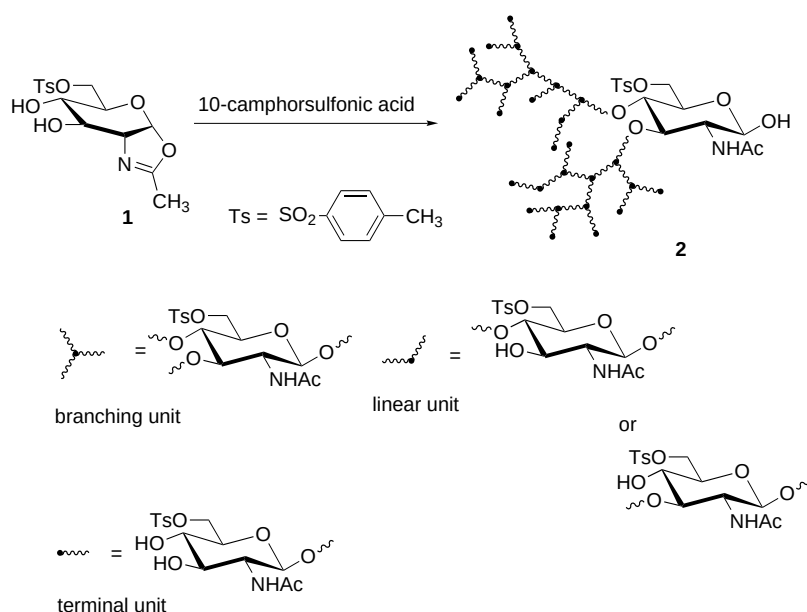
Hyperbranched polymers can be prepared more easily than dendrimers by the polymerization of AB_x monomers, where x is generally 2 or 3. Although the concept of such materials was described by Flory in 1952,^[2] synthesis and characterization of this class of polymers have been undertaken only in recent years.^[3] Interest has since increased, and several new hyperbranched polymers have been described.^[4] Recently, sugar-carrying multibranched glycopolymers and glycodendrimers with terminal sugar residues have been prepared.^[5] However, synthesis of a hyperbranched polysaccharide has so far not been reported.

Various oligosaccharides with branched chain structures are found in glycoproteins at cell surfaces and in intercellular systems.^[6] Examples include oligosaccharides isolated from calf thyroglobulin,^[7] immunoglobulin glycopeptide,^[8] and ovalbumin.^[9] Chemical syntheses of these oligosaccharides have been achieved, which has allowed further study of their biological functions and unique structures.^[10] Synthesis of a hyperbranched polysaccharide would also be very interesting, for such a polysaccharide can be expected to have unusual properties.

We have recently reported that benzyl-protected sugar dihydrooxazole monomers with a free hydroxyl group at position 4 or 6 undergo acid-catalyzed polymerization to give aminopolysaccharides.^[11] The polymerization proceeds by stereoregular glycosylation of an alcohol group with the dihydrooxazole ring^[12] to give aminopolysaccharides with natural (dibenzylchitin) and nonnatural structures. This polymerization method is not limited to the synthesis of linear polysaccharides, but can be extended to the formation of a hyperbranched compound from an AB_2 saccharide monomer. Here we report the synthesis of such a hyperbranched aminopolysaccharide **2** by the acid-catalyzed polymerization of a sugar dihydrooxazole monomer, 2-methyl-(6-*O*-tosyl-1,2-dideoxy- α -D-glucopyrano)-[2,1-*d*]-4,5-dihydrooxazole (**1**; tosyl = 4-toluenesulfonyl) with two hydroxyl groups at positions 3 and 4 (Scheme 1), which can be considered as an AB_2 monomer.

The polymerization of **1** was carried out in 1,2-dichloroethane at reflux temperature out with 10-camphorsulfonic acid (CSA, 10 mol %)^[13] as catalyst.^[14] The polysaccharide was isolated as a diethyl ether insoluble fraction. It was soluble in highly polar organic solvents such as *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and pyridine, but insoluble in organic solvents of low polarity and water. The ¹H and ¹³C NMR spectroscopic data of the product supported that each unit has the β -D-glucopyranan structure **2**.^[15] As no peak attributable to C1 of an α -glycoside (δ = 90–95) was observed in the ¹³C NMR spectrum, only the β configuration was tenable within the sensitivity of the method.

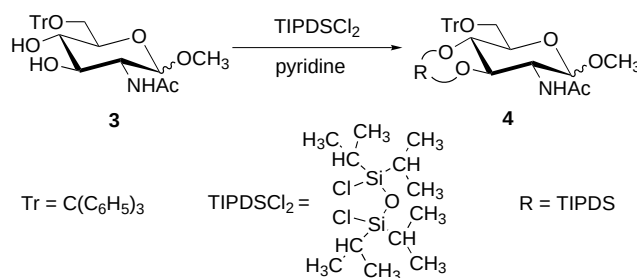
The number-average molecular weight (M_n) obtained by the reaction time of 3 h was calculated to be 6300 (degree of



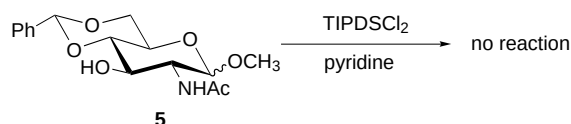
Scheme 1. Synthesis of hyperbranched aminopolysaccharide.

polymerization ca. 17.6) by gel permeation chromatography (GPC) with polystyrene as standard and DMF as eluent. On the other hand, the weight-average molecular weight (M_w) of the same product determined by the light-scattering method with RI detector and DMF as eluent was 4.5×10^5 . Branched polymers are known to be of spherical conformation in solution.^[16] Therefore, it may be considered that the actual M_n value of the present polysaccharide is larger than that estimated by GPC.

The degree of branching (DB) can be defined as the number of branched units relative to the number of total units. For polymers of high molecular weight, the number of branching points is nearly equal to the number of terminal units. To determine the DB value by the molar ratio of terminal units to total units, **2** was treated with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (TIPDSCl₂), a reagent for the protection of two adjacent hydroxyl groups in a saccharide.^[17] Each terminal unit in **2** has two hydroxyl groups, whereas only one hydroxyl group exists in each linear unit. To confirm the reactivity of TIPDSCl₂ toward the terminal and linear units, the reactions of methyl 2-acetamido-2-deoxy-6-*O*-trityl-D-glucopyranoside (**3**) and methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (**5**) with TIPDSCl₂ were carried out (Schemes 2 and 3); **3** and **5** are model compounds for the terminal and linear units, respectively.

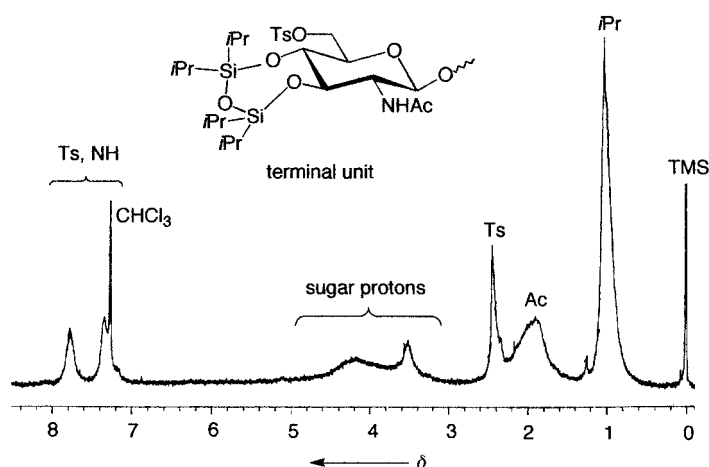


Scheme 2. Model reaction of **3** with TIPDSCl₂.

Scheme 3. Model reaction of **5** with TIPDSCl₂.

The results of the model reactions indicated that the terminal units in **2** should be able to react quantitatively with TIPDSCl₂ to give disiloxane-bridged derivatives, whereas the linear and branched units should not react with TIPDSCl₂.^[18] The reaction of **2** with TIPDSCl₂ was carried out in pyridine, and the product was isolated as a hexane-insoluble fraction.

The ¹H NMR spectrum (CDCl₃) of the reaction product shown in Figure 1 contains in comparison to **2** a new peak at around $\delta = 0.7$ –1.4 for isopropyl groups. From the integrated ratio of this peak and the methyl peaks of the acetamido and

Figure 1. ¹H NMR spectrum (CDCl₃) of the reaction product of **2** with TIPDSCl₂.

tosyl groups, the content of the terminal units in the polymer could be calculated as 0.51. In the complete hyperbranched polymer, the content of the terminal units is nearly a half of the total units when the molecular weight of the polymer is high. Therefore, the DB of **2** synthesized here can be considered to be almost perfect.^[19]

Table 1 summarizes the polymerization results under various reaction times. The DB of the polymers obtained with reaction times of 3–5 h was almost perfect, as, in each case, the ratio of the terminal units to the total units was about 0.5 (determined by ¹H NMR spectroscopic analysis after the reaction with TIPDSCl₂, entries 3 and 4). The ratio of the terminal units in the polymers obtained with reaction times of 1–2 h was 0.44–0.45, which indicates incomplete DB in these polymers (entries 1 and 2).

Polysaccharide **2** can be expected to have unusual properties because of the hyperbranched structure. The thermal properties of **2** were examined by thermogravimetric analysis (TGA). Decomposition of the tosyl group started at 166 °C and showed a 45% weight loss up to 337 °C. The residual material exhibited thermal resistance above 337 °C, but a second weight loss occurred at 510 °C. Decomposition was

Table 1. Polymerization of (**1**).^[a]

Entry	<i>t</i> ^[a] [h]	Yield ^[b] [%]	<i>M_w</i> 10 ^{−5} ^[c]	<i>M_n</i> ^[d]	<i>M_w</i> / <i>M_n</i> ^[c]	<i>y</i> ^[e]
1	1	57.3	2.3	5500	1.44	0.45
2	2	48.5	2.9	4800	1.23	0.44
3	3	49.4	4.5	6300	1.31	0.51
4	5	57.5	7.6	6600	1.93	0.49

[a] Polymerization was carried out with **1** (0.20 mmol) and 10-camphorsulfonic acid (10 mol% relative to **1**) in 1,2-dichloroethane (2.0 mL) at reflux. [b] Fraction insoluble in diethyl ether. [c] Determined by the light-scattering method with DMF as eluent. [d] Determined by GPC with DMF containing lithium chloride (0.02 mol L^{−1}) as eluent and polystyrene standards. [e] Ratio *y* of terminal units to total number of units determined by ¹H NMR spectroscopy.

complete at 600 °C. The TGA trace of **2** indicated that the thermal stability of **2** was much higher than that of normal, linear polysaccharides. For example, chitin showed a significant weight loss at 275–428 °C.

Finally, detosylation of **2** was carried out under alkaline conditions (sodium hydroxide) in aqueous ethanol at reflux temperature to yield a free hyperbranched aminopolysaccharide. The product was isolated as a methanol-insoluble fraction, and is insoluble in common organic solvents and water, but soluble in formic acid. The IR spectrum of the product showed the disappearance of the absorptions at 1358 and 1176 cm^{−1} for the tosyl S=O group. These IR data strongly supported the conclusion that complete detosylation had taken place to give the free hyperbranched aminopolysaccharide. Partial deacetylation of the acetamido groups of **2** is possible, although the absorption at 1647 cm^{−1}, attributable to the C=O moiety of the acetamido group, was present in the IR spectrum of the product. More detailed studies on the optimum conditions for detosylation are in progress.

In conclusion, we have synthesized a hyperbranched aminopolysaccharide **2** by acid-catalyzed polymerization of the AB₂-type saccharide monomer **1**. This polymerization provides the first example of the synthesis of a hyperbranched polysaccharide.

Experimental Section

Monomer 1: A solution of *p*-toluenesulfonyl chloride (7.56 g, 40.0 mmol) in pyridine (24 mL) was added to a solution of *N*-acetyl-D-glucosamine (8.80 g, 40.0 mmol) in pyridine (60 mL) under argon, and the mixture was stirred overnight at 40 °C. After the reaction mixture had cooled to room temperature, acetic anhydride (40 mL) was added, and the solution was stirred for a further 4 h. The pyridine was evaporated under reduced pressure, and the concentrated solution was poured into a large amount of ice water. The precipitate was isolated by decantation, washed several times with water, and dissolved in chloroform. The solution was successively washed with 1 M sulfuric acid, aqueous sodium hydrogen carbonate, and water. The chloroform layer was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was dried under reduced pressure to give 2-acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-6-*O*-tosyl-D-glucopyranose (7.73 g, 14.6 mmol, 36.5%). ¹H NMR (CDCl₃): δ = 1.98, 2.03, 2.19 (s, 12 H; CH₃C=O), 2.46 (s, 3 H; CH₃C₆H₄), 4.03–4.39 (m, 4 H; H₂, H₅, H₆), 5.02–5.53 (m, 3 H; H₃, H₄, NH), 5.64, 6.04 (d, *J* = 2.07, 8.92 Hz, 1 H; H₁ (β and α , respectively)), 7.36, 7.77 (d, *J* = 8.11 Hz, 4 H; C₆H₄). The product (2.81 g, 5.63 mmol) was dissolved in 1,2-dichloroethane (20.0 mL) under argon and treated with trifluoromethanesulfonic acid (0.900 g, 6.00 mmol). The mixture was stirred overnight at 50 °C, cooled to room temperature, and treated dropwise with triethylamine (4.0 mL). After an additional 20 min the mixture was diluted with chloroform, washed with water, dried

over anhydrous sodium sulfate, and evaporated. The syrupy residue was subjected to chromatography on silica gel with ethyl acetate/hexane/triethylamine (100/50/1, v/v/v) to give 2-methyl-(3,4-di-*O*-acetyl-6-*O*-tosyl-1,2-dideoxy- α -D-glucopyranosyl)-[2,1-*d*]-4,5-dihydrooxazole (0.895 g, 2.03 mmol, 39.5%). ^1H NMR (CDCl_3): δ = 1.99 (s, 3H; $\text{CH}_3\text{C}=\text{N}$), 2.03, 2.08 (s, 6H; $\text{CH}_3\text{C}=\text{O}$), 2.44 (s, 3H; $\text{CH}_3\text{C}_6\text{H}_4$), 3.60–4.12 (m, 4H; H2, H5, H6), 4.78–5.22 (m, 2H; H3, H4), 5.90 (d, J = 7.30 Hz, 1H; H1), 7.35, 7.78 (d, J = 8.11 Hz, 4H; C_6H_4). The product was dissolved in dry methanol (3.0 mL) under argon and treated with sodium methoxide (10.0 mg, 0.185 mmol) at room temperature. The reaction mixture was stirred at that temperature, and sodium methoxide (10.0 mg, 0.185 mmol) in dry methanol (3.0 mL) was added to the mixture every 1 h until complete consumption of the starting material was confirmed by thin layer chromatography (TLC). The reaction mixture was then poured into a large amount of ice water, and the aqueous phase was extracted three times with chloroform. The chloroform extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated at room temperature. The residue was dried under reduced pressure to give **1** (0.600 g, 1.68 mmol, 82.6%). ^1H NMR (CDCl_3): δ = 1.99 (s, 3H; $\text{CH}_3\text{C}=\text{N}$), 2.43 (s, 3H; $\text{CH}_3\text{C}_6\text{H}_4$), 3.62–3.90 (m, 5H; H3–H6), 4.08–4.28 (m, 1H; H2), 5.89 (d, J = 7.02 Hz, 1H; H1), 7.34, 7.79 (d, J = 8.11 Hz, 4H; C_6H_4); ^{13}C NMR (CDCl_3): δ = 13.6 ($\text{CH}_3\text{C}_6\text{H}_4$), 21.1 ($\text{CH}_3\text{C}=\text{N}$), 68.2 (C2), 69.0 (C6), 70.2, 70.6, 72.4 (C3, C4, C5), 99.7 (C1), 127.7, 130.3, 132.1, 145.1 (C_6H_4), 163.9 (N=C=O).

Polymerization of **1** (Table 1, entry 3): monomer **1** (0.0715 g, 0.20 mmol) and 10-camphorsulfonic acid (0.00465 g, 0.020 mmol) were dissolved in 1,2-dichloroethane (1.0 mL) under argon at room temperature, and the reaction mixture was heated under reflux for 3 h. The reaction mixture was cooled to room temperature and neutralized with pyridine. The solution was poured into a large volume of diethyl ether, and the precipitate was collected by filtration and washed with water. The material was dried under reduced pressure, dissolved in methanol, and the solution was poured into a large amount of diethyl ether. The precipitated product was isolated by filtration and dried under reduced pressure to give **2** (0.0353 g, 49.4%).

Reaction of **2** with TIPDSCl_2 : polymer **2** (0.100 g, 0.280 mmol) was dissolved in pyridine (2.2 mL) under argon, and TIPDSCl_2 (0.0397 g, 0.126 mmol) was added at room temperature. After the reaction mixture was stirred overnight, methanol was added. The solution was poured into a large amount of water, and the aqueous phase was extracted with 2-butanone. The extract was dried over anhydrous sodium sulfate, filtered, evaporated and dried in vacuo. Hexane was added to the residue, and the insoluble product was isolated by filtration and dried in vacuo (0.125 g).

Detosylation of **2**: Sodium hydroxide (0.300 g) and **2** (0.103 g) were dissolved in 50% aqueous ethanol (10.0 mL). The solution was heated under reflux for 5 h, cooled, neutralized with acetic acid, and concentrated under the reduced pressure. Methanol was added to the residue and the insoluble material was isolated by filtration and dried in vacuo to give the detosylated product (0.0426 g).

Received: January 9, 1998

Revised version: May 18, 1998 [Z11348IE]

German version: *Angew. Chem.* **1998**, *110*, 2540–2543

Keywords: carbohydrates • dendrimers • glycosylations

- 1996**, 2, 1115; d) D. Zanini, R. Roy, *J. Org. Chem.* **1996**, *61*, 7348; e) D. Zanini, R. Roy, *J. Am. Chem. Soc.* **1997**, *119*, 2088.
- [6] R. Kornfeld, S. Kornfeld, *Annu. Rev. Biochem.* **1976**, *45*, 217.
- [7] S. Ito, D. Yamashita, R. G. Spiro, A. Kobata, *J. Biochem. (Tokyo)* **1977**, *81*, 1621.
- [8] a) J. Baenziger, S. Kornfeld, S. Kochwa, *J. Biol. Chem.* **1974**, *249*, 1897; b) J. Baenziger, S. Kornfeld, *J. Biol. Chem.* **1974**, *249*, 7260.
- [9] a) T. Tai, K. Yamashita, S. Ito, A. Kobata, *J. Biol. Chem.* **1977**, *252*, 6687; b) K. Yamashita, Y. Tachibana, A. Kobata, *J. Biol. Chem.* **1978**, *253*, 3862.
- [10] T. Ogawa, K. Katano, K. Sasajima, M. Matsui, *Tetrahedron* **1981**, *37*, 2779.
- [11] a) J. Kadokawa, Y. Watanabe, M. Karasu, H. Tagaya, K. Chiba, *Macromol. Rapid Commun.* **1996**, *17*, 367; b) J. Kadokawa, S. Kasai, Y. Watanabe, M. Karasu, H. Tagaya, K. Chiba, *Macromolecules* **1997**, *30*, 8212.
- [12] S. E. Zurabyan, T. P. Volosyuk, A. J. Khorlin, *Carbohydr. Res.* **1969**, *9*, 215.
- [13] S. Nishimura, K. Matsuo, K. Kurita, *Macromolecules* **1990**, *23*, 4182. It has been reported that 10-camphorsulfonic acid is a more effective catalyst than, for example, *p*-toluenesulfonic acid and trifluoromethanesulfonic acid in glycosylations with a dihydrooxazole glycosyl donor.
- [14] Nucleophilic attack of a nitrogen atom in the dihydrooxazole group of **1** onto *p*-toluenesulfonate group at position 6 could take place during the polymerization. However, an acetyl-protected derivative of **1** was stable when heated under reflux in 1,2-dichloroethane, which indicates no reaction had occurred between the dihydrooxazole and *p*-toluenesulfonate groups.
- [15] ^1H NMR (270 MHz, $[\text{D}_6]\text{DMSO}/\text{D}_2\text{O}$, 20 °C): δ = 1.62–2.18 (br, 3H; $\text{CH}_3\text{C}=\text{O}$), 2.40 (s, 3H; $\text{CH}_3\text{C}_6\text{H}_4$), 3.09–5.00 (br, 7H; sugar protons), 7.46, 7.76 (2s, 4H, C_6H_4); ^{13}C NMR (67.8 MHz, $[\text{D}_6]\text{DMSO}$, 80 °C): δ = 19.2–26.2 (CH_3), 46.9–57.9 (C2), 68.0–71.7 (C3–C6), 99.5 (C1), 125.4–146.4 (C_6H_4), 168.4–171.4 (C=O).
- [16] a) S. Bywater, *Adv. Polym. Sci.* **1979**, *30*, 89; b) P. Rempp, E. Franta, J. E. Herz, *Adv. Polym. Sci.* **1988**, *86*, 145.
- [17] a) C. H. M. Verdegaa, P. L. Jansse, J. F. M. de Rooij, J. H. van Boom, *Tetrahedron Lett.* **1980**, *21*, 1571; b) W. T. Markiewicz, B. Nowakowska, K. Adrych, *Tetrahedron Lett.* **1988**, *29*, 1561; c) M. D. Hagen, C. S. Happ, E. Happ, S. Chládek, *J. Org. Chem.* **1988**, *53*, 5040.
- [18] In the reaction of **3** with TIPDSCl_2 , complete consumption of **3** and the formation of a single product were detected by TLC analysis. The product **4** was isolated in 60.0% yield by chromatography on silica gel, and the structure was determined by ^1H NMR spectroscopy. In contrast, no reaction of **5** with TIPDSCl_2 was observed by TLC, and 75.6% of **5** was recovered from the reaction mixture as a hexane-insoluble fraction.
- [19] This method for the determination of the DB value may contain some inconsistencies owing to errors in the calculation of the integrated ratio in the ^1H NMR spectrum. Furthermore, in the reaction of **2** with TIPDSCl_2 some formation of the nonbridged units by the reaction of the linear units with TIPDSCl_2 is possible. It has been reported, however, that TIPDSCl_2 reacts almost exclusively with two adjacent hydroxyl groups, and that the reaction favors the formation of cyclic disiloxane-bridged structures rather than nonbridged structures.^[17]

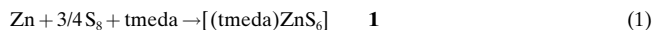
- [1] a) D. A. Tomalia, A. M. Naylor, W. A. Goddard III, *Angew. Chem.* **1990**, *102*, 119; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138; b) P. R. Dvornic, D. A. Tomalia, *Macromol. Symp.* **1994**, *88*, 123.
- [2] P. J. Flory, *J. Am. Chem. Soc.* **1952**, *74*, 2718.
- [3] a) Y. H. Kim, O. W. Webster, *J. Am. Chem. Soc.* **1990**, *112*, 4592; b) Y. H. Kim, O. W. Webster, *Macromolecules* **1992**, *25*, 5561.
- [4] a) B. I. Voit, S. R. Turner, *Angew. Makromol. Chem.* **1994**, *223*, 13; b) J. M. J. Fréchet, C. J. Hawker, *React. Funct. Polym.* **1995**, *26*, 127; c) B. I. Voit, *Acta Polymer.* **1995**, *46*, 87; d) A. R. Brenner, B. I. Voit, D. J. Massa, S. R. Turner, *Macromol. Symp.* **1996**, *102*, 47.
- [5] For example, a) R. Roy, D. Zanini, S. J. Meunier, A. Romanowska, *J. Chem. Soc. Chem. Commun.* **1993**, 1869; b) K. Aoi, K. Itoh, M. Okada, *Macromolecules* **1995**, *28*, 5391; c) P. R. Ashton, S. E. Boyd, C. L. Brown, N. Jayaramen, S. A. Nepogodiev, J. F. Stoddart, *Chem. Eur. J.*

A New Allotrope of Elemental Sulfur: Convenient Preparation of *cyclo*-S₁₄ from S₈**

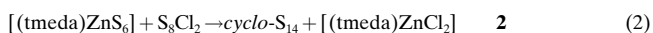
Ralf Steudel,* Oliver Schumann, Jürgen Buschmann, and Peter Luger

Sulfur forms far more allotropes than any other element. At present, at least 21 sulfur allotropes are known to exist at ambient pressure, 17 of which have been characterized by X-ray crystallography.^[1] They all contain sulfur atoms with a coordination number (CN) of 2. The densities of these compounds range between 1.9 and 2.2 g cm⁻³, and the internuclear distances between 200 and 218 pm.^[2] All investigated low-pressure allotropes are excellent electrical insulators (band gap ca. 2.9 eV). At high pressures, at least four additional allotropes have been obtained, three of which have been studied by X-ray diffraction. At 33 GPa sulfur becomes a semiconductor (of unknown structure), and at 83 GPa a metallic conductor. This "sulfur metal" crystallizes in an orthorhombic layer structure with CN = 4, but at 162 GPa the structure transforms into that of β -polonium with CN = 6. At 206 GPa the density reaches 6.6 g cm⁻³; however, the internuclear distances of 207.9 pm are "normal"^[3] (α -S₈: 205 pm^[4]). The two metallic sulfur modifications become superconductors below 10 and 17 K, respectively.^[5]

Here we report on a new monotropic low-pressure allotrope of sulfur which can be prepared in three steps from the thermodynamically stable form α -S₈. The starting material is the hexasulfido complex **1**, which was prepared by Rauchfuss et al.^[6] from zinc powder, orthorhombic α -S₈, and *N,N,N',N'*-tetramethylethylenediamine (tmeda) at 90 °C in 75 % yield [Eq. (1)].



Complex **1** forms yellow air-stable crystals, and its molecules contain a seven-membered metallacycle with the chelating ligand S₆²⁻. Like [(C₅H₅)₂TiS₅] the zinc complex acts as a sulfur-transfer reagent. For instance, treating a suspension of **1** in CS₂ with Se₂Cl₂ at -60 °C afforded the heterocycle 1,2-Se₂S₆.^[7] We studied the reaction of a solution of **1** in CS₂ at 0 °C with dichlorooctasulfane S₈Cl₂ [Eq. (2)], which is accessible by careful chlorination of *cyclo*-S₈ with elemental chlorine.^[8] The HPLC analysis^[9] of the mixture indicated the formation of *cyclo*-tetradecasulfur in high concentration.



However, on attempting to isolate S₁₄ from the mixture, decomposition to S₈ occurred regularly. This may be due to the presence of the strong nucleophile tmeda (p*K*_a = 5.85/8.97),^[10] which is only partly removed by the insoluble zinc complex **2**. Strong nucleophiles are known to catalyze the decomposition of thermodynamically unstable sulfur homocycles.^[11] After addition of P₄O₁₀ to the reaction mixture to remove the remaining amine, pure S₁₄ could be isolated in 11 % yield (based on **1**). As side product S₁₂ was isolated, which apparently originates from the reaction of **1** with the S₆Cl₂ that was present in S₈Cl₂ as another chlorination product.

S₁₄ forms intense yellow rodlike crystals, which intergrow to form bundles and melt at 117 °C with decomposition. The primary decomposition products are S₇ and S₈, but not S₆; therefore, a reaction sequence S₁₄ → 2S₇ → S₈ is likely. At 20 °C S₁₄ is stable for days in the crystalline state and as a solution in CS₂. The solubility in CS₂ is greater than that in CHCl₃. The EI mass spectrum (70 eV) exhibits only peaks for the sulfur ions S_n⁺ (*n* = 1–9). It contains no other elements, and the molecular ion was not observed. The Raman spectrum at -100 °C (Table 1)^[12] differs from those of all

Table 1. Wavenumbers [cm⁻¹] of the Raman bands of crystalline S₁₄ at -100 °C (krypton laser, 674 nm; relative intensities in parentheses).

Stretching modes	Bending modes	Torsional and lattice modes
483 (7)	270 (7)	122 (7)
474 (5)	252 (2)	90 (23)
468 (25)	243 (5)	79 (14)
462 sh	234 (23)	69 (59)
460 (59)	212 (2)	61 (41)
453 sh	198 (18)	57 (36)
447 (11)	189 (7)	47 (100)
444 (11)	177 (11)	34 (23)
	163 (25)	
	153 (16)	
	128 (48)	

other cyclic sulfur allotropes, but is consistent with expectations. Besides eight lines, two of which are shoulders, in the S–S stretching region (440–485 cm⁻¹), several bands for the deformation, torsion, and lattice vibrations are present in the region below 290 cm⁻¹. Signals due to S₈ and S₁₂ are not detectable.

The reversed-phase HPLC chromatogram of pure S₁₄ shows only one large peak, the retention time of which lies between those of S₁₃^[8] and S₁₅.^[14] With this technique S₁₄ was identified previously as a trace component in quenched sulfur melts and in synthetic sulfur mixtures.^[9, 15]

The cyclic structure of S₁₄ was confirmed by a single-crystal X-ray structure analysis.^[16] At 20 °C the crystals decomposed rapidly in the X-ray beam. Therefore, the sample was cooled to -100 °C, and at this temperature the reflection intensities remained constant. The structure is triclinic with two molecules in the unit cell and a density of 2.045 g cm⁻³ at -100 °C. The S₁₄ molecules occupy general sites but have approximately C_s molecular symmetry (Figure 1). The noncrystalline

[*] Prof. Dr. R. Steudel, Dipl.-Chem. O. Schumann
Institut für Anorganische und Analytische Chemie
der Technischen Universität
Skr. C2, Strasse des 17. Juni 135, D-10623 Berlin (Germany)
Fax: (+49) 30-314-26519
E-mail: steudel@schwefel.chem.tu-berlin.de.

Dr. J. Buschmann, Prof. Dr. P. Luger
Institut für Kristallographie der Freien Universität
Takustrasse 6, D-14195 Berlin (Germany)

[**] Sulfur Compounds, part 206. This work was supported by the Deutsche Forschungsgemeinschaft, the Deutschen Akademischen Austauschdienst, and the Verband der Chemischen Industrie. Part 205: R. Steudel, O. Schumann, J. Buschmann, P. Luger, *Angew. Chem.* **1998**, *110*, 515; *Angew. Chem. Int. Ed.* **1998**, *37*, 492.

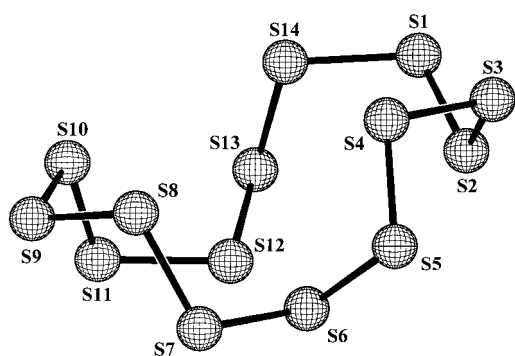


Figure 1. Structure of *cyclo-S*₁₄ in the crystal. Bond lengths [pm], angles [°], and torsional angles [°]: S1–S2 205.5(4), S2–S3 205.1(3), S3–S4 205.4(3), S4–S5 206.1(4), S5–S6 205.0(4), S6–S7 204.7(4), S7–S8 205.6(4), S8–S9 204.7(3), S9–S10 204.9(3), S10–S11 206.0(3), S11–S12 205.5(4), S12–S13 205.2(4), S13–S14 205.9(3), S14–S1 205.1(4); S1–S2–S3 108.4(2), S2–S3–S4 107.8(2), S3–S4–S5 104.4(2), S4–S5–S6 104.0(2), S5–S6–S7 104.95(14), S6–S7–S8 108.3(2), S7–S8–S9 106.95(13), S8–S9–S10 109.32(14), S9–S10–S11 106.0(2), S10–S11–S12 107.1(2), S11–S12–S13 105.0(2), S12–S13–S14 104.5(2), S13–S14–S1 105.1(2); S1–S2–S3–S4 +96.0(2), S2–S3–S4–S5 +72.5(2), S3–S4–S5–S6 –100.8(2), S4–S5–S6–S7 –94.9(2), S5–S6–S7–S8 +82.7(2), S6–S7–S8–S9 +107.1(2), S7–S8–S9–S10 –100.7(2), S8–S9–S10–S11 +95.9(2), S9–S10–S11–S12 –100.7(2), S10–S11–S12–S13 –75.9(2), S11–S12–S13–S14 +101.7(2), S12–S13–S14–S1 +101.5(2), S13–S14–S1–S2 –77.9(2), S14–S1–S2–S3 –94.7(2).

graphic mirror plane contains S2 and S9. The internuclear distances vary from 204.7 to 206.1 pm; the arithmetic mean of 205.3 pm is only insignificantly larger than that of orthorhombic α -S₈.

The conformation of sulfur homocycles is best described by the “motif”, which is the order of the signs of the torsional angles around the ring. The motif of S₁₄ is ++ – – ++ – – ++ – – + –. Since the first 12 signs are the same as those of the S₁₂ molecule,^[17] the structure of S₁₄ can be generated from that of *cyclo-S*₁₂ by opening any bond and inserting an S₂ fragment (S9 and S10). The absolute values of the torsional angles in S₁₄ are in the range of 72.5–101.7°; the arithmetic mean of 93.1° is also close to the corresponding value of S₁₂ (89°). The mean bond energy of S₁₂ is only 1 kJ mol^{–1} smaller than that of S₈. Therefore, S₁₂ is only second to S₈ in thermodynamic stability. The difference between the mean bond energy of S₁₄ and that of S₈ is 2 kJ mol^{–1}.^[18]

Experimental Section

*cyclo-S*₁₄: Solvents were dried over P₄O₁₀ and distilled. Under an atmosphere of dry nitrogen, S₈Cl₂ (4.2 g, 12.8 mmol) in CS₂ (17.5 mL) was added dropwise over 1 h to **1** (4.8 g, 12.8 mmol) in CS₂ (70 mL) at 0 °C. The temperature was then allowed to rise to 20 °C over 1 h. The colorless precipitate of **2** was collected by filtration and washed with 50 mL of CS₂; the filtrate and wash solutions were combined. To remove dissolved tmeda P₄O₁₀ (ca. 0.4 g) was added to the clear yellow solution (the hygroscopic P₄O₁₀ contains strongly acidic POH groups which protonate the amine). CHCl₃ (10 mL) was added to precipitate sparingly soluble S₁₂. After cooling to –35 °C the mixture of S₁₂ and P₄O₁₀ was filtered off. Addition of a further 10 mL of CHCl₃ to the filtrate and cooling to –35 °C for several days afforded yellow bundles of S₁₄ (yield 650 mg).

Received: April 6, 1998 [Z11685IE]

German version: *Angew. Chem.* **1998**, *110*, 2502–2504

Keywords: allotropy • sulfur • zinc

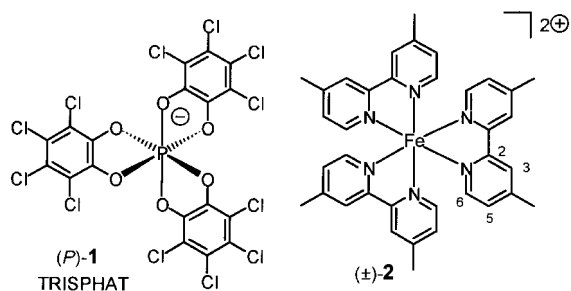
- [1] The following phases consist of cyclic molecules: S₆, S₇ (α – δ), S₈ (α – γ), S₉ (α , β), S₁₀, S₁₁, S₁₂, S₁₃, S₁₅, S₁₈ (α , β), S₂₀, S₆·S₁₀. In addition, two polymeric allotropes S_∞ are known (also termed S_μ or S_ω).
- [2] a) R. Steudel, *Chemie der Nichtmetalle*, 2nd ed., de Gruyter, Berlin, **1998**; b) R. Steudel, K. Bergemann, J. Buschmann, P. Luger, *Inorg. Chem.* **1996**, *35*, 2184; c) R. Steudel in *Sulfur—Its Significance for Chemistry, for the Geo-, Bio- and Cosmospere and Technology* (Eds.: A. Müller, B. Krebs), Elsevier, Amsterdam **1984**, p. 3.
- [3] H. Luo, S. Desgreniers, Y. K. Vohra, A. L. Ruoff, *Phys. Rev. Lett.* **1991**, *67*, 2998; Y. Akahama, M. Kobayashi, H. Kawamura, *Phys. Rev. B* **1993**, *48*, 6862; H. Luo, R. G. Greene, A. L. Ruoff, *Phys. Rev. Lett.* **1993**, *71*, 2943.
- [4] P. Coppens, Y. W. Yang, R. H. Blessing, W. F. Cooper, F. K. Larsen, *J. Am. Chem. Soc.* **1977**, *99*, 760.
- [5] V. V. Struzhkin, R. J. Hemley, H. Mao, Y. A. Timofeev, *Nature* **1997**, *390*, 382.
- [6] A. K. Verma, T. B. Rauchfuss, S. R. Wilson, *Inorg. Chem.* **1995**, *34*, 3072.
- [7] A. K. Verma, T. B. Rauchfuss, *Inorg. Chem.* **1995**, *34*, 6199.
- [8] R. Steudel, J. Steidel, T. Sandow, *Z. Naturforsch. B* **1986**, *41*, 958.
- [9] R. Strauss, R. Steudel, *Fresenius Z. Anal. Chem.* **1987**, *326*, 543.
- [10] L. Spialter, R. W. Moshier, *J. Am. Chem. Soc.* **1957**, *79*, 5955.
- [11] R. E. Davis in *Inorganic Sulphur Chemistry* (Ed.: G. Nickless), Elsevier, Amsterdam, **1968**, p. 85.
- [12] Investigating unstable sulfur allotropes by Raman spectroscopy requires the use of a laser beam with low-energy radiation (red or infrared); otherwise, photochemical conversion into S₈ may occur. For experimental details, see ref. [8].
- [13] R. Steudel, H.-J. Mäusle, *Z. Naturforsch. A* **1978**, *33*, 951.
- [14] R. Strauss, R. Steudel, *Z. Naturforsch. B* **1988**, *43*, 1151.
- [15] R. Steudel, H.-J. Mäusle, D. Rosenbauer, H. Möckel, T. Freyholdt, *Angew. Chem.* **1981**, *93*, 402; *Angew. Chem. Int. Ed. Engl.* **1981**.
- [16] Crystal structure analysis of S₁₄: 0.55 × 0.16 × 0.15 mm, triclinic, space group *P*1̄ (no. 2), *Z* = 2, *a* = 5.469(3), *b* = 9.662(5), *c* = 14.331(7) Å, α = 95.97(4), β = 98.96(4), γ = 100.43(4)°, *V* = 728.8(7) Å³, μ = 2.044 mm^{–1}, MoK α radiation, λ = 0.71068 Å. Of 4440 measured reflections (2.16 ≤ θ ≤ 30.00°), 54% with *I* ≤ 2 σ (*I*), 4270 were independent; *R*_{int} = 0.051. Due to the large width (1.7°, ω scan) and irregular form of the reflection profiles the ω scan mode was used, the background on both sides of the reflections was measured point by point. Initial coordinates of the sulfur atoms from direct methods with SIR92. Refinement on *F*² (SHELXL93), 127 refined parameters, *R*1 = 0.084, *R*1 = $\Sigma |F_o| - |F_c|$ / $\Sigma |F_o|$, *wR*2 = 0.25 with all independent reflections, *wR*2 = $\{\Sigma [w(F_o^2 - F_c^2)]^2 / \Sigma wF_o^4\}^{1/2}$, *w* = $[\sigma^2(F_o^2) + (0.1542P)^2]^{-1}$ with *P* = $[\max(F_o^2, 0) + 2F_c^2]/3$; max./min. residual electron density 1.51/–1.13 e Å^{–3}. Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depositary number CSD-408504.
- [17] J. Steidel, R. Steudel, A. Kutoglu, *Z. Anorg. Allg. Chem.* **1981**, *476*, 171.
- [18] R. Steudel, R. Strauss, L. Koch, *Angew. Chem.* **1985**, *97*, 58; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 59.

Diastereoselective Ion Pairing of TRISPHAT Anions and Tris(4,4'-dimethyl-2,2'-bipyridine)iron(III)**

Jérôme Lacour,* Jonathan J. Jodry, Catherine Ginglinger, and Sonya Torche-Halldimann

The induction of optical activity on configurationally labile racemic molecules by a chiral environment is an essential phenomenon that has been studied on several systems.^[1] For instance, optically active anions can induce optical activity onto cationic organic molecules or coordination complexes.^[2] The extent of the asymmetric induction was determined in these examples by chiroptical measurements, which gave qualitative but not quantitative information. The magnitude of the induction (diastereoselectivity) is not known, and the efficiency of the chiral inducers is difficult to appreciate. Herein we report that the asymmetric induction from chiral anions onto a chiral cation can indeed be an extremely efficient process.

Recently we showed that the anion TRISPHAT (**1**), which is easily prepared and resolved, is configurationally stable as an ammonium salt in solution.^[3] We decided to study its asymmetric ion pairing with a cation of similar shape and geometry, namely, the easily prepared *D*₃-symmetric [Fe(4,4'-Me₂bpy)₃]²⁺ (**2**; bpy = 2,2'-bipyridine). Complexes **3** are made up of two host anions **1** (racemic, *M* or *P*) and one configurationally labile^[4] guest cation **2**, and were synthesized in a



single step: Treatment of Fe(NH₄)₂(SO₄)₂·6H₂O with 4,4'-dimethyl-2,2'-bipyridine (3 equiv) in hot water and extraction of the resulting purple solution with TRISPHAT^[5] (2 equiv) afforded the desired complexes **3** as the major products along with minor amounts of bipyridine ligand in the organic layer (CH₂Cl₂/acetone 25/1).^[6] Further purification by recrystallization gave pure complexes **3** in decent yields (56–71 %).^[7] Racemic **3**, (**2**)(rac-**1**)₂, is insoluble in CH₂Cl₂ or CHCl₃, as opposed to the corresponding salts with *M* or *P* anions.

The highly asymmetric ion pairing of anions **1** (*P* or *M*) and cation **2** was simply demonstrated: ¹H NMR spectra of (**2**)(*P*-**1**)₂ and (**2**)(*M*-**1**)₂ in [D₆]DMSO (0–50 %)/CDCl₃ (1.0 mM) showed partial or complete resolution in the region containing signals of the cation (Figure 1).^[8] We were able to distinguish

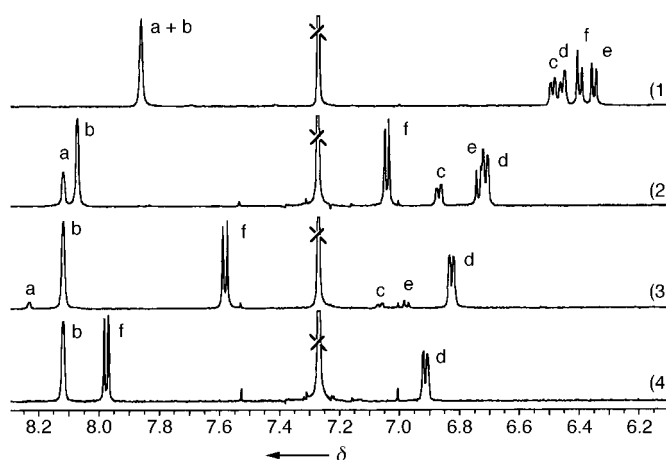


Figure 1. Sections of ¹H NMR spectra of (**2**)(*P*-**1**)₂ in [D₆]DMSO/CDCl₃ as a function of the percentage of [D₆]DMSO: 1) 50 %, 8 % *ds*; 2) 20 %, 47 % *ds*; 3) 7.5 %, 87 % *ds*; 4) 0 %, > 96 % *ds*. The signals a, c, e and b, d, f correspond to the hydrogen atoms 3, 5, 6 in **3**_M and **3**_P, respectively.

between the diastereomeric pairs (*P*-**2**)(*P*-**1**)₂ ≡ **3**_P and (*M*-**2**)(*P*-**1**)₂ ≡ **3**_M for compound (**2**)(*P*-**1**)₂, and (*M*-**2**)(*M*-**1**)₂ ≡ ent-**3**_P and (*P*-**2**)(*M*-**1**)₂ ≡ ent-**3**_M for compound (**2**)(*M*-**1**)₂. The diastereoselectivity of the asymmetric ion pairing between [**3**_P, **3**_M] and [ent-**3**_P, ent-**3**_M] was then directly calculated by integration of the respective signals (Table 1).

Table 1. Diastereoselectivity for (**2**)(*P*-**1**)₂ and (**2**)(*M*-**1**)₂ as a function of the percentage of [D₆]DMSO in CDCl₃.

% [D ₆]DMSO	(2)(1) ₂ ^[a]	
	<i>de</i> [%]	<i>dr</i> ^[b]
0	> 96	> 50:1
1.0	96	50:1
2.5	95	40:1
5.0	92	23:1
7.5	87	14:1
10	80	9.3:1
12.5	73	6.5:1
15	66	4.9:1
20	47	2.8:1
25	19	1.9:1
50	8	1.2:1

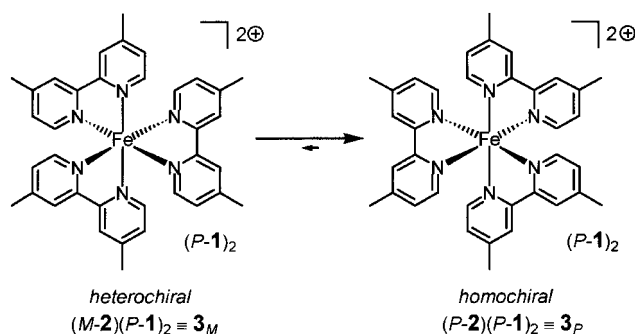
[a] Compound **1** of *P* or *M* configuration. [b] Diastereomeric ratio.

Upon decreasing the solvent polarity (by lowering the portion of DMSO), one diastereomer became predominant; a diastereoselectivity (*ds*) of up to 96% was achieved in pure CDCl₃ (Figure 1, Table 1). The circular dichroism (CD) spectrum of a solution of (**2**)(*P*-**1**)₂ (0.1 % DMSO in CHCl₃, 4.6 × 10⁻⁶ M) revealed strong exciton coupling in the π–π* region (Δε₂₈₈ = +168, Δε₃₀₅ = –260 M⁻¹ cm⁻¹), and the metal-to-ligand charge transfer (MLCT) transitions in the visible range showed opposite Cotton effects (Δε₄₉₁ = –17, Δε₅₉₂ =

[*] Dr. J. Lacour, J. J. Jodry, C. Ginglinger, S. Torche-Halldimann
Département de Chimie Organique
Université de Genève
quai Ernest Ansermet 30, CH-1211 Genève 4 (Switzerland)
Fax: (+41) 22-328-73-96
E-mail: lacour@sc2a.unige.ch

[**] We are grateful for financial support of this work by the Swiss National Science Foundation. We thank Dr. P. Kamalaprija, Mr. A. Pinto, Mr. J.-P. Saulnier, Mr. W. Kloeti, and Mrs. E. Sandmeyer for NMR and MS measurements.

+19 M⁻¹ cm⁻¹). The CD spectrum of (2)(*M*-1)₂ is the mirror image of that of (2)(*P*-1)₂. These spectra can be assigned to the *P* and *M* configurations of the cationic complexes, demonstrating that 3_{*P*} and ent-3_{*P*} are the major diastereomers.^[9] Therefore, with the decrease of the polarity of solvent, a highly asymmetric induction has taken place in solution favoring the diastereomeric ion pairs 3_{*P*} and ent-3_{*P*}. As a consequence, the equilibria 3_{*P*} ⇌ 3_{*M*} and ent-3_{*P*} ⇌ ent-3_{*M*} have been shifted towards these two preferred complexes (Scheme 1). The increase in diastereoselectivity with decreasing polarity is interpreted as the result of closer interactions between the ions.^[10]



Scheme 1. Shift of the equilibrium in favor of the homochiral diastereomeric ion pair (P-2)(P-1)₂ ≡ 3_{*P*} rather than the heterochiral (M-2)(P-1)₂ ≡ 3_{*M*}.

The derivatives 3_{*P*} and ent-3_{*P*} correspond to the homochiral association of the chiral, helical ions: Octahedral tris-bidentate complexes such as 1 and 2 adopt propellerlike structures and exist as enantiomers, *P* (Δ) or *M* (Λ) (right- or left-handed propellers), which can combine in either a homochiral (Δ-Δ, Λ-Λ) or a heterochiral relationship (Δ-Λ). Prior to our study, it had been shown that the packing of molecular propellers depends on many parameters and particularly on their relative stereochemistry.^[11] Experimental and computer modeling studies on monolayers of tris(bisimine)ruthenium(II) complexes have shown that either homochiral or heterochiral association could be preferred depending upon the spatial arrangement of the propellers.^[11d, e, 12] Enantioselective quenching experiments on excited states and ion-association reactions recently demonstrated that both homochiral or heterochiral “encounter” pairs can be favored in solution depending upon the solvent and the structure of the molecular propellers involved: Low to good selectivities were obtained in those studies performed in polar protic media.^[13]

Herein we have shown that for the two particular molecular propellers 1 and 2, the homochiral mode of association is favored in a solvent of low polarity and proceeds with high selectivity. Further studies are being conducted to determine the nature of the supramolecular assembly of the ions^[14] and the geometric parameters favoring the high diastereoselectivity.

Keywords: asymmetric amplification • ion pairs • iron • phosphorus • supramolecular chemistry

- [1] P. Pfeiffer, K. Quehl, *Chem. Ber.* **1931**, 64, 2667–2671.
- [2] a) S. Kirschner, N. Ahmad, C. Munir, R. J. Pollock, *Pure Appl. Chem.* **1979**, 51, 913–923; b) D. J. Owen, G. B. Schuster, *J. Am. Chem. Soc.* **1996**, 118, 259–260; c) D. J. Owen, D. VanDerveer, G. B. Schuster, *J. Am. Chem. Soc.* **1998**, 120, 1705–1717; d) B. Norden, F. Tjernereld, *FEBS Lett.* **1976**, 67, 368–370.
- [3] J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem.* **1997**, 109, 660–662; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 608–609.
- [4] Typical barriers of inversion for tris(bisimine)iron(II) complexes are in the range of 20–28 kcal mol⁻¹: a) R. G. Wilkins, *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, 2nd ed., VCH, Weinheim, **1991**; b) L. Seiden, F. Basolo, H. M. Neumann, *J. Am. Chem. Soc.* **1959**, 81, 3809–3813; c) F. M. Van Meter, H. M. Neumann, *J. Am. Chem. Soc.* **1976**, 98, 1388–1394.
- [5] Salts [Bu₃NH⁺](rac-1), [Bu₃NH⁺](*M*-1) (83% ee^[6]) or (cinchonidium)(*P*-1) (100% de^[3, 8]) were used.
- [6] TRISPHAT is an efficient phase-transfer reagent for cationic species: J. Lacour, A. Londez, unpublished results.
- [7] Compounds (2)(1)₂ were fully characterised by NMR (¹H, ¹³C, ³¹P), IR, and UV spectroscopy as well as CD, mass spectrometry, and combustion analysis.
- [8] TRISPHAT is an efficient NMR chiral shift agent for tris(bisimine)-ruthenium(II) complexes: J. Lacour, C. Ginglinger, F. Favarger, S. Torche-Haldimann, *Chem. Commun.* **1997**, 2285–2286.
- [9] A. J. McCafferty, S. F. Mason, B. J. Norman, *J. Chem. Soc. A* **1969**, 1428–1441.
- [10] A. Loupy, B. Tchoubar, *Salt Effects in Organic and Organometallic Chemistry*, 1st ed., VCH, Weinheim, **1992**.
- [11] a) R. Kuroda, S. F. Mason, C. D. Rodger, R. H. Seal, *Mol. Phys.* **1981**, 42, 33–50; b) R. Kuroda, P. Biscarini, *J. Chem. Soc. Dalton Trans.* **1990**, 3393–3397; c) R. Kuroda, *Inorg. Chem.* **1991**, 30, 4954–4959; d) J. Breu, P. Belser, H. Yersin, *Acta Crystallogr. Sect. C* **1996**, 52, 858–861; e) J. Breu, A. J. Stoll, *Crystallogr. Sect. C* **1996**, 52, 1174–1177.
- [12] a) J. Breu, K. J. Range, *Monatsh. Chem.* **1994**, 125, 141–151; b) J. Breu, C. R. A. Catlow, *Inorg. Chem.* **1995**, 34, 4504–4510; c) H. Sato, A. Yamagishi, S. Kato, *J. Am. Chem. Soc.* **1992**, 114, 10933–10940; d) A. Yamagishi, Y. Goto, M. Taniguchi, *J. Phys. Chem.* **1996**, 100, 1827–1832.
- [13] a) A. G. Lappin, R. A. Marusak, *Coord. Chem. Rev.* **1991**, 109, 125–180; b) A. Tatehata, T. Mitani, *Chem. Commun.* **1996**, 1033–1034; c) C. L. Maupin, S. C. J. Meskers, H. P. J. M. Dekkers, J. P. Riehl, *Chem. Commun.* **1996**, 2457–2458; d) J. P. Bolender, D. H. Metcalf, F. S. Richardson, *Chem. Phys. Lett.* **1993**, 213, 131–138, and references therein.
- [14] J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, 1st ed., VCH, Weinheim, **1995**, pp. 138–197.

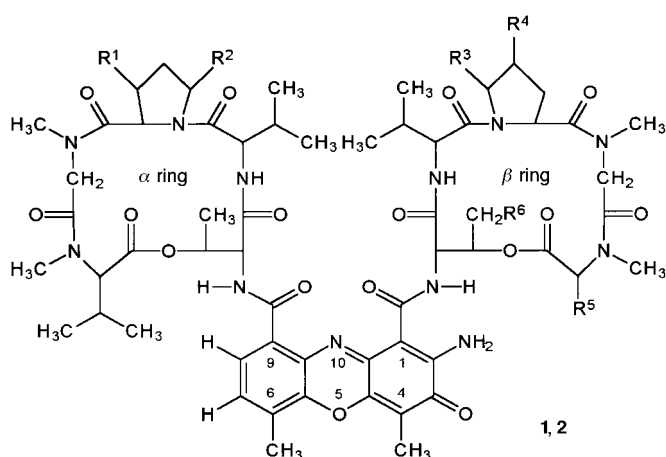
Received: February 11, 1998 [Z11466IE]
German version: *Angew. Chem.* **1998**, 110, 2522–2524

Crystal Structures of Actinomycin D and Actinomycin Z^{***}

Martina Schäfer, George M. Sheldrick,* Isabel Bahner, and Helmut Lackner*

In memory of Hans Brockmann

Actinomycins are antibiologically and cytostatically highly effective chromopeptides isolated from *Streptomyces* cultures, of which over thirty native and many synthetic variants are known.^[1] All possess the same chromophore, a 2-amino-phenoxazin-3-one system, which is coupled by acid amides to two identical or different pentapeptide lactone (depsipeptide) rings (*iso*- and *aniso*-actinomycins, respectively). Actinomycin D (= C₁, **1**; Scheme 1) has been most intensively investigated; in spite of its high toxicity it is employed inter alia for therapy of rare diseases such as the Wilms tumor. The mode of action of the actinomycins is particularly interesting from the standpoint of molecular biology.



Scheme 1. Actinomycin D (= C₁, **1**): R¹ = H, R² = H, R³ = H, R⁴ = H, R⁵ = CH(CH₃)₂, R⁶ = H; actinomycin Z₃ (**2**): R¹ = OH, R² = CH₃, R³ = CH₃, R⁴ = O, R⁵ = CH₃, R⁶ = Cl.

This involves—as proposed already in 1968^[2] and later verified by NMR spectroscopy^[3] and X-ray structural analysis of the actinomycin/deoxyguanosine^[4] and DNA octamer complexes^[5, 6]—an insertion (intercalation) of the chromophore between two guanine/cytosine (GC) base pairs of the double-stranded helical DNA. The two depsipeptide rings fit into the minor groove of the DNA, and each forms two hydrogen bonds between the NH and CO groups of the threonine units and the neighbouring nitrogen atoms of the

guanine bases; in addition there are two hydrogen bonds from the 2-amino group to a phosphate oxygen atom of the DNA. The hydrophobic amino acids of both depsipeptide rings (Pro, Sar, MeVal) lie on the GC base pairs on either side of the insertion position of the chromophore, whereby adjacent hydrophobic adenine/thymine base pairs have a stabilizing influence.^[7] These amino acid/DNA contacts protect the essential hydrogen bonds against competition reactions with nearby water molecules. As a result of intercalation of the actinomycin the spatial structure of the DNA is slightly distorted, which leads to an obstruction of the DNA-dependent RNA synthesis and DNA replication; one molecule in 1000 base pairs suffices for an effect.^[2] The activity of the antibiotic is extremely sensitive to chemical structural changes; it is reduced to zero by, for example, the opening of one depsipeptide ring or the replacement of the methyl groups on the chromophore by *tert*-butyl or CF₃ groups.^[8]

Attempts to solve the crystal structure of an uncomplexed actinomycin have been made since about 1960. Bachmann and Müller^[9] obtained one rhombohedral and two monoclinic forms of actinomycin C₃,^[10] which, however, appeared to be twinned about a pseudo-twofold axis. Palmer et al.^[11] found a further probably monoclinic crystal form with a similar twinning; a structural model could not be obtained. The first real crystal structure determination of actinomycin D occurred in 1988.^[12] Ginell et al. found the same crystal form as Palmer et al. had previously, but were able to solve the structure in the space group *P*1. However, as a result of the very weak data (maximum resolution 1.1 Å) as well as the twinning, it was only possible to refine the structure as a rigid group to an *R* value of 14%.

We have now been able to obtain for the first time untwinned crystals that diffracted to atomic resolution of two actinomycins, actinomycin D (**1**) and actinomycin Z₃ (**2**); the constitution of the latter was only recently elucidated by Shigamatsu et al.^[13] Of particular interest here are the conformations of the α - and β -depsipeptide rings in the uncomplexed state, their intramolecular interactions, and the packing of the actinomycin molecules in the crystal lattice, including their hydrophobic and hydrophilic contacts to one another and to solvent molecules.

Actinomycin D (**1**) crystallized out of ethyl acetate/methanol as orange-red single crystals with the triclinic space group *P*1.^[14] The unit cell of **1**, referred to subsequently as **1***, contains three independent molecules of **1** (A, B, and C) together with one methanol and seven ethyl acetate molecules. By way of example, Figure 1 shows three views of molecule C. The geometry of A, B, and C is almost identical, whereby A and B, with a root mean square deviation (rmsd) of only 0.29 Å, fit one another better than A and C (0.71 Å) or B and C (0.78 Å). Each molecule possesses approximately *C*₂ symmetry; the pseudo-twofold axis runs through the line joining O5 and N10. Only the unsymmetrical substitution at C2 and C3 of the chromophore prevents the presence of a genuine twofold axis. In each of the three molecules, two antiparallel hydrogen bonds are formed between the amide nitrogen atom of the D-valine residue of the α ring and the carbonyl oxygen atom of the D-valine residue of the β ring, and vice versa (Table 1). These hydrogen bonds stabilize the

[*] Prof. G. M. Sheldrick, Dr. M. Schäfer
Institut für Anorganische Chemie der Universität
Tammannstrasse 4, D-37077 Göttingen (Germany)
Fax: (+49) 551-392-582
E-mail: gsheldr@shelx.uni-ac.gwdg.de
Prof. Dr. H. Lackner, Dipl.-Chem. I. Bahner
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-399-660

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

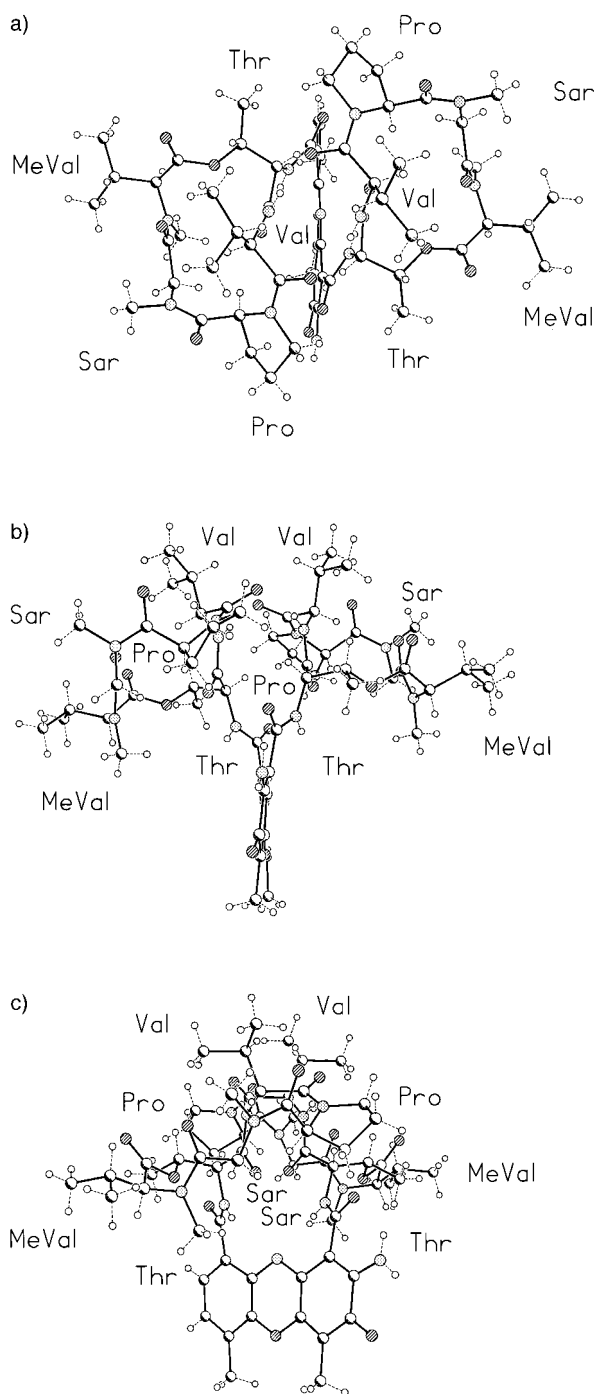


Figure 1. Three-dimensional structure of **1** (molecule C in the unit cell **1***). a) Top view: the β -depsipeptide ring is shown on the right, and the α ring on the left; the 2-amino group of the chromophore that lies under the depsipeptides points downwards. b) Side view: the β ring lies again on the right; the 2-amino group extends forwards. Underneath on the flat chromophore that is then inserted between the GC base pairs of the DNA one can recognize the methyl groups that are important for the stability of the complex. c) Front view: the chromophore (bottom) is bent slightly by the voluminous and conformationally stiff depsipeptide rings (see also b). Thr = L-threonine, Val = D-valine, Pro = L-proline, Sar = sarcosine, MeVal = *N*-methyl-L-valine. The dotted atoms are N, and the shaded are O atoms.

“A” conformation^[15] of the depsipeptide rings present here, and are thus consistent with all previously observed conformations in the solid state^[4–6, 16] and in solution.^[17] The

Table 1. Distances [Å] in several important intramolecular hydrogen bonds in **1*** and **2***.

	A	B	C	D	E
$N(\text{Val}_\beta) \cdots O(\text{Val}_\alpha)$	2.91	2.93	2.93	3.00	2.90
$N(\text{Val}_\alpha) \cdots O(\text{Val}_\beta)$	2.87	2.87	2.86	2.88	2.91
$N2 \cdots O(\text{C1} - \text{CO})$	2.74	2.77	2.62	2.68	2.68
$N(\text{Thr}_\beta) \cdots N10$	–	–	2.76	2.81	2.81
$N(\text{Thr}_\alpha) \cdots N10$	–	–	2.83	2.96	2.94

superposition of the six depsipeptide rings from A – C gives a maximum rmsd of only 0.29 Å.

Molecules A and B form a dimer across a pseudo-twofold axis. The chromophores are stacked parallel to one another with a shortest distance of 3.43 Å (Figure 2). The amide

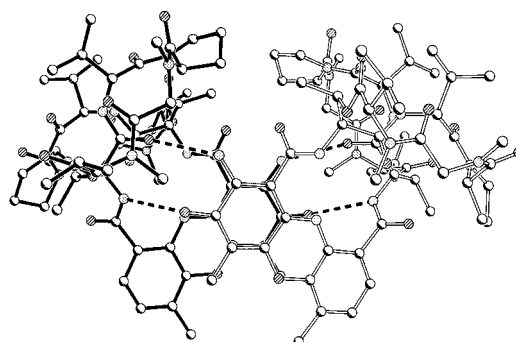


Figure 2. The dimer of the molecules A and B in **1***. Molecule A is indicated by solid bonds, and B by open bonds. The twofold axis runs perpendicular between the chromophore systems that are stacked with their quinone rings overlapping. The dashed bonds correspond to the hydrogen bonds.

nitrogen and carbonyl oxygen atoms of the threonine residue in the α -depsipeptide rings of A and B form two antiparallel hydrogen bonds to O3 and N2, respectively, of the chromophore of the corresponding other molecule ($N(\text{Thr}_\alpha) \cdots O3$ 3.07 and 3.13 Å, respectively; $N2 \cdots O(\text{Thr}_\alpha)$ 2.94 and 2.96 Å, respectively). Since, however, in the **1**/DNA complex these groups are bonding partners for the GC base pairs, the above dimerization is clearly only stable in the free actinomycin D.^[18] Molecule C shows no signs of dimerization; there is only a weak interaction between the 2-amino group of the chromophore and the carbonyl oxygen atom of the β -ring proline of molecule B of a neighboring asymmetric unit ($N2 \cdots O(\text{Pro}_\beta)$ 3.03 Å). This CO group also forms a hydrogen bond to a methanol molecule ($O(\text{Me}) \cdots O(\text{Pro}_\beta)$ 2.83 Å). The ethyl acetate molecules that are distributed throughout the cell do not enter into such interactions.

Actinomycin **Z₃** (**2**) was recently isolated in pure form as an important component of the actinomycin Z mixture, and the amino acid sequence of its α - and β -depsipeptide rings was elucidated.^[13] It is—together with actinomycin **Z₅**, which was first characterized at the same time—the first native chlorine-containing actinomycin, and displays the very rare 4-chloro-L-threonine (ClThr) instead of L-threonine in the β -depsipeptide ring. Furthermore the β ring contains *N*-methyl-L-alanine (MeAla) and *cis*-5-methyl-4-oxo-L-proline (MOPro) instead of *N*-methyl-L-valine and L-proline, respectively, and

the α ring contains *trans*-3-hydroxy-*cis*-5-methyl-L-proline (HMPPro) instead of L-proline.

Red single crystals of **2** suitable for X-ray analysis were obtained from benzene and have space group $P2_12_12_1$. Unlike the structure of **1** there are only two independent molecules (D and E) in the asymmetric unit,^[14] subsequently denoted by **2***. In addition, one water and twenty benzene molecules could be located in a difference Fourier synthesis; thus, this structure has a solvent content of 37.4% (**1***: 14.7%). Figure 3 shows the three-dimensional structure of molecule D in **2***.

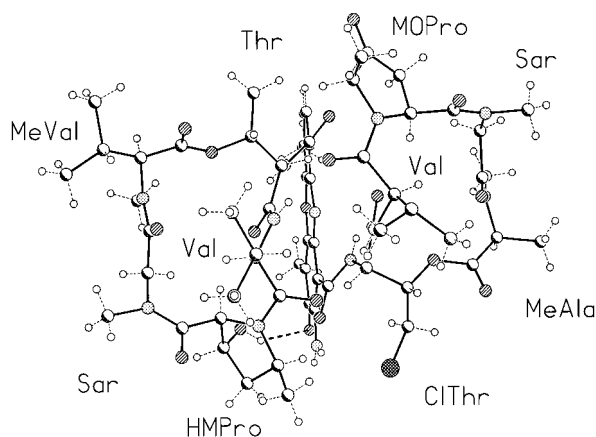


Figure 3. Three-dimensional structure of **2** in the unit cell **2***. The representation shown here with the β -depsipeptide ring on the right corresponds to that in Figure 2a. The thick dashed bond (bottom) marks the extra hydrogen bond from 3-O(HMPPro) to 1-CO on the chromophore. MeAla = *N*-methyl-L-alanine, MOPro = *cis*-5-methyl-4-oxo-L-proline, HMPPro = *trans*-3-hydroxy-*cis*-5-methyl-L-proline, CITHr = 4-chloro-L-threonine.

Although **2** also possesses pseudo- C_2 symmetry with the axis along the line connecting O5 and N10, it is much more strongly distorted than **1** as a result of the presence of different amino acids in the α - and β -depsipeptide rings. Both D-valine residues in **2** form, analogous in those in **1**, the reciprocal hydrogen bonds that stabilize the "A" conformation of the depsipeptide rings (Table 1). In addition, one finds an intramolecular hydrogen bond between the hydroxyl group of the hydroxymethylproline (α ring) and the 1-carbonyl oxygen atom on the chromophore (Figure 3; O(HMPPro) $\cdots$ O(1-CO) 2.82 Å in both D and E). The four depsipeptide rings in **2*** are again almost identical (maximum rmsd 0.33 Å); their conformations also correspond closely to those of the six depsipeptide rings in **1*** (rmsd 0.32 Å; Figure 4).

The independent molecules D and E in **2*** are also nearly identical (rmsd 0.24 Å). Their superposition onto molecule A in **1*** shows that the overall conformations of the two actinomycins **Z**₃ and D are comparable (rmsd 0.56 and 0.50 Å, respectively). A dimerization as in **1*** is, however, not to be found in **2***. Molecules D and E form a chain structure along the crystallographic a axis that is stabilized by intermolecular hydrogen bonds. The water molecule that had been located in the difference Fourier synthesis forms two hydrogen bonds, one to the carbonyl oxygen atom of the chlorothreonine (O(H₂O) $\cdots$ O(CITHr) 2.86 Å), and the other

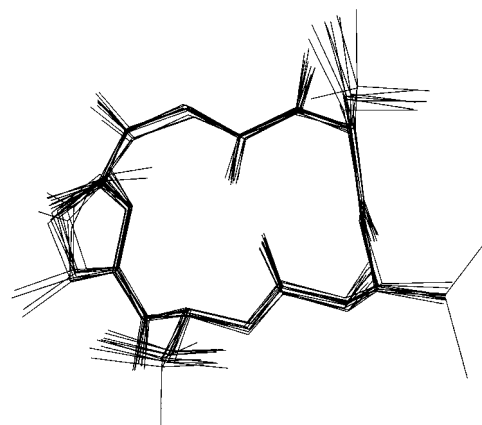


Figure 4. Least-squares fit of all ten depsipeptide rings of **1*** and **2*** on top of one another.

to the 9-carbonyl oxygen atom of the chromophore in molecule D (O(H₂O) $\cdots$ O(9-C) 2.99 Å).

Kamitori and Takusagawa^[6] showed in their study of an actinomycin/DNA complex that the depsipeptide rings can adapt their conformations by rotation about the bonds C1–CO and C9–CO in the chromophore, depending on the width of the minor groove. Thus, it is interesting to compare the corresponding torsion angles C2–C1–CO–N(Thr _{α}) and C8–C9–CO–N(Thr _{α}) (Table 2). One can recognize two trends here: The torsion angle in the β ring is larger than that in the α ring,

Table 2. Summary of the C2–C1–CO–N(Thr) and C8–C9–CO–N(Thr) torsion angles [°] in **1*** and **2*** (molecules A–E) as well as in the actinomycin/desoxyguanosine complex (F)^[4] and actinomycin/DNA complex (G).^[5]

	A	B	C	D	E	F	G
α ring	131.8	115.1	141.2	128.4	130.7	101	89.7
β ring	141.8	140.2	151.7	144.9	150.2	112	91.3

and from the free actinomycin (molecules C, D, E) through the dimer (A, B) to the complexed actinomycin (F, G), these angles become smaller.

In free actinomycin the threonine nitrogen atoms are forced towards each other in the direction of the chromophore plane, so that they have weak intramolecular interactions with N10 of the chromophore (Table 1). In the dimer the N(Thr) atoms are rotated further out of the chromophore plane (torsion angles 131.8 and 115.1°, respectively), the intramolecular saturation is lost,^[19] and the α -ring amide nitrogen atom can take part in intermolecular interactions. In the actinomycin/DNA complex (torsion angles about 90°) the amide nitrogen atoms stick right out of the chromophore plane and can now make the essential hydrogen bonds to the guanine residue of the DNA. The rotational freedom of the conformationally otherwise relatively inflexible depsipeptide rings about the C1–CO and C9–CO axes, together with that about the N–C bonds of the threonine residues,^[20] makes it possible for the actinomycin molecule to reorientate the α - and β -depsipeptide rings so far that they can be fitted optimally into the minor groove. When the depsipeptide rings are structurally appreciably different, as in the *aniso*-actinomycin **Z**₃ (**2**), the

resulting lack of symmetry of the whole molecule (Figure 3) should make the adaption and intercalation process more difficult. If then amino acid variants that are more hydrophilic weaken the important hydrophobic contacts of the depsipeptide rings with the adenine/thymine base pairs of the DNA, the reduction in the biological activity observed for actinomycins of the Z type becomes plausible.

Several factors played decisive roles in the final elucidation of the precise structure of the actinomycins: First, the growing of untwinned crystals, which was successful here for the actinomycins for the first time, was an essential precondition. The collection of high-resolution data sets was achieved by the use of low temperatures, an intensive X-ray beam, and an area detector, and led to much more detailed insights into the three-dimensional structures of the molecules. Finally the development of new ab initio methods of solving structures, as they are implemented in the program SHELXD,^[21] now makes the automated determination of structures with more than about 200 independent non-hydrogen atoms possible. The solution of these two structures on a Pentium processor required several hours. A solution of the structure of **1*** with 314 non-hydrogen atoms in the asymmetric unit with traditional direct methods would have been unthinkable. The determination of the structures of further actinomycins and other interesting "large small molecules" can thus be anticipated in the near future.

Received: March 23, 1998 [Z 11626IE]

German version: *Angew. Chem.* **1998**, *110*, 2482–2485

Keywords: actinomycins • antibiotics • dimerizations • structure elucidation

- [1] a) S. A. Waksman, H. B. Woodruff, *Proc. Soc. Exp. Biol. Med.* **1940**, *45*, 609–614; b) H. Brockmann, *Fortschr. Chem. Org. Naturst.* **1960**, *18*, 1–54; *Angew. Chem.* **1960**, *72*, 939–947; c) A. B. Mauger in *Topics in Antibiotic Chemistry*, Vol. 5 (Ed.: P. G. Sammes), Ellis Horwood, Chichester, **1980**, pp. 224–306.
- [2] W. Müller, D. M. Crothers, *J. Mol. Biol.* **1968**, *35*, 251–290.
- [3] a) D. J. Patel, *Biochemistry* **1974**, *13*, 2396–2402; b) C. Lian, H. Robinson, A. H.-J. Wang, *J. Am. Chem. Soc.* **1994**, *116*, 4154–4165; c) R. M. Wadkins, E. A. Jares-Erijman, R. Klement, A. Rüdiger, T. M. Jovin, *J. Mol. Biol.* **1996**, *262*, 53–68.
- [4] S. C. Jain, H. M. Sobell, *J. Mol. Biol.* **1972**, *68*, 1–20.
- [5] a) S. Kamitori, F. Takusagawa, *J. Mol. Biol.* **1992**, *225*, 445–456; M. Shinomiya, W. Chu, R. G. Carlson, R. F. Weaver, F. Takusagawa, *Biochemistry* **1995**, *34*, 8481–8491.
- [6] S. Kamitori, F. Takusagawa, *J. Am. Chem. Soc.* **1994**, *116*, 4154–4165.
- [7] Three different conformations of DNA/actinomycin D complexes are described in reference [6]; the depsipeptide rings adapt themselves to the appropriate "size" of the minor groove of the DNA.
- [8] a) H. Lackner, *Chem. Ber.* **1970**, *103*, 2476–2500; b) A. Giencke, H. Lackner, *Liebigs Ann. Chem.* **1990**, 569–579.
- [9] a) H. G. Bachmann, W. Müller, *Nature* **1964**, *201*, 261–264; b) M. F. Perutz, *Nature* **1964**, *201*, 814.
- [10] In actinomycin C₃ both D-valine subunits of actinomycin D are replaced by D-allo-isoleucine.
- [11] H. T. Palmer, R. A. Palmer, R. E. Dickerson, *Nature* **1964**, *202*, 1052–1057.
- [12] S. Ginell, L. Lessinger, H. M. Berman, *Biopolymers* **1988**, *27*, 843–864.
- [13] N. Shigematsu, L. K. Pannell, A. B. Mauger, I. Bahner, H. Lackner, *J. Nat. Prod.*, submitted.

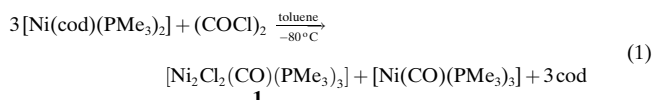
- [14] a) Crystallographic data for **1***: 3C₆₂H₈₆N₁₂O₁₆ + 7C₄H₈O₂ + CH₃OH, *M_r* = 4410, triclinic, space group *P*1, *a* = 15.737(5), *b* = 15.887(5), *c* = 25.156(10) Å, *α* = 85.93(1), *β* = 86.19, *γ* = 69.86(1), *V* = 5883.6(4) Å³, *Z* = 1, *ρ*_{calcd} = 1.246 Mg m^{−3}, *F*(000) = 2364, = 1.54178 Å, *T* = 133 K, *μ*(CuKα) = 0.76 mm^{−1}, min./max. transmission 0.7251/0.9276, crystal dimensions 0.45 × 0.45 × 0.1 mm³, 2.72° ≤ 2 θ ≤ 108.16°. Of 65014 measured data, 14126 were independent (*R*_{int} = 0.0444, Friedel mates merged), refinement: 2875 parameters, 3689 restraints, *R*1 = $\Sigma |F_o - F_c| / \Sigma F_o = 0.0545$ (*I* > 2 σ (*I*)) and *wR*2 = $[\Sigma w(F_o^2 - F_c^2)^2 / \Sigma wF_o^4]^{1/2} = 0.1477$ (all data); min./max. difference electron density −0.47/0.71 e Å^{−3}.^[14c] b) Crystallographic data for **2***: 2C₆₂H₈₃N₁₂O₁₈Cl + 20C₆H₆ + H₂O, *M_r* = 4219.8, orthorhombic, space group *P*2₁2₁2₁, *a* = 14.803(3), *b* = 24.780(5), *c* = 65.069 (10) Å, *V* = 23865(8) Å³, *Z* = 4, *ρ*_{calcd} = 1.174 Mg m^{−3}, *F*(000) = 9000, *λ* = 1.54178 Å, *T* = 173 K, *μ*(CuKα) = 0.838 mm^{−1}, min./max. transmission 0.7304/0.7871, crystal dimensions 0.4 × 0.3 × 0.3 mm³, 2.72° ≤ 2 θ ≤ 108.16°. Of 112696 data, 15653 were independent (*R*_{int} = 0.0602, Friedel mates merged). Refinement: 3024 parameters, 5470 restraints, *R*1 = $\Sigma |F_o - F_c| / \Sigma F_o = 0.0666$ (*I* > 2 σ (*I*)), *wR*2 = $[\Sigma w(F_o^2 - F_c^2)^2 / \Sigma wF_o^4]^{1/2} = 0.1820$ (all data); min./max. difference electron density: −0.343/0.357 e Å^{−3}. The chlorine atom in molecule E is disordered over two positions with occupancies of 0.85:0.15. Four of the twenty benzene molecules are also disordered over two positions and refined to occupancies of 0.55:0.45, 0.45:0.55, 0.57:0.43, and 0.63:0.37. Intensity data for **1*** and **2*** were recorded for shock-cooled crystals mounted in oil drops^[22] on a three-circle diffractometer with a multiwire proportional area detector with φ and ω scans. The reflections were integrated with the program SAINT. All data were corrected semi-empirically for systematic errors such as absorption. The structures were solved by direct methods (SHELXD)^[21] and refined against *F*² by least squares.^[23] All non-hydrogen atoms could be refined anisotropically. The hydrogen atoms were placed in geometrically ideal positions and refined with a riding model, in which the methyl groups (except those of solvent molecules) could rotate about their local threefold axes. All disorders could be resolved and refined anisotropically with the help of distance and ADP restraints. The crystallographic data of the structures described in this publication have been deposited with the Protein Data Bank (PDB), Brookhaven National Laboratory, under the codes 1A7Y und 1A7Z.
- [15] In the "A" form the peptide bonds from L-threonine up to L-methylvaline adopt the conformations *trans*, *cis*, *cis*, *trans*.^[17]
- [16] E. Pohl, G. M. Sheldrick, S. Fischer, H. Lackner, *Acta Crystallogr. Sect. C* **1994**, *50*, 100–103.
- [17] H. Lackner, *Angew. Chem.* **1975**, *87*, 400–411; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 375–386.
- [18] A different type of dimerization was deduced from NMR data for aqueous solutions of actinomycin D: The chromophores overlap more strongly, but no intermolecular hydrogen bonds are formed in this model.^[24]
- [19] The distances between the threonine nitrogen atoms and N10 (2.88 Å in A, 2.94 Å in B) are in the range for hydrogen bonds, but this is not true of the N(Thr)-H(Thr)⋯N10 angles.
- [20] The corresponding torsion angles H-N(Thr)-C(Thr)-H lie in the range of 146.6° to 155.2° in all five molecules.
- [21] G. M. Sheldrick, SHELXD, CCP4 Workshop, York, **1997**, 147–157.
- [22] T. Kottke, D. Stalke, *J. Appl. Crystallogr.* **1993**, *26*, 615–619.
- [23] G. M. Sheldrick, T. R. Schneider, *Methods Enzymol.* **1997**, *277*, 319–343.
- [24] N. S. Angerman, T. A. Victor, C. L. Bell, S. S. Danyluk, *Biochemistry* **1972**, *11*, 2402–2411.

Dichlorodinickel(0) Complexes with μ^2 -CO or μ^2 -CS Bridges and Trimethylphosphane Ligands: Homologous Composition, but Different Frameworks**

Hans-Friedrich Klein,* Andreas Schmidt, Ulrich Flörke, and Hans-Jürgen Haupt*

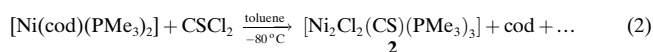
It has long been known that reduction of metal halides in the absence of suitable supporting ligands results in cluster formation if metal–metal bonds and/or additional ligand bridges can be formed.^[1] In the first steps of such condensation reactions highly reactive dinuclear intermediates with low coordination numbers of metals in low oxidation states play an important role. Starting with nickel in the presence of trimethylphosphane and an appropriate source of carbonyl or thiocarbonyl ligands, we have found conditions which lie on the border of metal deposition and allow the isolation and characterization of coordinatively unsaturated dinickel compounds in the formal oxidation state +I.

At -80°C in the absence of coordinating solvents, $[\text{Ni}(\text{cod})(\text{PMe}_3)_2]$ (cod = 1,5-cyclopentadiene) reacts with oxalyl chloride according to Equation (1) to give a violet solution which is stable at 20°C . Addition of pentane and cooling led to precipitation of black crystals of **1**.^[2]



Complex **1** dissolves readily in diethyl ether or THF to give a deep blue solution. However, the clear solutions in THF deposit a brown solid after 30 min at 20°C , and after 3 h $[\text{Ni}(\text{CO})(\text{PMe}_3)_3]$ and NiCl_2 are found as main products. Solutions in diethyl ether or toluene are more stable and afford single crystals on cooling.

Parallel to the carbonyl complex **1**, we obtained the thiocarbonyldinickel complex **2** of analogous composition which, however, differs substantially from **1** with respect to chemical properties and structure. At -80°C in the absence of coordinating solvents $[\text{Ni}(\text{cod})(\text{PMe}_3)_2]$ reacts with thiophosgene according to Equation (2) to give a red solution which is stable at 20°C and produces a red oil on evaporation. Within a few hours or after some days, the oily phase forms shiny black needles of the toluene solvate $\mathbf{2} \cdot \text{C}_7\text{H}_8$. Under diethyl ether **2** forms a sparingly soluble red oil. Clear solutions in THF are stable up to 70°C , in contrast to the carbonyl compound **1**.



[*] Prof. Dr. H.-F. Klein, Dipl.-Ing. A. Schmidt
Institut für Anorganische Chemie der Technischen Universität
Petersenstrasse 18, D-64287 Darmstadt (Germany)
Fax: (+49) 6151-164173
E-mail: hfklein@hrz2.hrztu-darmstadt.de
Prof. Dr. H.-J. Haupt, Dr. U. Flörke
Anorganische und Analytische Chemie der Universität-GH
Warburger Strasse 100, D-33095 Paderborn (Germany)

[**] Support of this work by the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie is gratefully acknowledged.

The molecular structure of **1**^[3] (Figure 1) consists of a hook-shaped backbone of two nickel and two chlorine atoms in a plane which also accommodates the μ^2 -CO ligand and, at the

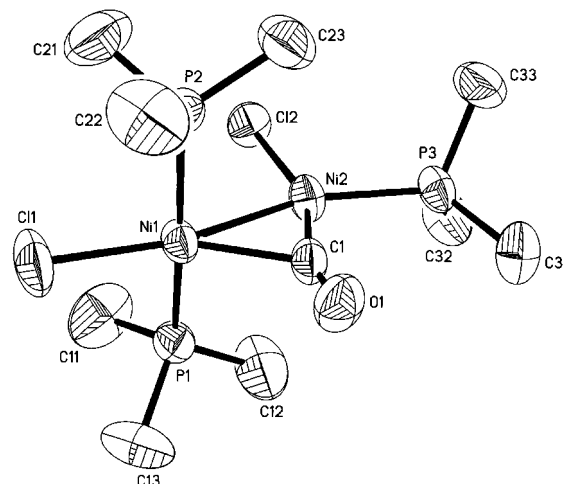


Figure 1. Molecular structure of **1**; selected bond lengths [Å] and angles [°]: Ni1–Ni2 2.3642(14), Ni1–C1 1.999(6), Ni2–C1 1.730(8), Ni1–P1 2.212(2), Ni1–P2 2.215(2), Ni2–P3 2.169(2), Ni1–Cl1 2.223(2), Ni2–Cl2 2.252(2), C1–O1 1.167(8); C1–Ni1–P1 93.2(2), C1–Ni1–P2 91.1(2), C1–Ni2–P3 103.5(2), P1–Ni1–P2 168.70(8), C1–Ni1–Ni2 45.8(2), C1–Ni2–Ni1 55.9(2), C1–Ni1–Cl1 150.3(2), C1–Ni2–Cl2 155.1(2), P3–Ni2–Ni1 159.37(7), Cl1–Ni1–Ni2 163.98(9), Cl2–Ni2–Ni1 99.34(7), P1–Ni1–Ni2 86.93(6), P2–Ni1–Ni2 88.59(6), P3–Ni2–Cl2 101.26(8), P1–Ni1–Cl1 90.73(8), P2–Ni1–Cl1 90.71(8), O1–C1–Ni1 122.3(5), O1–C1–Ni2 159.2(6), Ni1–C1–Ni2 78.3(3).

corner of the hook (Ni1–Ni2–Cl2 $99.34(7)^\circ$), one of the three P donor atoms. The remaining trimethylphosphane ligands are perpendicularly coordinated to Ni1. Disregarding the Ni–Ni interaction, one of the metal centers (Ni1) has an approximately square-planar coordination geometry, and the second (Ni2) a T-shaped environment. The angles within the T piece (Cl2–Ni2–C1 $155.1(2)^\circ$, Ni2–C1–O1 $159.2(6)^\circ$) are consistent with a highly unsymmetrical carbonyl bridge (semibridging mode), while the bridge angle Ni2–C1–Ni1 $78.3(3)^\circ$ leads to an Ni–Ni contact (2.3634(14) Å) in the region of a single bond, which is shorter than those reported for comparable dinickel complexes (2.439(1)–2.694(1) Å).^[4] The central bonding in the molecule may be described by a metal–metal bond of the donor–acceptor type and/or a three-center, two-electron bridge bond.

While the bridging carbonyl ligand of **1** is represented in the IR spectrum by a strong $\nu(\text{CO})$ band at 1830 cm^{-1} , which lies well within the range of terminal CO ligands and is in accord with an almost linear Ni2–C1–O1 angle, the fingerprint region of the spectrum down to 400 cm^{-1} displays the few absorptions typical for coordinated trimethylphosphane but without the expected band splitting.^[5] In the ^1H , ^{13}C , and ^{31}P NMR spectra (298–230 K) singlet resonances for trimethylphosphane are observed. At first sight these findings are inconsistent with the low molecular symmetry (Figure 1). Broadening and splitting of the ^{31}P signals (2:1, $\Delta\delta = 1.2$), which is independent of dilution, begin only at -80°C . This indicates extraordinarily high mobility of the ligands.^[6] To obtain a time-averaged

molecular C_{2v} symmetry in the atomic framework $Ni_2Cl_2COP_3$ on the NMR time scale, both metal centers must exchange their coordination geometries by shifting the CO bridge and by intramolecular migration of all other ligands. A schematic trajectory for the process is shown in Figure 2.

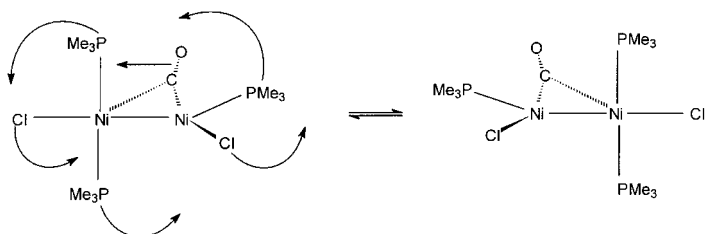


Figure 2. Intramolecular ligand migrations in **1**.

In contrast to the hook-shaped Cl–Ni–Ni–Cl framework of **1**, the structure of **2**^[7] (Figure 3) contains a roof-shaped Cl–Ni–Ni–Cl unit with a dihedral angle Cl1–Ni1–Ni2–Cl2 of 125.1°. A

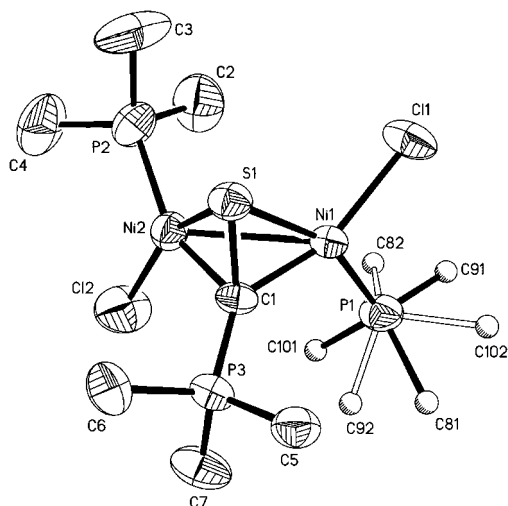
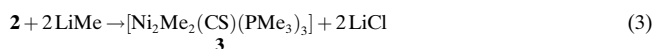


Figure 3. Molecular structure of **2**; selected bond lengths [Å] and angles [°]: Ni1–C1 1.874(7), Ni2–C1 1.918(7), Ni1–P1 2.149(2), Ni2–P2 2.179(3), Ni1–S1 2.201(2), Ni2–S1 2.158(2), Ni1–Cl1 2.205(2), Ni2–Cl2 2.187(3), Ni1–Ni2 2.7169(14), S1–C1 1.743(7), C1–P3 1.736(7); C1–Ni1–P1 107.0(2), C1–Ni1–S1 49.9(2), P1–Ni1–S1 156.43(10), C1–Ni1–Cl1 156.7(2), P1–Ni1–Cl1 95.99(9), S1–Ni1–Cl1 106.89(9), C1–Ni1–Ni2 44.9(2), P1–Ni1–Ni2 111.66(8), S1–Ni1–Ni2 50.74(6), Cl1–Ni1–Ni2 122.56(8), C1–Ni2–S1 50.2(2), C1–Ni2–P2 154.7(2), S1–Ni2–P2 107.76(10), C1–Ni2–Cl2 104.0(2), S1–Ni2–Cl2 152.71(11), P2–Ni2–Cl2 99.31(11), C1–Ni2–Ni1 43.6(2), S1–Ni2–Ni1 52.17(6), P2–Ni2–Ni1 115.32(8), Cl2–Ni2–Ni1 118.36(9), C1–S1–Ni2 57.7(2), C1–S1–Ni1 55.3(2), Ni2–S1–Ni1 77.10(7), P3–C1–S1 122.0(4), P3–C1–Ni1 138.2(4), S1–C1–Ni1 74.9(3), P3–C1–Ni2 129.1(4), S1–C1–Ni2 72.1(3), Ni1–C1–Ni2 91.5(3).

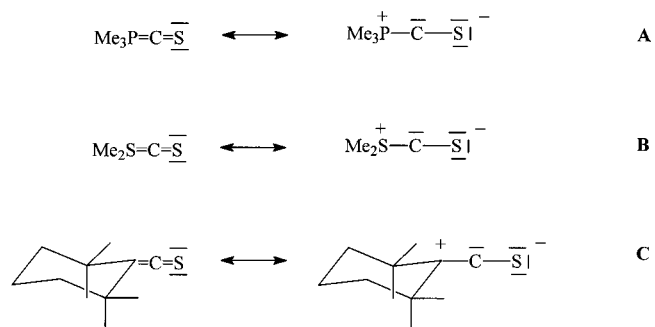
symmetrically bridging trimethylphosphonio- μ^2 -(CS) ligand is attached to the roof perpendicular to the Ni–Ni vector. The other two trimethylphosphane groups are coordinated to the ends of the dinickel unit in a transoid configuration. As the bridge angles (Ni2–C1–Ni1 91.5(3)°, Ni2–S1–Ni1 77.10(7)°) do not allow for a bonding Ni–Ni interaction (Ni1–Ni2 2.7169(14) Å), coordination of both metal centers can be described as quasitetrahedral. The ^1H NMR spectrum (298–

230 K) contains a doublet for the phosphonio group and two doublets for the trimethylphosphane ligands.

By reaction with methyllithium, which with **1** under the mildest conditions invariably leads to a deposition of elemental nickel, **2** is transformed into the novel dimethyldinickel compound **3** [Eq. (3)].



Brown crystals which are thermally stable up to 84 °C were obtained from pentane. Spectroscopic data in solution closely resemble those of **2** apart from the expected effects of higher electron density. Therefore, **3** is likely to arise from a substitution of the chloride ligands with retention of the remaining atomic framework. The dinuclear complexes **2** and **3** coordinate and stabilize one of the smallest representatives of the so-far unknown thiocarbonylphosphoranes **A**. As in the isoelectronic thiocarbonyl systems **B**^[8] and **C**,^[9, 10] the dipolar resonance form is favored by μ^2 -C μ^2 -S coordination perpendicular to the metal–metal vector (six-electron donor) and is largely independent of the bond angles in the bridge.



In contrast to **2** the NMR spectra of **3** suggest either a cisoid arrangement of methylnickel groups or fast exchange of ligands in solution gives the appearance of molecular C_s symmetry.

Experimental Section

1: Solutions of $[Ni(cod)(PMe_3)_2]$ (7.78 g, 24.4 mmol) in 80 mL of toluene and of oxalyl chloride (1.03 g, 8.11 mmol) in 30 mL of toluene were mixed at –80 °C. A yellow-brown color developed that, after warming to 20 °C, changed to violet. The solution was filtered, 70 mL of pentane was added, and the solution was kept at –27 °C for 14 h. The crystalline product was recrystallized from 400 mL of diethyl ether at –27 °C to give shiny black crystals; yield 1.57 g (44% with respect to oxalyl chloride), m.p. 153–155 °C (decomp); elemental analysis: calcd: C 27.03, H 6.12, Ni 26.41, P 20.90; found: C 27.35, H 5.88, Ni 26.35, P 20.86; ^1H NMR (200 MHz, $[D_8]$ toluene, 25 °C, TMS): δ = 1.39 (s); ^1H NMR (200 MHz, $[D_8]$ toluene/ CD_2Cl_2 , –80 °C, TMS): δ = 1.08 (s, 9H, PCH_3), 1.36 (s, 18H, PCH_3); ^{13}C NMR (75.4 MHz, CD_2Cl_2 , 25 °C, TMS): δ = 13.9 (s, PCH_3); ^{31}P NMR (81 MHz, CD_2Cl_2 , 25 °C, H_3PO_4): δ = –14.9 (s); ^{31}P NMR (81 MHz, $[D_8]$ toluene/ CD_2Cl_2 , –80 °C, H_3PO_4): δ = –0.8 (s, 1P), 0.4 (s, 2P).

2: Solutions of $[Ni(cod)(PMe_3)_2]$ (4.00 g, 12.5 mmol) in 40 mL of toluene and of freshly condensed thiophosgene (0.66 g, 5.70 mmol) in 30 mL of toluene were combined at –80 °C with vigorous stirring. The color changed from brown to red within a few minutes. After warming to 20 °C, the mixture was stirred for 1 h and filtered. Reducing the volume of the filtrate in vacuo afforded a red oil, which spontaneously crystallized within three days. Recrystallization from toluene at –70 °C afforded black needles of **2**.

C₇H₈; yield 1.15 g (36% with respect to thiophosgene), m.p. 88–90 °C, elemental analysis: calcd: C 36.94, H 6.38%, P 16.81; found: C 37.08, H 6.55, P 16.81; ¹H NMR (200 MHz, [D₆]acetone, 25 °C, TMS): δ = 1.28 (d, ³J(P,H) = 7.4 Hz, 9H, PCH₃), 1.42 (d, ³J(P,H) = 9.2 Hz, 9H, PCH₃), 1.98 (d, ³J(P,H) = 13.7 Hz, 9H, ⁺PCH₃), 2.30 (s, 3H, CCH₃), 7.17 (m, 5H, CH); ³¹P NMR (81 MHz, [D₆]acetone, 25 °C, H₃PO₄): δ = -9.9 (d, ³J(P,P) = 9 Hz, 1P, PCH₃), -4.5 (s, 1P, PCH₃), 26.9 (s, ³J(P,P) = 9 Hz, 1P, ⁺PCH₃).

3: To a solution of **2** (1.45 g, 2.62 mmol) in 40 mL of THF was added a solution of methylolithium in diethyl ether (3.3 mL, 1.6 M, 5.3 mmol) at -80 °C with vigorous stirring. The mixture turned light brown. Removing the volatile materials in vacuo, extracting the residue with 50 mL of pentane, and cooling to -27 °C for 10 h gave brown crystals; yield 0.68 g (62%); m.p. 84–88 °C (decomp), elemental analysis calcd for C₁₂H₃₃Cl₂Ni₂P₃S (419.8): C 34.36, H 7.92, P 22.14; found C 34.33, H 7.86, P 22.10; ¹H NMR (200 MHz, [D₈]THF, 25 °C, TMS): δ = -0.78 (s, 6H, NiCH₃), 1.18 (d, ²J(P,H) = 6.3 Hz, 18H, PCH₃), 1.66 (d, ²J(P,H) = 12.9 Hz, 9H, ⁺PCH₃); ¹³C NMR (75.4 MHz, [D₈]THF, 25 °C, TMS): δ = -24.1 (s, NiCH₃), 15.5 (d, ¹J(P,C) = 55.7 Hz, ⁺PCH₃), 17.0 (d, ¹J(P,C) = 9.5 Hz, PCH₃); ³¹P NMR (81 MHz, [D₈]THF, 25 °C, H₃PO₄): δ = -4.8 (s, PCH₃), 23.1 (s, ⁺PCH₃).

Received: April 8, 1998 [Z11704IE]

German version: *Angew. Chem.* **1998**, *110*, 2499–2502

Keywords: fluxional systems • metal–metal interactions • nickel • P ligands

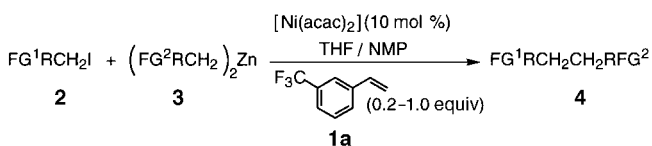
- [1] R. B. King, *Progr. Inorg. Chem.* **1972**, *15*, 287–473.
- [2] In toluene **1** is also obtained by treating [NiCl₂(PMe₃)₂] with [Fe₂(C₃H₅)₂(CO)₃(μ-SnMe₂)] or Na₂[Fe(CO)₄]·1.5 dioxane in 15% and 28% yield, respectively.
- [3] Crystal data for **1**: C₁₀H₂₇Cl₂Ni₂OP₃, *M_r* = 444.6; crystal dimensions: 0.55 × 0.45 × 0.15, monoclinic, space group *P*₂₁/*c*, *a* = 10.902(3), *b* = 16.923(4), *c* = 12.323(3) Å, β = 115.05(2)°, *V* = 2059(7) Å³, *Z* = 4, ρ_{calcd} = 1.434 g cm⁻³, *F*(000) = 920; 4611 reflections with 4.8 < 2θ < 55.0°, Siemens R3 diffractometer, MoK_α radiation (μ = 2.309 mm⁻¹), graphite monochromator. The structure was solved with direct methods (SHELXTLV5), refinement with 4413 independent reflections (*R*_{int} = 0.0344) for 173 parameters against |*F*²| with SHELXTLV5 gave *R* = 0.063, *wR*₂ = 0.192 (all data); max./min. residual electron density 1.143/–0.531 e Å⁻³. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at calculated positions.^[7b]
- [4] L. Manojlovic-Muir, K. W. Muir, W. M. Davis, H. A. Mirza, R. J. Puddephatt, *Inorg. Chem.* **1992**, *31*, 904–909.
- [5] Strong sharp bands were registered at 737 (ν_{as}(PC)) and 671 cm⁻¹ (ν_s(PC)).
- [6] A nickel complex in which two chelating (Ph₂P)₂CH₂ ligands are attached to a related atomic framework (μ-CO)Ni₂Cl₂ also shows fluxional behavior.^[4]
- [7] a) Crystal data for **2**: C₁₀H₂₇Cl₂Ni₂P₃S·C₇H₈, *M_r* = 552.7; crystal dimensions: 0.30 × 0.22 × 0.20 mm, monoclinic, space group *P*₂₁/*n*, *a* = 11.572(2), *b* = 9.229(1), *c* = 25.949(4) Å, β = 99.10(1)°, *V* = 2736.4(7) Å³, *Z* = 4, ρ_{calcd} = 1.342 g cm⁻³, *F*(000) = 1152; 6440 reflections with 5.4 < 2θ < 55.1°, Siemens R3 diffractometer, MoK_α radiation (μ = 1.824 mm⁻¹), graphite monochromator. The structure was solved by direct methods (SHELXTLV5), refinement of 6308 independent reflections (*R*_{int} = 0.0445) for 224 parameters against |*F*²| with SHELXTLV5 gave *R*₁ = 0.063, *wR*₂ = 0.171 (all data); max./min. residual electron density 0.599/–0.424 e Å⁻³. All non-hydrogen atoms except for the C atoms at P1 were refined anisotropically. Atoms C8–C10 were refined on split positions with mutual half occupation at a fixed distance *d*(PC). Hydrogen atoms were fixed at calculated positions. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC-101260 and -101267. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [8] D. Seyferth, G. B. Womack, M. Cowle, B. W. Hames *Organometallics* **1983**, *2*, 1696–1698.
- [9] H. Umland, F. Edelmann, D. Wormsbächer, U. Behrens *Angew. Chem.* **1983**, *95*, 148–149; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 152–153; *Angew. Chem. Suppl.* **1983**, 156–168.
- [10] W. Ziegler, H. Umland, U. Behrens, *J. Organomet. Chem.* **1988**, *344*, 235–247.

An Efficient Nickel-Catalyzed Cross-Coupling Between sp³ Carbon Centers

Riccardo Giovannini, Thomas Stüdemann, Gaëlle Dussin, and Paul Knochel*

The cross-coupling reaction between an organometallic species and an organic halide is an important method for forming a new carbon–carbon bond. Whereas transition metal catalyzed cross-coupling reactions between sp² carbon centers are well established^[1] and routinely applied even in complex syntheses,^[2] the cross-coupling reaction between two sp³ carbon centers often requires the use of stoichiometric amounts of organocuprates,^[3] which has several drawbacks. A nontransferred or nontransferable functional group is often wasted, and the moderate functional group diversity of lithium or magnesium cuprates^[4] often limits their application. Recently, we have shown that the presence of a double bond in the position γ to the carbon–halogen bond considerably facilitates the reductive-elimination step of the cross-coupling.^[5] The remote double bond coordinates to the nickel center and in this way removes electron density from the metal atom.^[6] Although it is mechanistically interesting, the required presence of the double bond in the iodoalkane reduces the synthetic scope of the reaction. Herein, we report that the addition of catalytic amounts of an unsaturated additive such as **1a** allows an efficient [Ni(acac)₂]-catalyzed cross-coupling reaction to be performed between various polyfunctional organic halides **2** and diorganozinc compounds **3** to give the cross-coupling products **4** (Scheme 1); this considerably extends the scope of the reaction.

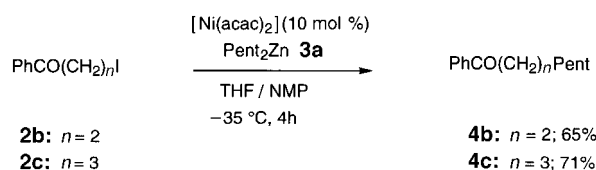


Scheme 1. Cross-coupling between sp³ carbon centers in the presence of cocatalysts **1a**. FG = functional group; NMP = *N*-methylpyrrolidone.

[*] Prof. Dr. P. Knochel, Dr. R. Giovannini, Dr. T. Stüdemann, Dipl.-Ing. G. Dussin
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
Fax: (+49) 6421-28-2189
E-mail: knochel@ps1515.chemie.uni-marburg.de

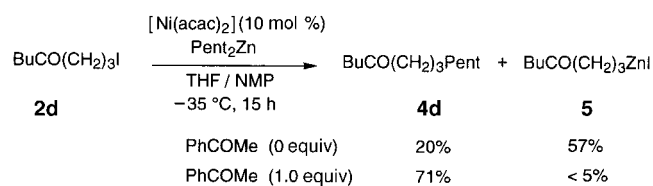
[**] We thank the Deutsche Forschungsgemeinschaft (SFB 260, Leibniz-program) and the Fonds der Chemischen Industrie for generous financial support. We thank Witco AG, BASF AG, Bayer AG, Chemetall GmbH, and SIPSY SA (France) for the generous gift of chemicals.

Preliminary results have shown that the Ni-catalyzed cross-coupling between an iodoalkane that does not contain a double bond for complexing to the nickel center could be improved upon adding an external olefin bearing an electron-withdrawing group. Thus, the reaction of 3-phenylpropyl iodide (**2a**) with dipentylzinc (Pent_2Zn ; **3a**) in the presence of $[\text{Ni}(\text{acac})_2]$ (7.5 mol %) in THF/NMP (2/1) at 25 °C (40 h) provides the cross-coupling product octylbenzene (**4a**) in a modest yield of 34 %. Upon addition of ethyl crotonate (**1b**; 1.0 equiv), the product **4a** can be isolated in 64 % yield (–25 °C, 24 h). Further evidence for cocatalysis by an external unsaturated ligand was obtained in the study of the cross-coupling reaction of 3-keto- and 4-ketoiodoalkanes (**2b–d**) with **3a**. The cross-coupling of **2b** and **2c** were fast and yielded the desired products **4b** (65 %) and **4c** (71 %; Scheme 2).



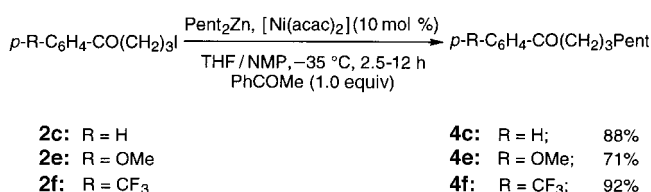
Scheme 2. Cross-coupling with oxygen group containing iodoalkanes **2b** and **2c**.

The reaction of the related iodoalkane **2d** with **3a** was, however, sluggish and provided a mixture of the cross-coupling product **4d** and the organozinc iodide **5**, which results from an iodine–zinc exchange reaction.^[7] This result shows that the keto group may play the same coordinating role as a double bond and that the organic group attached to the carbonyl moiety is important. Thus the addition of acetophenone (**1c**; 1.0 equiv) as an external ligand accelerates the reaction considerably and also suppresses completely the iodine–zinc exchange side reaction (less than 5 %) and provides the desired product **4d** in a 71 % yield (Scheme 3).



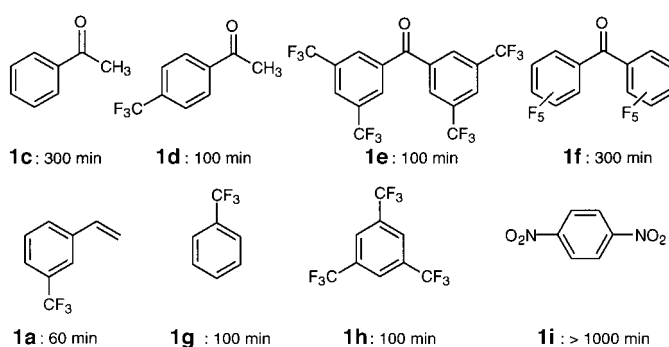
Scheme 3. Influence of acetophenone on the reaction of **2d** under the coupling conditions.

To evaluate the importance of the substitution pattern of the remote arylcarbonyl group, we have submitted the keto-substituted iodides **2c** and **2e–f** to our cross-coupling conditions and have observed that the most efficient cross-coupling was obtained with the iodide **2f**, in which the phenyl group bears a strong electron-withdrawing trifluoromethyl group (→**4f**, 92 %, Scheme 4). On the other hand, the cross-coupling with a methoxy-substituted phenyl ring was slow, and affords the lowest yield with the longest reaction time (**4e**, 71 % yield).



Scheme 4. Influence of the R group on the arylcarbonyl group on the coupling.

This study encouraged us to study more systematically the nature of the cocatalyst **1** by using the cross-coupling of 1-iodo-4-octanone (**2d**) with **3a** as a test reaction ($[\text{Ni}(\text{acac})_2]$ (10 mol %), THF/NMP, –35 °C) and adding between 0.2 and 1.0 equivalent of the cocatalysts **1a** or **1c–i**. The selection criteria for determining the best additive (**1**) was the conversion time and the amount of iodine–zinc exchange (Scheme 5). The introduction of trifluoromethyl substituents

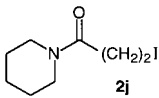
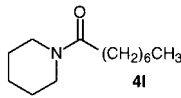
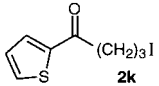
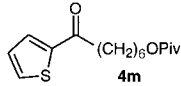
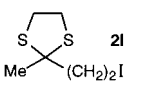
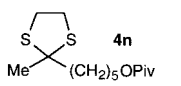
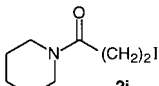
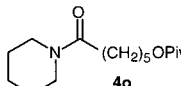
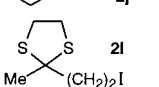
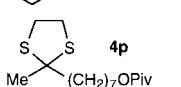
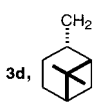
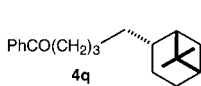
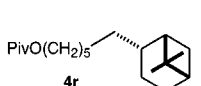


Scheme 5. Different cocatalysts and their influence of the cross-coupling of **2d** with **3a**.

increases the reaction rate (compare **1c** with **1d**, **1e**). The use of perfluorinated benzophenone (**1f**) was less efficient than that of various CF_3 -substituted benzenes such as **1g**^[8] or **1h**. Interestingly, 1,4-dinitrobenzene (**1i**) inhibits the cross-coupling reaction completely, thus indicating a possible radical pathway for the oxidative-addition step of the haloalkane to the nickel catalyst.^[9]

Although various additives such as **1d** or **1g** lead to fast cross-coupling reactions, all of these reactions were accompanied by the formation of iodine–zinc exchange products. However, *m*-trifluoromethylstyrene (**1a**) showed an exceptional activity and gave the fastest reactions. Remarkably almost no iodine–zinc exchange could be detected in the presence of **1a**. The use of substoichiometric amounts of the cocatalyst **1a** (20–50 mol %) gave in many cases the same results as when stoichiometric amounts were used. It was now possible to perform a variety of cross-coupling reactions with this optimized catalytic system. All of these reactions were complete within a few hours at –35 °C and proceeded very cleanly (see Table 1 and Experimental Section). The presence of a thioether or a thioacetal functionality had a favorable effect on the reaction rate, which may imply that a complexation of the nickel catalyst with the sulfur atom occurs.^[10] The cross-coupling with ester-functionalized iodoalkanes with various promoters **1** proved unsatisfactory. However with *m*-trifluoromethylstyrene (**1a**) the desired product was ob-

Table 1. Nickel-catalyzed cross-coupling reaction between dialkylzinc compounds and polyfunctional alkyl iodides in the presence of the cocatalyst **1a** or **1c**.

Entry	Iodoalkane 2	R ₂ Zn 3 , R =	4	Yield [%] ^[a]	Co-cat. (equiv)
1	PhS(CH ₂) ₃ I 2g	3a , Pent	PhS(CH ₂) ₇ CH ₃ 4g	71	1a (0.5)
2	PivO(CH ₂) ₃ I 2h ^[b]	3a	PivO(CH ₂) ₉ CH ₃ 4h	78	1a (0.3)
3	PhCO(CH ₂) ₃ I 2c	3b , PivO(CH ₂) ₃	PhCO(CH ₂) ₆ OPiv 4i	76	1a (0.2)
4	BuCO(CH ₂) ₃ I 2d	3b	BuCO(CH ₂) ₆ OPiv 4j	68	1c (0.5)
5	BnO ₂ C(CH ₂) ₂ I 2i ^[c]	3a	BnO ₂ C(CH ₂) ₆ CH ₃ 4k	76	1a (1.0)
6	 2j	3a	 4l	70	1c (1.0)
7	 2k	3b	 4m	70	1c (0.5)
8	 2l	3b	 4n	70	1a (0.5)
9	 2j	3b	 4o	68	1a (1.0)
10	 2l	3c , PivO(CH ₂) ₅	 4p	67	1a (0.3)
11	PhCO(CH ₂) ₃ I 2c	 3d	 4q	66	1c (1.0)
12	PivO(CH ₂) ₃ I 2h	3d	 4r	74	1a (1.0)

[a] Yields of the isolated, analytically pure products. [b] Piv = pivaloyl. [c] Bn = benzyl.

tained (**4k**, 76% yield; entry 5 of Table 1). A similar result was obtained with an iodoalkane bearing an amide functional group **2j**. The test cross-coupling reaction between the ester-containing iodoalkane **2h** with **3a** clearly demonstrates the functional group tolerance of this cross-coupling reaction. The pivaloxy group is too far from the carbon–iodine bond to facilitate the oxidative addition or reductive elimination by coordination; nevertheless the cross-coupling proceeds to furnish **4h** in a satisfactory yield (78%, entry 2). Various keto-containing iodoalkanes (**2c**, **d**, **j**, **k**) underwent the cross-coupling reaction smoothly with the functionalized zinc reagent ((PivO(CH₂)₃)₂Zn (**3b**); entries 3, 4, 7, and 9). The iodothioketal **2l** reacts as well with the zinc reagent **3b**; (entry 8).

In summary, we have developed a new nickel-catalyzed cross-coupling reaction between polyfunctional primary iodoalkanes and primary diorganozinc compounds in the presence of a promoter. *m*-Trifluoromethylstyrene proves to be an exceptionally active promoter leading to clean and fast cross-coupling reactions. The study of the scope, its mechanistic implications, and further synthetic applications of this reaction are currently being investigated in our laboratory.

Experimental Section

Typical procedure: Preparation of benzyl octanoate (**4k**): A 25-mL two-necked flask equipped with an argon inlet and a rubber septum was charged with [Ni(acac)₂] (0.128 g, 0.5 mmol, 10 mol %), THF (3.4 mL), NMP (1.7 mL), *m*-trifluoromethylstyrene (**1a**, 0.15 mL, 1 mmol, 20 mol %), and

benzyl 3-iodopropanoate (**2i**; 1.45 g, 5 mmol) at room temperature. The flask was cooled to –78 °C, and dipentylzinc (**3a**, 2 mL, 10 mmol) was added carefully. The reaction mixture was allowed to warm to –35 °C, and stirred for 2.5 h before being poured into an ice-cold saturated aqueous solution of NH₄Cl and extracted with diethyl ether. The organic phase was washed with brine and dried over Na₂SO₄. The resulting crude oil, obtained after evaporation of the solvents, was purified by flash chromatography (hexanes/diethyl ether, 10/1) to give the desired product **4k** (0.89 g, 3.8 mmol, 76% yield) as a colorless oil.

Received: March 25, 1998 [Z11639IE]
German version: *Angew. Chem.* **1998**, *110*, 2512–2515

Keywords: cross-coupling • homogeneous catalysis • nickel • styrene • zinc

- [1] *Metal-catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), WILEY-VCH, Weinheim, **1998**.
- [2] K. C. Nicolaou, E. J. Sorensen in *Classics in Total Synthesis*, VCH, Weinheim, **1996**, pp. 565–631.
- [3] B. H. Lipshutz, S. Sengupta, *Org. React. (N.Y.)* **1992**, *41*, 135–631.
- [4] For the stoichiometric use of zinc–copper reagents in cross-coupling between sp³ carbon centers, see C. E. Tucker, P. Knochel, *J. Org. Chem.* **1993**, *58*, 4781–4782.
- [5] A. Devasagayaram, T. Stüdemann, P. Knochel, *Angew. Chem.* **1995**, *107*, 2952–2954; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2723–2725.
- [6] a) T. Yamamoto, A. Yamamoto, S. Ikeda, *J. Am. Chem. Soc.* **1971**, *93*, 3350–3359; b) R. Sustmann, J. Lau, M. Zipp, *Tetrahedron Lett.* **1986**, *27*, 5207–5210; c) R. Sustmann, J. Lau, *Chem. Ber.* **1986**, *119*, 2531–2541; d) R. Sustmann, J. Lau, M. Zipp, *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 356–359; e) R. Sustmann, P. Hopp, P. Holl, *Tetrahedron Lett.* **1989**, *30*, 689–692; f) R. van Asselt, C. J. Elsevier, *Tetrahedron*

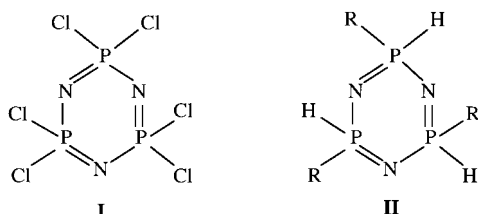
- 1994, 50, 323–334; g) P. L. Castle, D. A. Widdowson, *Tetrahedron Lett.* **1986**, 27, 6013–6016; h) K. Yuan, W. J. Scott, *Tetrahedron Lett.* **1989**, 30, 4779–4782; i) K. Yuan, W. J. Scott, *J. Org. Chem.* **1990**, 55, 6188–6194.
- [7] For Ni- or Pd-catalyzed iodine or bromine–zinc exchange reactions, see a) H. Stadtmüller, A. Vaupel, C. E. Tucker, T. Stüdemann, P. Knochel, *Chem. Eur. J.* **1996**, 2, 1204–1220; b) A. Vaupel, P. Knochel, *J. Org. Chem.* **1996**, 61, 5743–5753; c) E. Riguet, I. Klement, K. C. Reddy, G. Cahiez, P. Knochel, *Tetrahedron Lett.* **1996**, 37, 5865–5868.
- [8] For the use of $C_6H_5CF_3$ for accelerating the reductive elimination of $[NiEt_2(bpy)]$, see T. Yamamoto, M. Abila, *J. Organomet. Chem.* **1997**, 535, 209–211.
- [9] L. S. Hegedus, D. H. P. Thompson, *J. Am. Chem. Soc.* **1985**, 107, 5663–5669.
- [10] For an excellent review on nickel-catalyzed reaction of thioacetals, see T.-Y. Luh, *Synlett* **1996**, 201–208.

Synthesis and Crystal Structure of a *P*-Hydridophosphoraniminato–Zirconium Complex and Reaction to the First Tris(hydrido)cyclotriphosphazene**

Gerold Schick, Michael Raab, Dietrich Gudat, Martin Nieger, and Edgar Niecke*

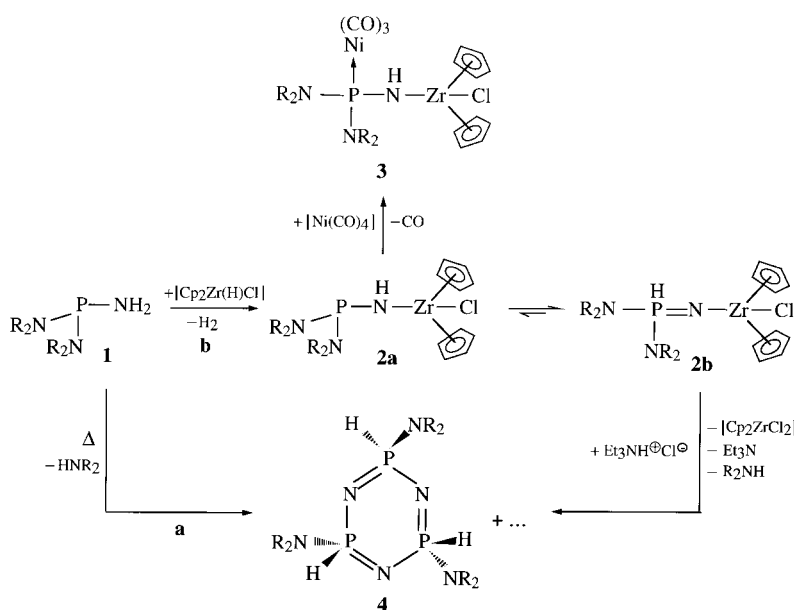
Dedicated to Professor Heinrich Nöth
on the occasion of his 70th birthday

Cyclophosphazenes belong to the best characterized compounds of main group elements and play a key role in the construction of inorganic polymers.^[1] In particular, ring-opening polymerization (ROP) of hexachlorocyclotriphosphazene (Cl_2PN)₃ (**I**) and subsequent substitution reactions give way to specifically substituted polymers whose high thermal stability and elastomeric and/or thermoplastic properties have been utilized for various special applications. In contrast, attempts to synthesize hydridocyclophosphazenes and study their reactivity are rare and have been confined to a limited number of compounds containing only a single PH functionality.^[2] Here we report on the



synthesis of the first representative of a tris(hydrido)cyclotriphosphazene of type **II** (according to our investigations, the previously described^[3] compound $[(Me_2N)(H)PN]_3$ is actually not a cyclophosphazene, but a hydridophosphazene polymer; the synthesis and characterization of this and further poly(hydrido)phosphazenes of the type $[(R_2N)(H)PN]_n$ will be reported elsewhere^[4]).

In solution the aminophosphane **1**, which is accessible by ammonolysis of the corresponding diaminochlorophosphane,^[5] decomposes at ambient temperature under cleavage of dicyclohexylamine to give mixtures of oligomeric and polymeric amino(hydrido)phosphazenes (Scheme 1, path a).^[4] Chromatographic separation affords the *cis,trans,trans*-configured cyclic trimer **4** in low yields (ca. 10%).^[6] The



Scheme 1. R = *cyclo*-Hexyl.

tris(hydrido)cyclophosphazenes are obtained in higher yields by controlled cleavage of the *P*-hydridophosphoraniminato–zirconium complex **2b** with triethylammonium chloride (Scheme 1, path b).

Complex **2b** is easily accessible by treatment of **1** with $[Cp_2Zr(H)Cl]$. The reaction proceeds by elimination of H_2 and formation of a Zr–N bond, and affords primarily a mixture of the two tautomers **2a** and **2b** in a ratio of 1:20. Compound **2b** can be isolated in pure form by crystallization at low temperature. Its reaction with tetracarbonylnickel affords in quantitative yield the phosphanylamido– $Ni(CO)_3$ complex **3**, whose formation is presumably preceded by conversion of **2b** into the thermodynamically less favored tautomer **2a**. An intramolecular cyclization of **2a** under formation of a zirconaazaphosphirane as was recently reported by Majoral et al.^[7] is not observed in this case.

The composition and constitution of **2b** and **3** follow from high-resolution mass spectra and ^{31}P , ^1H , and ^{13}C NMR spectra. The presence of a hydridophosphorane moiety in **2b** is proven in the ^{31}P NMR spectrum by the significant shielding of the phosphorus atom with respect to that in **1**, and by the

[*] Prof. Dr. E. Niecke, Dr. G. Schick, Dipl.-Chem. M. Raab, Priv.-Doz. Dr. D. Gudat, Dr. M. Nieger
Anorganisch-chemisches Institut der Universität
Gerhard-Domagk-Strasse 1, D-53121 Bonn (Germany)
Fax: (+49) 228-73-5327

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

occurrence of a characteristic P,H coupling ($^1J(\text{P,H}) = 529 \text{ Hz}$).^[2b, 8] The phosphanylamido configuration of the tautomer **2a** and the nickel complex **3** is suggested by the downfield shift of the ^{31}P NMR signals ($\delta = 94.0$ (**2a**), 128.1 (**3**)) and the absence of $^1J(\text{P,H})$ coupling. In the case of **3**, the proposed constitution is further confirmed by observation of coupling between phosphorus and the carbonyl carbon atoms ($^2J(\text{P,C}) = 2.9 \text{ Hz}$) and the occurrence of ν_{CO} absorptions whose frequencies ($2041, 1980 \text{ cm}^{-1}$) and intensities are characteristic for a phosphane–Ni(CO)₃ complex.

The molecular structure of the zirconium complex **2b** is further proven by a crystal structure analysis (Figure 1).^[9] The transition metal features a distorted tetrahedral coordination

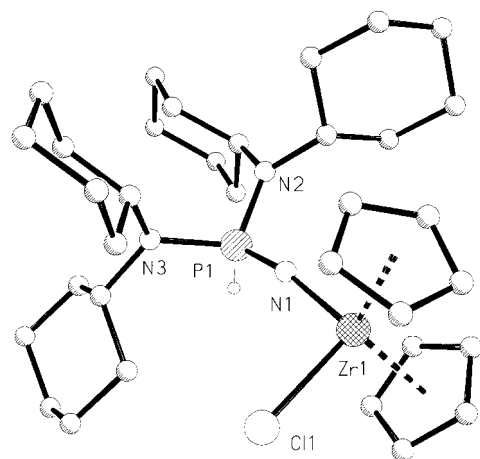


Figure 1. Structure of **2b** in the crystal. Selected bond lengths [pm] and angles [°]: Zr1–N1 195.1(3), Zr1–Cl1 247.9(1), Zr1–Cp(centroid) 224.9(2), 227.0(2), P1–N1 156.0(3), P1–N2 165.8(3), P1–N3 166.0(2); Zr1–N1–P1 165.5(2), Cl1–Zr1–N1 100.8(1), Cp1–Zr1–N1 107.4(1), Cp1–Zr1–Cp2 127.5(1), Cp1–Zr1–Cl1 104.4(1), Cp2–Zr1–Cl1 105.2(1), N1–P1–N2 110.9(1), N1–P1–N3 114.7(1), N2–P1–N3 110.3(1).

by two η^5 -coordinated cyclopentadienyl ligands, a chlorine atom, and the iminato N atom. The large bond angle in the Zr1–N1–P1 fragment ($165.5(2)^\circ$) and the short Zr1–N1 distance (195.1(3) pm) suggest, in accord with analogous findings in phosphoraniminato–transition metal complexes^[10] as well as related alkylideneamido^[11] and imido metallocenes,^[12] a high share of p character in the Zr–N bond. The P1–N1 distance of 156.0(3) pm falls into the typical range for P–N double bonds^[13] and thus mirrors the invariance of the P–N bond distance with respect to alterations of the metal–nitrogen bond, which is characteristic of phosphoraniminato complexes.^[10] The remaining bond distances and angles display no peculiarities.

The constitution and configuration of the tris(hydrido)cyclophosphazene **4** are unequivocally proven by the results of NMR and MS studies. The observation of the ^{31}P NMR signals in the characteristic region for hydridophosphazenes^[2, 8] and the occurrence of $^1J(\text{P,H})$ couplings ($^1J(\text{P,H}) = 589.4, 580.0 \text{ Hz}$) exclude a formulation as an isomeric cyclotriphosphazane. The observed A_2M -type splittings for the signals of the nuclei in the (PH)₃ moiety in both the $^1\text{H}\{^{31}\text{P}\}$ and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra prove clearly a non-geminal *trans* attachment of the hydrogen atoms at the ring. Since the magnetic equiv-

alence in the A₂ moieties is removed under the effect of the heteronuclear PH coupling, the ^1H NMR spectrum displays the more complicated splitting pattern of a [AK]₂NX spin system (A, N = ^1H ; K, X = ^{31}P), whose simulation enables the determination of the magnitudes of the remaining homo- and heteronuclear coupling constants (Figure 2).

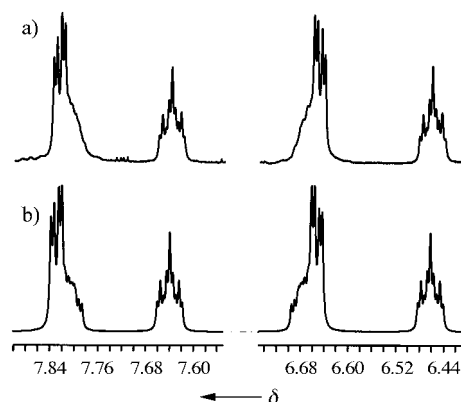


Figure 2. Experimental (a) and simulated ^1H NMR spectrum (b) of the P-bound protons of **4**. The parameters of the simulation are listed in the Experimental Section.

An inspection of the results of the simulation reveals remarkably large values for the $^4J(\text{H,H})$ coupling constants ($^4J(\text{H,H}) = -5.2 \text{ Hz}$ (*cis*), $+2.8 \text{ Hz}$ (*trans*)); the P,H and P,P coupling constants (see the Experimental Section) are as expected.^[2b, 8] The presence of chirality centers at the two isochronous phosphorus atoms leads further to a diastereotopy of the methine and methylene groups in the cyclohexyl substituents at these positions, and thus to a doubling of the corresponding ^1H and ^{13}C NMR signals.

Experimental Section

2b: To a solution of aminophosphane **1** (4.07 g, 10 mmol) in toluene (75 mL) is added $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$ (2.58 g, 10 mmol) under stirring at 25°C , and the mixture is then stirred for 3 d under exclusion of light. Any remaining white solids are subsequently separated from the yellow solution by filtration. The filtrate is then evaporated in vacuo, and the remaining yellow air- and moisture-sensitive solid residue is recrystallized at -78°C from pentane/diethyl ether; yield: 5.63 g (85%). M.p. $43-46^\circ\text{C}$ (decomp); ^{31}P NMR (121.5 MHz, CDCl_3): $\delta = -4.7$ (quint, $^1J(\text{P,H}) = 529$, $^3J(\text{P,H}) = 16.5 \text{ Hz}$); ^1H NMR (300 MHz, CDCl_3): $\delta = 7.2$ (d, $^1J(\text{P,H}) = 529 \text{ Hz}$, PH, 1H), 6.1 (s, Cp, 10H), 3.1 (m, NCH, 4H), 1.9–0.9 (m, CH_2 , 40H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 112.3$ (s, Cp), 54.7 (d, $^2J(\text{P,C}) = 5.3 \text{ Hz}$, NCH), 35.1 (d, $^3J(\text{P,C}) = 3 \text{ Hz}$, NCCCH_2), 35.0 (d, $^3J(\text{P,C}) = 1.7 \text{ Hz}$, NCCH_2), 27.7 (s, NCCCH_2), 26.4 (s, NCCCCCH_2); MS (EI, 70 eV): m/z (%): 661(3) [M^+], 626(1) [$M^+ - \text{Cl}$], 578(21) [$M^+ - c\text{-Hex}$], 481(53) [$M^+ - \text{N}(c\text{-Hex})_2$], 255(32) [Cp_2ZrCl^+], 180(100) [$\text{N}(c\text{-Hex})_2^+$].

3: To a solution of **2b** (0.63 g, 1 mmol) in toluene (10 mL) is added at 25°C $[\text{Ni}(\text{CO})_4]$ (0.17 g, 1 mmol). After the evolution of CO has ceased, the mixture is further stirred for 12 h. The light brown solution is then evaporated in vacuo, and the colorless air- and moisture-sensitive residue recrystallized from diethyl ether at -78°C ; yield: 0.70 g (87%). M.p. 137°C (decomp); $^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3): $\delta = 128.1$ (s); ^1H NMR (300 MHz, CDCl_3): $\delta = 6.3$ (s, Cp, 10H), 3.4 (m, NCH, 4H), 2.2 (d, $^2J(\text{P,H}) = 2.9 \text{ Hz}$, NH, 1H) 1.9–1.0 (m, CH_2 , 40H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): $\delta = 197.4$ (d, $^2J(\text{P,C}) = 2.7 \text{ Hz}$, CO), 114.5 (s, Cp), 57.0 (d, $^2J(\text{P,C}) = 14.1 \text{ Hz}$, NCH), 37.1 (d, $^3J(\text{P,C}) = 1.5 \text{ Hz}$, NCCH_2), 34.8 (d, $^3J(\text{P,C}) = 1.5 \text{ Hz}$, NCCCH_2), 27.9, 27.7 (s, NCCCH_2), 26.5 (s, NCCCCCH_2); IR: $\tilde{\nu}_{\text{CO}}$ (cm^{-1}) = 2041, 1980.

4: a) Aminophosphane **1** (5 g) is dissolved in a mixture of pentane (150 mL) and diethyl ether (50 mL), and the resulting solution is stirred for 2 d at ambient temperature. After all volatile components have been removed in vacuo, the obtained crude product mixture is subjected to chromatography on silica gel that has been pretreated with chlorotrimethylsilane. Elution with pentane furnishes **4** ($R_f = 0.9$) as a colorless solid; yield: 0.2 g (10.5 %). M.p. 80 °C. b) Alternatively, the zirconium complex **2b** (4 g, 6 mmol) is dissolved in diethyl ether (150 mL) and treated at ambient temperature under stirring with triethylammonium chloride (0.83 g, 6 mmol). After the mixture has been stirred for 4 h, all volatile components are removed in vacuo, and the remaining solid residue is extracted with pentane. The combined extracts are evaporated to dryness, and **4** is obtained after chromatographic workup as described above; yield: 0.29 g (23 %). $^1\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, CDCl_3): $\delta = 4.7$ (t, $^2J(\text{P,P}) = 17.6$ Hz, P_X), -0.5 (d, $^2J(\text{P,P}) = 17.6$ Hz, P_K); $^1\text{H}\{^31\text{P}\}$ NMR (300 MHz, CDCl_3): $\delta = 7.23$ (d, $^4J(\text{H,H}) = 2.7$ Hz, H_A), 7.05 (t, $^4J(\text{H,H}) = 2.7$ Hz, 1H , H_N); ^1H NMR (500 and 300 MHz, CDCl_3): $\delta = 7.23$ (m, 2H , H_A), 7.05 (m, 1H , H_N), (iteration with WINDAISO gave the following coupling constants (the signs given are based on a positive sign for $^1J(\text{P,H})$): $^1J(\text{P}_\text{K},\text{H}_\text{A}) = +580.0$, $^3J(\text{P}_\text{X},\text{H}_\text{A}) = +6.4$, $^3J(\text{P}_\text{K},\text{H}_\text{A}) = +8.8$, $^4J(\text{H}_\text{A},\text{H}_\text{A}) = -5.2$, $^4J(\text{H}_\text{A},\text{H}_\text{N}) = +2.8$, $^2J(\text{P}_\text{K},\text{P}_\text{X}) = +10.6$, $^2J(\text{P}_\text{K},\text{P}_\text{X}) = +16.9$, $^1J(\text{P}_\text{X},\text{H}_\text{N}) = +589.4$, $^3J(\text{P}_\text{K},\text{H}_\text{N}) = +7.8$, 3.1 (m, $^3J(\text{P,H}) + ^3J(\text{P,H}) = 6$, $^3J(\text{H,H}) = 11.7$, 3.6 Hz, NCH , 4H), 3.0 (dt, $^3J(\text{P,H}) = 8$, $^3J(\text{H,H}) = 11.7$, 3.5 Hz, NCH , 2H), 1.9 – 0.9 (m, CH_2 , 60H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): $\delta = 54.9$ (d, $^2J(\text{P,C}) = 5.4$ Hz, NC), 54.2 (pseudo t, $^2J(\text{P,C}) + ^4J(\text{P,C}) = 5.4$ Hz, NC), 34.4 (pseudo t, $^3J(\text{P,C}) + ^3J(\text{P,C}) = 1.5$ Hz, NCCCH_2), 34.3 (d, $^3J(\text{P,C}) = 3.2$ Hz, NCCCH_2), 34.1 (pseudo t, $^3J(\text{P,C}) + ^5J(\text{P,C}) = 1.5$ Hz, NCCCH_2), 27.25 , 27.20 , 27.15 (s, NCCCH_2), 26.3 , 26.2 (s, NCCCH_2); MS (EI, 70 eV): m/z (%): 678 (1) [M^+], 595 (2) [$\text{M}^+ - \text{c-Hex}$], 498 (7) [$\text{M}^+ - \text{N}(\text{c-Hex})_2$], 180 (100) [$\text{N}(\text{c-Hex})_2^+$]; HR-MS (EI, 70 eV): calcd for $\text{C}_{36}\text{H}_{69}\text{N}_6\text{P}_3$: 678.4797, found: 678.4797.

Received: April 7, 1997 [Z 11695 IE]

German version: *Angew. Chem.* **1998**, *110*, 2486–2488

Keywords: phosphazenes • phosphorus heterocycles • zirconium

- [1] a) H. R. Allcock, *Phosphorus–Nitrogen Compounds*, Academic Press, New York, **1972**; b) S. S. Krishnamurthy, A. C. Sau, *Adv. Inorg. Chem. Radiochem.* **1978**, *21*, 41; c) R. A. Shaw, *Phosphorus and Sulfur* **1978**, *4*, 101; d) “Inorganic and Organometallic Polymers”: *ACS Symp. Ser.* **360**, ACS, Washington, **1988**; e) R. H. Neilson, P. Wisian-Neilson, *Chem. Rev.* **1988**, *88*, 541–562; f) J. E. Mark, H. R. Allcock, R. West, *Inorganic Polymers*, Prentice-Hall, Englewood Cliffs, **1992**; g) “Inorganic and Organometallic Polymers II”: *ACS Symp. Ser.* **572**, ACS, Washington, **1994**; h) I. Manners, *Angew. Chem.* **1996**, *108*, 1712–1731; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1602–1635.
- [2] a) A. Schmidpeter, J. Ebeling, *Angew. Chem.* **1968**, *80*, 197; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 197; b) A. Schmidpeter, J. Ebeling, H. Stary, C. Weingand, *Z. Anorg. Allg. Chem.* **1972**, *394*, 171–186; c) H. R. Allcock, P. J. Harris, *J. Am. Chem. Soc.* **1978**, *101*, 21, 6221–6228; d) H. R. Allcock, M. S. Connolly, P. J. Harris, *J. Am. Chem. Soc.* **1982**, *104*, 2483–2490; e) H. R. Allcock, M. S. Connolly, R. R. Whittle, *Organometallics* **1983**, *2*, 1514–1523; f) H. R. Allcock, J. L. Descorcie, G. H. Riding, *Polyhedron* **1987**, *6*, 119–157.
- [3] A. Schmidpeter, H. Rossknecht, *Chem. Ber.* **1974**, *107*, 3146–3148.
- [4] E. Niecke, M. Raab, G. Schick, D. Gudat, K. Müllen, unpublished results.
- [5] G. Schick, A. Loew, M. Nieger, E. Niecke, K. Airola, *Chem. Ber.* **1996**, *129*, 211–217.
- [6] Chromatographic workup furnished a further fraction consisting of **4** and another cyclophosphazene which gives rise to singlets in both the $^31\text{P}\{^1\text{H}\}$ and $^1\text{H}\{^31\text{P}\}$ spectra ($\delta(^1\text{H}) = 7.36$, $\delta(^31\text{P}) = 0.6$). Since the mass spectrum of this mixture proved to be identical with that of pure **4**, and a simulation of the signal attributable to the PH moiety in the ^1H NMR spectrum as a $[\text{AX}]_3$ spectrum was in satisfactory agreement with the experimental data, we assume the presence of a mixture of **4** and an isomeric *cis,cis,cis*-tris(hydrido)cyclotriphosphazene.

- [7] a) J.-P. Majoral, M. Zablocka, A. Igau, N. Cénac, *Chem. Ber.* **1996**, *129*, 879–886; b) N. Dufour, J.-P. Majoral, A.-M. Caminade, R. Choukron, Y. Dromzée, *Organometallics* **1991**, *10*, 45–48.
- [8] S. S. Krishnamurthy, M. Woods, *Annual Reports on NMR Spectroscopy* **1987**, *19*, 175–320.
- [9] Crystal structure analysis of **2b**: $\text{C}_{34}\text{H}_{55}\text{ClN}_3\text{PZr}$, colorless crystals, $0.10 \times 0.20 \times 0.25$ mm; $M_r = 663.5$; triclinic, space group $P\bar{1}$ (no. 2), $a = 1042.4(2)$, $b = 1144.8(3)$, $c = 1648.5(2)$ pm, $\alpha = 105.70(2)$, $\beta = 94.77(2)$, $\gamma = 114.77(2)^\circ$, $V = 1.6756(6)$ nm ^{3} , $Z = 2$, $\mu(\text{Cu}_{\text{K}\alpha}) = 4.06$ mm $^{-1}$, $T = 200(2)$ K, $F(000) = 704$. Of 5371 reflections ($2\theta_{\text{max}} = 120^\circ$) measured on an Enraf-Nonius CAD4 diffractometer with $\text{Cu}_{\text{K}\alpha}$ radiation, 4973 were independent and used for all calculations. The structure was solved with direct methods and refined anisotropically on F^2 . Hydrogen atoms were refined with a riding model (program: SHELXL-93, 364 parameters, 1 restraint); $wR2(F^2) = 0.101$, $R(F) = 0.037$. An empirical absorption correction (DIFABS, N. Walker, D. Stuart, *Acta Crystallogr.* **1983**, *A39*, 158–166) was applied. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100765. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [10] K. Dehnicke, J. Strähle, *Polyhedron* **1989**, *8*(6), 707.
- [11] G. Erker, W. Frömberg, J. L. Atwood, W. Huttner, *Angew. Chem.* **1984**, *96*, 72–73; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 68.
- [12] P. J. Walsh, F. J. Hollander, R. G. Bergman, *J. Am. Chem. Soc.* **1988**, *110*, 8729–8731.
- [13] A. F. Wells, *Structural Inorganic Chemistry*, 5. ed., Clarendon, Oxford, **1984**.

Catalytic Asymmetric Allenylation: Regulation of the Equilibrium between Propargyl- and Allenylstannanes during the Catalytic Process**

Chan-Mo Yu,* Sook-Kyung Yoon, Kwangwoo Baek, and Jae-Young Lee

Dedicated to Professor Elias J. Corey on the occasion of his 70th birthday

The availability of efficient synthetic methods for achieving absolute stereoselectivity by catalytic processes in the production of enantiomerically pure compounds is of considerable current interest because such products can be used as chiral building blocks for the synthesis of valuable chiral substances.^[1] In this regard, allyl-transfer reactions provide excellent stereoselective routes for converting aldehydes into the corresponding alcohols.^[2] Subsequent to early studies by Hoffmann et al.^[3] on the use of chirally modified allyl boranes to accomplish asymmetric induction, many research groups have made important contributions to the extension of this

[*] Prof. Dr. C.-M. Yu, S.-K. Yoon, K. Baek, J.-Y. Lee
Department of Chemistry and Institute of Basic Science
Sungkyunkwan University, Suwon 440–746 (Korea)
Fax: (+82) 331-290-7075
E-mail: cmyu@chem.skku.ac.kr

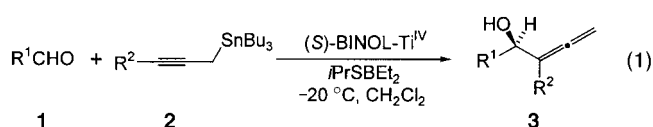
[**] This research was supported by grants from the Ministry of Education (BSRI 97-3420) and the Korea Science and Engineering Foundation (KOSEF 97-0501-02-01-3).

protocol to achieve high levels of stereoselectivity.^[4] The exceptional power of the allyl transfer reactions in forming enantioenriched alcohols from aldehydes has been enhanced by newly developed catalytic variations, especially the chiral Lewis acid catalyzed addition of allyl-transfer reagents to carbonyl functionalities.^[5] Although there have been several elegant reports regarding the enhancement of the catalytic ability for practical use,^[6] the scope of the catalytic allyl-transfer reactions is still limited to allyl systems.

Recently, we demonstrated that the utilization of molecular synergetic reagents, designed on the basis of mechanistic speculation, for catalytic asymmetric allylation and propargylation resulted in not only a significant increase in the reaction rate but also a reduced dosage of the chiral catalyst.^[7] This strategy should prove to be effective for the catalytic allenylation of achiral aldehydes—an efficient method should enable the many useful functional group transformations of allenyl alcohols to be realized.^[8]

Practical methods for the synthesis of allenyl alcohols are often limited by the tendency of propargylic reagents to couple with carbonyl groups to produce allenyl alcohols, which is mainly a consequence of their lack of regiochemical selectivity.^[9] An efficient method for the enantioselective synthesis of allenyl alcohols through the self-immolative transfer of chirality by the use of stoichiometric amounts of nonracemic propargylstannanes with aldehydes has been reported.^[10] While the reaction of some propargylboranes with stoichiometric chiral auxiliaries has been developed to achieve a highly enantio- and regioselective synthesis of allenyl alcohols,^[11] a catalytic version of the allenylation of aldehydes has not yet been realized. Described herein is an extension of the molecular accelerating strategy aimed at finding new reagents and realizing useful and practical ways to advance to new levels of asymmetric synthesis. In the present research, two major observations have been made in the enantioselective synthesis of allenyl alcohols: 1) bifunctional synergetic reagents expedite the catalytic process of asymmetric allenylation of achiral aldehydes in high enantioselectivity, and 2) the reaction proceeds with dramatic regiochemical selectivities as a result of the equilibrium between the tin reagents.

The starting point of this investigation was the availability of the tin reagent **2** in a regiochemically pure form. This compound was prepared by the following reaction in large quantities and purified by distillation: The treatment of 1-bromo-2-butyne (1.2 equiv) with magnesium (2.0 equiv) and Bu₃SnCl (1 equiv) in the presence of PbBr₂ (5 mol %) in THF afforded 2-butyntributylstannane (**2**, R² = Me) in 81 % yield after purification by distillation with a regioselectivity of over 98 %.^[12] The first study focused on the feasibility of **2** for the catalytic asymmetric allenylation of achiral aldehydes that were promoted by a chiral Lewis acid catalyst. Our initial studies were carried out with **1** (R¹ = PhCH₂CH₂) and **2** (R² = Me) in the presence of a (*S*)-BINOL–Ti^{IV} complex together with various bifunctional synergetic reagents R_nMSR¹ (M = B, Al, Si) [Eq. (1); BINOL = 2,2'-dihydroxy-1,1'-binaphthyl]. Several key findings emerged from the study: 1) the control experiment revealed that the reaction proceeded only marginally in the absence of a synergetic reagent (10 mol % of



catalyst, –20°C, 20 h, <10 % yield); 2) *i*PrSBET₂ exhibited quite high efficiency for the catalytic process; 3) a 2:1 mixture of the BINOL–Ti(O*i*Pr)₄ complex in the presence of 4-Å molecular sieves provided the most efficient catalyst;^[13] and 4) the best chemical yields and enantioselectivities were obtained at –20°C in CH₂Cl₂.

Under optimal conditions, the catalytic allenyl-transfer reaction was conducted by the dropwise addition of *i*PrSBET₂ (1.2 equiv) in CH₂Cl₂ at –20°C to a mixture of **1** (R = CH₂CH₂Ph, 1 equiv) and **2** (R = Me, 1.2 equiv) in the presence of the (*S*)-BINOL–Ti^{IV} complex (10 mol %) in CH₂Cl₂. After 9 h at –20°C, the reaction mixture was quenched by the addition of a saturated aqueous solution of NaHCO₃. Workup and chromatography on silica gel afforded alcohol **3a** in 85 % yield and with 93 % *ee*. This discovery prompted us to carry out more experiments with other aldehydes and tin reagents (Table 1).

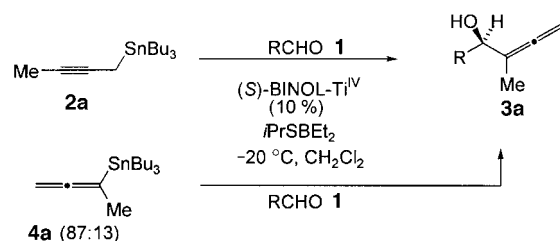
Table 1. Catalytic asymmetric allenylation of achiral aldehydes [Eq. (1)].^[a]

Entry	R ¹	R ²	3	yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	PhCH ₂ CH ₂	Me	a	85	93
2	PhCH ₂ CH ₂	Et	b	77	96
3	PhCH ₂ CH ₂	Pr	c	71	93
4	<i>n</i> -C ₆ H ₁₃	Me	d	97	92
5	<i>n</i> -C ₆ H ₁₃	Et	e	82	95
6	<i>n</i> -C ₆ H ₁₃	Pr	f	72	90
7	Me ₂ CHCH ₂	Me	g	62 ^[d]	81
8	Me ₂ CHCH ₂	Et	h	49 ^[d]	81
9	Me ₂ CHCH ₂	Pr	i	41 ^[d]	85
10	Ph	Me	j	74	90
11	Ph	Et	k	78	97
12	Ph	Pr	l	73	91

[a] All reactions were carried out at –20°C; (*S*)-BINOL:Ti(O*i*Pr)₄ = 2:1 (10 mol %); reaction times *t* = 9 h, unless otherwise stated. [b] Yields refer to isolated and purified products. [c] Enantiomeric excesses were determined by preparation of (+)-MTPA ester derivatives, analysis by ¹H NMR (all entries) and/or ¹⁹F NMR spectroscopy (entries 3, 6), and by HPLC analysis on a chiral stationary phase (Chiracel OD-H, *i*PrOH/hexane 10/90, entries 11, 12). [d] *t* = 11 h.

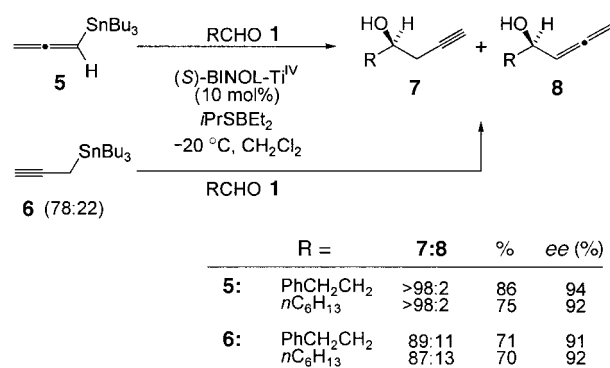
The absolute configuration of the predominating enantiomer of the adducts was unambiguously established by comparison of their specific rotations with that of known alcohols.^[11b] The absolute sense of the asymmetric induction parallels previous observations on catalytic asymmetric allylations that employed the (*S*)-BINOL–Ti^{IV} complex.^[7] Table 1 shows that the catalytic process is effective for a variety of aldehydes and tin reagents in terms of chemical yield and enantioselectivity. However, a reduced dosage of chiral catalyst (5 mol %) resulted in diminished chemical yields and longer reaction times (**3a**, –20°C, 24 h, 41 % yield). The reaction also produced none or only trace amounts of isomeric propargylic carbinols (<3 %) as judged by ¹H (500 MHz) NMR analysis of the crude products.

We turned our attention next to the application of this approach with other allenic or propargylic tin reagents to enlarge the scope of allylic transfer reactions. During our investigations, we observed the remarkable regulation of the equilibrium between allenyl- and propargylstannane reagents under the reaction conditions used. We were surprised to find that the reaction of **4a** (87:13 mixture) with **1** ($R = \text{PhCH}_2\text{CH}_2$, 1 equiv) under the same conditions afforded the alcohol **3a** ($R = \text{PhCH}_2\text{CH}_2$) in 81% yield and with 91% *ee*.^[14] This high regio- and enantioselectivity in the formation of allenyl alcohol **3a** from allenyltin **4a** at -20°C mediated by the BINOL– Ti^{IV} complex is virtually identical to that seen with propargyltin **2a** (Scheme 1). This is not the common case; allenyltin reagents usually convert aldehydes



Scheme 1. Catalytic asymmetric allenylation of aldehydes; **3a** is precipitated in over a 97% purity together with the isomers of propargyl alcohol. For yields and *ee* values with **2a**, see Table 1. With **4a**: $R = \text{PhCH}_2\text{CH}_2$: 81%, 91% *ee*; $R = n\text{-C}_6\text{H}_{13}$: 78%, 92% *ee*.

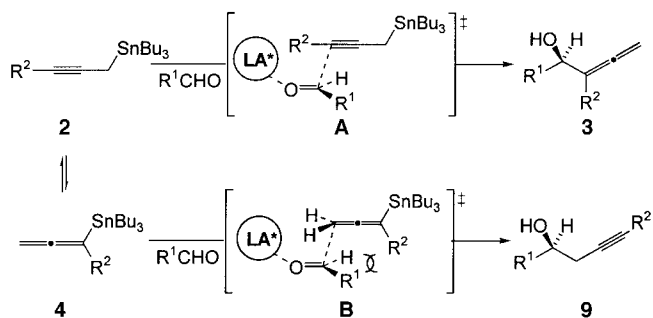
into propargyl alcohols in a reaction mediated by a Lewis acid catalyst in the absence of equilibrating reagents such as BuSnCl_3 .^[15] On the other hand, both allenyltin **5** and propargyltin **6**, under identical conditions, produced the same propargyl carbinol **7** as a major component (Scheme 2). In general, allenyl reagents lead mainly to propargylic adducts,



Scheme 2. Catalytic asymmetric propargylation with **5**^[7c] and **6**.

and propargylic reagents to allenyl adducts by $S_{\text{E}}2'$ addition to the aldehyde. These apparent contradictions could be explained by products being formed in the reaction that originated from the equilibrium between allenyl- and propargyltin reagents under the reaction conditions. Since anti-periplanar attack would lead to the particular product **3** or **9** via transition state **A** or **B**, the major reaction pathway could be dependent on the stability of the transition state under kinetic control or on orientations and steric factors, without a

necessary link to the product stability (Scheme 3). Thus, the origin of regiochemical selectivity for these transformations might be a result of the thermodynamic stability of the tin



Scheme 3. Formation of **3** and **9** from the equilibrium between **2** and **4**. LA^* = chiral Lewis acid catalyst.

reagents as well as subtle geometrical preferences for orientation in the transition states offered by the complex catalytic system rather than the original concentration of the reaction.

Experimental Section

Typical procedure for the catalytic allenylation (entry 12 of Table 1): A flame-dried flask containing (S)-BINOL (57.3 mg, 0.2 mmol) and activated powdered 4-Å molecular sieves (0.7 g) was evacuated and carefully purged with nitrogen three times, and then charged with dry CH_2Cl_2 (2 mL) followed by freshly distilled $\text{Ti}(\text{O}i\text{Pr})_4$ (freshly prepared, 0.5 M in CH_2Cl_2 , 0.2 mL, 0.1 mmol). The mixture was stirred at 25°C for 3 h. The red-brown mixture was cooled to -20°C in a dry ice– CCl_4 bath, and a solution of benzaldehyde (**1**, $R^1 = \text{Ph}$, 0.11 g, 1.0 mmol) in CH_2Cl_2 (0.5 mL) was added. A solution of tributyl-2-hexynylstannane (**2**, $R^2 = \text{Pr}$, 0.45 g, 1.2 mmol) in CH_2Cl_2 (1 mL) was added dropwise to this mixture, followed by the addition of $i\text{PrSBET}_2$ (0.18 g, 1.25 mmol) in CH_2Cl_2 (1 mL); by gas-tight syringe with a syringe pump) over 1 h along the wall of the flask while keeping the temperature below -20°C . After the reaction mixture was stirred for 8 h at -20°C , aqueous NaHCO_3 (5 mL) was added and then CH_2Cl_2 (5 mL). The molecular sieves were removed by filtration, and the aqueous layer was extracted with CH_2Cl_2 (ca. 20 mL). The combined organic solution was dried over anhydrous Na_2SO_4 , and the solvents were then removed under reduced pressure. Purification of the residue by column chromatography (EtOAc/hexanes 15/85) afforded **3** ($R^1 = \text{Ph}$, $R^2 = \text{Pr}$; 0.137 g, 0.73 mmol, 73%) as a colorless liquid; TLC: $R_f = 0.33$ (hexane/EtOAc 85/15); $[\alpha]_D^{20} = -120$ ($c = 1.75$, CHCl_3); FT-IR (neat): $\tilde{\nu} = 3389$, 1956 cm^{-1} ; EI-MS: m/z (%): 188 (M^+ , 30.6), 173 (24.2), 106 (37.8), 79 (100); ^1H NMR (500 MHz, CDCl_3): $\delta = 0.86$ (t, $J = 7.5$ Hz, 3H), 1.36–1.46 (m, 2H), 1.70–1.86 (m, 2H), 2.24 (d, $J = 4.5$ Hz, 1H), 4.96–5.04 (m, 2H), 5.09 (ddd, $J = 4.5$, 2.5, 2.5 Hz, 1H), 7.20–7.50 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3): $\delta = 13.74$, 20.70, 30.01, 74.11, 79.57, 108.05, 126.67, 127.70, 128.26, 142.15, 204.21.

Received: March 31, 1998 [Z11670IE]
German version: *Angew. Chem.* **1998**, *110*, 2504–2506

Keywords: aldehydes • asymmetric catalysis • Lewis acids • synthetic methods • titanium

- [1] General discussions: a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1993**, pp. 1–364; b) K. Maruoka, H. Yamamoto in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**, pp. 413–440; c) K. Mikami in *Advances in Catalytic Process* (Ed.: M. P. Doyle), JAI, Greenwich, **1995**, pp. 1–44.
- [2] Comprehensive discussions: a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293; b) D. Hoppe, W. R. Roush, E. J. Thomas in

Stereoselective Synthesis, Vol. 3 (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, 1996, pp. 1357–1602.

- [3] a) T. Herold, U. Schrott, R. W. Hoffmann, *Chem. Ber.* **1981**, *114*, 359–374; b) R. W. Hoffmann, *Angew. Chem.* **1982**, *94*, 569–580; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555–566.
- [4] Reviews: a) W. R. Roush in *Comprehensive Organic Synthesis*, Vol. 2 (Ed.: C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 1–53; b) M. Santell, J.-M. Pons, *Lewis Acids and Selectivity in Organic Chemistry*, CRC, New York, **1996**, pp. 91–184.
- [5] a) K. Ishihara, M. Mouri, Q. Gao, T. Maruyama, K. Furuta, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 11490–11495; b) J. A. Marshall, Y. Tang, *Synlett* **1992**, 653–654; c) A. L. Costra, M. G. Piazza, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Am. Chem. Soc.* **1993**, *115*, 7001–7002; d) G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468; e) S. Aoki, K. Mikami, M. Terada, T. Nakai, *Tetrahedron* **1993**, *49*, 1783–1792; f) J. W. Fallor, D. W. Sams, X. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 1217–1218; g) A. Yanagisawa, H. Nakashima, A. Ishiba, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 4723–4724; h) D. R. Gauthier, Jr., E. M. Carreira, *Angew. Chem.* **1996**, *35*, 2521–2523; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2363–2365; i) S. Weigand, R. Brückner, *Chem. Eur. J.* **1996**, *2*, 1077–1084; j) P. G. Cozzi, P. Orioli, E. Tagliavini, A. Umani-Ronchi, *Tetrahedron Lett.* **1997**, *38*, 145–148.
- [6] a) S. Casolari, P. G. Gozzi, P. Orioli, E. Tagliavini, A. Umani-Ronchi, *Chem. Commun.* **1997**, 2123–2124; b) K. Mikami, S. Matsukawa, *Nature* **1997**, *385*, 613–615; c) S. Matsukawa, K. Mikami, *Tetrahedron: Asymmetry* **1997**, *8*, 815–818.
- [7] a) C.-M. Yu, H.-S. Choi, W.-H. Jung, S.-S. Lee, *Tetrahedron Lett.* **1996**, *37*, 7095–7098; b) C.-M. Yu, H.-S. Choi, W.-H. Jung, H.-J. Kim, J. Shin, *Chem. Commun.* **1997**, 761–762; c) C.-M. Yu, S.-K. Yoon, H.-S. Choi, K. Baek, *Chem. Commun.* **1997**, 763–764; d) C.-M. Yu, H.-S. Choi, S.-K. Yoon, W.-H. Jung, *Synlett* **1997**, 889–890.
- [8] a) J. A. Marshall, M. A. Wolf, E. M. Wallace, *J. Org. Chem.* **1997**, *62*, 367–371; b) R. W. Friesen, C. Vanderwal, *J. Org. Chem.* **1996**, *61*, 9103–9110, and references therein.
- [9] Reviews: a) H. Yamamoto in *Comprehensive Organic Synthesis*, Vol. 2 (Ed.: C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 81–98; b) C. Bruneau, P. H. Dixneuf in *Comprehensive Organic Functional Group Transformations*, Vol. 1 (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Elsevier, Oxford, **1995**, pp. 953–998.
- [10] J. A. Marshall, R. H. Yu, J. P. Perkin, *J. Org. Chem.* **1995**, *60*, 5550–5555.
- [11] a) E. J. Corey, C.-M. Yu, D.-H. Lee, *J. Am. Chem. Soc.* **1990**, *112*, 878–879; b) H. C. Brown, S. V. Kulkarni, *Tetrahedron Lett.* **1996**, *37*, 4125–4128.
- [12] Allenyltin compounds are reported (H. Tanaka, A. K. M. Abdul Hai, H. Ogawa, S. Torri, *Synlett* **1993**, 835–836) to be obtained under conditions similar to those we used to obtain propargyltin compounds from 3-substituted propargyl bromides.
- [13] The role of molecular sieves for the Ti^{IV} -promoted reaction was reported; see a) ref. [5c]; b) M. Terada, Y. Matsumoto, Y. Nakamura, K. Mikami, *Chem. Commun.* **1997**, 281–282.
- [14] The reagent **4** was prepared by the reaction of 2-butylnyl pivaloate with $(Bu_3Sn)_2CuLi$ at $-78^\circ C$ in THF. Although the literature procedure can be used to prepare regiochemically pure triphenyltin analogues of **4** and **6**, it turned out to be unpromising for this purpose mainly because of the lack of reactivity.
- [15] J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31–47, and references therein.

Monocyclic $(CH)_5^+$ —A Heilbronner Möbius Aromatic System Revealed**

Michael Mauksch, Valentin Gogonea, Haijun Jiao, Paul von Ragué Schleyer*

Dedicated to Professor Edgar Heilbronner

In 1964 Heilbronner predicted that singlet $[4n]$ annulenes would be aromatic systems in twisted conformations where the p orbitals lie on the surface of a Möbius strip (Figure 1).^[1]

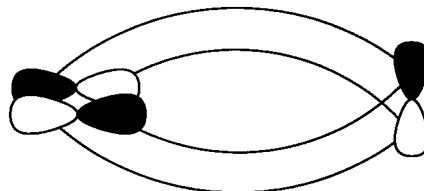


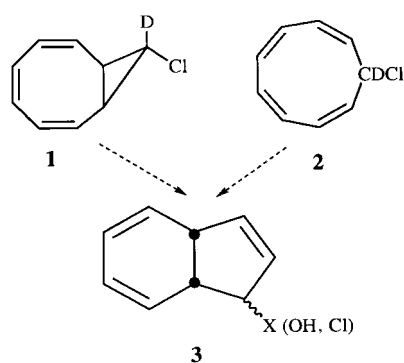
Figure 1. Schematic representation of the Möbius type overlapping p orbitals in $(CH)_5^+$. The C_2 axis lies horizontally; the carbon atom on it (right) is across from the phase inversion (left).

Although the Möbius concept has been employed extensively to interpret reactions and bonding,^[2,3] Möbius annulenes conforming to Heilbronner's original idea have still not been reported. Heilbronner pointed out that rings with twenty atoms or more might adopt Möbius geometries "without any apparent angle or steric repulsion strain".^[1] However, we have discovered computationally that Möbius aromaticity is possible in a much smaller ring system, namely, the cyclonona-trayenyl cation. Moreover, judging from early experimental evidence,^[4,5] this species may actually have been encountered more than once almost three decades ago!

A monocyclic $(CH)_5^+$ cation of unspecified nature, but which allowed isotope label scrambling, was first postulated in 1971 as a short-lived intermediate in the solvolysis of *exo*-9-chlorobicyclo[6.1.0]nona-2,4,6-triene in aqueous acetone at $75^\circ C$.^[4] The reactant containing deuterium at C9 (**1**, Scheme 1) gave a bicyclic product, *cis*-8,9-dihydroindene-1-ol (**3**, X = OH), with uniformly distributed deuterium label.^[4] Shortly afterwards Anastassiou and Yakali succeeded in preparing 9-chlorocyclononatetraene (**2**, stereochemistry undetermined).^[6] Under ionizing conditions (liquid SO_2 at $-66^\circ C$), D-labeled **2** gave **3** (X = Cl) by ion-pair return, again with complete statistical distribution of the label (1/9 D per C atom).^[5]

[*] Prof. Dr. P. von R. Schleyer, Dipl.-Chem. M. Mauksch, Dr. V. Gogonea, Dr. H. Jiao
Computer-Chemie-Centrum
Institut für Organische Chemie der Universität Erlangen-Nürnberg
Henkestrasse 42, D-91054 Erlangen (Germany)
Fax: (+49)9131-85-9132
E-mail: pvrs@organik.uni-erlangen.de

[**] We thank Prof. Emel Yakali (Raymond Walters College, Cincinnati, OH) for helpful discussions and Holger Bettinger (CCQC, Athens, GA) for the CCSD(T) computations. We are grateful to the Deutsche Forschungsgemeinschaft, the Humboldt Foundation (fellowship for V.G.), and the Fonds der Chemischen Industrie for their financial support.



Scheme 1. Reaction of deuterated **1** and **2** to the dihydroindenenes **3** with complete statistical distribution of the label.

In view of the expected antiaromaticity of the planar cyclononatetraenyl cation, Anastassiou and Yakali wondered why the ion forms so easily and how the positions could become equivalent.^[5a,7] They represented $(\text{CH})_8^+$ in a coiled conformation (**4** in Figure 2, structure on the right),^[5b] which was felt to be “incapable of skeletal inversion without experiencing again the adverse effects of antiaromaticity.”^[5a] We now report computational evidence that the eight-electron monocyclic cation $(\text{CH})_8^+$ actually does prefer this helical C_2 -symmetrical structure and is Möbius aromatic rather than nonaromatic.

Exploration of the potential energy surface of singlet $(\text{CH})_8^+$ with density functional theory^[8] located the Möbius conformation **4** (C_2) besides a second monocyclic minimum **5** (C_s), which is 21.6 kcal mol⁻¹ higher in energy (Table 1).^[9] As expected for antiaromatic singlet species, both **5** and especially planar C_{2v} -symmetric **6** (a second-order saddle point, 26.3 kcal mol⁻¹ less stable than **4**) show strong bond length alternations,^[10] positive nucleus-independent chemical shift (NICS) values ($\delta = +8.6$ and $+42.0$, respectively),^[11] and average ¹H chemical shifts of $\delta = 7.5$ (**5**) and 2.3 (**6**). In contrast, Möbius compound **4** has a small range of C–C bond lengths (maximum difference 0.043 Å, Table 1), the most negative NICS of $\delta = -13.4$ (the value for benzene is -9.7 at the same level!^[11]), and an average ¹H chemical shift of $\delta = 8.5$. The diamagnetic susceptibility of **4**^[12] is exalted ($A = -18.8$ ppm cgs) relative to that of nonaromatic **7** (NICS = -0.9), the reference structure (Table 1). In sharp contrast, the antiaromatic conformations **5** and **6** have paramagnetic susceptibility exaltations of $A = +18.1$ and $+112.5$ ppm cgs (Table 1). The low-lying transition state **7** (0.9 kcal mol⁻¹; confirmed to be 1.1 kcal mol⁻¹ at the CCSD(T)/DZP level^[13]) permits the facile enantiomerization of **4** (Table 1). Despite the loss of Möbius aromaticity during interconversion of the enantiomers of **4**, the barrier is small since **7** is less strained than the highly twisted **4**.

Möbius conformation **4** also can undergo disrotatory ring closure via the C_1 -symmetric transition state **8**. The computed barrier for the rearrangement (8.1 kcal mol⁻¹) of **4** via **8** into bicyclic **9** is in accord with the experimentally estimated half-life of **4** ($t_{1/2} < 10$ min at -66°C in liquid SO_2).^[5a,c] Although modest in magnitude, the aromaticity of transition state **8** (NICS = -6.0 , $A = -7.0$ ppm cgs; Table 1) is as expected for a pericyclic transition state.^[14] The bicyclic C_s -symmetric 1,4-

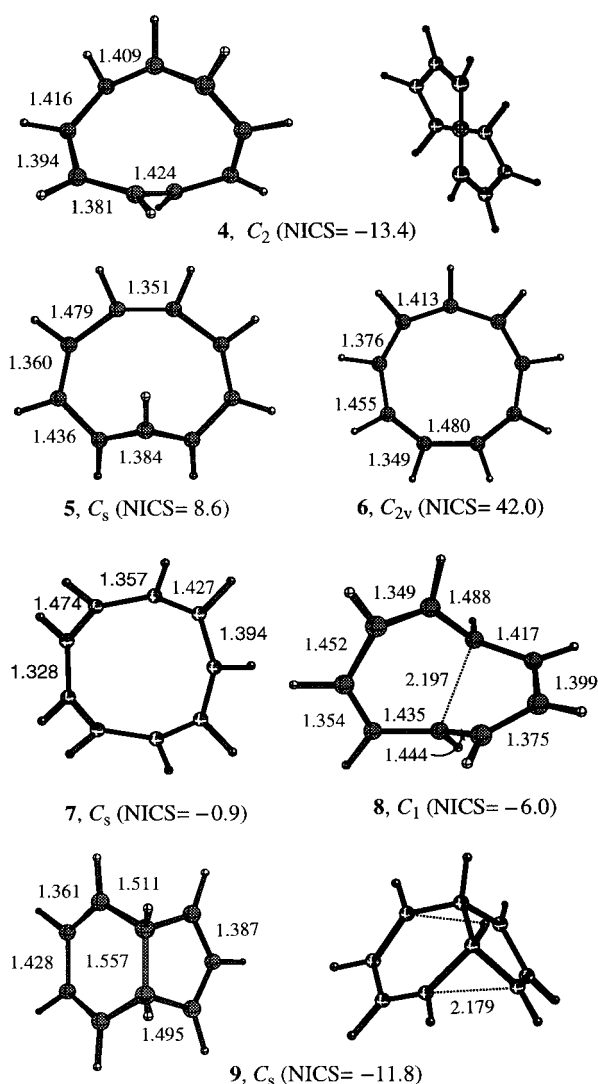


Figure 2. Conformations of $(\text{CH})_8^+$: The Möbius conformation **4** (C_2) and the strongly bond alternating form **5** (C_s); the planar antiaromatic singlet **6** (C_{2v}); **7** and **8** are transition states for enantiomerization and disrotatory ring closure of **4**, respectively. The latter connects to the bicyclic bishomoaromatic **9** (C_s). For further details, see text.

Table 1. Relative energies E_{rel} [kcal mol⁻¹] at the B3LYP/6-311 + G** and CCSD(T)/DZP level (including ZPE corrections at the B3LYP/6-31G* level), NICS [ppm], maximum differences in C–C bond lengths $\Delta R_{\text{C-C}}$ [Å], magnetic susceptibilities χ_{tot} , and diamagnetic susceptibility exaltations A [ppm cgs] of singlet $(\text{CH})_8^+$ species.

Species	NIMAG ^[a]	E_{rel}	ZPE	NICS ^[b,c]	$\Delta R_{\text{C-C}}$	χ_{tot} ^[d,e]	A ^[e]
4 , C_2	0	0.0	94.4	-13.4	0.043	-67.7	-18.8
5 , C_s	0	+21.6	94.3	+8.6	0.128	-30.8	+18.1
6 , C_{2v}	2	+26.3	93.6	+42.0	0.131	+63.6	+112.2
7 , C_s	1	+0.9 +1.1 ^[f]	94.1	-0.9	0.146	-48.9	0.0
8 , C_1	1	+8.1	93.9	-6.0	0.139	-55.9	-7.0
9 , C_s	0	-16.6	95.9	-11.8	0.067	-67.4	-18.5

[a] Vibrational analysis at the B3LYP/6-31G* level. [b] GIAO method in G94. [c] At the RHF/6-31 + G**/B3LYP/6-311 + G** level. [d] CSGT method in G94. [e] Relative to **7**. [f] Energy at the CCSD(T)/DZP//B3LYP/6-311 + G** level relative to **4** (including ZPE corrections at the B3LYP/6-31G* level).

bishomotropylium cation **9** (16.6 kcal mol⁻¹ more stable than **4**), was confirmed to be bishomoaromatic by Cremer based on geometric and magnetic criteria.^[15] The NICS at the geometric center of **9** (–11.8) and **1** = –18.5 ppm cgs (i.e., similar to that of **4**^[16]), corroborate this conclusion. This cation reacts to give the observed *cis*-8,9-dihydroindenes **3** (X = OH or Cl).^[4,5]

In summary, the geometric and magnetic criteria (NICS and **1**) exhibited by **4** now reveal this species to be the first Möbius aromatic system in the Heilbronner sense, for which there is experimental evidence.^[4,5] Without such evidence, the nature of **4** was not recognized originally. Furthermore, early speculations were incorrect: While conformation **6** is avoided, transition state **7** is not high in energy.^[5b] The complete scrambling of the deuterium label, observed for **3** even at –66 °C, is consistent with the low barrier computed for **7**, permitting rapid interconversion of the helical **4** enantiomers. Ninefold repetition of the enantiomerization results in complete distribution of a deuterium label in **4**. In conclusion, the experimental findings reported nearly three decades ago^[4,5] are explained by assuming that the (CH)₅⁺ intermediates were 4*n*-electron Möbius aromatic systems. Our prediction that **4** is the most stable monocyclic (CH)₅⁺ cation might be verified by applying modern experimental techniques such as laser flash photolysis, which has been employed to observe short-lived carbocations.^[17]

Received: March 16, 1998 [Z11593IE]

German version: *Angew. Chem.* **1998**, *110*, 2515–2517

Keywords: aromaticity • carbocations • density functional calculations • magnetic properties • Möbius strips

- [1] E. Heilbronner, *Tetrahedron Lett.* **1964**, 1923.
- [2] a) H. E. Zimmerman, *J. Am. Chem. Soc.* **1966**, *88*, 1564; b) H. E. Zimmerman, *Acc. Chem. Res.* **1971**, *4*, 272; c) H. Jiao, P. von R. Schleyer, *Angew. Chem.* **1993**, *105*, 1833; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1763; d) H. Jiao, P. von R. Schleyer, *J. Chem. Soc. Perkin Trans. 2* **1994**, 407.
- [3] D. P. Craig, *J. Chem. Soc.* **1959**, 997.
- [4] J. C. Barborak, T. M. Su, P. von R. Schleyer, G. Boche, G. Schneider, *J. Am. Chem. Soc.* **1971**, *93*, 279.
- [5] a) A. G. Anastassiou, E. Yakali, *J. Chem. Soc. Chem. Commun.* **1972**, 92; b) “The Cyclononatetraenyl Cation”: A. G. Anastassiou, *Topics in Nonbenzoid Aromatic Chemistry, Vol. 1*, Wiley, New York, **1973**, p. 18; c) E. Yakali, Dissertation, Syracuse University, NY, **1973**.
- [6] A. G. Anastassiou, E. Yakali, *J. Am. Chem. Soc.* **1971**, *93*, 3803.
- [7] We learned only recently that Anastassiou and Yakali actually considered the possibility of a Möbius cation (CH)₅⁺ in 1969, and this anticipation might have been also the incentive to carry out the early investigations outlined here: A. G. Anastassiou, E. Yakali, private communication (see also reference [5c]).
- [8] a) Geometries were optimized at the B3LYP/6-311+G** level. Frequencies and ZPE corrections are computed at the B3LYP/6-31G* level with Gaussian 94. The NICS and magnetic susceptibilities were calculated with GIAO and CSGT methods, respectively (as implemented in G 94); b) GAUSSIAN 94, Revision C.3: M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1995**.

- [9] The most stable triplet species (C_s) is 20.7 kcal mol⁻¹ higher in energy than **4** (UB3LYP/6-31G*): V. Gogonea, unpublished results.
- [10] a) For the application of geometric aromaticity criteria, see P. von R. Schleyer, P. Freeman, H. Jiao, B. Goldfuss, *Angew. Chem.* **1995**, *107*, 332; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 337; b) V. I. Minkin, M. N. Glukhovtsev, B. Y. Simkin, *Aromaticity and Antiaromaticity*, Wiley, New York, **1994**.
- [11] a) P. von R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao, N. J. v. E. Hommes, *J. Am. Chem. Soc.* **1996**, *118*, 6317; b) P. von R. Schleyer, H. Jiao, N. J. R. van E. Hommes, V. G. Malkin, O. Malkin, *J. Am. Chem. Soc.* **1997**, *119*, 12669.
- [12] a) For the use of diamagnetic susceptibility exaltations as aromaticity criteria, see H. J. Dauben, J. D. Wilson, J. L. Laity in *Nonbenzoid Aromaticity, Vol. II* (Ed.: J. P. Snyder), Academic Press, New York, **1971**, pp. 166–206; b) P. von R. Schleyer, H. Jiao, *Pure Appl. Chem.* **1996**, *68*, 209; c) see also reference [10a].
- [13] The Aces II program system: J. F. Stanton, J. Gauss, J. D. Watts, W. J. Lauderdale, R. Bartlett, *Int. J. Quantum Chem.* **1992**, *S26*, 879.
- [14] a) M. S. J. Dewar, *Angew. Chem.* **1971**, *83*, 859; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 761; b) H. Jiao, P. von R. Schleyer, *J. Phys. Org. Chem.* **1998**, in press.
- [15] D. Cremer, P. Svensson, E. Kraka, Z. Konkoli, P. Ahlberg, *J. Am. Chem. Soc.* **1993**, *115*, 7457.
- [16] Magnetic susceptibilities depend on the area of the delocalized system. This complicates comparisons among molecules with different sizes and shapes: B. Maoche, J. Gayoso, O. Ouamerli, *Rev. Roum. Chem.* **1984**, *26*, 613.
- [17] a) F. L. Cozens, R. A. McClelland, S. Steenken, *J. Am. Chem. Soc.* **1993**, *115*, 5050; b) M. Patz, H. Mayr, J. Bartl, S. Steenken, *Angew. Chem.* **1995**, *107*, 519; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 490; c) R. A. McClelland, F. L. Cozens, J. Li, S. Steenken, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1531.

Cp₃*Al₅I₆: An Intermediate in Reactions Leading to Elemental Aluminum and Al^{III} Species?*

Christoph Üffing, Elke Baum, Ralf Köppe, and Hansgeorg Schnöckel*

Dedicated to Professor Heinrich Nöth on the occasion of his 70th birthday

As we have demonstrated in earlier work, Al^I species are reactive both in solid noble gases and under preparative synthetic conditions,^[1] and often react to give thermodynamically more stable Al^{III} products and metallic aluminum. [Cp₂*Al]⁺[Cp*AlCl₃][–] is thus formed as the final product from Cp*Al and AlCl₃ with simultaneous deposition of aluminum. This isomer of the sesquichloride [Cp₃*Al₂Cl₃] contains the aluminocenium ion [Cp₂*Al]⁺ as a structural peculiarity.^[2] To understand this reaction mechanism and to find out how Al^I species can react in general, we carried out investigations with the aim of capturing intermediate products of the disproportionation.

[*] Prof. Dr. H. Schnöckel, Dr. C. Üffing, Dr. E. Baum, Dr. R. Köppe
Institut für Anorganische Chemie der Universität
Engesserstrasse, Geb. 30.45, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4854
E-mail: hg@achpc9.chemie.uni-karlsruhe.de

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

To prepare as stable an intermediate as possible, we selected AlI_3 instead of AlCl_3 and treated the iodide with $[\text{Cp}^*\text{Al}]_4$ under the exclusion of donors; that is, we provided soft substituents that have a proven capability for stabilizing elements in low oxidation states. It became apparent that the presence of Al_2I_6 dramatically increased the tendency of $[\text{Cp}^*\text{Al}]$ to disproportionate: Whereas pure $[\text{Cp}^*\text{Al}]$ can be heated in solution to almost 90°C without visible decomposition, it disproportionates in the presence of Al_2I_6 even below room temperature. This means that even a relatively stable Al^{I} compound such as $[\text{Cp}^*\text{Al}]$ reacts so rapidly at room temperature that intermediate products cannot normally be intercepted.^[3] In view of this, proof of the participation of other Al^{I} species in the reaction between Al^0 and Al^{III} should be even more difficult if not altogether impossible to obtain. Therefore, the structurally characterized intermediate product presented here— $[\text{Cp}_3^*\text{Al}_5\text{I}_6]$ (**1**), which could be isolated at -20°C —is of particular significance (Figure 1a).

Compound **1** is formed from a suspension of $[\text{Cp}^*\text{Al}]_4$ and Al_2I_6 (molar ratio 1:2) in toluene at -20°C . It is a colorless

substance and very sensitive to hydrolysis. Crystals of **1** thus obtained contain toluene such that the formula may be written as $\mathbf{1} \cdot 0.5\text{C}_7\text{H}_8$. The X-ray structure analysis^[5] at -73°C shows that **1** has a cage-like framework comprising five Al and two I atoms, in which the aluminum atom Al(1) is coordinated in a tetrahedral fashion by two iodine atoms (Al(1)–I(1) 257, Al(1)–I(2) 254 pm) and two Cp^* -substituted aluminum atoms (Al(2), Al(3); Al–Al 252–253, Al–C 214–224 pm) (Figure 1a). The iodine atoms I(3) and I(4) lie at a considerably larger distance from Al(1) (Al(1)–I(3) 398, Al(1)–I(4) 388 pm) and form a plane with I(1) and I(2); Al(1) also lies in this plane.

An Al_2 unit (Al(4), Al(5); Al–Al 254 pm) is arranged almost perpendicular to the Al_3 group. One of the metal atoms of this Al_2 unit is coordinated by three iodine atoms (Al(5)–I(3) 260, Al(5)–I(5) 254, Al(5)–I(6) 257 pm), and the other by one iodine atom and a Cp^* substituent (Al(4)–I(4) 281, Al(4)–C 215–234 pm). The iodine atoms I(3) and I(4) occupy an eclipsed conformation with respect to the Al_2 unit. In addition, there are interactions between these iodine atoms and the Al atoms Al(2) and Al(3) of the Al_3 unit. The atomic distances are shown in Figure 1b.^[6] In agreement with the average oxidation number 1.8 for aluminum, the Al–Al and Al–I distances in **1** resemble those in donor-stabilized aluminum(II) diiodides.^[10] The structure of **1** provides a first indication of the reaction mechanism for the reaction of $[\text{Cp}^*\text{Al}]$ with Al_2I_6 (Scheme 1).

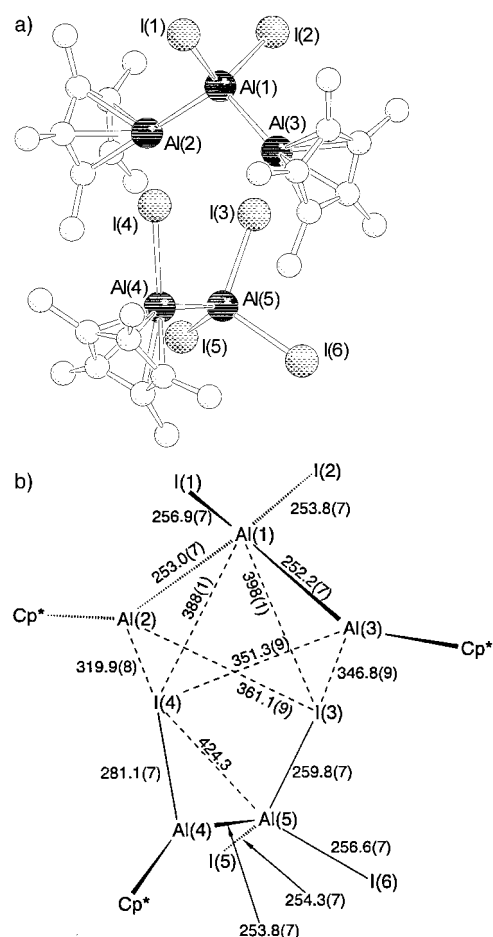
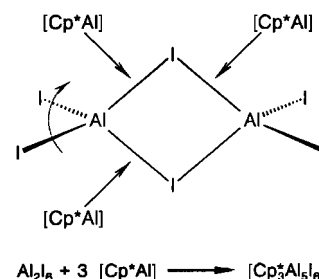


Figure 1. a) Structure of **1** in the crystal (SCHAKAL^[4]). Hydrogen atoms are not shown. b) Schematic representation of the structure of **1** with several distances [pm]. Further distances [pm] and angles [°]: Al(2)–Al(3) 407(1), Al(2)/Al(3)– Cp^* 214.4(6)–224.4(7), Al(4)–C(21) 233.6(6), Al(4)–C(22) 227.1(6), Al(4)–C(23) 215.2(5), Al(4)–C(24) 215.6(6), Al(4)–C(25) 225.3(7), Al(1)–Al(5) 597(2), Al(1)–Al(4) 608(2); Al(2)–Al(1)–Al(3) 107.23(7), I(1)–Al(1)–I(2) 111.73(9), Cp^* –Al–Al(1) 117.3(2)–176.9(2), Al(5)–Al(4)–I(4) 104.83(7), Al(4)–Al(5)–I(6) 111.10(8), Al(4)–Al(5)–I(3) 111.27(7), I(6)–Al(5)–I(3) 108.04(13).



Scheme 1. Reaction of three molecules of $[\text{Cp}^*\text{Al}]$ with one molecule of Al_2I_6 . Schematic representation (top) and reaction equation (bottom).

It is apparent that monomeric $[\text{Cp}^*\text{Al}]$ has a tendency to undergo insertion reactions. Even at -20°C —that is, at very low $[\text{Cp}^*\text{Al}]$ concentrations^[11]—three $[\text{Cp}^*\text{Al}]$ molecules are inserted into bridging Al–I bonds. At the same time, three bridging Al–I bonds of Al_2I_6 are expanded so much that only the weak Al–I–Al bridging interactions mentioned above remain.

To decide whether the experimentally observed species should be described as separated ions $[\text{Cp}_2^*\text{Al}_3\text{I}_2]^+[\text{Cp}^*\text{Al}_2\text{I}_4]^-$, as an ion pair, or as a donor–acceptor complex, we carried out extensive quantum-chemical calculations.^[9] These show that the calculated geometry parameters (e.g., several Al–I distances and the angle $\text{Al}_{\text{Cp}^*}\text{–Al–Al}_{\text{Cp}^*}$) for isolated ions do not agree with the observed structural data. Additional calculations were therefore carried out for the model compounds $[\text{Cp}_3\text{Al}_5\text{I}_6]$ (**1a**), $\text{Br}_3\text{Al}_5\text{I}_6$ (**1b**), and $\text{H}_3\text{Al}_5\text{I}_6$ (**1c**).^[9] It became clear that the geometry is decisively influenced by the Cp^* groups, because both the hydrogen-

and the bromine-substituted compounds have quite different Al–I distances in the bridges and very acute Al–Al–Al angles in the Al_3 unit when compared with **1a**. The compounds **1a–c** also differ from one another considerably with regard to the population analyses. Whereas the calculations for **1a** result in a clear charge separation between the Al_3 and Al_2 units (± 0.38) and negatively charged bridging iodine atoms (-0.15), there are virtually no charge separations (Al_3 : approx. -0.04 ; Al_2 : ca. $+0.04$). Furthermore, there are only very weakly negatively polarized bridging iodine atoms (ca. -0.04) in **1b** and **1c**.^[9c]

The compounds **1a–c** also differ in their energy balance. The insertion of three AlH units into a Al_2I_6 molecule is, with 438 kJ mol^{-1} , highly exothermic, whereas the insertion of the CpAl units leads to an energy gain of just 199 kJ mol^{-1} . These thermodynamic results are plausible in view of the calculated charge separation in **1a**. In conclusion, the quantum-chemical calculations, which in the case of **1a** produce results that are in good agreement with the experimental structural data of **1**, permit the following bonding description for this intermediate. In contrast to the donor–acceptor complexes **1b** and **1c**, **1** and **1a** are best described as contact ion pairs that disproportionate at room temperature to give elemental aluminum and Al^{III} species.^[12]

This type of insertion of Al^{I} species can also occur in technically relevant electrochemical reductions^[13] of organic aluminum(III) compounds. The resulting primary products can insert themselves into the reagents and react in an analogous manner to **1** to give species rich in aluminum. Unstable intermediates such as these can then spontaneously disproportionate to give elemental aluminum. The starting compound (Al^{III}) is also formed, which can then go through the reaction cycle again. In a similar manner, Al^{I} species could also be important intermediates in the preparation of organic aluminum compounds from aluminum and alkyl halides, whereby the insertion of Al^{I} compounds into Al^{III} species already formed could possibly lead to compounds analogous to **1**.^[14]

Experimental Section

AlI_3 (50 mg, 0.12 mmol) was combined with $[(\text{Cp}^*\text{Al})_4]$ (20 mg, 0.03 mmol), and toluene was added. The suspension was stored at -20°C . After a few days clear, colorless crystals of **1** were formed along with solid $[(\text{Cp}^*\text{Al})_4]$. Elemental aluminum was not deposited under these conditions. To transfer the crystals quickly from the cold suspension onto the goniometer head, they were warmed to room temperature in mineral oil (Aldrich) under an argon stream. (The crystals decompose slowly in this oil; the color changes from colorless to yellow and then to red.) In the cold N_2 stream (200 K) on the goniometer head, a glass-like protective coating is formed around the crystal, thus preventing attack by air and moisture.

Received: December 11, 1997

Revised version: May 4, 1998 [Z11252]

German version: *Angew. Chem.* **1998**, *110*, 2488–2491

Keywords: aluminum • disproportionations • insertions • intermediates • structure elucidation

[1] C. Dohmeier, D. Loos, H. Schnöckel, *Angew. Chem.* **1996**, *108*, 141–161; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 129–149.

- [2] a) C. Dohmeier, H. Schnöckel, C. Robl, U. Schneider, R. Ahlrichs, *Angew. Chem.* **1993**, *105*, 1714–1716; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1655; b) C. Dohmeier, Dissertation, Universität München, **1994**.
- [3] An example for an insertion of $[\text{Cp}^*\text{Al}]$ into a Si–F bond is known, however: S. Schulz, T. Schoop, H. W. Roesky, L. Häming, A. Steiner, R. Herbst-Irmer, *Angew. Chem.* **1995**, *107*, 1015–1016; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 919–920.
- [4] E. Keller, SCHAKAL92, Universität Freiburg, **1992**.
- [5] Crystal structure analysis of $\text{C}_{30}\text{H}_{45}\text{AlI}_6 \cdot 0.5 \text{ C}_7\text{H}_8$ (**1**· $0.5 \text{ C}_7\text{H}_8$): $M_r = 1348.09$; crystal dimensions: $0.51 \times 0.35 \times 0.27 \text{ mm}^3$, $T = 200(2) \text{ K}$, monoclinic, space group $\text{C}2/c$, $a = 21.974(5)$, $b = 27.730(70)$, $c = 17.107(4) \text{ Å}$, $\beta = 117.16(6)^\circ$, $V = 9274.6(236) \text{ Å}^3$, $Z = 8$, $\rho_{\text{calc}} = 1.931 \text{ g cm}^{-3}$, $\mu = 4.093 \text{ mm}^{-1}$, $F(000) = 5064$. Of 9952 reflections measured on a four-circle diffractometer (STOE-STADI-4; $\text{MoK}\alpha$ radiation, $\lambda = 0.71073 \text{ Å}$; graphite monochromator), 8147 were independent ($R(\text{int.}) = 0.0252$); $-18 \leq h \leq 26$; $-23 \leq k \leq 32$; $-20 \leq l \leq 20$; $3.98 \leq 2\theta \leq 49.96^\circ$. The structure was solved by direct methods (SHELXS-86),^[5a] and 6929 reflections ($F > 4\sigma(F)$) were used for full-matrix refinement of 402 parameters by the least-squares method against $|F^2|$ (SHELXL-93).^[5b] Hydrogen atoms were treated using a rider model with fixed isotropic U values; weighting scheme: $\omega^{-1} = \sigma^2 F_o^2 + (0.0430 P)^2 + 32.1956 P$, with $P = (F_o^2 + 2F_c^2)/3$; ω scan (scan width 0.82 – 1.48°); semi-empirical absorption correction (min./max. transmission $0.2131/0.2579$); $R1 = 0.0327$ ($F > 4\sigma(F)$); $wR2$ (all data) = 0.0894 ; max./min. residual electron density $1.666/-1.202 \text{ e Å}^{-3}$. Further details on the crystal structure analysis may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-408058. a) SHELXS-86: G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473; b) SHELXL-93: G. M. Sheldrick, Universität Göttingen, **1993**.
- [6] With respect to the Al–I distances to the terminal I atoms in dimeric AlI_3 ($245^{[7a]}$ as well as 244.7 and $245.9 \text{ pm}^{[7b]}$), the distances from Al(1) and Al(5) to their nearest neighboring iodine atoms are 9 – 15 pm longer. The Al–I(4) and Al–I(3) distances in the bridges are also considerably elongated with respect to those in Al_2I_6 . These results seem reasonable, however, when one considers that a) Al atoms in low oxidation states have a much greater radius (the Al–I distance in $[\text{AlI} \cdot \text{NEt}_3]_4$ is 264 pm ,^[8] in a bridging bond an Al–I distance of 283 pm has been calculated for $\text{Al}_2\text{I}_2^{[9]}$) and b) higher coordination numbers (in comparison to the examples listed under a)) lead to a further increase in the interatomic distances in **1**.
- [7] a) A. F. Wells, *Structural Inorganic Chemistry*, 5th ed., Clarendon, Oxford, **1984**; S. I. Troyanov, *Zh. Neorgan. Khim.* **1994**, *39*, 552–555; b) R. Kniep, P. Blees, W. Poll, *Angew. Chem.* **1982**, *94*, 370; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 386.
- [8] A. Ecker, H. Schnöckel, *Z. Anorg. Allg. Chem.* **1996**, *622*, 149–152.
- [9] All ab initio calculations were carried out with the RI-DFT module^[9a] (B–P parametrization) of the program TURBOMOLE^[9b] using SVP basis sets.^[9c] Population analyses were carried out with the method of Mulliken. Atomic numbering for **1**: see Figure 1; energies (E) [a.u.]; distances [pm]; angles [$^\circ$]; partial charges (δ): $[\text{Cp}_3\text{Al}_5\text{I}_6]$ (**1a**; C_1 symmetry): $E = -1861.284917$; Al(1)–Al(2) 257.0, Al(1)–Al(3) 257.2, Al(2)–I(3) 326.8, Al(2)–I(4) 357.8, Al(3)–I(3) 346.0, Al(3)–I(4) 332.1, Al(4)–I(4) 278.4, Al(5)–I(3) 268.0, Al(4)–Al(5) 256.4, Al(2)–Al(3) 389.0; Al(2)–Al(1)–Al(3) 98.3, I(4)–Al(4)–Al(5) 109.9, Al(4)–Al(5)–I(3) 108.5; $\delta(\text{Cp}_{\text{Al}(4)}) = 0.02$, $\delta(\text{Cp}_{\text{Al}(2)}) = 0.10$, $\delta(\text{Cp}_{\text{Al}(3)}) = 0.09$, $\delta(\text{Al}(1)) = 0.30$, $\delta(\text{Al}(2)) = 0.25$, $\delta(\text{Al}(3)) = 0.25$, $\delta(\text{Al}(4)) = 0.29$, $\delta(\text{Al}(5)) = 0.39$, $\delta(\text{I}(3)) = -0.17$, $\delta(\text{I}(4)) = -0.27$, $\delta(\text{I}(5)) = -0.33$, $\delta(\text{Al}_3) = 0.38$, $\delta(\text{Al}_2) = -0.38$; that is, **1a** should be considered as an ion pair due to the clear charge separation and the strongly charged bridging iodine atoms ($\delta(\text{I}) > -0.15$). $\text{Br}_3\text{Al}_5\text{I}_6$ (**1b**; C_1 symmetry): $E = -9003.663100$; Al(1)–Al(2) 260.2, Al(1)–Al(3) 260.2, Al(2)–I(3) 297.5, Al(3)–I(3) 297.5, Al(2)–I(4) 310.8, Al(3)–I(4) 310.8, Al(4)–I(4) 269.4, Al(5)–I(3) 281.0, Al(4)–Al(5) 257.1, Al(2)–Al(3) 335.3; Al(2)–Al(1)–Al(3) 80.2, I(4)–Al(4)–Al(5) 116.2, Al(4)–Al(5)–I(3) 99.0; $\delta(\text{Br}_{\text{Al}(4)}) = -0.18$, $\delta(\text{Br}_{\text{Al}(2)}) = -0.20$, $\delta(\text{Br}_{\text{Al}(3)}) = -0.20$, $\delta(\text{Al}(1)) = 0.39$, $\delta(\text{Al}(2)) = 0.23$, $\delta(\text{Al}(3)) = 0.23$, $\delta(\text{Al}(4)) = 0.39$, $\delta(\text{Al}(5)) = 0.37$, $\delta(\text{I}(3)) = -0.04$, $\delta(\text{I}(4)) = -0.05$, $\delta(\text{I}(5)) = -0.23$, $\delta(\text{Al}_3) = -0.04$, $\delta(\text{Al}_2) = 0.04$; that is, **1b** should

be regarded as a donor–acceptor complex, as there is no charge separation between the Al units and the bridging iodine atoms are only weakly charged.^[9d] $[\text{H}_3\text{Al}_3\text{I}_6]$ (**1c**; C_1 symmetry): $E = -1282.817496$; Al(1)–Al(2) 259.7, Al(1)–Al(3) 259.7, Al(2)–I(3) 291.9, Al(2)–I(4) 305.3, Al(3)–I(3) 292.2, Al(3)–I(4) 305.4, Al(4)–I(4) 268.4, Al(5)–I(3) 282.0, Al(4)–Al(5) 256.4, Al(2)–Al(3) 333.0; Al(2)–Al(1)–Al(3) 79.8, I(4)–Al(4)–Al(5) 114.2, Al(4)–Al(5)–I(3) 100.2; $\delta(\text{H}_{\text{Al}(4)}) = -0.02$, $\delta(\text{H}_{\text{Al}(2)}) = 0.09$, $\delta(\text{H}_{\text{Al}(3)}) = 0.09$, $\delta(\text{Al}(1)) = 0.40$, $\delta(\text{Al}(2)) = 0.04$, $\delta(\text{Al}(3)) = 0.04$, $\delta(\text{Al}(4)) = 0.28$, $\delta(\text{Al}(5)) = 0.35$, $\delta(\text{I}(3)) = -0.03$, $\delta(\text{I}(4)) = -0.05$, $\delta(\text{I}(5)) = -0.24$, $\delta(\text{“Al}_3\text{”}) = -0.05$, $\delta(\text{“Al}_2\text{”}) = 0.05$; that is, **1c** should be regarded as a donor–acceptor complex, as there is no charge separation between the Al units and the bridging iodine atoms are only weakly charged.^[9d]

$\text{Al}_2\text{I}_6 + 3\text{AlH} \rightarrow \text{H}_3\text{Al}_3\text{I}_6$; $\Delta E = -438\text{ kJ mol}^{-1}$. $\text{Al}_2\text{I}_6 + 3[\text{CpAl}] \rightarrow [\text{Cp}_3\text{Al}_3\text{I}_6]$; $\Delta E = -199\text{ kJ mol}^{-1}$. a) K. Eichkorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chem. Phys. Lett.* **1995**, *240*, 283–290; *Chem. Phys. Lett.* **1995**, *242*, 652–660; b) R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165–169; c) A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571–2577. d) A similar polarization was also calculated for Al_2I_6 : donor–acceptor complex; D_{2h} symmetry; Al–I_{bridge} 270.7, Al–I_{terminal} 250.2, Al–Al 367.8; $\delta(\text{I}_{\text{bridge}}) = -0.05$, $\delta(\text{I}_{\text{terminal}}) = -0.21$; $\delta(\text{Al}) = 0.47$.

- [10] a) A. Ecker, E. Baum, M. A. Friesen, M. A. Junker, C. Üffing, R. Köppe, H. Schnöckel, *Z. Anorg. Allg. Chem.* **1998**, *624*, 513–516; b) A. Ecker, H. Schnöckel, *Z. Anorg. Allg. Chem.*, in press.
- [11] In the ^{27}Al NMR spectrum, monomeric $[\text{Cp}^*\text{Al}]$ can only be identified in equilibrium with $[[\text{Cp}^*\text{Al}]_4]$ above about 60°C , because the energy for the tetramerization to $[[\text{Cp}^*\text{Al}]_4]$ is around -150 kJ mol^{-1} .^[1]
- [12] The NMR spectrum of a mixture of $[[\text{Cp}^*\text{Al}]_4]$ and Al_2I_6 in deuterated toluene shows signals at the following shifts: ^1H NMR (Bruker AC-250 spectrometer (250.134 MHz); room temperature; reference: $\delta(\text{C}_7\text{D}_7\text{H})$): $\delta = 2.09$; ^{27}Al NMR (Bruker AMX-300 spectrometer; room temperature; external reference: $\delta([\text{Al}(\text{H}_2\text{O})_6]^{3+})$): $\delta = 0$. After a reaction period of a few days at -20°C : ^1H NMR: $\delta(\omega_{1/2}[\text{Hz}]) = 2.07$ (10), 2.03 (10) (both with low intensity), 1.93 (2), 1.85 (3), 1.78 (3), 1.60 (3) (the latter in a ratio of about 3:3:2); ^{27}Al NMR: $\delta(\omega_{1/2}[\text{Hz}]) = 110$ (br, weak), -21 (550), -83 (260). After about one month at -20°C : ^1H NMR: $\delta(\omega_{1/2}[\text{Hz}]) = 1.85$ (2), 1.74 (2), 1.60 (2) (in a ratio of about 2:3:4); ^{27}Al NMR: $\delta(\omega_{1/2}[\text{Hz}]) = 110$ (br, weak), -21 (520), -82 (260). After about three months and intermediate tempering at 120°C : ^1H NMR: $\delta(\omega_{1/2}[\text{Hz}]) = 1.57$ (sharp, s); ^{27}Al -NMR: $\delta(\omega_{1/2}[\text{Hz}]) = -19$ (500, weak), -81 (360), -114 (very weak, $[\text{Cp}_2^*\text{Al}]^+$).^[2a] These NMR spectroscopic results indicate a more complex reaction sequence than for the reaction between $[[\text{Cp}^*\text{Al}]_4]$ and AlCl_3 .^[2a]
- [13] See, for example, the electrochemical reduction of Al^{III} species to elemental aluminum or the preparation of simple organic aluminum(III) compounds from aluminum and alkyl halides: K. Ziegler, H. Lehmkuhl, *Z. Anorg. Allg. Chem.* **1956**, *283*, 414–424; W. Kautek, W. Fromberg, J. A. de Hek, *Metallüberfläche* **1992**, *46*, 67–74; J. Fischer, *Metallüberfläche* **1996**, *50*, 183–184; A. Ecker, H. Schnöckel, *VDI-Nachrichten* **1996**, *50*, 22; H. Köhnlein, H. Schnöckel, *Aluminum* **1997**, *73*, 766–767.
- [14] Additional Al^{III} species are formed by their subsequent disproportionation. This should lead to an increase in the reaction rate for the formation of the desired end products.

Average Octet Radical Polymer: A Stable Polyphenoxyl with Star-Shaped π Conjugation**

Hiroyuki Nishide,* Makoto Miyasaka, and Eishun Tsuchida

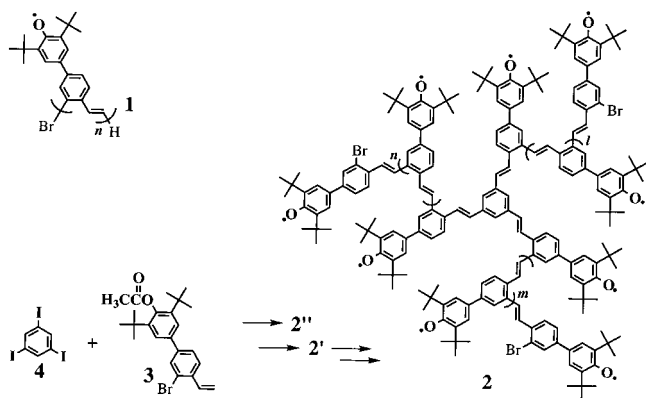
The search for syntheses of organic molecules with very high spin resulting from intramolecular through-bond magnetic ordering is driven by the desire to realize magnetism based purely on organic components.^[1] High-spin alignment in the ground state has been demonstrated for cross-conjugated polyradicals or radical polymer main chains, such as poly(1,3-phenylenecarbene)^[1b] and poly(1,3-phenylenephenylmethine).^[1c] Pseudo-two-dimensional branched, cyclic, and ladder homologues have also been synthesized to increase the spin quantum number S at low temperature.^[2] The aim was to diminish the damage of a radical or spin defect, which is fatal for the cross-conjugated polyradicals. In addition, these polyradicals lacked chemical stability at room temperature.

There is another approach to the high-spin molecules that makes use of π -conjugated linear polymers bearing pendant radical groups on the polymer backbone which are π -conjugated with the backbone to ensure the ferromagnetic connectivity of the radicals.^[1e] In this type of polyradical, the spin alignment between the pendant unpaired electrons is not sensitive to a spin defects, which are unavoidable for radical polymers of increasing molecular size because the magnetic interaction is transmitted through the π -conjugated polymer backbone. A further advantage is that the pendant, built-in radical groups could be chosen from a series of chemically stable organic radicals. We recently synthesized poly(1,2-phenylenevinylene) containing di-*tert*-butylphenoxyl as the pendant radical group (**1**) which has a through-conjugated backbone bond and allows long-range ferromagnetic exchange interaction between the pendant unpaired electrons: With a spin concentration of 0.7 per monomer unit, **1** displays values for S of $4/2$ to $5/2$.^[3] We report here our successful improvement of both S and the stability of the polyradical by extending **1** to the star-shaped homologue **2** (Scheme 1).

The precursor acetoxypolymer **2'** was synthesized in a one-pot reaction by the Pd-catalyzed Heck reaction of styrene **3** with 1,3,5-triiodobenzene (**4**), the core of the star-shaped polymer (see the Experimental Section). The molecular weight and degree of polymerization ($\text{DP} = l + m + n + 6$ for **2**) of the star-shaped polymer was controlled by the feed ratio of **3** to **4** during the polymerization. The iodide groups had completely reacted in every polymer. The DP measured by

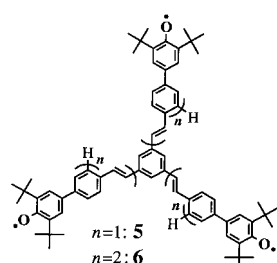
[*] Prof. H. Nishide, M. Miyasaka, Prof. E. Tsuchida
Department of Polymer Chemistry
Waseda University, Tokyo 169–8555 (Japan)
Fax: (+81) 3-3209-5522
E-mail: nishide@mn.waseda.ac.jp

[**] This work was partially supported by Grants-in-Aid for Scientific Research (nos. 277/08246101 and 09305060) from the Ministry of Education, Science and Culture, Japan, and by the NEDO R&D Project on Precision Polycondensation. The authors thank Prof. A. Rajca (University of Nebraska) for his productive comments on this study.



Scheme 1.

light scattering was in agreement with the final bromide content determined by elemental analysis, which supports a linear structure of the side chains. Fourteen peaks in the ^{13}C NMR spectrum, which could be ascribed to the benzene rings and vinylene groups, supported both the head-to-tail linkage



structure of the side chains and the 1,3,5-trisubstituted benzene structure of the core. Polymer $2''$ was completely hydrolyzed to the corresponding hydroxypolymer $2'$. Tri- and hexaradical compounds **5** and **6** were also synthesized.

With a small excess of $n\text{Bu}_4\text{NOH}$ in 2-methyltetrahydrofuran (2Me-THF), hydroxypolymer $2'$ (DP = 33, 42, 70) was converted into the phenolate polymer, which was then heterogeneously oxidized with an aqueous solution of $\text{K}_3[\text{Fe}(\text{CN})_6]$ to yield the polyradical **2**. This polyradical is also soluble in common solvents such as benzene, THF, and chloroform. The UV absorption was shifted bathochromically to $\lambda_{\text{max}} = 450$ nm relative to those of **5**, **6**, and **1** ($\lambda_{\text{max}} = 420$, 423, and 425 nm, respectively), which suggested π conjugation in the backbone of **2**.

A solution of **2** in chloroform was cast under an oxygen-free atmosphere to yield a transparent, brown-green, brittle film; the glassy property^[4] is ascribed to the rigid structure of **2**. In the solid state **2** is stable even at room temperature. The half-life of the radicals **2**, **1**, and **3** was 3.4, 1.2, and 0.1 d, respectively. The conjugation with and/or the relatively planar skeleton structure of the star-shaped backbone improved the chemical stability of the pendant phenoxyl radical in **2**.

The ESR spectrum of **2** at a low spin concentration shows a broad hyperfine structure at $g = 2.004(2)$, which is attributed to the 5–7 protons of the phenoxyl ring and phenylenevinylene backbone. The distribution of spin density into the core of **2** was indicated by the hyperfine structure of the core model compound **5** at a low spin concentration (Figure 1 a). These ESR results suggested an effectively delocalized spin distribution over the entire star-shaped polyradical, most likely because of its sterically less hindered or relatively planar structure. The ESR spectra of frozen glasses in toluene of **2**, **5**,

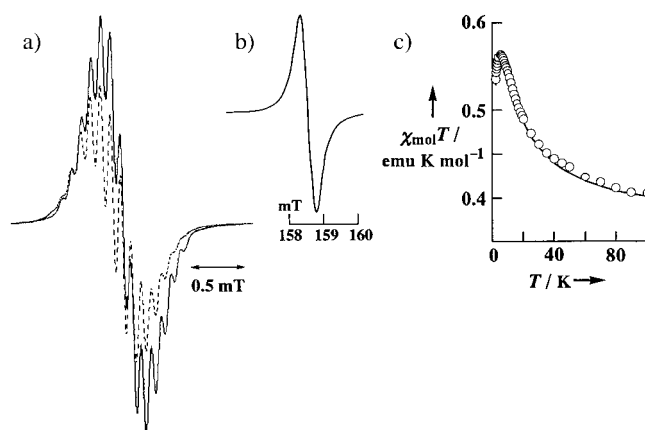


Figure 1. a) ESR spectrum of the core model compound **5** at a low spin concentration in toluene at room temperature (the dashed line represents the simulation, $a_{\text{H}} = 0.10$, 0.09, and 0.08 mT) b) ESR $\Delta M_s = \pm 2$ signal of **5** at a high spin concentration at 77 K. c) Plot of $\chi_{\text{mol}}T$ versus T for **5** (spin concentration 0.9) in 2Me-THF. The solid line is the theoretical curve calculated with Equation (1) for $2J = 19 \text{ cm}^{-1}$, $\theta = -0.29 \text{ K}$, $x_1 = 0$, $x_2 = 0.13(2)$, and $x_3 = 0.86(8)$.^[5]

and **6** with a high spin concentration showed a $\Delta M_s = \pm 2$ forbidden transition ascribed to a triplet species at $g = 4.021(8)$ (Figure 1 b).

Static magnetic susceptibility and magnetization of the polyradicals in frozen 2Me-THF or toluene were measured with a SQUID magnetometer (Quantum Design MPMS-7). The magnetization plots of triradical **5** were presented close to the Brillouin curve for $S = 3/2$ at temperatures lower than 3 K and indicated a quartet ground state of the triradical. Figure 1 c shows a plot of the product of molar magnetic susceptibility χ_{mol} and T versus T for **5**: as in the case for ferromagnetic species, $\chi_{\text{mol}}T$ increases at low temperature from the theoretical value ($\chi_{\text{mol}}T = 0.375$) for $S = 1/2$, which was analyzed using the van Vleck expression^[5] [Eq. (1)] to obtain the spin exchange coupling constant (J , positive for ferromagnetic compound) of the ferromagnetic interaction. The value $2J = 19 \pm 2 \text{ cm}^{-1}$ for **5** is larger than that ($6 \pm 1 \text{ cm}^{-1}$) for the corresponding diradical analogue 1-[2'-methyl-5-(3'', 5''-di-*tert*-butyl-4''-oxyphenyl)styryl]-2-[4'-(3'', 5''-di-*tert*-butyl-4''-oxyphenyl)styryl]benzene. This result indicates that the 1,3,5-benzene core acts as an effective coupler for connecting three polyradical side chains.

$$\chi_{\text{mol}}T = \frac{(N_A g^2 \mu_B^2 T) / (k(T - \theta))}{[x_3 \{1 + \exp(-2J/kT) + 10 \exp(J/kT)\} / 12 + \{1 + \exp(-2J/kT) + 2 \exp(J/kT)\} + x_2 / (3 + \exp(-2J/kT)) + x_1 / 4]} \quad (1)$$

The inset in Figure 2 gives the $\chi_{\text{mol}}T$ plots for the polyradicals **2** and **6**, which have the same spin concentration of about 0.7 and different degrees of polymerization. As is typical of ferromagnetic species, the increase in $\chi_{\text{mol}}T$ at low temperature is enhanced for the polyradical with a higher molecular weight; that is, it corresponds to the number of spins in the polyradical molecule. The star-shaped polyradical exhibits a more effective interaction than the corresponding linear polyradical. Figure 2 shows the magnetization M plots for the star-shaped polyradical **2** (DP = 70), normalized with saturated magnetization M_s . The M/M_s curves for **2** even with a spin concentration of 0.80 lie almost on the theoretical

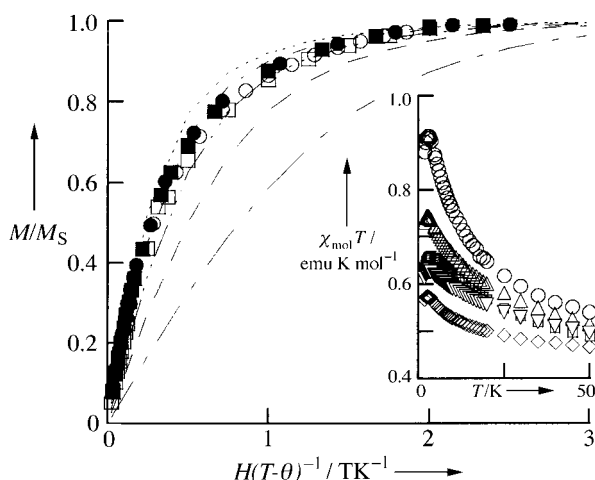


Figure 2. Normalized plots of magnetization M/M_s versus the ratio of magnetic field to temperature for **2** (DP = 70) with a spin concentration 0.80 per monomer unit in 2Me-THF at 1.8 K (●), 2.0 (■), 2.5 (○), and 3 (□) as well as the theoretical curves corresponding to the Brillouin functions for $S = 1/2, 3/2, 5/2, 7/2$, and $9/2$. Inset: Plots of $\chi_{\text{mol}} T$ versus T for **2** with different degrees of polymerization (DP) and spin concentrations. DP = 70, 0.75 spins/unit (○); DP = 42, 0.68 (Δ); DP = 33, 0.65 (□). For **1** with DP = 29 and 0.68 spins/unit (▽). For **6** with 0.75 spins/unit (◇).

Brillouin curve for $S = 9/2$ and $6/2$ at low and high magnetic field, respectively. This characterizes the polyradical **2** as a mixture of molecular high-spin assemblages^[2b, 6] or a disperse spin system with $S = 7/2$ on average.

Experimental Section

Polymerization: Palladium acetate (0.6 mmol), tri-*o*-tolylphosphane (1.2 mmol), 1,3,5-triiodobenzene^[7] (0.1 mmol), and triethylamine (3.08 mmol) were added to a solution of monomer **3**^[2b] (6.06 mmol) in DMF (12.3 mL). The solution was warmed to 45 °C for 6 h and then heated at 90 °C for 18 h. The mixture was separated on a polystyrene gel column and purified by reprecipitation from chloroform in methanol to yield the polymer as a yellow powder in 42 % yield. The molecular weight of the polymer was estimated by a light-scattering measurement (Tosoh LS-8000).

2'': ¹H NMR (500 MHz, CDCl₃): δ = 1.42 (s, 54H; C(CH₃)), 2.38 (s, 9H; OCOCH₃), 7.23–7.74 (m, 24H; Ar, CH=CH); ¹³C NMR (125 MHz, CDCl₃): δ = 22.53, 31.98, 36.20, 125.85, 127.40, 127.72, 128.05, 129.18, 129.39, 132.11, 135.97, 137.66, 138.45, 138.67, 142.17, 143.68, 170.76; IR (KBr): $\tilde{\nu}$ = 1765 ($\nu_{\text{C=O}}$), 960 cm⁻¹ ($\delta_{\text{C=C}}$); correct elemental analysis. Iodine content less than 0.01 %, as determined by the combustion method. The fluorescence at 450 nm (λ_{ex} = 420 nm) was ascribed to the *trans*-stilbene structure.

2': Polymer **2''** was converted into **2'** after complete elimination of the protecting acetyl groups with KOH in DMSO/THF. ¹H NMR (500 MHz, CDCl₃): δ = 1.45 (s, 54H; C(CH₃)), 5.24 (s, 3H; OH), 7.39–7.78 (m, 24H; Ar, CH=CH); ¹³C NMR (125 MHz, CDCl₃): δ = 29.85, 33.96, 123.43, 123.55, 126.25, 126.51, 126.78, 127.64, 128.12, 131.66, 133.68, 134.72, 135.78, 136.12, 141.44, 153.17; IR (KBr): $\tilde{\nu}$ = 3640 ($\nu_{\text{O-H}}$), 960 cm⁻¹ ($\delta_{\text{C=C}}$); M_n = 2.1×10^4 (M_w/M_n = 1.2) for DP = 70, 1.3×10^4 (M_w/M_n = 1.2) for DP = 42, 1.0×10^4 (M_w/M_n = 1.2) for DP = 33.

Oxidation: The hydroxypolymer **2'** was completely converted into the phenolate anion with a small excess of *n*Bu₄NOH in 2Me-THF and carefully oxidized with an aqueous alkaline solution of K₃[Fe(CN)₆] under an inert atmosphere at room temperature to yield the corresponding polyradicals.

5: 1,3,5-Tris[4'-(3'',5''-di-*tert*-butyl-4'-acetoxyphenyl)styryl]benzene (**5''**) was prepared by the Heck reaction of 4-(3',5'-di-*tert*-butyl-4'-acetoxyphenyl)styrene and **4** in 63 % yield. Correct elemental analysis; ¹H NMR (500 MHz, CDCl₃): δ = 1.42 (s, 54H; C(CH₃)), 2.38 (s, 9H; OCOCH₃),

7.22–7.74 (m, 27H; Ar, CH=CH); ¹³C NMR (125 MHz, CDCl₃): δ = 22.68, 31.50, 35.58, 125.21, 126.98, 127.60, 128.30, 129.09, 136.05, 137.74, 138.33, 140.99, 142.10, 142.73, 147.64, 171.12; IR (KBr): $\tilde{\nu}$ = 1765 ($\nu_{\text{C=O}}$), 960 cm⁻¹ ($\delta_{\text{C=C}}$); FAB-MS: m/z = 1122.7 (found), 1122.7 (calcd). Compound **5''** was deprotected in alkaline solution to yield the hydroxyprecursor **5'**, which was oxidized as described above to give **5**.

6: Compound **6''** was prepared by treating 2-[4'-(3'',5''-di-*tert*-butyl-4'-acetoxyphenyl)styryl]-4-(3',5'-di-*tert*-butyl-4'-acetoxyphenyl)styrene with **4**. ¹H NMR (500 MHz, CDCl₃): δ = 1.32 (s, 108H; C(CH₃)), 2.38 (s, 18H; OCOCH₃), 7.22–7.82 (m, 48H; Ar, CH=CH); ¹³C NMR (125 MHz, CDCl₃): δ = 22.54, 22.68, 31.43, 35.59, 124.52, 125.22, 125.37, 125.44, 126.58, 126.78, 126.94, 126.99, 127.58, 129.18, 130.51, 131.12, 134.63, 135.24, 135.98, 136.31, 137.76, 138.01, 140.98, 141.36, 142.55, 142.73, 147.43, 147.67, 171.03, 171.11; IR (KBr): $\tilde{\nu}$ = 1765 ($\nu_{\text{C=O}}$), 962 cm⁻¹ ($\delta_{\text{C=C}}$); FAB-MS: m/z = 2167 (found), 2167.3 (calcd). Compound **6''** was then deprotected and oxidized to give **6**.

Received: March 26, 1998 [Z11648IE]
German version: *Angew. Chem.* **1998**, *110*, 2497–2499

Keywords: EPR spectroscopy • magnetic properties • polymers • polyradicals • radicals

- [1] a) D. A. Dougherty, *Acc. Chem. Res.* **1991**, *24*, 88–94; b) H. Iwamura, N. Koga, *Acc. Chem. Res.* **1993**, *26*, 346–351; c) A. Rajca, *Chem. Rev.* **1994**, *94*, 871–893; d) J. S. Miller, A. Epstein, *Angew. Chem.* **1994**, *106*, 399–429; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 385–415; e) H. Nishide, *Adv. Mater.* **1995**, *7*, 937–941.
- [2] a) N. Nakamura, K. Inoue, H. Iwamura, *Angew. Chem.* **1993**, *105*, 900–903; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 872–874; b) A. Rajca, S. Utamapanya, *J. Am. Chem. Soc.* **1993**, *115*, 10688–10694; c) A. Rajca, K. Lu, S. Rajca, *J. Am. Chem. Soc.* **1997**, *119*, 10335–10345; d) A. Rajca, J. Wongsriratanakul, S. Rajca, *J. Am. Chem. Soc.* **1997**, *119*, 11674–11686; e) D. Ruiz-Molina, J. Veciana, F. Palacio, C. Rovira, *J. Org. Chem.* **1997**, *62*, 9009–9017; f) R. J. Bushby, D. R. McGill, K. M. Ng, N. Taylor, *J. Mater. Chem.* **1997**, *7*, 2343–2354.
- [3] a) H. Nishide, T. Kaneko, T. Nii, K. Katoh, E. Tsuchida, K. Yamaguchi, *J. Am. Chem. Soc.* **1995**, *117*, 548–549; b) H. Nishide, T. Kaneko, T. Nii, K. Katoh, E. Tsuchida, P. M. Lahti, *J. Am. Chem. Soc.* **1996**, *118*, 9695–9704.
- [4] The polyradical **2** was amorphous and glassy. No glassy → rubbery transition was observed by differential scanning calorimetry up to the thermal decomposition temperature (the temperature for the 10 % weight loss was 283 °C under N₂, as measured by thermogravimetry differential thermal analysis (TG-DTA)).
- [5] J. H. van Vleck, *The Theory of Electric and Magnetic Susceptibilities*, Oxford University Press, London, **1932**. x_1 , x_2 , and x_3 are the fractions of the doublet, triplet, and quartet, respectively ($x_1 + x_2 + x_3 = 1$). μ_B is the Bohr magneton, and θ the Weiss constant.
- [6] H. Nishide, *ACS Symp. Ser.* **1996**, *644*, 247–257.
- [7] A. Willgerodt, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3347–3351.

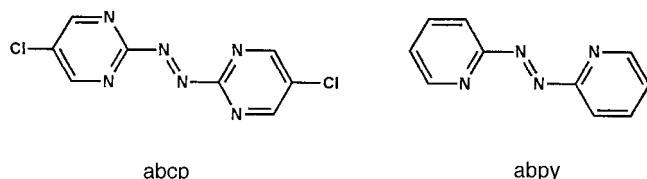
The First Structural Characterization of an Azoaromatic Radical Anion Stabilized by Dicopper(I) Coordination**

Nataša Doslik, Torsten Sixt, and Wolfgang Kaim*

Dedicated to Professor Hans Bock
on the occasion of his 70th birthday

In contrast to the hyperoxide (superoxide) radical anion O_2^- , which has long been isolated in various forms and structurally characterized ($d_{O-O} = 1.26-1.36 \text{ \AA}$),^[1] the related ($O \rightleftharpoons NR$) radical anions $RNNR^{\cdot-}$ of azo compounds have so far been detected only by EPR and other spectroscopic techniques.^[2] This absence of structural information is all the more conspicuous as the occupation of the low-lying π^* orbital of azo compounds by one electron is also invoked in the excited-state formulation of the numerous azo-containing dyes.^[3]

In the course of developing new bis-bidentate bridging ligands for molecule-mediated metal-metal communication,^[4] we have recently synthesized the new compound 2,2'-azobis(5-chloropyrimidine) (abcp)^[5a] and prepared its dinuclear bis(triphenylphosphane)copper complex by reaction with $[(Ph_3P)_4Cu](PF_6)$. Surprisingly, the main fraction of the isolated reaction mixture was the singly reduced compound $[(\mu-abcp)\{Cu(PPh_3)_2\}_2](PF_6)$ (**1-PF₆**),^[5b] which could be characterized by EPR and UV/Vis spectroscopy and X-ray crystal structure analysis.^[6]



The cation **1**⁺ exhibits a familiar pattern of "S-frame" dimetal coordination ($d_{Cu-Cu} = 4.866(1) \text{ \AA}$) as was similarly observed for $[(\mu-abpy)\{Cu(PPh_3)_2\}_2](PF_6)_2$ (abpy = 2,2'-azobispyridine).^[7] However, whereas the dicopper(I) complex dication in the latter compound exhibits an $N=N$ bond length of $1.248(11) \text{ \AA}$ corresponding to a nonreduced azoaromatic ligand,^[8] the monocation **1**⁺ displays a longer $N=N$ bond length of $1.345(7) \text{ \AA}$ and shorter $C-N(-N)$ bond lengths of $1.360(5) \text{ \AA}$ (Figure 1). On the other hand, the bonding parameters within the 5-chloropyrimidine rings are fairly normal (Figure 1), suggesting only minor participation of these π systems in the accommodation of the additional electron. The structural results strongly support the formulation of a bond order of 1.5 for the $N=N$ bond, with the length of $1.345 \text{ \AA}$ lying between the values for $HN=NH$ (calculated

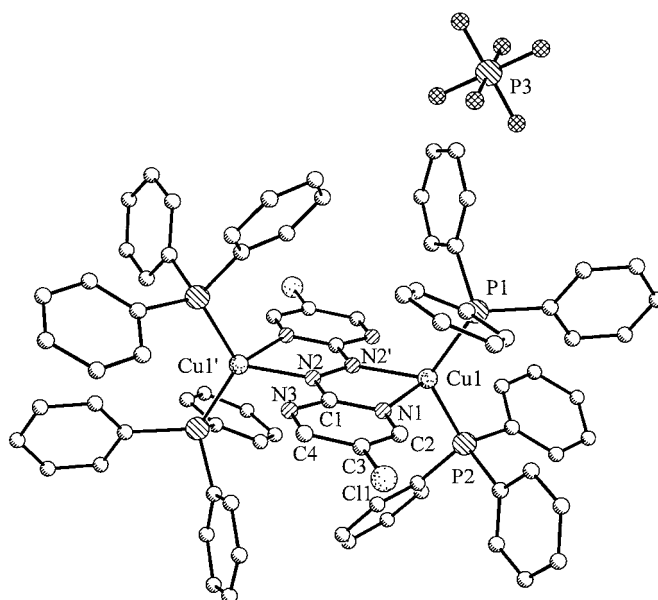


Figure 1. Molecular structure of **1-PF₆** in the crystal. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Cu1–N2' 2.045(3), Cu1–N1 2.098(3), Cu1–P2 2.2462(13), Cu1–P1 2.2636(12), N1–C2 1.337(5), N1–C1 1.360(5), N2–N2' 1.345(7), N2–C1 1.363(5), N3–C4 1.322(6), N3–C1 1.344(5), C2–C3 1.379(6), C3–C4 1.402(6), C3–C11 1.720(4), Cu1–Cu1' 4.866(1); N2'–Cu1–N1 76.58(14), N2'–Cu1–P2 113.05(10), N1–Cu1–P2 108.09(10), N2'–Cu1–P1 118.54(10), N1–Cu1–P1 103.40(10), P2–Cu1–P1 124.10(5), C1–N1–Cu1 112.2(3), N2'–N2–C1 113.6(4), N2–N2'–Cu1 117.8(4), N1–C1–N2 119.2(4).

as $1.21 \text{ \AA}$) and H_2N-NH_2 ($1.45 \text{ \AA}$).^[9] Furthermore, this value coincides with the $O-O$ bond distances found for MO_2 ($M = Na, K$).^[1]

EPR and UV/Vis spectroelectrochemical results support the formulation of a dicopper(I) complex containing an azoaromatic anion radical ligand: An EPR signal at $g = 2.0077$ with only insufficiently resolved hyperfine structure at 298 K (anisotropic line broadening^[2a, g]) and a single feature at 110 K rule out any significant contribution from a formulation with copper-centered spin.^[10] The long-wavelength absorptions at 700 and 560 nm for the radical species and at 930 nm for the electrogenerated dication **1**²⁺ are characteristic of metal-to-ligand charge-transfer transitions $d(Cu) \rightarrow \pi^*(N=N)$.^[10]

We attribute the unexpected formation and high stability of **1**⁺ mainly to the anodically shifted reduction potential of abcp (-1.01 V versus ferrocenium/ferrocene (Fc^+/Fc^0) in $CH_3CN/0.1 \text{ M Bu}_4NPF_6$); the lowering of the π^* level in comparison to abpy ($E_{red} = -1.46 \text{ V}$ versus Fc^+/Fc^0 in $CH_3CN/0.1 \text{ M Bu}_4NPF_6$) arises as a consequence of the introduction of chlorine substituents and of additional nitrogen functionalities. Furthermore, the twofold metal coordination^[11] clearly facilitates the reduction of abcp; relative to the ligand, the reduction potential of the dicopper complex ($+0.06 \text{ V}$ versus Fc^+/Fc^0 in $CH_2Cl_2/0.1 \text{ M Bu}_4NPF_6$) is shifted by more than 1 V to positive values. Finally, the metal complex fragments effectively protect the reduced azo functionality from attack by electrophiles such as H^+ .^[12]

[*] Prof. Dr. W. Kaim, Dipl.-Chem. N. Doslik, Dipl.-Chem. T. Sixt
Institut für Anorganische Chemie der Universität
Pfaffenwaldring 55, D-70550 Stuttgart (Germany)
Fax: (+49) 711-685-4165
E-mail: kaim@iac.uni-stuttgart.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Volkswagen-Stiftung.

Received: February 12, 1998 [Z11470IE]
German version: *Angew. Chem.* **1998**, *110*, 2521–2522

Keywords: azo compounds • bond order • copper • EPR spectroscopy • radical ions

- [1] A. F. Holleman, E. Wiberg, N. Wiberg, *Lehrbuch der Anorganischen Chemie*, 101st ed., de Gruyter, Berlin, **1995**, pp. 508, 1555, 1624, and references therein.
- [2] a) C. S. Johnson, R. Chang, *J. Chem. Phys.* **1965**, *43*, 3183; b) U. Krynitz, F. Gerson, N. Wiberg, M. Veith, *Angew. Chem.* **1969**, *81*, 745; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 755; c) T. Shida, *Adv. Radiat. Res. Phys. Chem.* **1973**, *2*, 469; d) R. Sustmann, R. Sauer, *J. Chem. Soc. Chem. Commun.* **1985**, 1248; e) G. A. Russell, R. Konaka, E. T. Strom, W. C. Danen, K. Chang, G. Kaupp, *J. Am. Chem. Soc.* **1968**, *90*, 4646; f) F. A. Neugebauer, H. Weger, *Chem. Ber.* **1975**, *108*, 2703; g) W. Kaim, S. Kohlmann, *Inorg. Chem.* **1986**, *25*, 3442; h) T. Shida, *Electronic Absorption Spectra of Radical Ions*, Elsevier, Amsterdam, 1988, p. 194.
- [3] Cf. H. Zollinger, *Color Chemistry*, 2nd ed., VCH, Weinheim, **1991**.
- [4] W. Kaim, R. Reinhardt, J. Fiedler, *Angew. Chem.* **1997**, *109*, 2600; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2493.
- [5] a) Synthesis of abcp: A solution of lithium hypochlorite (50 g, 0.856 mol) in water (300 mL) was cooled until it began to solidify (external bath temperature -30°C). A solution of 2-aminopyrimidine (5 g, 52.5 mmol) in H_2O (100 mL) was then added slowly and carefully. After completion, the orange-red reaction mixture was warmed to room temperature and extracted several times with dichloromethane. The organic phase was then purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 2/1) to yield the separated red mono- and dichlorinated azo compounds. The ligand abcp was obtained in a yield of 1.20 g (18%). Correct C,H,N analysis; ^1H NMR (250 MHz, 300 K, CDCl_3): $\delta = 8.93$ (s). b) Synthesis of **1**-PF₆: The ligand abcp (51 mg, 0.20 mmol) and $[\text{Cu}(\text{PPh}_3)_4](\text{PF}_6)$ (503 mg, 0.40 mmol) were treated for two hours at -70°C in dichloromethane (10 mL). The addition of Et_2O after the mixture had warmed to room temperature precipitated the dark blue product, which was then redissolved in THF (10 mL). Careful addition of Et_2O (about 1 mL) produced a dark blue, partially crystalline material (178 mg, 54%). We attribute the reduction to the presence of excess PPh_3 (see J. W. Hersberger, R. J. Klingler, J. K. Kochi, *J. Am. Chem. Soc.* **1983**, *105*, 61). EPR (CH_2Cl_2 , 298 K or 110 K): $g = 2.0077$; UV/Vis (CH_2Cl_2 , 300 K): λ_{max} (ϵ) = 700 (1560), 560 (2350), 403 (6400), 373 (6270) nm ($\text{M}^{-1}\text{cm}^{-1}$); cyclic voltammetry ($\text{CH}_2\text{Cl}_2/0.1\text{M}$ Bu_4NPF_6): $E_{\text{pa}}(\text{ox}) = 1.42\text{ V}$, $E_{1/2}(\text{red1}) = 0.06\text{ V}$, $E_{1/2}(\text{red2}) = -0.75\text{ V}$ versus Fc^+/Fc^0 at a scan rate of 100 mV s^{-1} .
- [6] Crystal structure analysis of **1**-(PF₆) $\cdot 2\text{THF}$: $\text{C}_{80}\text{H}_{64}\text{Cl}_2\text{Cu}_2\text{F}_{16}\text{N}_6\text{P}_5\cdot 2\text{C}_4\text{H}_8\text{O}$, $M_r = 1720.50\text{ g mol}^{-1}$, crystal size $0.4 \times 0.3 \times 0.6\text{ mm}$, triclinic, space group $P\bar{1}$, $a = 11.5353(9)$, $b = 14.4228(10)$, $c = 14.8086(11)\text{ \AA}$, $\alpha = 88.040(5)^{\circ}$, $\beta = 70.643(6)^{\circ}$, $\gamma = 66.855(5)^{\circ}$, $V = 2124.2(3)\text{ \AA}^3$, $Z = 1$, $\rho_{\text{calcd}} = 1.439\text{ g cm}^{-3}$, $3.08^{\circ} < 2\theta < 50^{\circ}$; 8694 reflections (7472 independent; $h = -14$ to 14 , $k = -17$ to 18 , $l = -18$ to 19) were collected at -90°C , 7198 reflections were used for the refinement. $R = 0.0578$ [$I > 2\sigma(I)$], $wR_2 = 0.1748$; Siemens P4 diffractometer with graphite monochromator and $\text{MoK}\alpha$ radiation ($0.71073\text{ \AA}$). The structure was solved by direct methods (Siemens SHELXS-86) and refined with full-matrix least-square methods (SHELXL-93). Two solvent molecules had to be included, one of which was disordered. Anisotropic thermal parameters were refined for all non-hydrogen atoms. Hydrogen atoms were introduced at calculated positions and refined freely (riding model). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101074. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [7] W. Kaim, S. Kohlmann, J. Jordanov, D. Fenske, *Z. Anorg. Allg. Chem.* **1991**, *598/599*, 217.
- [8] H. S. Freeman, S. A. McIntosh, P. Singh, *Dyes Pigm.* **1997**, *35*, 11.
- [9] A. F. Holleman, E. Wiberg, N. Wiberg, *Lehrbuch der Anorganischen Chemie*, 101st ed., de Gruyter, Berlin, **1995**, pp. 661, 672.

- [10] M. Moscherosch, J. S. Field, W. Kaim, S. Kohlmann, M. Krejci, *J. Chem. Soc. Dalton Trans.* **1993**, 211.
- [11] An alternative formulation would be the "triple ion" description $\text{Cu}^+ (\text{abcp}^-)/\text{Cu}^+$; see H. Bock, H.-F. Herrmann, *J. Am. Chem. Soc.* **1989**, *111*, 7622. See also H. Bock, K. Ruppert, C. Näther, Z. Havlas, H.-F. Herrmann, C. Arad, I. Bögel, A. John, J. Meuret, S. Nick, A. Rauschenbach, W. Seitz, T. Vaupel, B. Solouki, *Angew. Chem.* **1992**, *104*, 564; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 550.
- [12] Note added in proof (July 24, 1998): The molecular structure of Ru complexes of azoaromatic radical anions will be reported by A. Chakravorty et al.

Highly Enantioselective Catalytic Hetero-Diels–Alder Reaction with Inverse Electron Demand**

Jacob Thorhauge, Mogens Johannsen, and Karl Anker Jørgensen*

The hetero-Diels–Alder reaction of α,β -unsaturated carbonyl compounds with electron-rich alkenes gives excellent access to substituted 3,4-dihydro-2H-pyrans that are very useful precursors for the synthesis of carbohydrates and natural products.^[1] The reaction is controlled by the LUMO of the α,β -unsaturated carbonyl compound and the HOMO of the dienophile; electron-withdrawing substituents on the former greatly enhances the reactivity.^[1, 2]

Although the reaction usually is highly regioselective, Lewis acids can improve both regioselectivity and reaction rate.^[1c] A variety of different achiral Lewis acids, such as EtAlCl_2 ,^[3] Me_2AlCl ,^[3] ZnCl_2 ,^[3] TiCl_4 ,^[3] $\text{Eu}(\text{fod})_3$,^[4] $\text{Yb}(\text{fod})_3$,^[5] LiClO_4 ,^[6] $\text{Mg}(\text{ClO}_4)_2$,^[6] and SnCl_4 ^[7] have been shown to catalyze inverse hetero-Diels–Alder reactions ($\text{fod} = 6,6,7,7,8,8\text{-heptafluoro-2,2-dimethyl-3,5-octadiene}$).

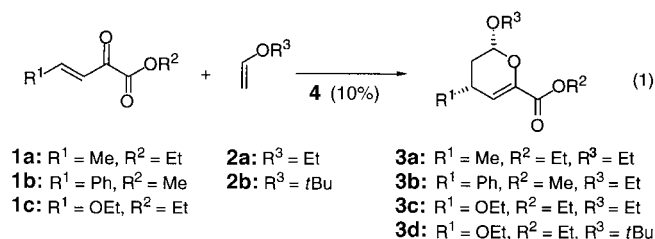
Although much work has been devoted to the diastereoselective hetero-Diels–Alder reaction with inverse electron demand,^[3a, b, 8] the enantioselective addition of electron-rich alkenes to α,β -unsaturated carbonyl compounds with chiral Lewis acids as catalysts is still a relatively unexplored field and only very few reactions have been reported. Examples include the intramolecular cycloaddition of an oxadiene with a diisopropylideneglucose–titanium complex as catalyst (33–88% *ee* for the tetracyclic product),^[9] and a reaction catalyzed by *trans*-(4,5-dihydro-4,5-diphenyloxazole)– $\text{Mg}(\text{ClO}_4)_2$ which yields both ene and hetero-Diels–Alder products in a 89:11 ratio (89% *ee* for the ene product).^[1c] Kanemasa has reported an intermolecular hetero-Diels–Alder reaction with inverse electron demand in which the enantioselective addition of (*E*)-oxo-phenylsulfonyl-3-alkenes to enol ethers

[*] K. A. Jørgensen, J. Thorhauge, M. Johannsen
Center for Metal Catalyzed Reactions
Department of Chemistry, Aarhus University
Langelandgade 140, DK-8000 Aarhus C (Denmark)
Fax: (+45) 8619-6199
E-mail: kaj@kemi.aau.dk

[**] The work was made possible by a grant from the Danish National Science Foundation. Thank are expressed to Professor R. G. Hazell for performing the X-ray analysis.

gives dihydropyran adducts in good yields (77–96%) and with enantioselectivities of 59–97% with TiBr_2 –TADDOL as the catalyst (TADDOL = tetraphenyl-1,3-dioxolan-4,5-dimethanol).^[4b, 10] During the writing of this paper, we became aware of recent work by Evans et al., who have studied the copper(II) bis(dihydrooxazole) catalyzed hetero-Diels–Alder reaction between α,β -unsaturated acylphosphonates and vinyl ethers.^[11]

We report here a novel and highly diastereo- and enantioselective catalytic hetero-Diels–Alder reaction of β,γ -unsaturated α -keto esters **1**, substituted in the γ position with alkyl, aryl, and alkoxy substituents, with the electron-rich alkenes **2** to give very attractive dihydropyran adducts **3** [Eq. (1)]. The products thus formed are very useful precursors for the synthesis of carbohydrates and natural products.



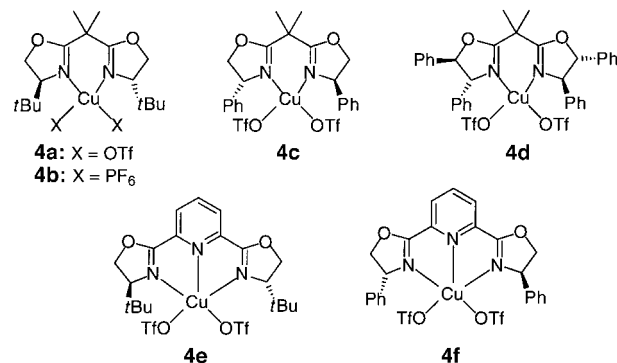
The results of the [4+2] cycloaddition reaction of **1a** with **2a** in the presence of various copper(II) catalysts **4a**, **c–f**^[12] are presented in Table 1 (OTf = trifluoromethylsulfonate).

Table 1. Results of the reaction **1a** + **2a** → **3a** in the presence of the catalysts **4a**, **c–f** (10 mol %).

Entry	Catalyst	Solvent	T [°C]	Conv. [%]	ee [%] ^[a]
1	4a	CH_2Cl_2	–45	100	95.6
2	4a	CH_2Cl_2	–78	100	97.5
3	4a	THF	–45	100	99.0
4	4a	THF	–78	100 (89) ^[b]	99.7
5	4a	CH_3NO_2	–20	100	75.8
6	4c	CH_2Cl_2	–78	100	63.8
7	4d	CH_2Cl_2	–78	95	72.4
8	4e	CH_2Cl_2	–78	< 10	< 5
9	4f	CH_2Cl_2	–78	10	64.9

[a] Determined by GC on a chiral stationary phase. [b] Yield of isolated product.

The enantioselectivity induced with **4a** is superior to that induced by **4c–f**. The reaction of **1a** and **2a**, catalyzed by **4a** in CH_2Cl_2 at –45°C, shows complete conversion, and gives



the hetero-Diels–Alder product **3a** with 95.6% ee (Table 1, entry 1). This is improved to 97.5% when the reaction temperature is reduced to –78°C (entry 2). The use of THF as solvent leads to a further improvement; **3a** is obtained with 99.0% ee at –45°C, and at –78°C it is isolated in 89% yield and with 99.7% ee (entries 3 and 4). A high conversion is also observed with nitromethane as the solvent, but the ee value drops to 75.8% (entry 5). The two phenyl-substituted copper(II) bis(dihydrooxazole)s **4c**, **d** also catalyze the reaction of **1a** with **2a**, but although high conversion is obtained, the ee value of **3a** is only moderate (entries 6 and 7). Catalysts **4e**, **f** are much less effective than **4a**, **c**, **d**, and only a low ee value of **3a** is observed (entries 8 and 9).

The absolute stereochemistry of the hetero-Diels–Alder product **3a** is dependent on the catalyst; both **4a** and **4c** give the same enantiomer of **3a**—an opposite stereochemistry in the ligand leads to the same absolute stereochemistry in the product.^[13] In contrast, **4d** and **4f** give opposite absolute stereochemistries of **3a**.

The scope and the potential of the hetero-Diels–Alder reaction catalyzed by the copper(II) bis(dihydrooxazole)s **4a**, **b** are demonstrated for the reaction of various γ -substituted β,γ -unsaturated α -keto esters **1a–c** with the electron-rich alkenes **2a**, **b** [Eq. (1)] and **2c** [Eq. (2)]. The results for the reactions are presented in Table 2.

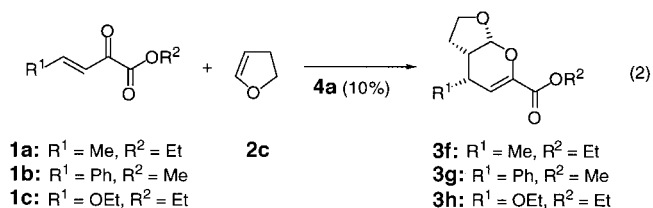


Table 2. Results of the hetero-Diels–Alder reaction of **1a–c** with **2a–c** in the presence of the catalysts **4a**, **b** (10 mol %) at –78°C in THF.

Entry	Catalyst	1	2	Product ^[a]	Yield [%] ^[b]	ee [%]
1	4a	1a	2a	3a	89	> 99.5 ^[c]
2	4a	1b	2a	3b	95	99.5 ^[d]
3	4a	1c	2a	3c	93	> 99.5 ^[c]
4	4b	1c	2a	3c	88	96.8 ^[c, e]
5	4a	1c	2b	3d	61 ^[f]	90.4 ^[c]
6	4a	1a	2c	3f	51 ^[14]	> 99.5 ^[c]
7	4a	1b	2c	3g	96	99.5 ^[c]
8	4a	1c	2c	3h	84	97.5 ^[c, g]

[a] All de values are greater than 98%, except for **3g** (95%). [b] Yield of isolated product. [c] Determined by GC on a chiral stationary phase. [d] Determined by HPLC on a chiral stationary phase. [e] CH_2Cl_2 as solvent. [f] Two diastereomers: 4:1, < 10% ee for the minor diastereomer. [g] Reaction temperature –45°C.

The β,γ -unsaturated α -keto esters **1a–c** react with **2a** in the presence of **4a** (10 mol %) in THF at –78°C to give the hetero-Diels–Alder products **3a–c** in high yields and with very high enantiomeric excess ($\geq 99.5\%$ ee ; Table 2, entries 1–3). When the anion of the catalyst is changed from OTf^- to PF_6^- , a small decrease in the yield and enantioselectivity of **3c** is observed (88%, 96.8% ee , entry 4). The use of **2b** as the alkene decreases the diastereoselectivity, as now two

diastereomers are formed in a ratio of 4:1 (60% *de*). The hetero-Diels–Alder product **3d** is isolated in 61% yield, and the major diastereomer has an *ee* value of 90.4% (entry 5). The drop in the *ee* value is probably due to steric repulsion between the *tert*-butyl substituent and the chiral catalyst in the preferred *endo* transition state for the reaction.

The cyclic enol ether **2c** is also an excellent substrate for the enantioselective reaction catalyzed by **4a**. Reaction of **2c** with **1a** leads to the formation of adduct **3f** in 51% yield,^[14] and only one enantiomer can be detected by GC on a chiral stationary phase (*ee* > 99.5%; Table 2, entry 6). The reaction of **1b** is also highly enantioselective, and **3g** is isolated in 96% yield and with 99.5% *ee* (entry 7). The introduction of an ethoxy substituent in the substrate, **1c**, leads likewise to a very selective reaction, as **3h** is obtained in 84% yield and with 97.5% *ee*. The *endo* approach of the alkene was confirmed by an X-ray analysis of the cycloadduct **3h**.

The generality and potential of these highly enantioselective hetero-Diels–Alder reactions with inverse electron demand catalyzed by **4a** are evident from the results presented in Table 2. High yields and very high enantiomeric excess are obtained with alkyl-, aryl-, and alkoxy-substituted oxadienes, and both acyclic and cyclic dienophiles can be used. The reaction thus offers a new and promising method for the synthesis of natural compounds and novel carbohydrates.

Experimental section

3b: Catalyst (**S**)-**4a** was prepared by the addition of Cu(OTf)₂ (36 mg, 0.1 mmol) to 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (31 mg, 0.105 mmol) dissolved in dry THF (2 mL) under N₂, followed by stirring for 1 h. Compound **1b** (190 mg, 1.0 mmol) was added to the catalyst solution, which was then cooled to –78 °C. Freshly distilled **2a** (143 µL, 1.5 mmol) was added, and the solution was stirred at this temperature for 50 h. Pentane (2 mL) was then added, and the mixture was filtered through a silica plug with pentane/Et₂O (1/1). The solvent was evaporated, and the crude product was purified by flash chromatography (pentane/Et₂O 90/10) to give **3b** as a pale yellow oil in 95% yield and with 99.5% *ee*, determined by HPLC with a chiral OD column (hexane/*i*PrOH 98/2, 1.0 mL min^{–1}). [α]_D²⁰ = +2.1° (*c* = 1.06, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ = 7.34–7.20 (m, 5H; C₆H₅), 6.16 (dd, *J* = 3.2, 1.1 Hz, 1H; C=CH), 5.16 (dd, *J* = 7.7, 2.2 Hz, 1H; C-6H), 4.04 (dq, *J* = 9.3, 7.1 Hz, 1H; OCHHCH₃), 3.81 (s, 3H; OCH₃), 3.73 (ddd, *J* = 9.5, 7.0, 3.2 Hz, 1H; C-4H), 3.63 (dq, *J* = 9.3, 7.1 Hz, 1H; OCHHCH₃), 2.31 (dddd, *J* = 13.5, 7.0, 2.2, 1.1 Hz, 1H; C-5HH), 1.97 (ddd, *J* = 13.5, 9.5, 7.7 Hz, 1H; C-5HH), 1.23 (t, *J* = 7.1 Hz, 3H; OCH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 163.2, 142.8, 142.3, 128.6, 127.5, 126.8, 114.5, 100.0, 64.7, 52.2, 37.8, 36.0, 15.1. The reaction has also been run on a gram scale to give **3b** in quantitative yield and with high selectivity (> 99% *ee*, > 98% *de*).

3h: The catalyst was prepared as described above. Compound **1c** (172 mg, 1 mmol) was added to the catalyst solution, which was then cooled to –78 °C and treated with freshly distilled **2c** (151 µL, 2 mmol). The solution was warmed to –45 °C and stirred for 50 h. Pentane (2 mL) was then added, and the mixture was filtered through a silica plug with pentane/Et₂O (1/1). After evaporation of the solvent, the crude product was purified by flash chromatography (pentane/Et₂O, 75/25) to give **3h** as a highly crystalline, colorless solid in 84% yield and with 97.5% *ee* (determined by GC with a Chropack Chirasil-DEX CB column). One recrystallization from Et₂O gave the enantiopure product. X-ray spectroscopy confirmed the expected *endo* structure of the product. [α]_D²⁰ = –32.1° (*c* = 1.06, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ = 6.01 (dd, *J* = 2.2, 1.5 Hz, 1H; C=CH), 5.66 (d, *J* = 4.0 Hz, 1H; C-2H), 4.50 (dd, *J* = 6.6, 2.2 Hz, 1H; C-4H), 4.26 (dq, *J* = 4.4, 7.1 Hz, 2H; OCH₂CH₃), 4.24 (ddd, *J* = 17.9, 9.2, 3.5 Hz, 1H; C-7aHH), 3.97 (dt, *J* = 9.2, 8.1 Hz, 1H; C-7aHH), 3.60 (q, *J* =

7.1 Hz, 2H; OCH₂CH₃), 2.75 (m, 1H; C-3H), 2.01 (m, 2H; C-3aHH), 1.31 (t, *J* = 7.1 Hz, 3H; OCH₂CH₃) 1.24 (t, *J* = 7.1 Hz, 3H; OCH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 162.1, 141.6, 108.6, 102.2, 70.6, 68.4, 64.3, 61.4, 42.5, 23.7, 15.4, 14.2.

Received: May 13, 1998 [Z11854IE]

German version: *Angew. Chem.* **1998**, *110*, 2543–2546

Keywords: asymmetric catalysis • cycloadditions • copper • Lewis acids • synthetic methods

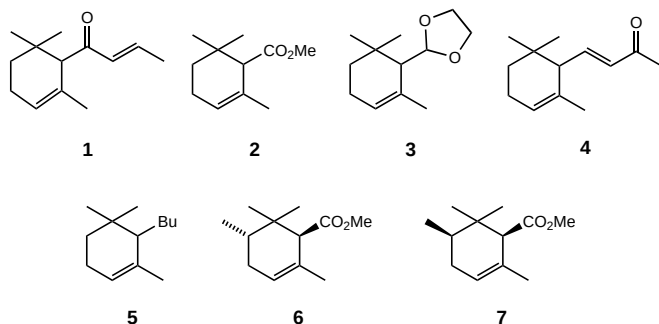
- For example, a) G. Desimoni, G. Tacconi, *Chem. Rev.* **1975**, *75*, 651; b) D. L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, New York, **1987**. c) L. F. Tietze, G. Ketschau in *Stereoselective Heterocyclic Synthesis I*, Vol. 189 (Ed.: P. Metz), Springer, Berlin, **1997**, pp. 1–120.
- For example, J. Sauer, R. Sustmann, *Angew. Chem.* **1980**, *92*, 773; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779.
- For example, a) D. L. Boger, K. D. Robarge, *J. Org. Chem.* **1988**, *53*, 3373; b) L. F. Tietze, C. Schneider, A. Grote, *Chem. Eur. J.* **1996**, *2*, 139; c) L. F. Tietze, C. Schneider, A. Montenbruck, *Angew. Chem.* **1994**, *106*, 1031; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 980; d) B. B. Snider, Q. Zhang, *J. Org. Chem.* **1991**, *56*, 4908; e) L. F. Tietze, S. Brand, T. Pfeiffer, J. Antel, K. Harms, G. M. Sheldrick, *J. Am. Chem. Soc.* **1987**, *109*, 921; f) E. Wada, S. Kanemasa, O. Tsuge, *Chem. Lett.* **1989**, 675.
- For example, a) E. Wada, H. Yasuoka, S. Kanemasa, *Chem. Lett.* **1994**, 145; b) E. Wada, W. Pei, H. Yasuoka, U. Chin, S. Kanemasa, *Tetrahedron* **1996**, *52*, 1205.
- J.-Y. Mérou, L. Chichereau, E. Desabre, P. Gadonneix, *Synthesis* **1996**, 519.
- For example, a) G. Desimoni, G. Faita, P. P. Righetti, G. Tacconi, *Tetrahedron* **1991**, *47*, 8399; b) G. Desimoni, G. Faita, P. P. Righetti, L. Toma, *Tetrahedron* **1990**, *46*, 7951; c) A. Corsico Coda, G. Desimoni, G. Faita, P. P. Righetti, G. Tacconi, *Tetrahedron* **1989**, *45*, 775; d) M. A. Forman, W. P. Dailey, *J. Am. Chem. Soc.* **1991**, *113*, 2761.
- For example, a) A. Sera, M. Ohara, H. Yamada, E. Egashira, N. Ueda, J. Setsune, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1912; b) L. F. Tietze, C. Schneider, *Synlett* **1992**, 755.
- For example, a) S. J. Johnson, C. Crasto, S. M. Hecht, *Chem. Commun.* **1998**, 1019; b) G. Dujardin, S. Rossignol, E. Brown, *Tetrahedron Lett.* **1996**, *37*, 4007; c) G. Dujardin, S. Rossignol, E. Brown, *Synthesis* **1998**, 763; d) R. R. Schmidt, M. Maier, *Tetrahedron Lett.* **1985**, *26*, 2065.
- a) L. F. Tietze, P. Saling, *Synlett* **1992**, 281; b) L. F. Tietze, P. Saling, *Chirality* **1993**, *5*, 329.
- E. Wada, H. Yasuoka, S. Kanemasa, *Chem. Lett.* **1994**, 1637.
- D. A. Evans, J. S. Johnson, *J. Am. Chem. Soc.* **1998**, *120*, 4895.
- a) A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339; b) D. A. Evans, S. J. Miller, T. Lectka, *J. Am. Chem. Soc.* **1993**, *115*, 6460; c) D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross, S. J. Miller, *Angew. Chem.* **1995**, *107*, 864; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798; d) A. K. Ghosh, P. Mathivanan, J. Caprello, *Tetrahedron: Asymmetry* **1998**, *9*, 1, and references therein.
- We have previously observed similar change in induction with copper(II) bis(dihydrooxazole)s as catalysts for normal hetero-Diels–Alder reactions of aldehydes and ketones: M. Johannsen, K. A. Jørgensen, *J. Org. Chem.* **1995**, *60*, 5979; M. Johannsen, S. Yao, K. A. Jørgensen, *Chem. Commun.* **1997**, 2169.
- The reaction gives 100% conversion, but the product is presumably unstable on the column during purification.^[3a]

Diastereoface-Selective Epoxidations: Dependency on the Reagent Electrophilicity**

Charles Fehr*

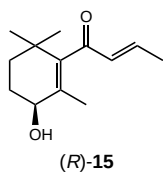
Stereoselective epoxidations have received great attention, as can be judged from the numerous reviews covering the subject.^[1] The vast majority of diastereocontrolled epoxidations is based on directing effects that favor the approach of the reagent onto the face containing a polar functional group.^[2] In the absence of a steering element, reaction normally takes place on the sterically less hindered side, and conformational analysis is thus essential to predict the π -face selectivity of reactions involving flexible substrates.^[3] Mechanistic studies carried out on systems devoid of sterically discriminating groups have evidenced hyperconjugative effects^[4] as well as electrostatic (polar) interactions between reagent and substrate as playing a role in the selectivity.^[5]

Whereas most of the relevant studies compare substrate reactivities under given conditions, we examined the relationship between the electrophilicity of the reagent (peracid) and the π -facial selectivity for α -damascone (**1**) and six structurally related cyclogeranyl derivatives (**2–7**). Remarkably, we



found the same trend for all of the cases studied: The stronger the peracid, the higher the *syn* selectivity. These results are rationalized by an increase in the electrostatic interactions between the alkene and the strong peracids, which result from the increased electrostatic potential of the latter.

From a synthetic viewpoint, the diastereocontrolled epoxidation of chiral α -cyclogeranyl systems is of prime importance. Several approaches towards the forskolin^[6] and taxane skeleton^[7] have taken advantage of this possibility for the construction of the epoxide-cleaved, isomeric alcohol displaying the structural features of (*R*)-**15**. Furthermore, this transformation has proven its usefulness in the synthesis of carotenes,^[8] edulanes,^[9] strigol,^[10] and other terpenoids.^[11]



[*] Dr. C. Fehr
Firmenich SA, Corporate R&D Division
P.O. Box 239, CH-1211 Geneva 8 (Switzerland)
Fax: (+41) 22-780-33-34
E-mail: charles.fehr@firmenich.com

[**] O. Etter and S. Chappuis are thanked for their skilful experimental work, W. Thommen for the NOE experiments, and Dr. J.-Y. de Saint Laumer for the calculations (PM3).

In the course of this project we became aware of repeated erroneous attributions of epoxide configurations,^[6b, 9b, 10b, 11b] in spite of the authoritative work of Eugster.^[8] In view of the planned chirality transfer sequence in which (*S*)-**1** is converted into (*R*)-**15**,^[12] this stereochemical question is essential.

The known preferential *syn* epoxidation of α -ionone (**4**) with 3-chloroperbenzoic acid (*m*CPBA) in CHCl_3 (**11s/11a** = 86:14)^[8] prompted us to use the same reagent to selectively epoxidize α -damascone (**1**). Whereas *m*CPBA in CH_2Cl_2 afforded an 85:15 mixture of epoxy ketones **8s/8a** (66:34 in toluene), peracetic acid led to a slightly lower selectivity (80:20 in CH_2Cl_2 , 58:42 in toluene; Table 1).^[13] In contrast, the highly reactive permaleic acid gave rise to a diastereofacial selectivity of 99.3:0.7 (98:2 in toluene) in favor of **8s**. We therefore tested the strongest commonly used peracid, trifluoroperacetic acid, in CH_2Cl_2 . Even at -50°C the reaction was very fast and afforded **8s** with excellent diastereofacial selectivity (99.8:0.2) in a yield of 95%.^[14] A net reversal of selectivity was brought about with the system *tert*-butyl hydroperoxide/ $[\text{Mo}(\text{CO})_6]$:^[15] In 1,2-dichloroethane at 70°C , the *anti*-epoxide **8a** was largely favored (89:11).

Table 1. Ratios of *syn* and *anti* conformers (**8s–14s/8a–14a**) obtained from epoxidation of **1–7**.^[a]

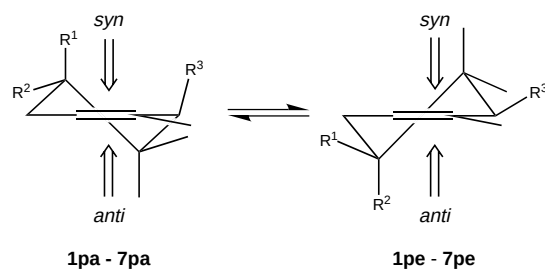
	1	2	3	4	5	6	7
$\text{CF}_3\text{CO}_3\text{H}^{[b]}$	99.8:0.2	99.5:0.5	100:0	95:5	96:4	100:0	81:19
permaleic acid ^[c]	99.3:0.7	97:3	—	—	—	—	22:78
<i>m</i> CPBA ^[d]	85:15	79:21	94:6	85:15	84:16	94:6	6:94
$\text{CH}_3\text{CO}_3\text{H}^{[e]}$	(58:42)	(47:53)	(88:12)	84:16	85:15	(88:12)	3:97
<i>t</i> BuO ₂ H/ $[\text{Mo}(\text{CO})_6]^{[f]}$	11:89	14:86	(71:29)	(60:40)	74:26	(71:29)	2:98

[a] Qualitative rate indications: *fast*, moderate, (slow); [b] CH_2Cl_2 , Na_2CO_3 , -50°C . [c] Maleic anhydride, 70% aqueous H_2O_2 ; CH_2Cl_2 , 20°C . [d] CH_2Cl_2 , $0-20^\circ\text{C}$. [e] Toluene, Na_2CO_3 , $20-50^\circ\text{C}$. [f] $\text{ClCH}_2\text{CH}_2\text{Cl}$, 70°C .

In view of these fascinating results, we extended our study to substrates **2–7**, which were submitted to the same epoxidation reagents. Interestingly, all of the alkenes **1–7** follow the same reagent-dependent selectivity trend: The highest *syn* preference is found with trifluoroperacetic acid followed by permaleic acid and *m*CPBA. In comparison, peracetic acid in toluene is less reactive and always affords a higher proportion of the *anti* epoxide. The highest preference for *anti* epoxidation is achieved with *tert*-butyl hydroperoxide in the presence of catalytic amounts of $[\text{Mo}(\text{CO})_6]$.

As stated by Eugster, the most stable conformer of α -ionone (**4**) is that with a pseudoaxial side chain (**4pa**), and the

syn-selective epoxidation was explained by the fact that the axial methyl group sterically hinders the approach of the peracid from below (*anti*, Scheme 1). This reasoning can

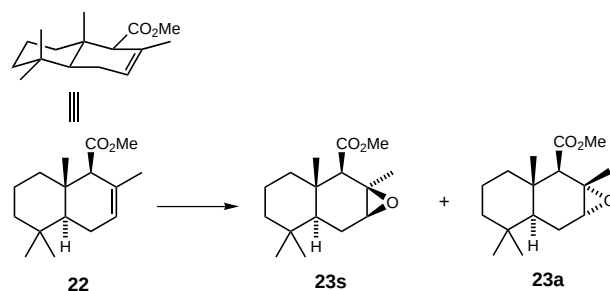


Scheme 1. Conformers of **1–7**. ΔH [kcal mol⁻¹] in favor of pseudoaxial conformer (PM3): **1** (1.35), **2** (1.47), **3** (3.18), **4** (0.93), **5** (1.28), and **6** (2.09); in favor of pseudoequatorial conformer: **7** (1.60).

equally be applied to the herein reported epoxidations using *m*CPBA, where both conformers—which are in equilibrium with each other in the case of **1**, **2**, **4**, and **5**—react with great ease. In addition, we can deduce that the pseudoaxial conformers react essentially with *syn* selectivity and the pseudoequatorial conformers with high *anti* selectivity, as the observed diastereofacial discriminations approximately parallel the conformational preferences (Table 1). The trends observed by using peracetic acid instead of *m*CPBA are diminished reactivity and decreased *syn* selectivity.^[13] Presumably, the more weakly electrophilic peracetic acid is more sensitive to steric factors. As a result, *anti* epoxidations of the pseudoequatorial conformers are faster than *syn* epoxidations of the pseudoaxial conformers. The increased reactivity of **7** relative to its diastereomer **6** (competition experiment) reflects the intrinsic preference of the bis-pseudoequatorial reaction conformer in this system. This trend in favor of *anti* epoxidation is most pronounced with the sterically most demanding Mo-catalyzed epoxidations that lead, for substrates **1** and **2**, to a distinct reversal of diastereofacial selectivity.

Trifluoroperacetic acid is by far the most reactive epoxidation agent and displays an outstanding preference for *syn* epoxidation for all the substrates investigated (followed by permaleic acid). Remarkably, this statement holds even for hydrocarbon **5**, which is devoid of any polar groups that are able to undergo complexation by hydrogen bonding.

The preferential *syn* epoxidation of alkenes **1–6**, in which the pseudoaxial conformers dominate, is not surprising. However, the extent of *syn* selectivity in **1** and **2** (>200:1) implies that the pseudoequatorial conformers **1pe** and **2pe** also undergo preferential *syn* epoxidation. Indeed, ester **7**, with a pseudoequatorial groundstate conformation, gives an epoxide mixture that is rich in the *syn* conformer (**14s**:**14a** = 81:19). To confirm the contrasteric reactivity of **7**, the rigid *trans*-decalin derivative **22**^[16] with a pseudoequatorial ester group was submitted to epoxidation. Whereas the epoxidation with *m*CPBA affords the *anti* epoxide **23a**,^[16] CF₃CO₃H preferentially reacts from the more hindered face (**23s**:**23a** = 82:18). Permaleic acid shows an intermediate reactivity (22:78, Scheme 2).



Scheme 2. Epoxidation of *trans*-decalin derivative **22**, which possesses a pseudoequatorially fixed ester group. *syn*:*anti* = 82:18 (with CF₃CO₃H in CH₂Cl₂), 22:78 (with permaleic acid in CH₂Cl₂), 5:95^[16] (with *m*CPBA in CH₂Cl₂), 3:97 (with CH₃CO₃H in toluene).

This result is contrasteric (and probably contraelectronic),^[17] but can be rationalized on the basis of the electrostatic interactions, which become important with CF₃CO₃H, possessing a very high electrostatic potential (partial positive charge). In these very fast and exothermic reactions, little polarization is required for attaining the early transition state, but the approach of CF₃CO₃H is governed by Coulombic attractions with the more electron-rich π face.^[18] This reactivity–selectivity relationship is contrary to the commonly accepted principle that a better discrimination between diastereomeric transition states is achieved with a reagent of moderate reactivity.

Houk et al.^[5a] have demonstrated that the *syn* additions of strong electrophiles (AcCl–AlCl₃ or :CCl₂) to isopropylidenebenzonorbornenes result from preassociations between the electrophiles and the aromatic ring, whereas weak electrophiles (for example *m*CPBA or NBS) preferentially react from the opposite side, where polarization is facilitated by involvement of the π orbital. The present work compares different electrophiles of the same reaction type and describes for the first time, how electrostatic effects can be exploited for improving the π -face selectivity of epoxidations.

syn-Selective epoxidations of certain pseudoaxially locked alkoxycyclohexenes using CF₃CO₃H have been observed,^[14a] but seemed to be limited to special cases. More recently, *m*CPBA has been shown to effect moderate to excellent *syn* epoxidations with various cyclohexenes and cyclopentenones possessing an amide, ester,^[2a, b] or ketone^[2c] functionality.

To illustrate that our findings are not limited to particular substrate classes, esters **24** and **25** as well as ketone **26** were epoxidized using either CF₃CO₃H or *m*CPBA (Table 2). Because the *anti* epoxides **27a–29a** are prone to cleavage reactions in the presence of acids, these epoxidations were performed in aqueous NaHCO₃/CH₂Cl₂. Careful analysis by gas chromatography (GC) indicated that the *syn*:*anti* ratios increase during the reaction and isolation. Contrary to the claim of Armstrong et al.,^[2c] ketone **26** only exhibits very high *syn* selectivity when CF₃CO₃H is used as the reagent.^[19]

Experimental Section

(–)-**8s**: A 70 % aqueous solution of H₂O₂ (1.62 g, 33.4 mmol) was added to a solution of (CF₃CO)₂O (14.8 g, 9.9 mL, 70 mmol) in CH₂Cl₂ (25 mL) at 0 °C. After 30 min this solution was added dropwise to a suspension of (*S*)-(-)-**1** (99 % *ee*)^[20] (4.80 g, 25.0 mmol) and Na₂CO₃ (7.80 g, 75.0 mmol) in

Table 2. Epoxidation of olefinic esters **24** and **25** as well as ketone **26** and comparison with literature results.

Reaction scheme: Olefinic ester **24-26** (where n is the number of methylene groups between the double bond and the ester group, and X is the ester group) reacts with a peracid to form a **syn:anti** mixture of epoxides **27s-29s** and **anti** products **27a-29a**.

	n	X	Peracid	syn:anti (yied [%])
24	–	OMe	CF ₃ CO ₃ H	94:6 ^[a]
			CF ₃ CO ₃ H	100:0 (84) ^[b]
			mCPBA	78:22 (91) ^[a, b] ($X = i\text{Pr}$: 3:1 ^[2b])
25	CH ₂	OMe	CF ₃ CO ₃ H	96:4 ^[a]
			CF ₃ CO ₃ H	99:1 (63) ^[b]
			mCPBA	68:32 (87) ^[a, b] (4:1 ^[2a])
26	CH ₂	Me	CF ₃ CO ₃ H	100:0 (77) ^[a, b]
			mCPBA	80:20 ^[a]
			mCPBA	88:12 (86) ^[b] (100:0 (61) ^[2c])

[a] First reaction sample. [b] Distilled product.

CH₂Cl₂ (30 mL) at –50 °C. After complete addition (30 min) the mixture was poured into aqueous Na₂SO₃ and extracted with diethyl ether. The organic phase was washed successively with H₂O, saturated NaHCO₃, and saturated NaCl, dried (Na₂SO₄), evaporated, and distilled bulb-to-bulb (oven temperature 80–90 °C/0.7 Torr). Yield: 5.06 g of (–)-**8s** (95 %); $[\alpha]_D^{20} = -136$ ($c = 0.03$ in CHCl₃), 99% *ee* by GC on a chiral phase; ¹H NMR (360 MHz, CDCl₃): $\delta = 2.59$ (C(6)H); ¹³C NMR (360 MHz, CDCl₃): $\delta = 31.8$ (C(2)).

(–)-**8a**: A mixture of [Mo(CO)₆] (56 mg, 0.21 mmol), dichloroethane (6 mL), and *t*BuOOH (3 M in isooctane, 6 mL, 18 mmol) was heated at 70 °C for 30 min and introduced within 15 min into a stirred, heated (80 °C) mixture of (S)-(–)-**1** (99% *ee*)^[20] (2.00 g, 10.4 mmol), Na₂HPO₄ (11 mg), and dichloroethane (12 mL). After 1 h the mixture was cooled and isolated as above. The distilled mixture (1.84 g; **8a/8s** = 89:11; GC: 90%, yield: 76%) was separated by chromatography (SiO₂; cyclohexane/AcOEt 98/2). (–)-**8a**: 1.32 g (61 %); $[\alpha]_D^{20} = -66$ ($c = 0.06$ in CHCl₃), 99% *ee* by GC on a chiral phase; ¹H NMR (360 MHz, CDCl₃): $\delta = 3.12$ (C(6)H); ¹³C NMR (360 MHz, CDCl₃): $\delta = 32.6$ (C(2)).

Received: February 17, 1998 [Z114741E]

German version: *Angew. Chem.* **1998**, *110*, 2509–2512

Keywords: conformation analysis • electrostatic interactions • epoxidations • peracids

- [1] a) A. H. Hoveyda, D. A. Evans, *Chem. Rev.* **1993**, *93*, 1307; b) A. S. Rao, *Comprehensive Organic Synthesis*, Vol. 3 (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, p. 357; c) B. Plesnicar, *Oxidation in Organic Chemistry, Part C* (Ed.: W. S. Trahanowsky), Academic Press, New York, **1978**, p. 211; d) V. G. Dryuk, *Tetrahedron* **1976**, *32*, 2855; e) G. Berti, *Top. Stereochem.* **1973**, *7*, 93.
- [2] a) P. Kocovsky, I. Stary, *J. Org. Chem.* **1990**, *55*, 3236; b) F. Mohamadi, M. M. Spees, *Tetrahedron Lett.* **1989**, *30*, 1309; c) A. Armstrong, P. A.

- Barsanti, P. A. Clarke, A. Wood, *Tetrahedron Lett.* **1994**, *35*, 6155; A. Armstrong, P. A. Barsanti, P. A. Clarke, A. Wood, *J. Chem. Soc. Perkin Trans. 1* **1996**, 1373; d) ref. [1a].
- [3] B. Rickborn, S.-Y. Lwo, *J. Org. Chem.* **1965**, *30*, 2212; E. Vedejs, D. M. Gapinski, *J. Am. Chem. Soc.* **1983**, *105*, 5058; S. L. Schreiber, T. Sannakia, B. Hulin, G. Schulte, *J. Am. Chem. Soc.* **1986**, *108*, 2106; ref. [1e].
- [4] S. Srivastava, W. J. le Noble, *J. Am. Chem. Soc.* **1987**, *109*, 5874; J. Lau, E. M. Gonikberg, J. Hung, W. J. le Noble, *J. Am. Chem. Soc.* **1995**, *117*, 11421; L. A. Paquette, G. J. Wells, M. C. Böhm, R. Gleiter, *J. Am. Chem. Soc.* **1981**, *103*, 7122.
- [5] a) J. D. Wu, Y. Li, J. Na, K. N. Houk, *J. Org. Chem.* **1993**, *58*, 4625; b) S. D. Kahn, C. F. Pau, W. J. Hehre, *J. Am. Chem. Soc.* **1986**, *108*, 7396; K. Bowden, E. J. Grubbs, *Chem. Soc. Rev.* **1996**, 171.
- [6] a) M. I. Colombo, J. Zinczuk, E. A. Ruveda, *Tetrahedron* **1992**, *48*, 963; b) K. C. Nicolaou, W. S. Li, *J. Chem. Soc. Chem. Commun.* **1985**, 421.
- [7] K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 38; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15.
- [8] P. Uebelhart, A. Baumeler, A. Haag, R. Prewé, J. H. Bieri, C. H. Eugster, *Helv. Chim. Acta* **1986**, *69*, 1986, and references therein.
- [9] a) W. Francke, S. Schulz, V. Sinnwell, W. A. König, Y. Roisin, *Liebigs Ann. Chem.* **1989**, 1195; b) H. Okawara, S. Kobayashi, M. Ohno, *Heterocycles* **1979**, *13*, 191.
- [10] a) D. W. Brooks, E. Kennedy, *J. Org. Chem.* **1983**, *48*, 277; b) E. M. Mangnus, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 155.
- [11] a) E. R. Koft, T. A. Broadbent, *Org. Prep. Proced. Int.* **1988**, *20*, 199; b) R. Kaiser, D. Lamparsky, *Helv. Chim. Acta* **1979**, *62*, 1878; A. Chakraborty, G. K. Kar, J. K. Ray, *Tetrahedron* **1997**, *53*, 8513; c) C. Chapuis, K. H. Schulte-Elte, *Tetrahedron* **1995**, *78*, 165.
- [12] Compound **15** of unknown enantiomeric composition was identified as a constituent of Virginia tobacco and recognized as a valuable flavor component: A. J. N. Bolt, S. W. Purkis, J. S. Sadd, *Phytochemistry* **1983**, *22*, 613; D. Helmlinger, V. Krasnobajew (Givaudan), CH654,567, **1986** [*Chem. Abstr.* **1986**, *105*, 113 607h].
- [13] These changes are more pronounced in toluene (and with a Na₂CO₃ buffer) than in CH₂Cl₂. For solvent effects, see H. Kropf, M. R. Yazdanmashch, *Tetrahedron* **1974**, *30*, 3455.
- [14] a) B. A. McKittrick, B. Ganem, *Tetrahedron Lett.* **1985**, *26*, 4895; b) W. D. Emmons, A. S. Pagano, *J. Am. Chem. Soc.* **1955**, *77*, 89.
- [15] B. E. Rossiter, T. R. Verhoeven, K. B. Sharpless, *Tetrahedron Lett.* **1979**, 4733.
- [16] F. E. Ziegler, B. H. Jaynes, *Tetrahedron Lett.* **1985**, *26*, 5875.
- [17] The *anti* π face of **7pe** displays a higher electron density in the HOMO than the *syn* face (PM3).
- [18] A calculation (PM3) of the electron density surfaces encoded by the electrostatic potential^[5] for **1pa–7pa**, **1pe–7pe**, and **22** showed that the *syn* faces exhibit a more negative electrostatic field.
- [19] A referee suggested citing the work of T. Linker, K. Peters, E.-M. Peters, and F. Rebien (*Angew. Chem.* **1996**, *108*, 2662; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2487) as an example of *syn*-selective epoxidation of a cyclohexene ester. According to these authors, the selectivity is entirely the result of the steric control exerted by the *trans*-oriented phenyl group. However, preliminary experiments performed in our laboratory show that the same facial selectivity is observed in the absence of the phenyl group, and that CF₃CO₃H gives the highest *syn* selectivity.
- [20] C. Fehr, J. Galindo, *Angew. Chem.* **1994**, *106*, 1967; *Angew. Chem. Int. Ed. Engl.* **1994**, *34*, 1023.



The interior of a flame generates small and large particles.

Fullerenes and Soot Formation— New Pathways to Large Particles in Flames**

Klaus-Heinrich Homann*

In memory of Wilhelm Jost

It is only rarely mentioned in the fullerene literature that there is a natural source for fullerenes, namely the combustion of certain hydrocarbons within rich mixtures with O₂. Under most combustion conditions, however, soot is the nearly exclusive high-molecular-weight product formed. This is probably the reason why fullerenes were not found earlier, even though soot extraction studies have been performed frequently in the past. As the first experimental conditions that led to the discovery of fullerenes—laser evaporation of graphite—were very different from conditions found in flames, combustion researchers did not expect to find

fullerenes among the products of combustion. As is so often the case, serendipity led to the discovery of fullerenes, even though the flames under investigation were studied for completely different reasons: namely to look for very large polycyclic aromatic hydrocarbons (PAHs) that were the assumed precursors of soot particles. These species could not be worked up after precipitation, so they were sampled with a molecular beam of a flame burning at low pressure. PAHs also have low ionization potentials; hence it was decided to study the natural flame ions of PAHs, as these are more readily detected. As it was also known that the flames of aromatic compounds contain

many PAHs, benzene was used as the fuel. These three conditions (low pressure, flame ions, and benzene as the fuel) turned out to be favorable for the detection of a large variety of fullerenes in flames. Even though it has not yet been possible to obtain larger quantities of fullerenes by combustion, it has been possible to get closer to answering the question as to how these uniquely built carbon molecules are formed together with the much less orderly structured soot particles.

Keywords: combustion • flames • fullerenes • polycycles • soot

1. Introduction

Soot is the best known high-molecular-weight product of combustion. The presence of fullerenes in flames was discovered in 1987,^[1] two years after their initial discovery.^[2a] During normal or industrial combustion the formation of fullerenes relative to soot is so low that they can only be detected with the most sensitive analytical techniques. By the use of special fuels and certain combustion conditions, however, flames can be created in the laboratory in which fullerenes and soot are formed in approximately equal proportions. This article will only deal with such laboratory flames. From this vantage point, fullerenes are certainly the

most spectacular high-molecular-weight products of incomplete combustion. After all, they have been on the front page of the New York Times, and the 1996 Nobel Prize was awarded for their discovery during the condensation of carbon vapor after laser bombardment of graphite.^[2b] Soot does not command the same degree of scientific respect. With respect to their economic importance, however, the relationship between these two substances is reversed.

At high temperatures, the thermodynamic driving forces in a C/H/O system that does not contain enough oxygen to oxidize all the carbon to CO favor edifices that are rich in carbon. Which mechanisms, however, can explain why large fullerene molecules, having a well-defined molecular formula and exhibiting very high symmetry such as the structure of buckminsterfullerene, are formed under the same conditions and at approximately the same time scales as comparatively huge soot particles, which have neither a molecular formula nor a defined structure? Could fullerenes be a product stemming from soot? Or could the situation be reversed, namely that a fullerene molecule, or something similar, is the

[*] Prof. Dr. K.-H. Homann
Institut für Physikalische Chemie der Technischen Universität
Petersenstrasse 20, D-64287 Darmstadt (Germany)
Fax: (+49) 6151-16-4717
E-mail: homann@pc2.chemie.tu-darmstadt.de

[**] This review evolved out of the 1995 Wilhelm Jost Memorial Lecture, given in Halle/Saale, Marburg, Göttingen, and Hannover.

starting point for the growth of a soot particle? Or are there parallel reaction steps that lead to soot particles and fullerenes?

The chemistry of combustion begins with the fuel, a pure, low-molecular-weight hydrocarbon such as methane, ethylene, acetylene, or an aromatic species such as benzene. It is necessary, therefore, to search from these beginnings for intermediates in the formation of large carbon-rich species. The formation of fullerenes by laser evaporation of graphite^[2b] or in the fullerene generator by Krätschmer,^[3] both of which are pure carbon/helium systems, will not be considered in this article.

2. Classification of Large Particles in Flames

There are five classes of large particles in rich hydrocarbon flames, including soot and fullerenes. Four of them have been known for some time. These four classes, which are depicted in Figure 1, do not only differ in their range of molecular

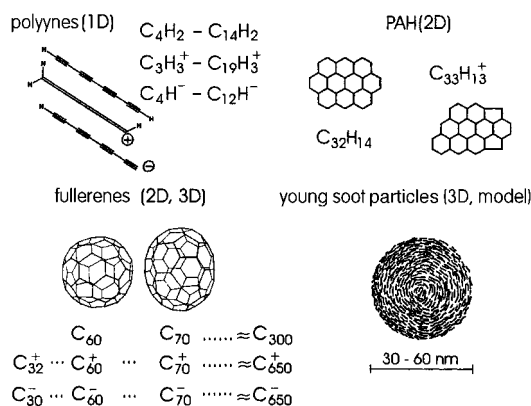


Figure 1. In rich hydrocarbon flames there are carbon-rich particles with one, two, and three-dimensional C backbones that also occur as intrinsic ions in the flame. The residual double bonds of the polycyclic compounds in the diagram are not shown.

masses, but also in the dimensionality of the arrangement of their C atoms. The fifth class was only found through the application of new analytical methods and is considered to be very important for soot and fullerene formation and will be discussed later.

2.1. Polyacetylenes

The first class is the extended polyynes or polyacetylenes. They possess a one-dimensional linear arrangement of carbon atoms and in the electrically neutral (normal) state they carry one hydrogen atom on each end of the chain; their generic formula is $C_{2n}H_2$. They have been detected with formulas up to $C_{14}H_2$. In flames they also exist as radicals, mainly with one additional H atom on one end;^[4] and formulas up to C_8H_3 have been detected. As all polyacetylenes have a high proton affinity and the longer ones also possess relatively low ionization potentials,^[5] they exist in flames in the protonated form and, with increasing chain length, also as simple positively charged ions, albeit in very low concentrations (e.g., $x_{\max}(C_6H_3^+) \approx 4 \times 10^{-11}$ or $[C_6H_3^+]/[C_6H_2] \approx 10^{-8}$). They can also exist as negatively charged ions, for example, $C_{2n}H^-$.^[6]

The most remarkable property of polyacetylenes in flames is that in the region of maximum temperature within the flame they are all in partial chemical equilibrium with each other and with acetylene and hydrogen. This is also true for their radicals and ions and their equilibria with the normal polyacetylenes.^[4, 7] These equilibria limit the growth of the polyacetylenes, as the large chains tend to degrade. This keeps their range of molecular masses far from that of fullerenes and soot particles, which means that polyacetylenes can be ruled out as potential precursors. There are, however, additional arguments for this assumption; for example, the polyacetylene concentration in rich acetylene flames is particularly high, while the fullerene formation is relatively low.^[8]

2.2. Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are two-dimensional carbon-rich molecules. Naphthalene can be looked on as the smallest PAH, while the largest PAHs have molecular formulas of around $C_{320}H_{50}$.^[9] By the use of authenticated materials, about 30 unsubstituted PAHs have been identified up to the molecular mass of coronene (300 u).^[10] Beyond this range only very little is known about their structures. As a consequence of the two-dimensional arrangement of their C atoms the multitude of structures is much larger than of one-dimensional species. The most common structural element of



Klaus-Heinrich Homann was born in Göttingen (Germany) in 1935. He studied Chemistry at the Universities of Freiburg/Breisgau and Göttingen from 1955 to 1961. He was awarded his doctorate at the University of Göttingen in 1964 and in 1969 finished his Habilitation in Physical Chemistry. He was a Fellow of the National Science Foundation, Washington, D.C. at Boston College 1969–70 before becoming a Lecturer (Universitätsdozent) at the Universität Göttingen. Since 1971 he has been Professor at the Technische Hochschule Darmstadt. In 1994 he received the Bernard Lewis Gold Medal and the Silver Medal of the International Combustion Institute. In 1995 he gave the Hottel Lecture at MIT, in Cambridge, MA (USA) and the Wilhelm Jost Memorial Lecture. His research interests include chemical kinetics and the chemistry of combustion.

PAHs is the hexagon of benzene. The structural variety is increased by the addition of pentagons. The existence of five-membered rings in PAHs is of particular interest with respect to fullerene formation. When five-membered rings are bordered by hexagons on not more than two adjacent edges, the molecule is still nearly planar as seen in dicyclopenta[*cd,fg*]pyrene. The bowl-shaped structure of corannulene is markedly different; here a five-membered ring is bordered on all sides by hexagons (Figure 2).

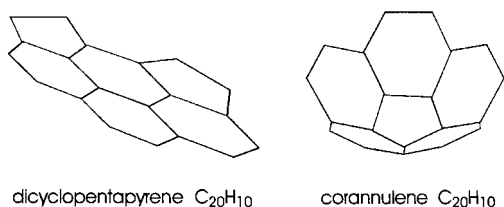


Figure 2. Five-membered rings only cause strong molecular distortions when they are bordered by condensed six-membered rings on more than two adjacent edges.

In flames, PAHs also exist as both σ and π radicals.^[11] In the former species, the unpaired electron is located in a σ orbital, while in the latter it is found in a π orbital. PAHs also exist in protonated or ionized form.^[7, 12] At 10^{-4} to 10^{-3} , their degree of ionization or protonation is markedly larger than for the polyene C₆H₂.^[9] PAHs apparently only exist as negatively charged ions if they contain one or more five-membered rings and/or one oxygen atom.^[13]

Even though the density of the large ions in flames is very low they can be readily detected by mass spectrometry. All large molecules occur as ions, whether as anions, cations, or in both forms. Hence, much information about their occurrence and growth stems from studies of these species that naturally occur in flames. This does not imply that reactions, which will later be discussed with measurements on ions, only apply to ion–molecule reactions. For the large particles under study these reactions also pertain to the corresponding neutral reactants.

2.3. Fullerenes

Fullerenes exhibit a three-dimensional closed-cage structure. In flames the neutral species have been detected on-line from C₆₀ up to about C₃₀₀. From C₇₀ onward, all even-numbered species have been found.^[11] The most prominent are always C₆₀ and C₇₀. Which of these two species is more common depends upon the combustion conditions and the fuel. Ordinarily, however, C₆₀ predominates. Regardless of form and size, all fullerenes must contain twelve pentagons in order to create a closed cage. Fullerene ions are much more readily detected in a flame than the neutral molecules. This can be gleaned from the fact that the ions are found in a mass range that is broader by a factor of about two relative to the neutral species (C₃₂⁺ up to approximately C₆₅₀⁺, C₃₀⁺ up to about C₆₀₀⁺). The ionized species C₆₂ to C₆₈ are found as well.^[14] It is not unambiguously clear whether the upper limit of about C₆₅₀

arises because of limitations of the measurement technique or stems from specific conditions within the flame. A mechanism of formation that will be discussed later indicates that the latter is true.

One could consider fullerenes to be two-dimensional species, as the C atoms only form a molecular surface. The upper mass limit, which is only about twice as high as that found for the planar PAHs, is relatively low for three-dimensional particles. This also supports the view that fullerenes are two-dimensional. The absolute lowest boundary appears to be C₃₂⁺ or C₃₀⁺; this has been observed during the photolytic degradation of fullerenes as well.^[15] The so-called nanotubes are related to fullerenes. These are elongated, fullerene-like cylindrical tubes which are closed at the rounded ends. They contain *several* layers of carbon atoms, possess much greater molecular masses, and have also been detected in flames.^[16]

2.4. Soot Particles

Soot particles are definitely three-dimensional. The smallest ones exhibit a mass of about 2×10^3 u, while the largest ones get as big as 10^8 u.^[17] This effectively unlimited growth, especially relative to one and two-dimensional particles, is characteristic of three-dimensional species. For some time, it has been known that the C/H ratio for very young soot particles is about 3.^[18] Relative to the largest PAHs (about C₃₂₀H₅₀), this corresponds to a rather high hydrogen content. Even if it were possible to assign a definite molecular formula C_xH_y to a given soot particle, this would be rather useless as it must be assumed that no two soot particles are alike. All soot particles, even the smallest ones, occur in flames as negatively and positively charged species.^[19, 20]

As is well known, fullerene molecules are hollow. Soot particles have filled interiors. A limited similarity can be found in the forms of the two species. One must, however, consider some special cases, both for fullerenes and for soot particles. There are soot particles that exhibit a nearly perfect spherical shape.^[21] While the closed, highly symmetrical shape of C₆₀ is intrinsic and a consequence of the particular arrangement of twelve pentagons and twenty hexagons, the spherical shape for soot particles is the result of a certain growth mechanism. These quite round particles were able to grow by the surface degradation of small hydrocarbon molecules. During growth, no coagulation with other soot particles occurred (quite accidentally). These turbostratically arranged layer segments exhibit an interlayer distance slightly larger than that found for graphite.^[22] During growth at flame temperatures, it is assumed that they can shift with respect to each other at the surface and thereby briefly form, in effect, a two-dimensional liquid. Hence, the eventually spherical shape arises from a dynamic process, which leads to other shapes when particles coagulate during growth.

The depiction of a soot particle in Figure 1 should not be taken literally. It is meant to indicate the (usually only approximate) spherical shape of the particle as well as the layer fragments that are visible under an electron microscope. These layers are oriented in a more or less parallel fashion

with respect to the surface and in exceptional cases are grouped around a common center. The considerations (see below) about the origins of soot and the appearance of the first soot particles are not really related to the structure of the finished particle. This structure is, in fact, created during the particle growth by the attachment and heterogeneous degradation of small unsaturated hydrocarbons (e.g., acetylene) at the surface, tempering processes in the interior accompanied by the loss of hydrogen, and coagulation with other soot particles. For this reason, the detailed knowledge about the morphology of some “finished” soot particles will not be taken into account for the following considerations. An extensive discussion of soot formation and its various aspects can be found in the review article by Haynes and Wagner.^[23]

3. The Flame as a Chemical Reactor

Premixed flames have proven successful for the detailed study of flame chemistry. These flames burn at low pressures (about 30 mbar) on a circular, cooled, porous metal plate (diameter 75 mm). Figure 3 shows a schematic representation

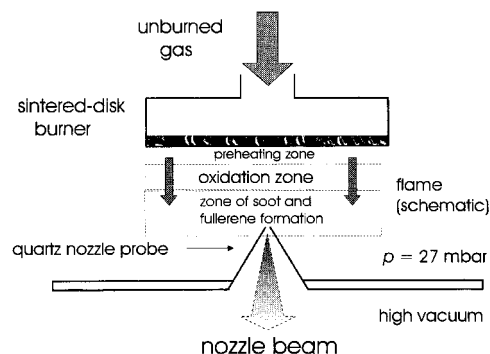


Figure 3. Schematic representation of a burner with a flat low-pressure flame and a nozzle beam probe.

of such a burner with a flame. The flame burns in a stationary fashion, which means that the spatial distribution of temperatures and concentrations remains unchanged. In the interior of the flame, these variables change primarily only with the distance from the burner. Therefore, such flames are also referred to as quasi one-dimensional. Further outward towards the edge of the flame, the temperature is not as high as in the center. These different temperature profiles (at the edge and at the axis) for the combustion of the same hydrocarbon/oxygen mixture is of importance for the study of fullerene and soot formation, which will be discussed in Section 8.

The fuels employed were acetylene, 1,3-butadiene, benzene, and naphthalene. The flames were continuously sampled using a cone-shaped probe with an opening of about 0.7 mm in diameter, behind which a strong vacuum was applied. The sample was initially in the form of an expanding nozzle beam. From this (continuous) nozzle beam, a molecular beam was separated by a skimmer (see Figure 4) and a second vacuum pump. The various components of this molecular beam were then analyzed with several different apparatus. The probe that extended into the flame is indicated

schematically in Figure 3. Even though the probe is not cooled and made of thin quartz glass, the flame is perturbed. The extent of this perturbation has been studied and consists mainly of a temperature drop of about 150–250 K at the probe tip, relative to the unperturbed flame, with the amount depending on the position in the flame.^[24, 25]

A discussion of the chemistry of the reactions that constitute the bulk of the combustion is beyond the scope of this article. However, the most important conditions with respect to temperature and concentrations of critical reactants will be discussed in a qualitative manner, as the precursors for soot particles or fullerenes are exposed to these conditions on their path through the flame into the exhaust gas. A larger distance from the burner corresponds to a longer total reaction time.

3.1. Temperature

The temperature increases steadily from slightly above room temperature up to the end of the oxidation zone, at a distance of about 11–13 mm from the burner surface, where the supply of added molecular oxygen is exhausted. (A typical temperature profile is shown in Figure 13.) The maximum temperature at the flame axis at the end of the oxidation zone is dependent on the fuel, the fuel/oxygen mixture, and its unburned gas velocity (throughput). For the experiments described herein, mainly acetylene and benzene were used in a mixture with pure oxygen, which lead to a maximum temperature of 2050 to 2200 K. Hence, the temperature increases steadily in the flame zone, in which the higher molecular weight hydrocarbons are formed alongside the oxidation reactions.

The larger the activation energy, the more rapidly the rate constants of elementary reactions increase with temperature. For competition to occur between bimolecular association reactions (growth reactions) and rearrangement and degradation reactions, which exhibit higher activation energies, the following is implied: At the relatively low temperatures at the beginning of the oxidation zone, the molecules grow but rearrangement and degradation reactions do not play a significant role. With increasing temperature, the growth reactions become faster, but the rates of the degradation and rearrangement reactions increase even more rapidly. Since the concentration of the oxidizing radicals (mainly OH) also increases with temperature, the effect of degradation reactions increase with temperature in any case. This means that, depending on the combustion conditions, the growth of the molecules or particles can be limited and soot formation can be inhibited. How the formation of fullerenes is affected under these conditions will be described. After the maximum temperature is reached, it drops by about 70 K for every 10 mm. In this region growth reactions can catch up again, provided that enough reactants remain available in the exhaust gas.

3.2. Smaller Molecules and Radicals

The addition of acetylene to hydrocarbon radicals is a known type of growth reaction.^[26] Under the conditions that

prevail when soot and fullerene formation sets in within C_2H_2/O_2 flames the concentration of C_2H_2 drops by a factor of about 50 from the burner to the end of the oxidation zone.^[24] This loss of a growth component is more than compensated for by the increase in the rate constants of the growth reactions, which grow by several orders of magnitude. Hence, growth reactions remain important throughout the entire flame.

During the combustion of benzene, the benzene molecule itself is an important reactant for the formation of higher molecular weight PAHs. In contrast to acetylene, benzene is completely consumed, even before the end of the oxidation zone. In the vicinity of the temperature maximum benzene is, therefore, no longer available as a building block for larger molecules or particles. Within a benzene flame, however, acetylene is formed with increasing temperature. At the end of the oxidation zone, acetylene is present in nearly the same concentrations as those found in acetylene flames.^[27]

The most important small radicals found in fuel-rich hydrocarbon flames are H, CH_3 , and OH,^[28] with OH being the most important oxidizing agent in flames. The maximum concentration of the three radicals is reached just before the end of the oxidation zone. As the OH concentration drops sharply outside the oxidation zone of fuel-rich flames, the rate of formation of the large particles in the oxidation zone determines how greatly they will be affected by oxidative degradation. If they are formed rapidly they effectively only represent a transformation of the fuel and most of them will undergo combustion. If formation is slower and still continues when the OH concentration is decreasing, the large particles can reach the exhaust gas and are emitted together with it from the flame. As the growth of the large molecules starts in any case inside the oxidation zone, all possible precursors of soot and fullerenes are more or less exposed to oxidative degradation.

The primary role of the free H atoms is the propagation of the driving force of flame chemistry, the chain branching reaction $H + O_2 \rightarrow OH + O$. They thereby indirectly influence the formation and combustion of large molecules. It is much more difficult to discern a potential direct effect of free H atoms on the formation reactions of large molecules. This is because until now very few experiments have been performed to study the fundamental reactions of H with, for example, large PAHs or even soot particles at temperatures comparable to those found in flames. Attempts to accelerate the growth of PAHs and soot particles by the addition of free H atoms to a flame have mostly had the opposite effect.^[29] Methyl radicals do not contribute to the formation of large molecules. This is apparent from the study of methane flames where methyl radicals reach a relatively high intermediate concentration, but do not lead to a significant formation of larger particles.

4. Apparatus and Experimental Methods

Our experimental methods are specially tailored to the on-line analysis of the just described medium-sized to large particles. Analytically speaking, trace analyses are performed. A further aspect was the ability to apply as many analytical

methods as possible to the same flame. The main problem was the separation and, if possible, identification of the single components, which numbered in the thousands. This goal was realized by examining the nozzle beam or the molecular beam of the flame with various methods. This will be briefly discussed by use of the schematic diagram shown in Figure 4.

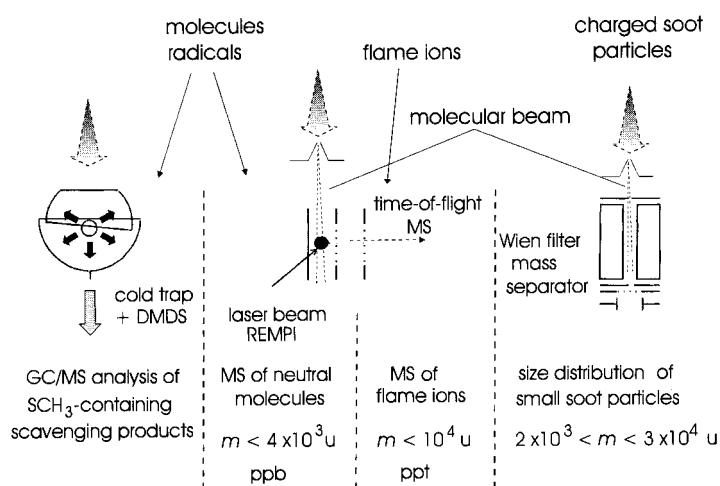


Figure 4. Methods for the analysis of molecular or nozzle beams from flames. From left to right: cold trap to trap radicals in frozen dimethyl disulfide (DMDS); time-of-flight mass spectrometry after resonance-enhanced laser photoionization (REMPI); time-of-flight mass spectrometry of flame ions; separation of very small electrically charged soot particles with a Wien filter mass separator.

The mass and sensitivity ranges of the methods employed are given in the figure. In the particle beam, indicated by an expanding arrow (nozzle beam) or dashed lines (molecular beam), we analyzed:^[30]

- *Free hydrocarbon radicals, PAHs as well as oxygen-containing PAHs*, by condensing them together with excess dimethyl disulfide in a special cold trap at the temperature of liquid nitrogen. The radicals are trapped according to the reaction $R^{\cdot} + CH_3SSCH_3 \rightarrow RSCH_3 + SCH_3$. After the contents of the cold trap are allowed to melt, the trapped radicals are identified and quantified by GC/MS analyses of the stable products $RSCH_3$. The largest thus found radical was pyrenyl. The nonradical condensable components were also determined quantitatively. In this case, the upper mass boundary was found to be coronene.
- *PAHs, PAH radicals, and fullerenes* by resonant (REMPI) and nonresonant multiphoton ionization with a frequency-doubled, pulsed dye laser and separation with a time-of-flight mass spectrometer, equipped with an ion reflector, which was specially designed for large ions. Photoionization is particularly effective for PAHs, and minimal fragmentation enables the detection of PAH radicals.
- *Positive and negative flame ions*, also with a reflectron time-of-flight mass spectrometer. As these species are already present in the molecular beam of the flame, a pulsed deflection voltage was used instead of the laser.

- *Very small positively and negatively charged soot particles* by employing a specially designed Wien filter mass separator (Wien filter + electrical deceleration field). This instrument does not yield single mass peaks but a (continuous) mass distribution, which is quite appropriate for small soot particles.

The procedure for all experiments was to take samples from the flames at various distances from the burner and to interpret the concentration profiles or mass distributions in terms of the combustion chemistry of the large particles.

5. Properties and Behavior of Large PAHs in Flames

As the mass range of large PAHs overlaps with that of the fullerenes as well as with that observed for small soot particles, it is an obvious choice to study the type of PAHs, their radicals and ions, as well as their development.

PAHs occur with any number of C atoms. The largest ones that have been detected in flames contained about 320 C atoms. Figure 5 shows the same segment of a mass spectrum of

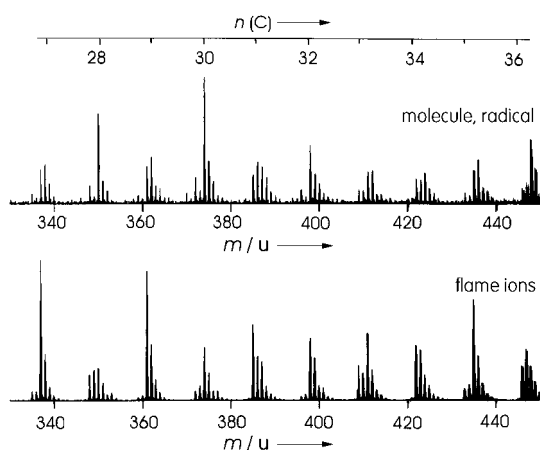


Figure 5. The mass spectra of a group of uncharged PAHs and their radicals show many similarities with those of corresponding positively charged flame ions. The upper abscissa shows the number n of C atoms per group of PAHs.

neutral PAHs (top) and PAH flame ions in a fashion that falsely suggests equal intensities, in reality the concentration of the neutral species is much higher. The mass spectrum of the flame ions is completely free of fragments and the spectrum of the neutral species nearly so. Both mass spectra show groups of PAHs with the same number of C atoms, ranging from 27 to 36. It is apparent, that in the range $C_{27}H_x$ to $C_{33}H_x$ the signals of ions containing odd numbers of C atoms are more intensive, while for the neutral species the even-numbered PAHs stand out. This difference in intensity becomes smaller with increasing mass of the PAHs, until it is only marginal for species with more than 50 C atoms. It is useful for other reasons as well (see below) to note whether PAHs contain an even or odd number of C atoms.

The different signals within a group stem primarily from molecules or ions with a different number of H atoms. In such

a group, there are relatively H-rich and H-poor PAHs. The true ratio of H-rich to H-poor PAHs is obtained once the ^{13}C isotope distribution in the groups has been evaluated and usually shows PAHs that clearly dominate a group together with PAHs of lower intensity. The PAHs with the highest intensity within a group are termed the main PAHs.

5.1. The Molecular Formulas

The mass spectra yield initially only the molecular formulas of the PAHs. It is known from other studies of flame PAHs that one molecular formula usually encompasses several isomers.^[31] The molecular formulas of the PAHs belonging to the isotope-corrected signals in the mass spectrum can be plotted in a C/H diagram, where each point corresponds to a certain formula C_xH_y . This is shown in Figure 6 for the PAHs from the flames of three different fuels. The PAHs of a group

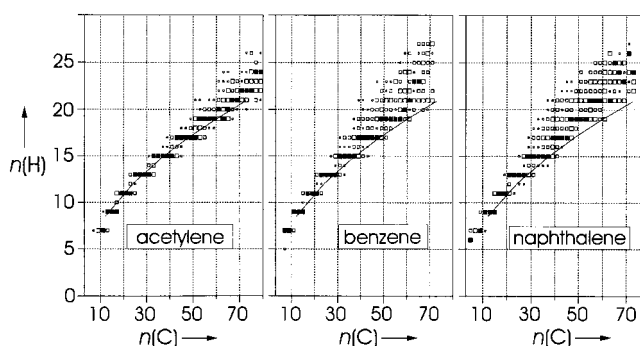


Figure 6. C/H diagram of the molecular formulas of positive PAH ions in the flames of three fuels. Black squares: PAH^+ ions at relatively high maximum concentrations; unfilled squares (according to size): PAH^+ ions at lower concentrations. PAHs exhibiting a structure having the maximum number of condensed six-membered rings fall on the solid line.

in the mass spectrum are listed in a vertical column in the C/H diagram. The most intensive ones within a group are denoted by the filled squares, weaker ones by the unfilled squares of decreasing size. In this diagram, the molecular formulas of the PAHs form a band that widens towards larger PAHs. This observation indicates that with an increase in the number of C atoms, the bandwidth for the H content becomes larger. This behavior becomes more pronounced when the fuel is changed from acetylene to benzene and finally to naphthalene. It is useful to provide an orientation aid in this diagram. Therefore, the solid line connects molecular formulas of PAHs or their ions that possess a highly condensed system of six-membered rings. These species are shown in Figure 7 up to a maximum of 59 C atoms. The odd-numbered ones also contain an odd number of H atoms. In the neutral state, these particles are π radicals. In ions with this structure the charge is delocalized, which contributes to their stability. These structures are the most C-rich or most H-poor PAHs formed solely from six-membered rings.

It is noteworthy that the dominant PAHs in acetylene flames, up to about $C_{70}H_x$, are densely grouped around this line. Hence, all PAHs above this line are richer in hydrogen

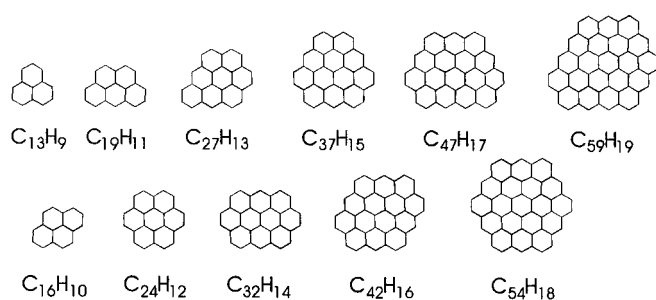


Figure 7. Odd- and even-numbered PAHs with a maximally condensed six-membered ring structure. In electrically neutral molecules the odd numbered species are π radicals.

than the highly condensed structures shown in Figure 7, for which there are no other isomers built solely from six-membered rings. Thus, there are some very hydrogen-rich large PAHs, particularly in flames of aromatic fuels.

The diagrams in Figure 6 have only been constructed from the formulas of odd-numbered PAHs and they refer to ions, which can be gleaned from the odd number of H atoms. It should be noted that a plot of even-numbered PAHs, either as neutral species or positively charged ions, is on this scale essentially indistinguishable from the one shown.

5.2. Probable Structures of Large PAHs

The molecular masses corresponding to the peaks in the mass spectra yield molecular formulas, but only knowledge of the structures leads to further progress with respect to the question about the precursors of soot and fullerenes. For this, it is necessary to use all available knowledge about the high-temperature reactions of known PAHs and their identified PAH products—not only from flames—as well as calculations of the thermodynamic stability of PAHs and the dependency on structure and temperature. Knowledge of proton affinities and ionization potentials is equally useful.

It becomes possible to draw reasonable conclusions about the structural types of flame PAHs from the mass spectrometric intensities and their repeat patterns with dependence on the molecular formulas, which can be correlated with similar repeat patterns for certain structural types. For this purpose, a section from the lower segment of the C/H diagram of the acetylene flame (which is the simplest one) and the intensities of the corresponding main PAH⁺ ions will be considered more closely (Figure 8). The *unfilled* squares, which represent the main PAH⁺ ions, form steps (in Figure 6, these species are denoted by filled squares for better clarity). At the beginning of a step, the intensities of two signals in a group are comparable, so that two main PAH⁺ ions can be registered. The PAH⁺ ions in Figure 7 that possess formulas corresponding to highly condensed structures are found roughly in the middle of the steps. The steps become broader with an increase in the number of C atoms.

Interesting correlations are obtained when the maximum densities of these main PAH⁺ ions in a flame are plotted separately for odd and even-numbered main PAH⁺ ions against the number of C atoms (Figure 9). Those points that

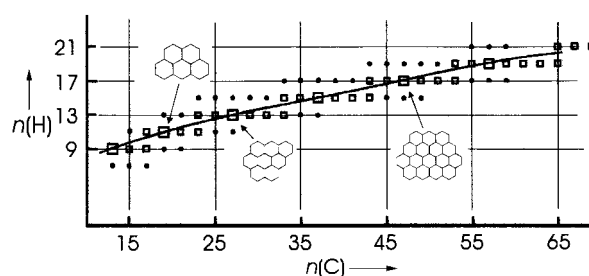


Figure 8. Segment of the C/H diagram of the PAH molecular formulas from an acetylene flame. The main PAHs (unfilled squares) form steps; the species exhibiting the maximally condensed six-membered ring structure lie in the center of these steps.

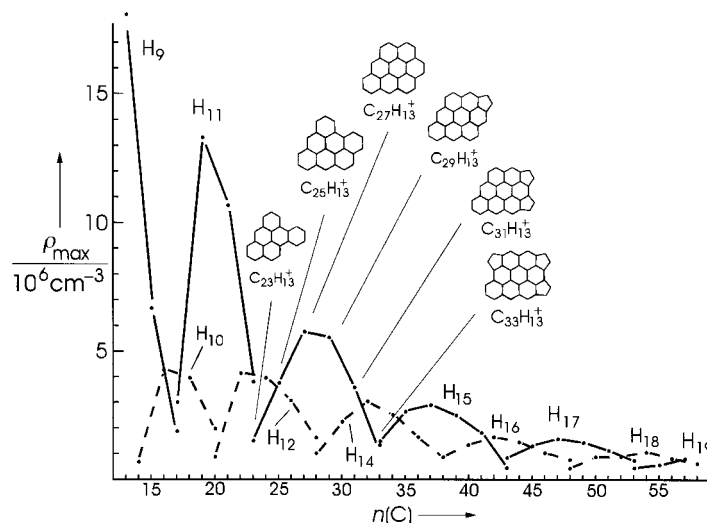


Figure 9. Maximum densities ρ of odd-numbered (solid line) and even-numbered (dashed line) PAH⁺ ions in a C_2H_2/O_2 flame as a function of the number of C atoms per molecule. For PAH⁺ ions with the same number of H atoms, there are maxima at the maximally condensed six-membered ring structures.

belong to PAH⁺ ions with the same number of H atoms are connected by the line to improve clarity. These curves exhibit maxima always for those PAH⁺ ions with molecular formulas corresponding to the structures shown in Figure 7. This is observed for odd and even-numbered PAH⁺ ions and include $C_{13}H_9^+$, $C_{19}H_{11}^+$, $C_{27}H_{13}^+$, etc., and $C_{16}H_{10}^+$, $C_{24}H_{12}^+$, $C_{32}H_{14}^+$, etc. Relatively high concentrations of particles at high temperatures indicate thermal stability. For this reason, it is likely that the PAH ions marked among the main PAH⁺ ions possess just these structures. It is, therefore, better to use the terms H-rich and H-poor PAHs and PAH⁺ ions with respect to these structural standards, that is, the line drawn in the C/H diagram, instead of solely using the main PAH in the groups as orientation. The points on the curves left of the maxima thus correspond to H-rich PAHs, those on the right to H-poor PAHs.

There are many different reasons for a change in the relative H content. A PAH becomes more H-rich, for example, by substituting a H by a methyl group, by hydrogenation with retention of the C arrangement, by a more open carbon backbone that exhibits coves, by a more oblong arrangement of hexagons without cove formation, or by the formation of biaryl species. More H-poor structures can be

generated by replacing an H with an ethynyl group and by incorporating one or more five-membered rings into the structure. All these structural characteristics have been found in PAHs from flames, however, some such as substituted or hydrogenated PAHs only in very small quantities. In the zones of the flame where these main PAHs reach their maximum concentration, the temperature is so high that changes in the relative H content (along one of the lines in Figure 9) must not affect the stability of the corresponding structures in an overly negative way. Taking this fact into account, of the possibilities just mentioned only the more open, cove-containing or more oblong arrangement of hexagons ($\rightarrow$ H-rich) and the incorporation of pentagons ($\rightarrow$ H-poor) remain viable. This has also been confirmed by theoretical studies.^[32] Possible structures are shown next to the line for 13 H atoms in Figure 9. While $C_{27}H_{13}^+$ has only one isomer, there are three for $C_{25}H_{13}^+$ and four for $C_{23}H_{13}^+$. For the more H-poor species $C_{29}H_{13}^+$, $C_{31}H_{13}^+$, and $C_{33}H_{13}^+$ there are also several possibilities for the peripheral arrangement of the pentagons.

Based on these arguments it becomes clear that PAHs from the same mass spectrometric groups, that is, with the same number of C atoms, but different numbers of H atoms, have very little in common in terms of structure and mechanisms of formation, even though they occasionally have a similar maximum concentration. For example, $C_{33}H_{13}^+$ probably contains three five-membered rings in a highly condensed structure, while $C_{33}H_{15}^+$ exhibits a structure containing only six-membered rings and probably two four-carbon coves. A rule of thumb can be formulated as: *Flame PAHs with the same number of C atoms but different numbers of H atoms have different C backbones.*

Up to now, only main PAHs stemming from acetylene flames and lying along the “steps” have been considered. The same considerations apply also to H-rich large PAHs from the flames of aromatic fuels. Many of these PAHs, however, are so H rich that they can only be viewed as biaryls or oligoaryls (mainly with phenyl and naphthyl groups). Smaller biaryls have been detected and identified in large numbers in naphthalene flames.^[31] They are not very thermally stable, which agrees with the observation that these components reach their maximum concentration at the beginning of the oxidation zone, where the temperature is not yet very high.

5.3. The Occurrence of Extremely Large PAHs

The largest PAHs and their ions are found, somewhat surprisingly, in acetylene flames and not in those of aromatic fuels. A slightly modified depiction of their H content with increasing number of C atoms in the molecule or ion is shown in Figure 10; Instead of the number of H atoms, the C/H ratio is employed. The reason for this lies in the better comparison with very young soot particles, for which this ratio has also been determined. Only main PAHs have been used in the plot, but both odd (unfilled dots) and even-numbered (filled dots) species are included in the diagram. As before, the curve drawn connects the maximally condensed species according to Figure 7. Some structures of large odd-numbered species are

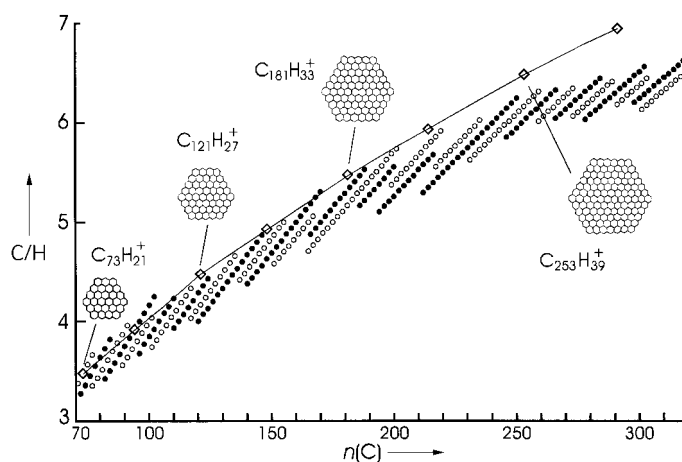


Figure 10. The atomic C/H ratio of the very large main PAH⁺ ions in a C_2H_2/O_2 flame, as a function of the number n of C atoms. Filled dots: even-numbered PAH⁺ ions; unfilled dots: odd-numbered PAH⁺ ions. For comparison, the structures and C/H ratios of some odd-numbered PAH⁺ ions with the maximally condensed six-membered ring structure are shown as well.

included as well. In this diagram, the H-rich PAHs lie below the line and the H-poor ones above it.

It is apparent, that for very large PAHs as well, there is no principal difference between odd and even-numbered species with respect to H content. In acetylene flames, the “band” of growth follows the line of maximally condensed hexagons fairly well up to about C_{100} PAHs. When the number of C atoms increases further, the PAHs become slightly more rich in hydrogen. The diamond at the upper end of the solid line represents $C_{294}H_{42}$. The main PAH for this C content is $C_{294}H_{46}$. This is only a small difference in H content. While $C_{294}H_{42}$ has an unambiguous structure (Figure 11), there are

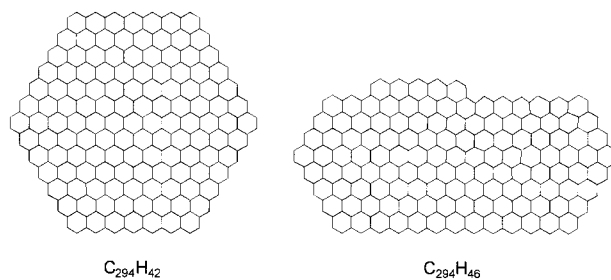


Figure 11. While the PAH $C_{294}H_{42}$ possesses only one unique, highly symmetrical structure, which is made up only of hexagons, the slightly more H-rich main PAH $C_{294}H_{46}$ exhibits numerous isomeric structures in a flame, which are most probably oblong and/or contain four C coves. One isomer is shown here.

many possible structural isomers for $C_{294}H_{46}$, one of which is also depicted in Figure 11. This demonstrates the kind of structural change that a slightly larger H content can cause for very large PAHs. The course of the “band” shows that very large H-poor PAHs and, hence, the incorporation of five-membered rings into the structure must be quite rare. Otherwise, the “band” would cross the line, as is observed for PAHs with $C_{100}H_x$ or lower. This means that large PAHs are essentially planar molecules. The existence of these very

large PAHs indicates that PAH growth does not stop with the onset of soot formation, as it clearly goes beyond the mass of the smallest soot particles ($\approx 2 \times 10^3$ u).

A detailed discussion of the relationship between PAH growth and structure is beyond the scope of this article. It suffices to note the relevant literature.^[9] Important characteristics of the growing PAHs in the different flames with respect to soot and fullerene formation should, however, be summarized. Hydrogen-poor PAHs are formed primarily in acetylene flames up to about $C_{100}H_x$. Only those structures, however, that contain at most three five-membered rings are observed in significant concentrations. The growth by continuing reactions with C_2H_2 can be represented by a “band” that consists of probably thousands of individual PAHs. There is, however, no such “band” in the C/H diagram that leads to fullerenes (located on the $n(C)$ axis).

In the flames of aromatic fuels, the situation is different. Fewer H-poor PAHs are formed, that is, those containing five-membered rings in their structure. In contrast, there is quite a number of H-rich PAHs, in particular in species with 30 or more C atoms. These have structures that must consist nearly exclusively of six-membered rings with four-carbon coves. In addition, one finds large biaryls. In benzene and naphthalene flames, relatively strong fullerene formation is observed, but no “band” in the C/H diagram that leads to fullerenes.^[33]

5.4. Profiles of PAHs and PAH Radicals

For some time now, PAH radicals have played a dominant role in the discussion of the growth reactions of PAHs and in the formation of soot and fullerenes. Only recently, however, has it been possible to determine the concentration profiles of such radicals in flames. In some cases, this was done quantitatively. The following surprising results were obtained. Figure 12 shows the concentration profiles of ethynylbenzene and PAHs as well as of the corresponding radicals with one H atom less.^[11, 31] All PAHs and their radicals are intermediates

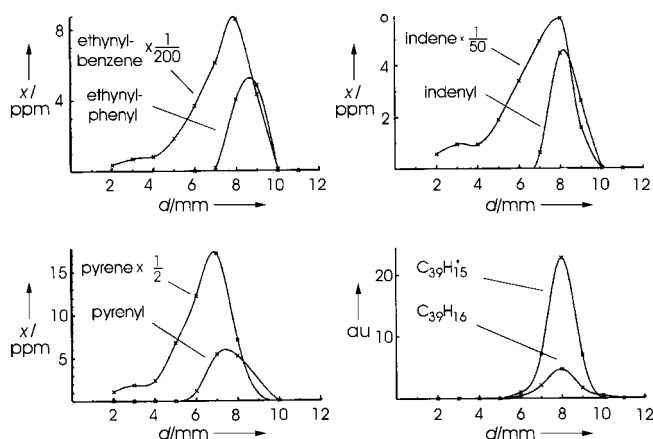


Figure 12. Profiles of the mole fractions x of PAHs and corresponding radicals ($-1H$) plotted against the distance d from the burner in a naphthalene/ O_2 /Ar flame. The relative concentration of the radicals increases strongly with the number of C atoms. For large odd-numbered PAHs, the radicals even become the more common species.

in the oxidation zone. The maximum concentration for ethynylphenyl reaches only 0.3 % of that of ethynylbenzene and the maximum is found at a larger distance to the burner, that is, at a higher temperature. For the larger indenyl radical, the maximum concentration is already 1.6 % and for the even larger pyrenyl radical about 20 % of the corresponding closed-shell PAH. The maxima also move closer together. For very large odd-numbered PAHs, the radical concentrations are surprisingly *larger* than those of the corresponding nonradical species. The maxima are reached at the same distance from the burner. In all probability, the latter species are π radicals like indenyl. For large even-numbered σ radicals, the radical concentrations also reach a high percentage, but they do not become larger than the concentrations of the closed-shell PAHs.^[11, 31]

As the reactivity of radicals is greater than that of the corresponding valence-saturated (by H) molecules, their concentration generally remains small. As a consequence of their higher enthalpies of formation, their maximum concentrations are expected to occur at higher temperatures. This is certainly also true for radicals of smaller PAHs. For very large PAHs and, assumably, for other large molecules with many internal degrees of freedom this well-known picture appears to change. The difference between the reactivity of radicals and their corresponding molecules vanishes with increasing size and increasing number of internal degrees of freedom. It is quite possible that the remaining differences in the reactivity between species having the same or very similar molecular formulas—whether molecule or radical—stem from other criteria, for instance the structure itself or some bonds weakened by steric effects. Very little is known about the elementary reactions of large molecules or clusters at high temperatures. It is unreasonable to expect, for example, that the rate constant of the reaction between naphthyl and acetylene is similar to that of the reaction between acetylene and a young soot particle, which also possesses one or more unpaired electrons. Research is still only just beginning in this area.

5.5. The Role of Oxidation Reactions in PAH Growth

The growth of PAHs occurs primarily in the oxidation zone of the flames. Therefore, all participating reactants, intermediates, products, and their ionized forms are more or less exposed, directly and indirectly, to the influence of oxidation reactions. The indirect influence stems from the change in the temperature profile of the flame by the more intense and more rapid (or slower) combustion of all oxidizable components. This leads to a change in the concentration profiles of the small radicals (H, OH, O, CH_3 , etc.) that participate in the chain-branching reactions. In contrast, the direct influence lies in the reactions of PAHs and their radicals or of fullerenes and their precursors with oxidizing reactants such as OH, O, or O_2 .

The oxidation of aromatic- and alkyl-substituted aromatic species in flames and under flamelike conditions, for example, in flow reactors at temperatures up to about 1200 K, as well as behind shock waves has been studied frequently.^[27, 34, 35, 36] Hydrocarbons with relatively small aromatic cores were

employed for these studies, with phenanthrene being the largest one used.^[37] The reactions of O and OH with benzene and substituted benzenes have also been studied.^[38] The presence of partially oxidized higher aromatic species in fuel-rich flames has also led to knowledge of the first intermediates of oxidative attack.^[31] This leads to the following general picture, in particular with respect to the effects on the growth reactions. Hydroxyl arenes (phenol, naphthols, hydroxyphenanthrenes, hydroxypyrenes) are the very early and dominant, if not primary, products of oxidation. This leads to the conclusion that corresponding compounds can also be formed from higher aromatic species.

In addition, oxygen is found in ketogroups (e.g., indene-1-one), aldehydes (e.g., benzaldehyde), or as a heteroatom in rings (e.g., benzofuran). Usually only one O atom is found in partially oxidized arenes, very rarely two O atoms are observed (quinones). On the other hand, carbon monoxide is found very early in the oxidation of arenes at temperatures around 1200 K. This gas results from cleavage of an hydroxy-arene or of the respective radical (e.g., the phenoxy radical). Concurrently, a PAH with a condensed five-membered ring is formed. This indicates that thermal degradation quickly follows the oxidative attack on a C atom, which leaves no time for the further attachment of another O atom. Such a degradation step, however, does not significantly perturb the growth reactions because, at temperatures that are not too high, a PAH containing a five-membered ring is formed, which just possesses one less C atom. It is also possible, that in the course of this oxidation/CO release reaction sequence a PAH σ radical is formed that could even favor further growth. Partially oxidized PAHs or their ions have only been detected up to a mass of about 400 u.^[13]

At higher temperatures, and primarily at the maximum temperature in a flame, no binding of OH or O to form hydroxyarenes takes place. Instead, an abstraction of H from the arene occurs, thus forming an aryl radical and H₂O or OH, respectively. This does not mean, however, that the C skeleton of the PAH is not further affected. Under these conditions, unimolecular degradation reactions are faster than bimolecular association reactions with small unsaturated hydrocarbons. In addition, the C–C bonds in radicals are much more readily broken than in intact molecules.^[39] Hence, there is not only the release of one C atom in a single step (as CO), but, after the cleavage of the six-membered ring, up to four C atoms are cleaved off simultaneously, as is known from the oxidation of alkylarenes. This leads to the formation of another aryl radical, and so on. A single oxidative attack (or the reaction with H; indirect influence) can therefore initiate a rapid succession of degradation reactions. The end products of such a degradation are acetylene and polyacetylenes.

In the flame zone, where relatively many PAHs are formed, their growth is not significantly hindered by oxidation; no O-containing PAHs accumulate since they rapidly decompose. For appropriately hot flames, the oxidative attack also acts as the initiator for rapid PAH degradation, which happens anyway at high temperatures. Under these conditions no soot is formed. Hence, the steep drop in the PAH profiles in Figure 12 at 8–10 mm is not only caused by consumption through growth but also by decomposition.

6. The Controversy Over Soot and Fullerenes in Flames

Already in 1986, one year after the discovery of fullerenes, Smalley, Kroto, and co-workers suggested that fullerene-like structures could be the “nuclei” for roughly spherical soot particles.^[40] These species would not be closed cages like C₆₀, C₇₀, or their larger analogues, but would have failed to achieve closure of the cage in *one* carbon layer during their growth. Growth would continue in a second layer, which places itself over the first one, and in several more layers, all of which would be curved by the incorporation of five-membered rings. In this way, only incompletely closed fullerene shells would be formed, which all in all would exhibit a roughly spherical shape. Kroto expanded these ideas in 1988 and proposed a so-called icospiral nucleation process.^[41] According to this mechanism, the first stages of soot particles resemble the shell of a nautilus. Free valences, which are unavoidable because of the nonclosure of the cage in an all-carbon system, would be saturated (primarily around the opening of the nautilus shell) by hydrogen atoms during soot formation in combustion processes. Only along the edge (along the opening of the nautilus shell) would growth proceed along a spatial spiral, thus increasing the volume of the particle and its otherwise fullerene-like surface.

In the meantime, in 1987, fullerenes were discovered in sooting hydrocarbon flames, initially in the form of positively and negatively charged ions.^[11] The fact that these ions were still also present in the soot-containing exhaust gas, lead to the conclusion that fullerenes in flames represented stable final products—albeit in small concentrations—and not just short-lived intermediates. Accordingly, in 1991, C₆₀ and C₇₀, were, for the first time, extracted from a premixed low-pressure flame and separated by HPLC.^[42]

In the past, there have been many hypotheses about the structure of the very first soot particles. These varied from tiny stacked graphite layers to droplets of high-boiling oil.^[43, 44] In 1941, Rummel and Veh had already proposed that soot formation is preceded by PAH formation.^[45] All these proposals were more or less well founded on experimental evidence. But none of these hypotheses caused such a controversy among some flame and soot researchers as Kroto's icospiral mechanism, which placed initial soot particles close to fullerenes.^[46, 47] The counter arguments were mainly: The growth of PAH molecules in flames, proven many times by experiments, which has also been subjected to model calculations, was completely ignored, as well as the fact that soot, with respect to its chemical reactions, is much more similar to arenes than to graphite. In addition, it had been shown that during the initial stages of soot formation, when the particles are small and particle number density relatively high, coagulation of particles played an important role. According to Kroto's model, however, even the larger particles grow only in a very specific manner, by the binding of smaller carbon clusters, so that more and more layers with a fullerene structure are formed. According to this mechanism, even the initial soot particles should be very H-poor. It was found, however, that young soot exhibits a C/H ratio of about

three.^[18] Baum has presented an impartial summary of this controversy.^[48]

The fact that fullerenes (or fullerene-like structures) had been predicted to occur in flames, as well as the reasonable idea that during the formation of fullerenes “errors” could occur that might prevent closure of the cage but not further growth, in addition to the general fascination associated with fullerenes, did lend some credibility to Kroto’s hypothesis. One of the major causes of the controversy, however, was that the chemical environments in hot, cluster-containing carbon vapor and in a sooting flame are very different, a fact that was probably not appropriately appreciated. The unfortunate term “fullerene soot” for the amorphous carbon formed during the Krätschmer process for fullerene synthesis later added more confusion to this matter, as this material has nothing in common with soot from flames.

Thus, at the end of the 1980s, there were roughly four models for the relationship between fullerenes and soot: soot particles are formed by the faulty growth of fullerenes; fullerenes are formed from soot particles; soot particles and fullerenes are formed simultaneously, side-by-side; both species are formed in the flame, but are not interconnected in any way. This situation could only be remedied by well-designed experiments.

7. Fullerenes in Flames

7.1. Properties and Behavior of Fullerenes in Flames

While the maxima of all PAHs are found within the oxidation zone—they are shifted to larger distances from the burner with increasing molecular mass because the larger ones are formed from the smaller ones—fullerenes are formed later. They reach their maximum concentrations at the end of the oxidation zone or just behind it. The exact location depends on the fuel and the combustion conditions. Figure 13 shows an example of one PAH and one fullerene

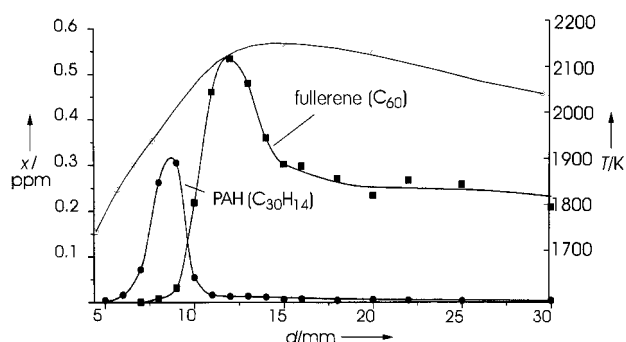


Figure 13. Temperature profile ○ and mole fractions ●, ■ of a PAH ($C_{30}H_{14}$) and a fullerene (C_{60}) in a benzene/ O_2 flame.

profile to demonstrate the characteristic concentration profile of the two classes of large molecules. A typical temperature profile is shown as well. While large PAHs show only very small concentrations in the exhaust gas, fullerenes reach a

nearly constant level after a small drop behind the maximum. The partial consumption of fullerenes after the maximum is caused by oxidation. The remaining constant concentration indicates that there is no further degradation of the thermally stable fullerenes in the range of 2100–1800 K.

Roth and co-workers have studied the thermal decay of C_{60} and its reaction with O_2 behind shock waves.^[49] This study leads to the conclusion that the oxidation of C_{60} with the remaining oxygen in the flame at temperatures of greater than 2000 K occurs on a time scale comparable to the other flame processes. Thermal degradation becomes significant only at temperatures above 2400 K.

The multitude of formed fullerenes can be gleaned from a mass spectrum of the positively charged fullerene flame ions from an acetylene flame (Figure 14). Above C_{100}^+ , the mass

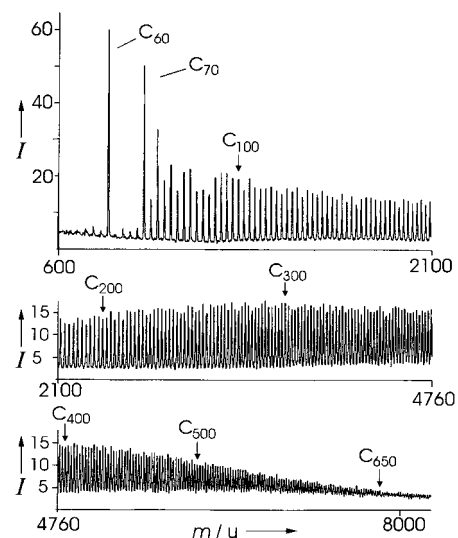


Figure 14. Mass spectrum of positive fullerene flame ions in a sooting acetylene/ O_2 -flame.

spectrum is quasi-continuous. Signals up to C_{650}^+ can be distinguished, albeit at decreasing intensity. The steady intensity development for very large fullerenes indicates that they are empty cages as well, not multiple-layer molecules (onion structure). If this were the case, one would expect discontinuities in the intensity development, for example, at the beginning of a new layer.

Recently, larger fullerenes up to C_{96} have been extracted from the soot of low-pressure benzene flames, separated by HPLC, and isolated.^[50] The obtained amounts of $C_{60}:C_{70}:C_{76}:C_{78}:C_{84}$ corresponded to 100:100:4:3:6, while those of $C_{84}:C_{86}:C_{90}:C_{92}:C_{94}:C_{96}$ followed a ratio of 100:0.5:5:0.5:1.25:1.

Fullerenes smaller than C_{60} are a peculiarity. They occur primarily in flames of aromatic fuels, but also during the combustion of butadiene. Figure 15 shows a mass spectrum of the positively charged ions of these particles in a benzene flame. It has thus far not been possible to isolate fullerenes smaller than C_{60} from flames or to detect them on line as neutral species with multiphoton ionization mass spectrometry. This method, however, is not very sensitive to fullerenes.

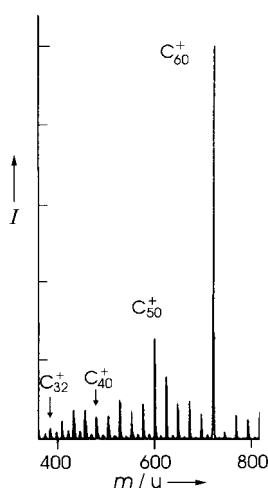


Figure 15. Mass spectrum of fullerene flame ions C_{32}^+ up to C_{66}^+ in a benzene/ O_2 flame. The very small signals between those of the fullerenes stem from residues of large PAH $^+$ ions.

The small fullerenes can be found as positively and negatively charged flame ions.

From all that is known about the relationship between charged and their corresponding neutral species in flames, it must be assumed that fullerenes smaller than C_{60} do actually exist in flames as neutral species. Apparently the sensitivity and separation capabilities of the currently employed on-line techniques are insufficient to detect these species. Their occurrence in ionized form indicates that they possess exceptionally high electron affinities and low ionization potentials. This makes them detectable, in contrast to their uncharged counterparts, which probably only exist in very small concentrations relative to C_{60} and C_{70} . All these small

fullerene ions must exhibit adjacent five-membered rings, those smaller than C_{50} even triples of five-membered rings. The reason that they have not been found during the extraction of soot could be their very low concentrations or their instability in the condensed phase. It is also possible that ionized and neutral small fullerenes exhibit different structures. It has only recently been observed that, in flames, very large odd-numbered PAHs preferable occur as radicals.

In flames, small fullerenes readily add one or more H atoms even at high temperatures. This reduces the stress on the cage.^[8] They are not precursors of C_{60} , C_{70} , and the larger fullerenes. In general, it has been found that fullerenes—in contrast to PAHs—do not grow by adding smaller hydrocarbons. The delayed formation of very large fullerenes, relative to C_{60} and C_{70} , has different reasons, which will be discussed together with their mechanism of formation.

A further peculiarity is the formation of “odd-numbered” fullerenes, which occur in low concentrations together with normal fullerenes.^[30c] They always carry at least one, sometimes two H atoms. Their structure is unknown, as it has thus far been impossible to isolate them. They have only been detected on-line in their ionized form. It is likely that the additional C atom is not integrated into the cage structure but exists as a CH or CH_2 bridge on the outside of the cage, where it is particularly sensitive to oxidative attack. Odd-numbered fullerenes are highly unstable and are quickly consumed in a zone where the concentration of even-numbered fullerenes decreases only partially.

7.2. Fullerene Precursors

The discovery of fullerene precursors was enabled by the fortunate fact that their detection in the form of negatively charged ions is very sensitive, while the large majority of

PAHs in the corresponding mass range does not form negatively charged ions at all. Therefore, there are no overlaps in the mass spectrum stemming from PAHs that occur in the corresponding flame zone with much higher concentrations. These overlaps do occur, however, in the mass spectra of positively charged flame ions and neutral molecules.

Figure 16 depicts a mass spectrum of negatively charged flame ions from a flame zone in which fullerenes are formed. The mass range spans from about C_{44} to C_{60} .^[51] Based on their

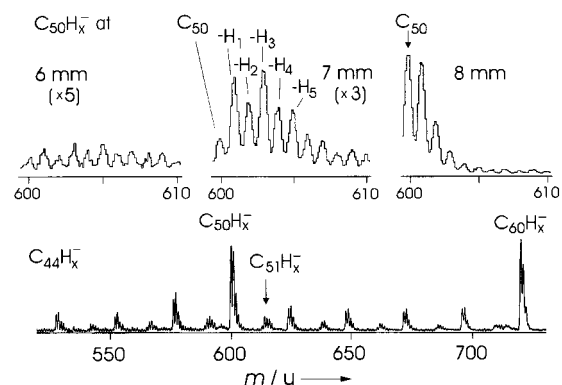


Figure 16. Section of a mass spectrum of negative ions of even-numbered ($C_{2n}H_x^-$) and odd-numbered ($C_{2n+1}H_x^-$) fullerene precursors. Top: mass spectrum of $C_{50}H_x^-$ upon increasing distance from the burner; bottom: $C_{44}H_x^-$ to $C_{60}H_x^-$ at a burner distance of 7 mm.

intensity, the groups of mass signals arise from $C_{60}H_x^- \approx C_{50}H_x^- > C_{2n}H_x^- > C_{2n+1}H_x^-$, where x varies from 0 to about 7 for the even-numbered species and from 1 to about 7 for the odd-numbered ones. The upper part of Figure 16 shows the development of the group $C_{50}H_x^-$ over 2 mm in the flame. At 6 mm the mass spectrum consists of weak signals at all masses, which do not differ much in intensity. From these, signal groupings grow, in which the signals belonging to hydrogen-containing ions decrease again and finally disappear completely (with the exception of the odd-numbered $C_{2n+1}H^-$). The formation and consumption of H-containing species occurs in distinct intervals. The most H-rich species can be detected first. Corresponding profiles of the signal intensities of the $C_{50}H_x^-$ group, after ^{13}C deconvolution, are shown as an example in Figure 17. Finally, only the hydrogen-free even-numbered fullerenes remain. Other fullerenes show the same

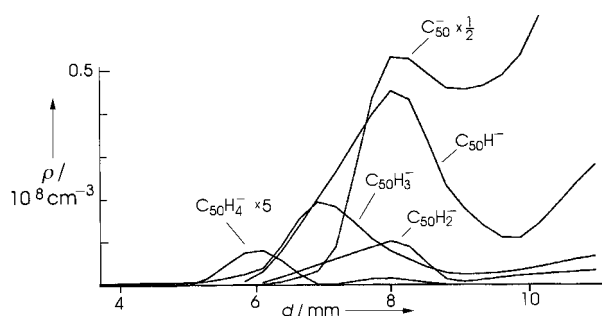


Figure 17. Profiles of the number density ρ of negative ions of hydrogen-containing fullerene precursors in a benzene/ O_2 flame, plotted against the distance d from the burner.

behavior. The signal groupings that first appear above the background of weak peaks in the mass spectrum belong to $C_{60}H_x^-$ and $C_{70}H_x^-$.

Another important observation with respect to fullerene precursors is the presence in the mass spectrum of a continuous background of negative ions in the mass range of less than 500 to far beyond 2×10^3 u. This can be seen clearly in the fullerene mass spectrum in Figure 18.^[51] This is a previously unknown observation during on-line analysis of flames with molecular beam mass spectrometry. Whenever fullerenes and/or soot are formed, the continuous mass spectrum is observed as an intermediate.

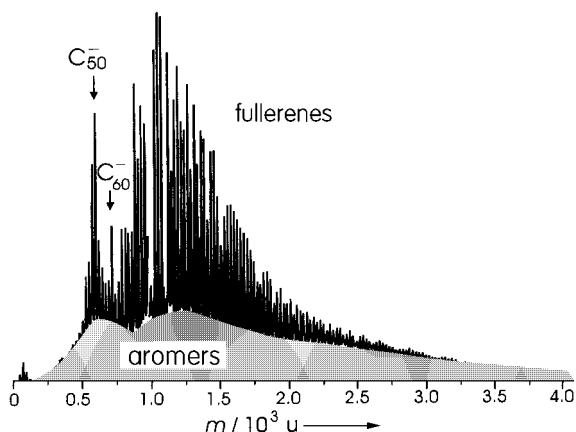


Figure 18. Mass spectrum of negative fullerene flame ions showing a continuous background of the negatively charged aromers (= aromatic oligomers) in a benzene/O₂ flame.

A plot of, for example, the integrated signal intensity over the mass range 720–750 u in the form of an intensity profile together with that of a PAH ion and C_{60}^+ (Figure 19) shows

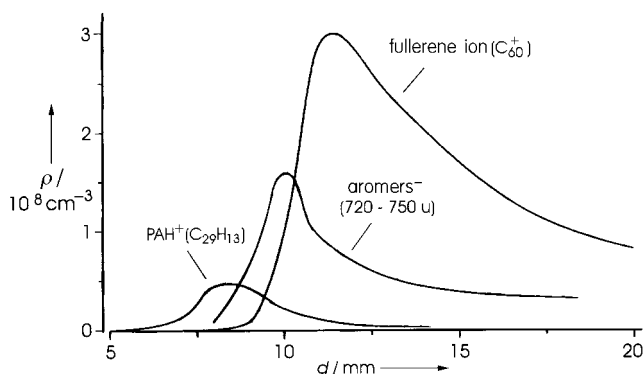


Figure 19. The intensity profile of the aromers in the range 720–750 u (intensity arbitrarily scaled) fits between the number density ρ profiles for large PAHs and C_{60} .

that the components that cause the background are very likely the precursors of fullerenes. We have termed this thus far unknown class of large particles in fuel-rich flames “aromers” (= aromatic oligomers). This is the fifth of the classes that were discussed in Section 2.

7.3. Probable Properties of Aromers

Aromers are characterized by the following properties:

- They form negatively charged ions particularly well in the flame, but can be photoionized externally to yield positively charged ions.
- They yield a continuous mass spectrum.
- Their mass distribution changes within a flame as well as with different fuels and combustion conditions.
- One can deduce their properties also from the type of molecules and ions, which show a discrete mass spectrum in the same mass range.

Aromers, or at least a substantial fraction of them, are very reactive particles, which behave in the mass spectrometer like ‘metastable ions’, long known from electron impact ionization.^[52] In contrast to these ions, which gain their internal energy from the ionization process, the big flame ions obtain their energy from simple internal thermal excitations in the flame.

When they no longer undergo collisions (molecular beam, ionic beam in MS), only intramolecular processes can occur, which are, at least in part, degradation reactions that change the mass of the particle. This exactly corresponds to the unimolecular degradation after thermal activation according to the Lindemann mechanism, the only difference being that it is possible to observe the effects of the *isolated* degradation step, namely the continuous mass spectrum. From the fact that, relative to the other large molecules (fullerenes, large PAHs), this mass spectrum is barely shifted in its mass range, it can be concluded that during unimolecular decay only small neutral particles are cleaved off (e.g., H₂), but that the aromer as a whole does not break up into two roughly equal halves. The observation that aromers are best detected as negatively charged ions indicates that they possess many five-membered rings and probably also adjacent five-membered rings in their structures. This increases their electron affinity. The well-known, very stable cyclopentadienyl anion is a good example for this effect.

The aromers occur initially together with stable particles, which yield a negatively charged flame ion mass spectrum in which every mass is observed at approximately equal intensities. This indicates the presence of C–H compounds that are quite hydrogen rich relative to the PAHs discussed so far. It is, therefore, assumed that the same is true for the aromers. The H-rich PAH ions discussed in section 5.1, on the other hand, yield discrete mass peaks, which means that they do not lose hydrogen in the mass spectrometer, even though among them there are some very large specimens with many internal degrees of freedom. This implies that aromers cannot be planar like PAHs, but must possess structures that facilitate the loss of H₂. This leads to their role as precursors for fullerenes.

7.4. Reactions of Aromers

These observations fit best to particles that are initially formed by the agglomeration of two large arenes. This agglomeration must occur in such a fashion that the arene

parts are not in the same plane, but can approach each other over a large range of their peripheries. A primary formation of the C–C single bond as in biaryls would be conceivable. An attractive interaction without localized bonding is also possible, such as between a large aromatic π radical and a large PAH molecule to give a type of radical π complex. Van der Waals forces have also been suggested for the agglomeration of two large PAH molecules.^[53] In any case, the intermediate would be relatively H rich, as it would exhibit a noncondensed structure, in contrast to the planar PAHs. These edifices are envisioned to be flexible enough so that the aromatic parts can get sufficiently close to each other to lose their hydrogen in the form of H_2 —not from two adjacent, but from two facing H atoms. Thus the original parts can be rapidly linked by C–C single bonds in a zipperlike fashion. The term “aromers” encompasses all possible structures from the initial edifice of two agglomerated PAHs (whether of the biaryl or the π complex type) to the nearly closed, but still H-containing cages. It is very possible that large radicals are among these species. Considering that PAH radicals have been detected in relatively large concentrations, this is actually quite likely.

It would now be possible to consider topological models of a large number of possibilities for the multiple peripheral linkages of two PAHs stemming from the large mass range that occurs in flames. Instead, however, only a few readily visualizable results as well as one surprising finding will be discussed. In terms of fullerene formation, the complete closure of the structure using only five and six-membered rings must be the goal. The simplest, but rare case, is that of two PAHs with the same number of H-carrying peripheral C atoms, but without four-carbon coves. Figure 20 depicts this

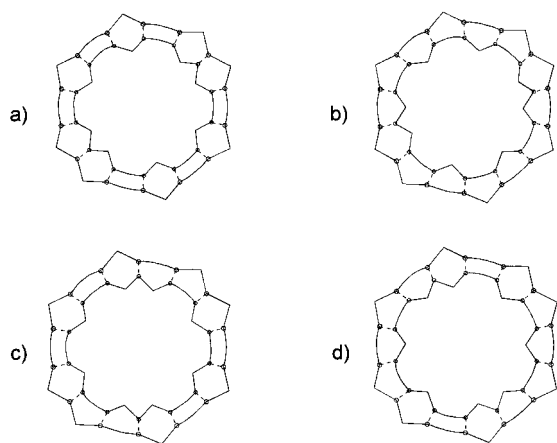


Figure 20. Topological considerations: connecting the peripheral H-carrying C atoms of two PAHs, in this example ovalene $C_{32}H_{14}$, results in several different polygons. In case (b), the twelve pentagons necessary for the closure of the fullerene cage are formed. (See text for explanation.)

situation using two ovalene molecules ($C_{32}H_{14}$) as the example. Only the peripheries of both PAHs are shown with their outer C atoms (solid lines, H atoms omitted). They are shown in a geometrically distorted fashion, but topologically correct, so that upon bond formation (dashed lines) between two facing C atoms, one can readily envision which types of polygons are formed.

In the first case (Figure 20a), six four-membered and eight six-membered rings are obtained. If one periphery is twisted with respect to the other until the next linkage situation is reached, two six-membered rings and twelve five-membered rings are formed (b). Further twisting leads, after link-up, to four four-membered, four five-membered, and six six-membered rings (c). The combination of two four-membered, eight five-membered, and four six-membered rings exists as well (d). Further rotations of either one PAH part leads to a repetition of these combinations. Case (b) would result in a fullerene, albeit a distorted one. This happens here in four out of fourteen situations (29%). As hydrocarbons incorporating four-membered rings have so far never been observed in flames, these cases can be excluded, unless one considers intramolecular rearrangements of a four-membered and an adjacent six-membered ring to form two five-membered rings.

This simple example demonstrates that not all linkages lead to twelve five-membered rings. The probability, however, increases with the size of two thus structured PAHs (PAHs on the solid lines in Figures 8 and 10). For two $C_{34}H_{18}$ molecules, it is 66%. The surprising result (less so for mathematicians familiar with Euler's work) is: If only five and six-membered rings are formed during a complete link-up, there will always be twelve five-membered rings, regardless of the size of the PAHs, that is, their number of peripheral C atoms.

7.5. Fullerene Formation

The initially unimolecular loss of hydrogen from the aromers occurs so rapidly that the concentration of the intermediates involved remain too small for detection. Therefore the C–H diagram shows no “band” in the direction of the fullerenes. Considering the multitude of different PAHs, the probability is not particularly large that just the right pair of aromers meet to have an exact fit after closure of the “zipper”. It is much more common that two PAHs combine that have different numbers of H-carrying peripheral C atoms. Even when this number is the same in both molecules, but one (or both) of the PAHs contains coves, the “zipper” does not close smoothly. This implies that before the final formation of actual fullerenes, there ought to be particles with a few remaining H atoms that are lost more slowly, so that the lifetime of these species is long enough to enable detection. These are now the direct precursors, $C_{50}H_x$, $C_{60}H_x$, $C_{70}H_x$, and many more, which can be analyzed as negatively charged ions. Their loss of the remaining hydrogen atoms can also be studied. According to this model, the final closure of the cage usually also requires the “removal” of excess C atoms, either pyrolytically or by oxidative means. If the number of peripheral C atoms in the two original PAHs is too different, a closure of the cage in this manner becomes unlikely.

This hypothesis of fullerene formation also raises the question of how five-membered rings within a system of six-membered rings can be rapidly shifted intramolecularly so that five-membered rings that initially were connected are finally isolated from each other (“isolated pentagon rule” of fullerenes). They cannot remain at the site of the zipper, as the strain in the closing structure would become too high. Scott,

Zimmermann, and co-workers have performed insightful experiments to resolve this question.^[54, 55]

This mechanism in itself is not limited to any number of C atoms, odd or even, in the finally formed fullerene molecule. This is in agreement with the initial observation of all fullerene groups (see Figure 16). Calculations with H-containing fullerenes indicate that it is likely that at least the even-numbered detectable fullerene precursors already exhibit the closed cage structure and that the H atoms are not located on adjacent C atoms.^[56] Otherwise, the H atoms would be lost too rapidly and the species could not be detected in the mass spectrometer. Without already closed cage structures, it would also be difficult to explain why it is that $C_{60}H_x$ and $C_{70}H_x$ appear as the first detectable fullerene precursors.

There are aromers formed from smaller and from larger PAHs; larger ones can lead to fullerenes containing more C atoms. This mechanism explains why there are large fullerenes that are formed somewhat later. The PAHs that subsequently form the aromers grow with time, while complete fullerenes do not. It is noteworthy, that the largest detectable fullerenes ($\approx C_{650}$) contain about twice as many C atoms as the largest PAHs that can be distinguished ($\approx C_{320}H_x$). This supports the model of their formation from aromers.

There are still many questions regarding the formation as well as the detection of smaller fullerenes, C_{30} to C_{58} . Because of the large ring strains involved, a zipper mechanism is difficult to conceive for smaller aromers. As the fullerenes that are smaller or equal to C_{50} , in particular, are formed *after* C_{60} and C_{70} and are favored by an increase in flame temperature, one working hypothesis has them formed by oxidative degradation of larger fullerenes. The effect of O_2 on solid or dissolved C_{60} and C_{70} in the range of 200 to 500 °C has been the subject of several studies,^[57, 58, 59] but the results (intercalation of oxygen, possible linkage of fullerene molecules by oxygen, formation of carbon-rich C–O polymers, degradation to the point of complete destruction of the fullerene structure) cannot be applied to oxidation reactions in flames. Low quantities of epoxides such as $C_{60}O$ and $C_{70}O$ can be detected together with fullerenes isolated from soot as well,^[60] while they are not found in situ analyses in flames. Anderson and co-workers have shown that the ion–molecule reaction $O^+ + C_{60}$ leads to smaller fullerene fragments and to species like $C_{59}O^+$,^[61] but the impact energies used in these studies were significantly larger than the thermal energy available in flames. It is, therefore, necessary to await the results of studies of thermal elementary reactions, such as $C_{60} + O_2$, O , and OH , at high temperatures before it can be determined whether, apart from possibly CO, smaller fullerenes are formed as well. The very exothermic oxidative degradation reactions of the larger fullerenes could overcome the energy barriers stemming from the cage strain. The absolute lower limit for this type of degradation should be around C_{32} to C_{30} .

As the entire process occurs in a flame zone in which every particle is still exposed to some extent to oxidative or thermal degradation, the principal “survival of the fittest” also plays a role. This certainly includes the even-numbered fullerenes and in particular C_{60} and C_{70} .

7.6. The Acetylene Mechanism of Fullerene Formation

The formation of fullerenes in flames via aromers is not the only mechanism under discussion. Howard and co-workers have proposed a different pathway and have tested it with model calculations.^[62] It also considers PAHs to be precursors of fullerenes, but it particularly stresses the importance of those PAHs that are derived from corannulene ($C_{20}H_{10}$). Parallel to the formation of large planar PAHs others are formed as well, also by acetylene binding, which not only contain a few five-membered rings along their periphery, but also in the interior, in between the six-membered rings. The continued incorporation of five-membered rings while simultaneously more and more H-poor hydrocarbons are formed leads to a bending of the forming PAHs that increases until the cage is closed with the formation of the twelfth five-membered ring. Intermediates in this mechanism are $C_{20}H_{10}$, $C_{30}H_{10}$, $C_{40}H_{10}$, and $C_{50}H_{10}$ on the way to C_{60} and additionally $C_{60}H_{10}$ on the way to C_{70} . A further crucial difference to the aromer mechanism is that the successive growth leading to C_{60} and C_{70} is primarily assumed to occur through *bimolecular* reactions, namely the binding of acetylene with essentially concomitant loss of H_2 . Even though model calculations show that fullerene formation is possible this way in the short time intervals available in flames, it has so far not been possible to detect the H-poor intermediates. This mechanism predicts a particularly strong formation of C_{60} and C_{70} in rich acetylene flames. This has also not been confirmed by observations.

8. Soot Formation versus Fullerene Formation

The same continuous mass spectra that are found in benzene flames during fullerene formation are observed in acetylene flames shortly before soot formation. It is, therefore, reasonable to assume that aromers do not only participate in fullerene formation, but also act as precursors to soot particles. Indeed, why should every half-closed aromer form a closed cage structure under all circumstances? From the growth of PAHs it is known that all particles with open edges can grow by binding acetylene, for example. An experiment is noteworthy in which large particles in the interior and at the edge of a flat benzene/oxygen flame were examined. The result is shown in Figure 21. In the relatively hot interior there are fullerenes, but no soot. Soot forms only in the less-hot edge zone, where only very few fullerenes are found.^[63]

In combination with the observation that acetylene-rich flames contain few fullerenes, but a lot of soot, as long as the temperature is not too high, this temperature effect, together with the model of aromers as precursors for both types of large particles, yields the following overall picture that is summarized in Figure 22. High temperature environments containing relatively low concentrations of small unsaturated hydrocarbons, favor *unimolecular* reactions of aromers. This includes the “zipper reactions” leading to fullerenes, but also general degradation reactions, so that it is conceivable that very large particles are not formed at all. If the temperature is lower and small growth components (such as acetylene) are

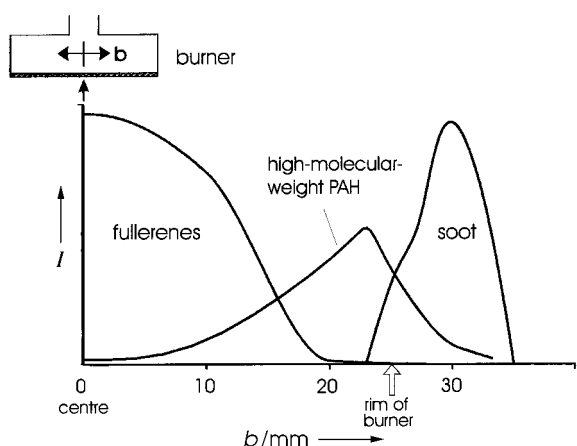


Figure 21. Cross section profile of large particles in a sooting benzene/O₂ flame at a burner distance of $d = 20$ mm plotted against the distance b from the middle of the flame. Within this flame, fullerenes are formed in the hot interior, while soot forms at the less hot edges. (Intensity I in arbitrary units.)

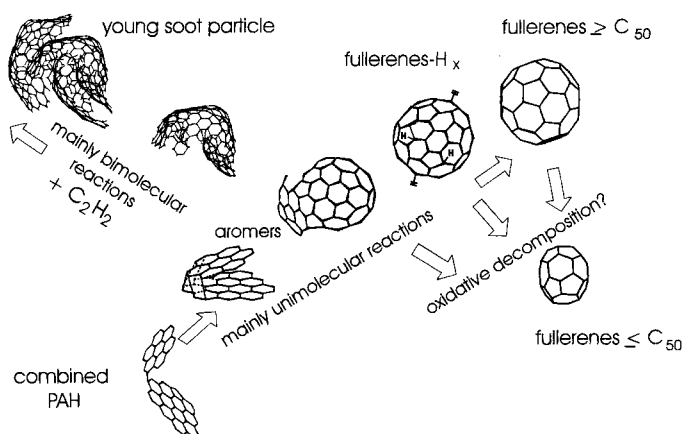


Figure 22. Paths to fullerenes and soot via aromers. While the formation of fullerenes from aromers occurs mainly through unimolecular reactions at high temperatures, soot particles are formed in bimolecular addition reactions of small unsaturated hydrocarbons (e.g., C₂H₂) at lower temperatures. Small fullerenes could possibly be formed in very small quantities by the oxidative degradation of larger fullerenes.

present in higher concentrations, *bimolecular* reactions of aromers dominate, which do not provide enough time for cage closure but instead rapidly lead to small soot particles. It is important to note that these reactions occur with particles that contain aromatic partial structures, but are no longer overall planar. In the case of normal PAHs, these alternatives would either lead only to degradation or to growth up to the stability limit for planar particles.

In the case of soot formation, continuous mass spectra are found somewhat below about 2×10^3 u, and then develop into the mass distribution of larger particles.^[30d] If the formation of the corresponding aromers requires that two large PAHs must first combine, this leads to an average PAH mass of nearly 1×10^3 u, corresponding to about 70 to 90 C atoms. According to Figure 10, these have a C/H ratio between 3.2 and 3.8, not very different from the C/H ratio found for very young soot, which was about 3. The formation of the first soot particles is, therefore, not a simple continuation of PAH growth, as the

mass of the largest PAHs, about 4.5×10^3 u, is significantly larger than that of the smallest soot particles. The C/H ratio of the largest PAHs, about 6.5, is also significantly larger.

9. Conclusion

The controversy, whether initial soot particles in flames are formed by a fullerene mechanism or vice versa, can be resolved by the currently available experimental studies that indicate that both species have common precursors. We have termed these precursor particles aromers. It has thus far only been possible to draw indirect conclusions with respect to their properties. They possess aromatic partial structures and are rich in hydrogen. Hence, they cannot resemble the intermediates in the Kroto icospiral mechanism. Once these aromers have formed, the conditions in the flame determine the further course of the reaction. Fuel-rich combustion under normal pressures (relatively high density of small unsaturated hydrocarbons) but with air instead of pure oxygen (lower temperature) favors the formation of soot. Special flames, however, allow the adjustment of conditions (low pressure, a specific temperature range, aromatic fuel) in such a manner that the large particles formed in small amounts are exclusively fullerenes, formed by essentially unimolecular reactions from aromer precursors, while no soot is formed.

As there are, however, other models of fullerene formation in flames as well, further specific experiments will be necessary before the mechanisms of formation and degradation of fullerenes can be finally clarified. It does, however, appear to be certain that reactions as well as intermediates are different in flames from those in the fullerene generator and the laser evaporation of graphite.^[64, 65] The species found under those conditions, medium-sized chains, rings, and (assumably) multiple-ring systems made of pure carbon, could not be detected in flames.^[66] While C₂ is found in fuel-rich flames, its concentration is not sufficient to model fullerene formation.^[67] The concentration of negative ions C_{2n+1}[−], $n = 1-5$, is also much too low, just several 10^6 cm^{−3}, in order for these species to initiate fullerene formation.^[6, 14]

The results presented in this article would not have been possible without the enthusiastic work, the imagination, and the experimental abilities of my co-workers, whose names could only be listed in the references. They are gratefully acknowledged. The research was supported by the Deutsche Forschungsgemeinschaft, the Federal Ministry for Education, Science, Research, and Technology as part of the research project Technical Flames (TECFLAM), the Stiftung Volkswagenwerk, the State of Hesse, the Fritz-und-Margot-Faudi Foundation, and last but not least by the Fonds der Chemischen Industrie. I am very grateful for this support.

Received: November 25, 1997 [A 260 IE]
German version: *Angew. Chem.* **1998**, *110*, 2572–2590

[1] P. Gerhardt, S. Löffler, K.-H. Homann, *Chem. Phys. Lett.* **1987**, *137*, 306.

[2] a) H. W. Kroto, J. R. Heath, S. C. O'Brien, R. F. Curl, R. E. Smalley, *Nature* **1985**, *318*, 162; b) R. F. Curl, *Angew. Chem.* **1997**, *109*, 1636;

- Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1566; H. W. Kroto, *Angew. Chem.* **1997**, 109, 1648; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1578; R. E. Smalley, *Angew. Chem.* **1997**, 109, 1666; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1594.
- [3] W. Krätschmer, L. D. Lamb, K. Fostiropoulos, D. R. Huffman, *Nature* **1990**, 347, 354.
- [4] M. Hausmann, K.-H. Homann, *Ber. Bunsen-Ges. Phys. Chem.* **1997**, 101, 651.
- [5] S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin, W. G. Mallard, *J. Phys. Chem. Ref. Data* **1988**, 17, Suppl. No. 1.
- [6] P. Gerhardt, K.-H. Homann, *Ber. Bunsen-Ges. Phys. Chem.* **1990**, 94, 1086, 1521.
- [7] P. Gerhardt, K.-H. Homann, *J. Phys. Chem.* **1990**, 94, 5381.
- [8] J. Ahrens, M. Bachmann, T. Baum, R. Kovacs, P. Weilmünster, K.-H. Homann, *Int. J. Mass Spectrom. Ion Processes* **1994**, 138, 133.
- [9] P. Weilmünster, A. Keller, K.-H. Homann, *Combust. Flame* **1998**, in press.
- [10] a) H. Bockhorn, F. Fetting, H. W. Wenz, *Ber. Bunsen-Ges. Phys. Chem.* **1983**, 87, 1067; b) T. G. Benish, A. L. Lafleur, K. Taghizadeh, J. B. Howard, *Symp. Int. Combust. Proc.* **1996**, 26, 2319.
- [11] R. Kovacs, *Dissertation*, Technische Hochschule Darmstadt, **1996**.
- [12] D. B. Olson, H. F. Calcote, *Symp. Int. Combust. Proc.* **1981**, 18, 453.
- [13] S. Löffler, K.-H. Homann, *Symp. Int. Combust. Proc.* **1990**, 23, 355.
- [14] T. Baum, S. Löffler, P. Löffler, P. Weilmünster, K.-H. Homann, *Ber. Bunsen-Ges. Phys. Chem.* **1992**, 96, 841.
- [15] S. C. O'Brien, J. R. Heath, R. F. Curl, R. E. Smalley, *J. Chem. Phys.* **1988**, 88, 220.
- [16] J. B. Howard, K. Das Chowdhury, *Nature* **1994**, 370, 603.
- [17] "Soot Formation in Combustion": K.-H. Homann in *Nachr. Akad. Wissensch. Göttingen, II. Math.-Physik. Klasse, No. 3* (Eds.: H. Jander, H. G. Wagner), Vandenhoeck & Ruprecht, Göttingen, **1989**, pp. 101–107.
- [18] K.-H. Homann, H. G. Wagner, *Symp. Int. Combust. Proc.* **1967**, 11, 371.
- [19] K. G. Payne, F. J. Weinberg, *Proc. R. Soc. London A* **1959**, 250, 316.
- [20] K.-H. Homann, *Ber. Bunsen-Ges. Phys. Chem.* **1979**, 83, 738.
- [21] a) J. Lahaye, G. Prado in *Particulate Carbon Formation During Combustion* (Eds.: D. C. Siegla, G. W. Smith), Plenum, New York, **1981**, pp. 33–55; b) L. L. Ban, P. C. Vegvari, W. M. Hess, *Norelco Reporter* **1973**, 20, 1.
- [22] J. Lahaye, G. Prado, *Chemistry and Physics of Carbon, Vol. XIV* (Eds.: P. L. Walker, P. A. Thrower), Dekker, **1978**, pp. 167–294.
- [23] B. S. Haynes, H. G. Wagner, *Prog. Energy Combust. Sci.* **1982**, 7, 229.
- [24] K.-H. Homann, H. G. Wagner, *Ber. Bunsen-Ges. Phys. Chem.* **1965**, 69, 20.
- [25] J. C. Biordi, C. P. Lazzara, J. F. Papp, *Combust. Flame* **1974**, 23, 73.
- [26] K. Guthier, P. Hebggen, K.-H. Homann, J. Hofmann, G. Zimmermann, *Liebigs Ann.* **1995**, 637.
- [27] J. D. Bittner, J. B. Howard, *Symp. Int. Combust. Proc.* **1981**, 18, 1105.
- [28] see for example P. R. Westmoreland, J. B. Howard, J. P. Longwell, *Symp. Int. Combust. Proc.* **1986**, 21, 773.
- [29] M. Bachmann, W. Wiese, K.-H. Homann, *Symp. Int. Combust. Proc.* **1994**, 25, 635.
- [30] a) M. Hausmann, K.-H. Homann, *Ber. Bunsen-Ges. Phys. Chem.* **1995**, 99, 853; b) J. Ahrens, R. Kovacs, E. A. Shafranovsky, K.-H. Homann, *Ber. Bunsen-Ges. Phys. Chem.* **1994**, 98, 265; c) P. Gerhardt, S. Löffler, K.-H. Homann, *Symp. Int. Combust. Proc.* **1988**, 22, 395; d) Ref. [6]; e) R. Wegert, W. Wiese, K.-H. Homann, *Combust. Flame* **1993**, 95, 61.
- [31] J. Griesheimer, *Dissertation*, Technische Hochschule Darmstadt, **1997**.
- [32] S. E. Stein, A. Fahr, *J. Phys. Chem.* **1985**, 89, 3714.
- [33] M. Bachmann, J. Griesheimer, K.-H. Homann, *Chem. Phys. Lett.* **1994**, 223, 506.
- [34] K. Brezinsky, G. T. Linters, T. A. Litzinger, I. Glassman, *Symp. Int. Combust. Proc.* **1986**, 21, 833.
- [35] C. R. Shaddix, K. Brezinsky, I. Glassman, *Symp. Int. Combust. Proc.* **1992**, 24, 683.
- [36] P. Frank, J. Herzler, T. Just, C. Wahl, *Symp. Int. Combust. Proc.* **1994**, 25, 833.
- [37] H. Frerichs, M. Tappe, H. G. Wagner, *Symp. Int. Combust. Proc.* **1990**, 23, 21.
- [38] K. Lorenz, R. Zellner, *Ber. Bunsen-Ges. Phys. Chem.* **1983**, 87, 629.
- [39] W. Müller-Markgraf, J. Troe, *Symp. Int. Combust. Proc.* **1986**, 21, 815.
- [40] Q. L. Zhang, S. C. O'Brien, J. R. Heath, Y. Lin, C. F. Curl, H. W. Kroto, R. E. Smalley, *J. Phys. Chem.* **1986**, 90, 525.
- [41] H. W. Kroto, *Science* **1988**, 242, 1139.
- [42] J. B. Howard, J. T. McKinnon, Y. Makarovsky, A. L. Lafleur, M. E. Johnson, *Nature* **1991**, 352, 139.
- [43] U. Hofmann, D. Wilm, *Z. Elektrochem.* **1936**, 42, 504.
- [44] a) S. C. Graham, J. B. Homer, J. L. J. Rosenfeld, *Proc. R. Soc. London A* **1975**, 344, 259; b) H. Jinno, S. Fukutani, A. Takaya, *Symp. Int. Combust. Proc.* **1976**, 16, 709.
- [45] K. Rummel, P. O. Voh, *Arch. Eisenhüttenwes.* **1941**, 14, 489.
- [46] L. B. Ebert, *Science* **1990**, 247, 1468.
- [47] M. Frenklach, L. B. Ebert, *J. Phys. Chem.* **1988**, 92, 561.
- [48] R. M. Baum, *Chem. Eng. News* **1990**, February 5, 30.
- [49] S. von Gersum, P. Roth, *Symp. Int. Combust. Proc.* **1994**, 25, 661.
- [50] H. Richter, K. Taghizadeh, W. J. Grieco, A. L. Lafleur, J. B. Howard, *J. Phys. Chem. B* **1997**, 101, 1556.
- [51] M. Bachmann, *Dissertation*, Technische Hochschule Darmstadt, **1997**.
- [52] J. A. Hipple, E. U. Condon, *Phys. Rev.* **1945**, 68, 54.
- [53] J. H. Miller, K. C. Smyth, W. G. Mallard, *Symp. Int. Combust. Proc.* **1984**, 20, 1139.
- [54] a) L. T. Scott, N. H. Roelofs, *J. Am. Chem. Soc.* **1987**, 109, 5461; b) L. T. Scott, *Pure Appl. Chem.* **1996**, 68, 291; c) L. T. Scott, A. Necula, *Tetrahedron Lett.* **1997**, 38, 1877.
- [55] a) S. Hagen, U. Nuechter, M. Nuechter, G. Zimmermann, *Polycyclic Aromat. Compd.* **1995**, 4, 209; b) S. Hagen, H. Christoph, G. Zimmermann, *Tetrahedron* **1995**, 51, 6961.
- [56] C. J. Pope, J. B. Howard, Massachusetts Institute of Technology, personal communication.
- [57] R. Assink, J. E. Schirber, D. A. Loy, B. Morosin, G. A. Carlson, *J. Mater. Res.* **1992**, 7, 2136.
- [58] J. A. Nisha, V. Sridharan, J. Janaki, Y. Hariharan, V. S. Sastry, C. S. Sundar, T. S. Radhakrishnan, *J. Phys. Chem.* **1996**, 100, 4503.
- [59] M. Wohlers, H. Werner, D. Herein, T. Schedel-Niedrig, A. Bauer, R. Schlögl, *Synth. Met.* **1996**, 77, 299.
- [60] J. B. Howard, *Symp. Int. Combust. Proc.* **1992**, 24, 933.
- [61] J. F. Christian, Z. Wan, S. L. Anderson, *Chem. Phys. Lett.* **1992**, 199, 373.
- [62] C. J. Pope, J. A. Marr, J. B. Howard, *J. Phys. Chem.* **1993**, 97, 11 001.
- [63] M. Bachmann, W. Wiese, K.-H. Homann, *Combust. Flame* **1995**, 101, 548.
- [64] R. F. Curl, *Philos. Trans. R. Soc. London A* **1993**, 343, 19.
- [65] H. Schwarz, *Angew. Chem.* **1993**, 105, 1475; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1412.
- [66] G. von Helden, M.-T. Hsu, N. Gotts, M. T. Bowers, *J. Phys. Chem.* **1993**, 97, 8182.
- [67] M. Hausmann, P. Hebggen, K.-H. Homann, *Symp. Int. Combust. Proc.* **1992**, 24, 793.

How Does Nature Cleave Sulfuric Acid Esters? A Novel Posttranslational Modification of Sulfatases

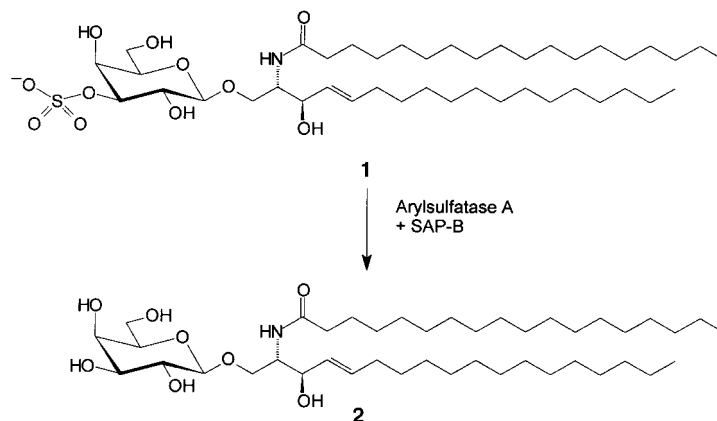
Gunther Uhlhorn-Dierks, Thomas Kolter, and Konrad Sandhoff*

Alkyl- and arylsulfates are relatively stable compounds that can only be cleaved under drastic conditions, for example by alkaline hydrolysis. They are widely used as anionic detergents. Sulfuric acid esters of alcohols exist as naturally occurring substances, for example in heparin, in the mucopolysaccharides chondroitin sulfate and keratan sulfate, in sulfated steroids, and as tyrosine sulfate in the peptide hormones gastrin and cholecystokinin. Conjugation with sulfate is also of relevance for drug metabolism. The analysis of an inherited disease by the group of Kurt von Figura has led to the basic understanding of the enzymatic reactions involved in sulfuric acid ester hydrolysis. A new posttranslational protein modification required for the catalytic mechanism has been identified.^[1]

Nine different sulfatases have been identified in humans that are necessary for the enzymatic degradation of organic sulfuric acid esters.^[2, 3] With the exception of steroid sulfatase they are localized in the lysosomes of the cell. Different inherited disorders are known that are caused by the deficiency of distinct sulfatases leading to a tissue-specific accumulation of the nondegradable sulfuric acid ester. Metachromatic leukodystrophy (MLD), mucopolysaccharidosis, and ichthyosis can be distinguished.

It was demonstrated in patients suffering from MLD that arylsulfatase A (ASA) is defect.^[4, 5] The name arylsulfatase is based on their ability to cleave artificial aromatic sulfuric acid esters. Arylsulfatase A cleaves sulfatides in the presence of a cofactor, a sphingolipid activator protein (SAP-B) (Scheme 1).^[6] MLD leads to the accumulation of sulfatide (galactocerebroside sulfate) in different organs, a loss of the cerebral white matter of the patients, and to death during childhood. The name "metachromatic leukodystrophy" results from the metachromatic stain of the storage material in histological sections, such that on staining with cresyl violet, the absorption maximum is changed so that the deposits appear brown.^[4]

In contrast to MLD, the activities of all known sulfatases are severely decreased in a rare disorder called Austin's disease or multiple sulfatase deficiency (MSD). The clinical manifestation is a combination of symptoms of individual sulfatase deficiencies. The genetic basis of MSD is still

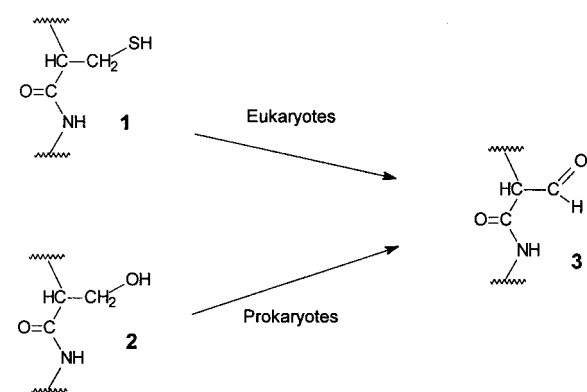


Scheme 1. Hydrolysis of sulfatide **1** to give galactosylceramide **2**. The reaction is catalyzed by arylsulfatase A. Sphingolipid activator protein B (SAP-B) is a necessary cofactor. The deficiency of arylsulfatase A leads to metachromatic leukodystrophy.

unknown. Complementation studies have shown that the genes for single sulfatases are not affected and that it is not a fortuitous common failure of two or more enzymes.^[7, 8] After expression of the complementary DNA (cDNA) from an intact sulfatase in MSD patient cells the resulting enzymatic activity appears to be severely reduced.^[9] These experimental results led to the proposal of a secondary defect such as an incomplete co- or posttranslational modification that is necessary for the catalytic activity of all sulfatases.

With this in mind the enzymatic active arylsulfatase A was purified and analyzed for the presence of such a posttranslational modification.^[1] After digestion with the protease trypsin and enzymatic removal of N-glycosidically linked oligosaccharides a peptide was isolated with a mass different from that predicted by the DNA sequence. The mass of this peptide, which comprises the amino acids 59 to 73 of ASA, was amazingly 74 Da less than expected after reductive carboxymethylation. In general posttranslational modifications result in mass increases—apart from proteolytic processing or glycane trimming. By sequencing, metabolic labeling with [³⁵S]methionine, and MALDI-MS it could be shown that this peptide (ASA 59 to 73) contains no cysteine residue at position 69 as predicted by the ASA cDNA, but a formylglycine residue (2-amino-3-oxopropanoic acid, Scheme 2). After reduction with NaBH₄ the peptide mass increased by two units and serine was identified at position 69 through sequencing.

[*] Prof. Dr. K. Sandhoff, G. Uhlhorn-Dierks, Dr. T. Kolter
Kekulé-Institut für Organische Chemie und Biochemie der Universität
Gerhard-Domagk-Strasse 1, D-53121 Bonn (Germany)
Fax: (+49) 228-73-7778
E-mail: sandhoff@uni-bonn.de



Scheme 2. Posttranslational modification of the amino acid cysteine **1** (in eukaryotes) and serine **2** (in specific prokaryotes: *Klebsiella pneumoniae* and *Escherichia coli*) to give formylglycine **3**.

The same modification was also detected in the human N-acetylgalactosamine-4-sulfatase (arylsulfatase B, ASB)^[1] and in the arylsulfatase from the green alga *Volvox carteri*.^[10] This indicates the evolutionary conservation of this protein modification in eukaryotes.

Which amino acids contain the sulfatases from patients with MSD, the starting point for this investigation? In arylsulfatase A and B overexpressed in MSD cells, mainly the unmodified cysteine residue instead of formylglycine was found. However up to 20% of the investigated sulfatases were modified.^[1] Therefore, MSD has to be regarded as a partial defect of a posttranslational modification resulting in an incomplete loss of catalytically active sulfatases.

The identity of the modifying enzyme that catalyzes the conversion of protein-bound cysteine to formylglycine is not yet known. Since it has been shown that the synthesis of the cysteine-containing precursors is not impaired, a modification on the level of a putative formylglycine containing aminoacyl tRNA can be excluded. The transformation of the cysteine residue occurs after synthesis of the peptide backbone and its translocation into the lumen of the endoplasmic reticulum, where N-glycosylation also takes place. With the aid of peptide constructs it could be demonstrated that formylglycine is formed after N-glycosylation.^[11]

The signal for posttranslational modification is often coded within the amino acid sequence. In the case of arylsulfatase A the trigger for modification was localized by construction of chimeric proteins from ASA sequences and non-ASA sequences. A linear sequence of sixteen amino acids (four in front of and eleven after the cysteine) is sufficient to initiate the oxidation of the cysteine residue to the formylglycine residue.^[11] The amino acid sequence in this region is strictly conserved among all eukaryotic sulfatases (Figure 1).

It is not directly evident, how a sulfuric acid ester can be cleaved with the assistance of an aldehyde. Two different reaction mechanisms are conceivable: first the nucleophilic attack of a sulfate oxygen at the aldehyde; second the nucleophilic substitution at the sulfur atom by an enol or hydrate of the aldehyde. The crystal structure of arylsulfatase A^[12] and B^[13] as well as a biologically verified site-directed mutated sulfatase^[14] provide information on this problem. The recently published crystal structure shows that arylsulfatase A exists as a homo-

Lower Eukaryotic Arylsulfatases

<i>Volvox carteri</i>	P	V	C	C	P	S	R	T	N	L	W	R	G	Q	F
<i>Chlamydomonas reinhardtii</i>	P	V	C	C	P	S	R	T	N	L	?	R	G	Q	F
<i>Hemicentrotus pulcherrimus</i>	A	V	C	T	P	S	R	S	A	I	M	T	G	R	L
<i>Strongylocentrotus purpuratus</i>	S	V	C	T	P	S	R	S	A	I	V	T	G	R	Q

Human Arylsulfatases

Arylsulfatase A	S	L	C	T	P	S	R	A	A	L	L	T	G	R	L
Arylsulfatase B	P	L	C	T	P	S	R	S	Q	L	L	T	G	R	Y
Steroidsulfatase	P	L	C	T	P	S	R	A	A	F	M	T	G	R	Y
N-Acetylglucosamin-6-sulfatase	A	L	C	C	P	S	R	A	S	I	L	T	G	K	Y
Iduronatsulfatase	A	V	C	A	P	S	R	V	S	F	L	T	G	R	R
N-Acetylgalaktosamin-6-sulfatase	P	L	C	S	P	S	R	A	A	L	L	T	G	R	L
Arylsulfatase D	P	L	C	T	P	S	R	A	A	F	L	T	G	R	H
Arylsulfatase E	S	L	C	T	P	S	R	A	A	F	L	T	G	R	Y

Figure 1. Comparison of the sequences from different sulfatases. The cysteine residue which is converted into formylglycine is marked by an arrow.

octamer composed of a tetramer of dimers (α_2)₄.^[12] The structure revealed great similarity to alkaline phosphatase although the sequence homology is rather low. In its assumed active site a magnesium ion is found which is coordinated to the oxygen atom of formylglycine (Figure 2). The observed

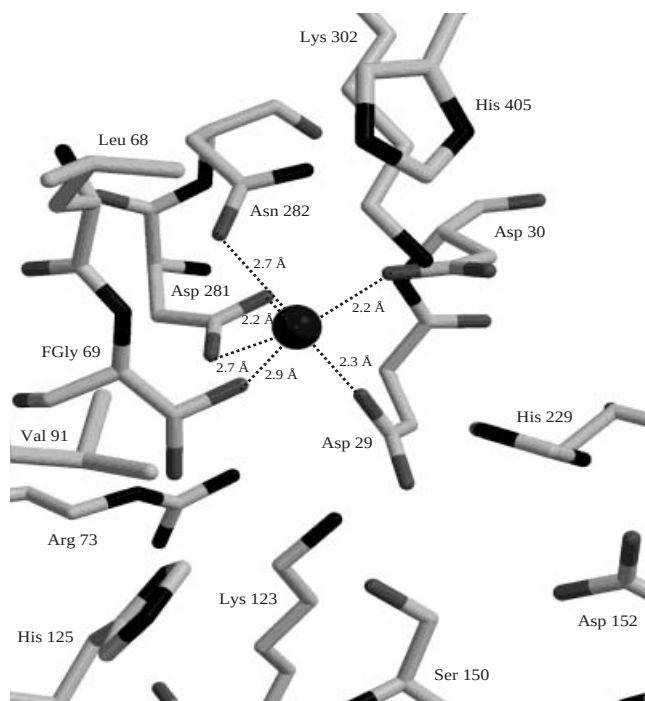
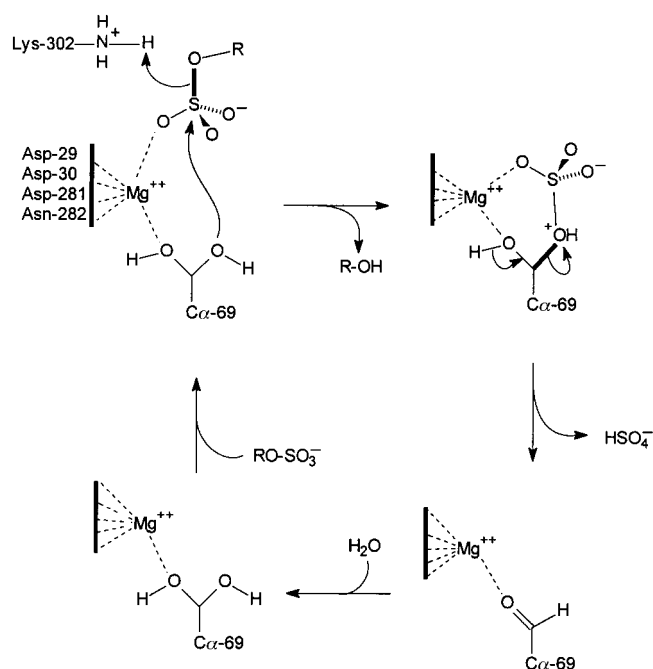


Figure 2. Part of the three-dimensional structure of human arylsulfatase A.^[12] The distances between selected side chain atoms and the central magnesium ion are given.

electron density was interpreted as an aldehyde hydrate by the authors. In alkaline phosphatase two zinc ions are in the active site and coordinate the phosphate; the catalytic active amino acid is a serine.

A hypothetical mechanism of sulfate cleavage is shown in Scheme 3. One of the geminal oxygen atoms of the aldehyde



Scheme 3. Hypothetical mechanism of sulfuric acid ester hydrolysis (modified according to ref. [12]).

performs a nucleophilic attack on the sulfur atom of the sulfate; the galactosyl ceramide residue serves as the leaving group. The magnesium ion increases the electrophilicity of the sulfur atom and facilitates the nucleophilic attack of the hydrate oxygen atom leading to the formation of a sulfated enzyme intermediate. Such an intermediate was postulated earlier on the grounds of the anomalous kinetics of arylsulfatase A.^[15] With [³⁵S]-labeled substrate it could be shown that ASA binds sulfate. Further characterization of the modified enzyme failed since the label was lost after denaturation. It was considered that the sulfate group is not present in an ester linkage which would be stable under denaturing conditions.^[16, 17]

Taking the recent findings into account an explanation is as follows: the driving force for the fission of the sulfated enzyme is the reformation of the carbonyl bond of formylglycine. No hydrolysis of a stable S–O bond is required, instead the less stable C–O bond is broken. The conclusions derived from the crystal structure concerning the catalytic mechanism are supported by experiments with a modified enzyme. The cysteine residue in the precursor protein of ASA and ASB was replaced by serine by site-directed mutagenesis. This serine residue is not oxidized to formylglycine in the cell lines used for the expression. The generated mutants are able to cleave [³⁵S]-labeled substrate, however the sulfate remains tightly bound to the enzyme.^[14] The serine oxygen atom is sufficiently nucleophilic to cleave the sulfuric acid ester but the assistance of a second oxygen atom to release the enzyme-bound sulfate is lacking. Only in alkaline environment and after the addition of galactose as acceptor for the released sulfate a desulfatation of the enzyme takes place and a catalytic cycle starts. The proposed mechanism is comparable to that of alkaline phosphatase. First a serine residue attacks the phosphoric acid ester of the substrate. In the second step the resulting phosphoserine is hydrolyzed by a water mole-

cule. In sulfatases, a second hydroxyl group of the hydrated formylglycine is required for sulfate release.

The cysteine residue, which is posttranslationally converted to formylglycine, is highly conserved in all known eukaryotic sulfatases (see Figure 1).^[10] However, among the five prokaryotic sulfatase sequences known to date there are two exceptions. In *Klebsiella pneumoniae* and *Escherichia coli*, the DNA codes for a serine instead of cysteine. The characterization of *Klebsiella pneumoniae* sulfatase on the protein level showed that the initially incorporated serine is converted to a formylglycine residue (see Scheme 2).^[18] The incomplete conversion is explained with saturation of the enzymes necessary for the transformation. In contrast to eukaryotic cells, which cannot convert a serine residue, this amino acid serves as a precursor for the catalytically active amino acid in prokaryotic cells. So far it is not known whether *Klebsiella pneumoniae* can also modify a cysteine residue into a formylglycine residue.

The recent results should enable the identification of the enzymes that catalyze the oxidation of cysteine residues or serine residues by suitable methods such as that of the two-hybrid system. This would also lead to an improved understanding of the molecular basis of multiple sulfatase deficiency which is assumed to be caused by a defective posttranslational modification. The quoted articles illustrate how the analysis of inherited diseases can lead to the discovery of new chemical and biochemical principles.

German version: *Angew. Chem.* **1998**, *110*, 2591–2594

Keywords: enzyme catalysis • glycolipids • proteins • sulfatases

- [1] B. Schmidt, T. Selmer, A. Ingendoh, K. von Figura, *Cell* **1995**, *82*, 271–278.
- [2] E. F. Neufeld, J. Muenzer in *The Metabolic Bases of Inherited Disease* (Eds.: C. Scriver, A. L. Beaudet, W. S. Sly, D. Valle), McGraw-Hill, New York, **1995**, S. 2465–2494.
- [3] A. Ballabio, L. J. Shapiro in ref. [2], pp. 2999–3022.
- [4] E. H. Kolodny, A. L. Fluharty in ref. [2], pp. 2693–2741.
- [5] J. H. Austin, A. S. Balasubramanian, T. N. Paattabiraman, S. Saraswathi, D. K. Basu, B. K. Bachhawat, *J. Neurochem.* **1963**, *10*, 805–816.
- [6] E. Mehl, H. Jatzkewitz, *Hoppe-Seyler's Z. Physiol. Chem.* **1964**, *339*, 260–276.
- [7] K. Fedde, A. L. Horwitz, *Am. J. Hum. Genet.* **1984**, *36*, 623–633.
- [8] A. Ballabio, G. Parenti, E. Napolitano, P. Di Natale, G. Andria, *Hum. Genet.* **1985**, *70*, 315–317.
- [9] W. Rommerskirch, K. von Figura, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 2561–2565.
- [10] T. Selmer, A. Hallmann, B. Schmidt, M. Sumper, K. von Figura, *Eur. J. Biochem.* **1996**, *238*, 341–345.
- [11] T. Dierks, B. Schmidt, K. von Figura, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 11 963–11 968.
- [12] G. Lukatela, N. Krauss, K. Theis, T. Selmer, V. Gieselmann, K. von Figura, W. Saenger, *Biochemistry* **1998**, *37*, 3654–3664.
- [13] C. S. Bond, P. R. Clements, S. J. Ashby, C. A. Collyer, S. J. Harrop, J. J. Hopwood, J. M. Guss, *Structure* **1997**, *5*, 277–289.
- [14] M. Recksiek, T. Selmer, T. Dierks, B. Schmidt, K. von Figura, *J. Biol. Chem.* **1998**, *273*, 6096–6103.
- [15] C. I. Prosser, A. B. Roy, *Biochim. Biophys. Acta* **1980**, *613*, 130–139.
- [16] A. Waheed, R. L. Van Etten, *Arch. Biochem. Biophys.* **1980**, *203*, 11–24.
- [17] A. B. Roy, T. J. Mantle, *Biochem. J.* **1989**, *261*, 689–697.
- [18] C. Miech, T. Dierks, T. Selmer, K. von Figura, B. Schmidt, *J. Biol. Chem.* **1998**, *273*, 4835–4837.

Towards a Rational Synthesis of Large-Pore Zeolite-Type Materials?

Duncan E. Akporiaye*

Until ten years ago, one of the main goals in the synthesis of zeolites and related crystalline microporous materials was the preparation of materials whose structures contain “large” and “extra-large” pores with dimensions equal to or greater than 12 T atoms (≥ 0.75 nm, T = tetrahedral framework cation). This search was driven by, among others, the desire to find replacements for the ubiquitous faujasite structure with 12-ring pores, as well as to generate new applications in catalysis, adsorption, and ion exchange. The determination of the structures of VPI-5 (18-ring) and $\text{AlPO}_4\text{-8}^{[1]}$ (14-ring) presaged the discovery of the range of aluminophosphate structures with extra-large pores listed in Table 1. The subse-

Table 1. Overview of zeolite-type materials with extra-large pores.

Pore size no. of T atoms	Aluminophosphate-based	Alumino- silicate-based
20	Cloverite ^[1] JDF-20 ^[13]	–
18	VPI-5 ^[1]	–
16	ULM-16 ^[14]	–
14	$\text{AlPO}_4\text{-8}^{[1]}$	UTD-1 ^[5] CIT-5 ^[6]

quent finding of a new class of ordered mesoporous materials, prepared by using surfactant-based structure-directing agents,^[2] might have invalidated the above approach to very large pore materials, since they extended the range of pore sizes achievable from approximately 1.8 nm to greater than 20 nm. However, these ordered mesoporous materials have found few catalytic applications owing to the weak acidity of the aluminosilicate variants.

The recent trend to develop rational synthetic strategies can provide a means for the discovery of new large-pore zeolite-type structures. This is well illustrated by the extensive work of Zones et al.^[3] on the synthesis of high-silica zeolites, which is based on understanding the role and interaction of the organic structure-directing agent (guest) in the gel chemistry, and the final crystalline structures (host) in terms of a host–guest relationship. Thus, in the hunt for high-silica materials with multidimensional channel systems, bulky polycyclic organic amines were used to give maximum stabilization of the hydrophobic inner silica surface of these compounds.

Large-pore materials such as SSZ-31 (12-ring)^[4] are the fruits of this work; however, the recent determination of the structure of this material also reveals the likely limitations of this approach. In the choice of bulky organic amines, the trend is towards low charge density on the organic compound and in the framework (high Si/Al ratio). With this strategy, it is evident that the organic compound will increasingly act as an inert space filler, and the challenge for the synthetic zeolite chemist will be to maximize the impact of the shape of the structure-directing agent on the structure of the product. The result of this is a tendency for the formation of one-dimensional channel systems and highly intergrown mixtures of polymorphs with closely related structures.

This trend is also evident in the novel conditions employed in the synthesis of the only two known 14-ring zeolites, UTD-1^[5] (Figure 1) and CIT-5.^[6] The former involves a bis-cyclopentadienyl complex of cobalt, and the latter is critically dependent on the presence of lithium in addition to the polycyclic amine.

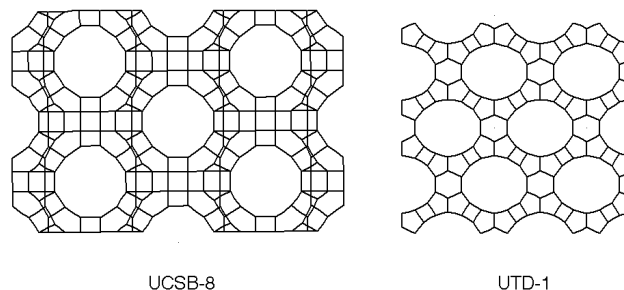


Figure 1. Structures of UCSB-8 and UTD-1.

In spite of these perceived limitations, the convergence of these experimental approaches with newly developed computational strategies may provide further breakthroughs. Thus, quantitative shape analysis of the guest and host^[7] following energy minimization of the organic molecule in a wide range of zeolite frameworks gives some insight into the relationship between shape and size. Following naturally from this, in a revolutionary development, the de novo design of the guest molecule^[8] was implemented with algorithms that maximize the stabilizing overlap of the van der Waals surfaces of the host and guest by means of the directed “growth” of the organic compound within the confines of the pore system.

In recent exciting work by Stucky et al.,^[9] an alternative strategy for the preparation of large-pore, multidimensional structures led to a range of novel metalloaluminophosphate

[*] Dr. D. E. Akporiaye
Sintef Applied Chemistry
P.O. Box 124 Blindern, N-0314 Oslo (Norway)
Fax: (+47) 22067350
E-mail: duncan.akporiaye@chem.sintef.no

structures. The basis of this new approach is in essence diametrically opposed to the routes used so far for aluminosilicate systems, and preliminary results appear to confirm a degree of rational design. Instead of reducing the charge density on the organic structure-directing agent through the use of bulky molecules, with the consequent weakening of the electrostatic interaction between host and guest, the approach of charge-density matching of host and guest has been introduced. Thus, following the analysis of known zeolite systems in which large multidimensional pores are associated with low Si/Al ratios and hence high framework charge density, the goal has been to use organic compounds with the desired high charge density. Diamines of the general formula $H_2N(CH_2)_nNH_2$ proved fruitful in this role and led to three novel structures UCSB-6, UCSB-8 (Figure 1), and UCSB-10 in a metalloaluminophosphate system in which, for the first time, aluminum is replaced to a large extent by cobalt, magnesium, manganese, and zinc in the tetrahedral structure. The hydrophobic hydrocarbon backbone of these diamines is believed to allow the separation of the charged inorganic wall from the cage/pore contents. This indicates a form of “self-assembly” during the crystallization of this system, in which the strong interaction between the inorganic species and the protonated amino groups at the end of the long hydrocarbon backbone direct the formation of large pores. If this mechanism is valid, it would point to an interesting correspondence with the charge-matching concepts that describe the formation of MCM and related mesoporous systems.^[10, 11]

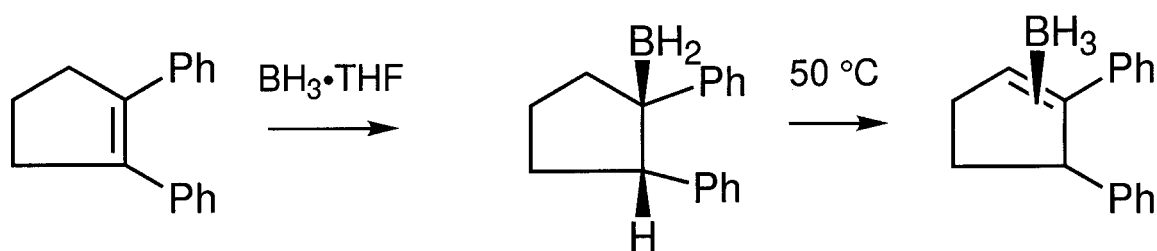
A natural progression following the success of this approach in preparing UCSB-*x* materials is to consider how this might now be applied to the aluminosilicate system, for which few structures with extra large pores are known (Table 1). This is important for the industrial application of this important class of acid catalysts and sorbents, since few

aluminophosphate-type microporous materials have sufficient thermal stability to be used in commercial processes.^[12] This is in contrast to the high thermal stability and extensive application of zeolites in refinery and petrochemical processes.

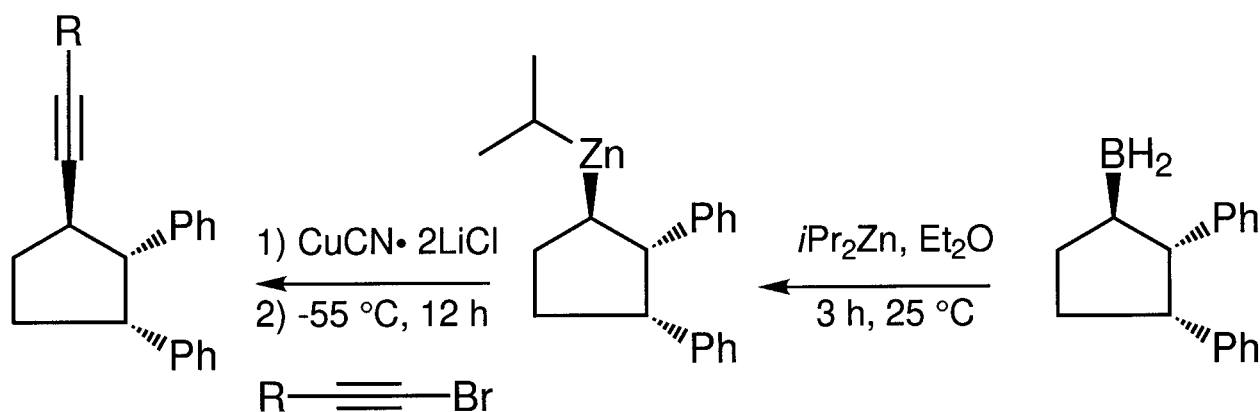
German version: *Angew. Chem.* **1998**, *110*, 2594–2595

Keywords: microporosity • synthesis design • zeolites • zeolite analogues

- [1] W. M. Meier, D. H. Olson, C. Baerlocher, *Atlas of Zeolite Structure Types*, Elsevier, Boston, MA, **1996**.
- [2] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710–712.
- [3] S. I. Zones, Y. Nakagawa, L. T. Yuen, T. V. Harris, *J. Am. Chem. Soc.* **1996**, *118*, 7558–7567.
- [4] R. F. Lobo, M. Tsapatsis, C. C. Freyhardt, I. Chan, C.-Y. Chen, S. I. Zones, M. E. Davis, *J. Am. Chem. Soc.* **1997**, *119*, 3732–3744.
- [5] R. F. Lobo, M. Tsapatsis, C. C. Freyhardt, S. Khodabandeh, P. Wagner, C.-Y. Chen, K. J. Balkus, S. I. Zones, M. E. Davis, *J. Am. Chem. Soc.* **1997**, *119*, 8474–8484.
- [6] P. Wagner, M. Yoshikawa, M. Lovallo, K. Tsuji, M. Tsapatsis, M. E. Davis, *Chem. Commun.* **1997**, *22*, 2179–2180.
- [7] R. E. Boyett, A. P. Stevens, M. G. Ford, P. A. Cox, *Zeolites* **1996**, *17*, 505–512.
- [8] D. J. Willock, D. W. Lewis, C. R. A. Catlow, G. J. Hutchings, J. M. Thomas, *J. Mol. Catal.* **1997**, *119*, 415–424.
- [9] X. Bu, P. Feng, G. D. Stucky, *Science* **1997**, *278*, 2080–2085.
- [10] Q. Huo, R. Leon, P. M. Petroff, G. D. Stucky, *Science* **1995**, *268*, 1324–1327.
- [11] P. Behrens, *Angew. Chem.* **1996**, *108*, 561–564; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 515–518.
- [12] B. V. Vora, T. L. Marker, P. T. Barger, H. E. Fullerton, H. R. Nilson, S. Kvisle, T. Fuglerud, *Stud. Surf. Sci. Catal.* **1997**, *107*, 87–98.
- [13] R. H. Jones, J. M. Thomas, J. S. Chen, R. R. Xu, Q. S. Huo, S. G. Li, Z. Ma, *J. Solid State Chem.* **1993**, *102*, 202–208.
- [14] T. Loiseau, G. Ferey, *J. Mater. Chem.* **1996**, *6*, 1073–1074.



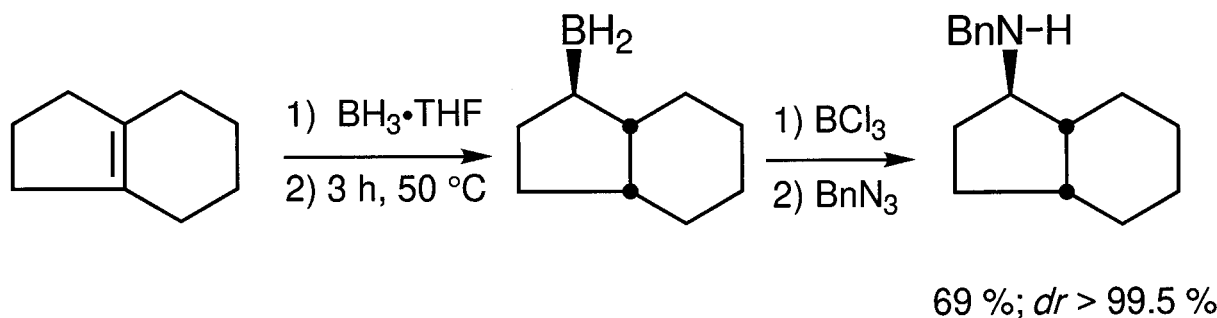
The hydroboration of tetrasubstituted cyclic alkenes produces tertiary organoboranes, which undergo a stereoselective rearrangement to furnish organoboranes bearing three adjacent stereocenters. These species can be converted into a variety of products.



1 diastereoisomer

With bicyclic systems, a preferential migration in the direction of the five-membered ring is observed.

Further details are given on the following pages.

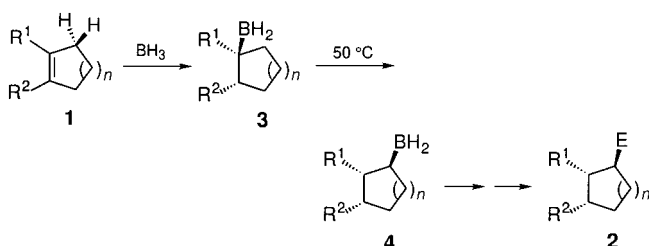


Stereoselective Allylic C–H Activation with Tertiary Alkylboranes: A New Method for Preparing Cycloalkyl Derivatives with Three Adjacent Stereocenters**

Frédéric Lhermitte and Paul Knochel*

*Dedicated to Professor Gernot Boche
on the occasion of his 60th birthday*

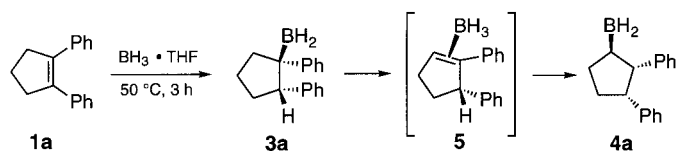
The functionalization of unreactive carbon–hydrogen bonds is an active field of investigation.^[1] Transition metal complexes have been used with great success for selectively activating C–H bonds,^[1, 2] and a few examples involving main group organometallic compounds have been described.^[3] Herein, we report a highly stereoselective C–H activation of an allylic position that allows the construction of three adjacent stereocarbon centers by making use of a rearrangement of a tertiary alkylborane. Whereas most organoboranes undergo rearrangements at elevated temperature,^[4] it was noticed by Rickborn and Wood^[5] and Field and Galagher^[6] that cyclic tetrasubstituted alkenes undergo such a dyotropic rearrangement^[7] under much milder conditions. We found that this approach allows a highly stereoselective conversion of various cyclic or acyclic tetrasubstituted alkenes of type **1** into polyfunctional products of type **2** in a one-pot reaction via the intermediate organoboranes **3** and **4** (Scheme 1).



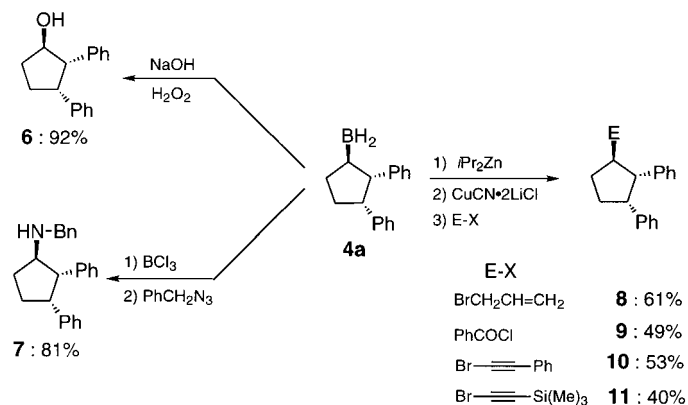
Scheme 1. Synthesis of **2** from **1** by hydroboration (→**3**) and migration (→**4**). *n* = 1, 2.

Thus, 1,2-diphenylcyclopentene (**1a**) was smoothly hydroborated with BH₃·THF (THF, 50 °C, 3 h) to provide the tertiary alkylborane **3a**, which undergoes a stereoselective *syn* migration leading to the less sterically hindered secondary organoborane **4a** (Scheme 2). The high stereochemical control is explained by assuming a dehydroboration of **3a** to form the alkene–borane complex **5**, which undergoes a second hydroboration. Here, there can be no dissociation from the alkene, as this would result in a decrease in stereoselectivity.^[5, 6]

The alkylborane **4a** was trapped with several electrophiles with retention of stereochemistry (Scheme 3). Thus, oxidation



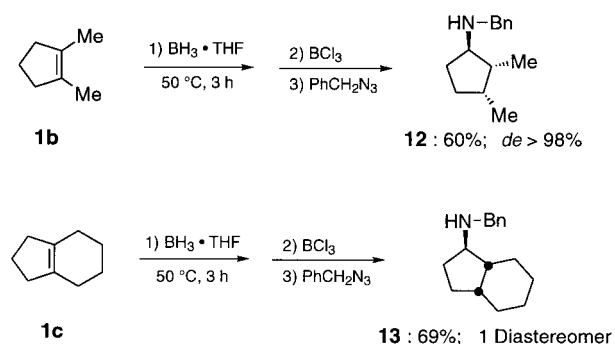
Scheme 2. Synthesis of **4a**.



Scheme 3. Synthesis of **6–11**.

of **4a** with 30% H₂O₂ affords the cyclopentanol **6** in 92% overall yield as a single stereoisomer. Treatment of **4a** with boron trichloride followed by benzyl azide^[8] (25 °C, 1 h) provides the amine **7** as one stereoisomer in 81% overall yield. Transmetalation of **4a** to the corresponding organozinc compound^[9] by treatment with *i*Pr₂Zn (2 equiv) and subsequent transformation to the zinc–copper reagent^[10] by addition of CuCN·2LiCl furnishes—after reaction with electrophiles such as allyl bromide, benzoyl chloride, 2-phenylethynyl bromide, or 1-bromo-2-trimethylsilylacetylene—the expected products **8–11** with diastereomeric excesses of greater than 97% and in 40–61% overall yield.

Extension of this rearrangement to other tetrasubstituted alkenes has been examined (Scheme 4). Both 1,2-dimethylcyclopentene (**1b**) and the bicyclic alkene **1c** undergo the



Scheme 4. Synthesis of **12** and **13**.

stereoselective rearrangement. Amination of **1b** and **1c** (1. BH₃·THF, 50 °C, 3 h; 2. BCl₃, 25 °C, 3 h; 3. PhCH₂N₃, 25 °C, 1 h)^[8] led to the desired stereoisomers **12** and **13** in 60–69% overall yield.^[11]

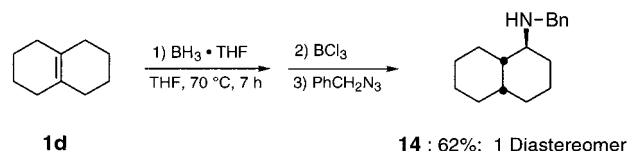
Interestingly, in the case of **1c** the migration takes place almost exclusively in the direction of the five-membered ring.

[*] Prof. Dr. P. Knochel, Dr. F. Lhermitte
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
Fax: (+49) 6421-28-21-89
E-mail: knochel@ps1515.chemie.uni-marburg.de

[**] We thank the DFG (SFB 260, Leibniz program) and the Fonds der Chemischen Industrie for financial support. F. L. thanks the Alexander Von Humboldt Foundation for a fellowship. We thank BASF AG, Bayer AG, and WITCO for the generous gift of chemicals.

This may be due to the proper alignment of the adjacent C–H bond with the C–B bond in the five-membered ring facilitating the dehydroboration. In a six-membered ring, there would be an angle of about 60° between the C–H and C–B bonds; this alignment would require a higher energy of activation.

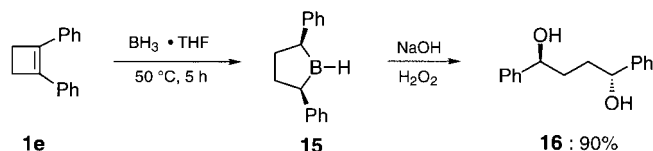
With bicyclo[4.4.0]dec-1(6)-ene (**1d**) the hydroboration must be carried out, as expected, at 70 °C in refluxing THF (Scheme 5). In this case also, a highly stereoselective migration takes place despite the elevated temperature. After



Scheme 5. Synthesis of **14**.

amination (1. $\text{BH}_3 \cdot \text{THF}$, 70 °C, 7 h; 2. BCl_3 , 25 °C, 3 h; 3. PhCH_2N_3 , 25 °C, 1 h)^[8] the bicyclic amine **14** was obtained in 62 % yield as a single stereoisomer.

A novel stereoselective borane rearrangement was found upon use of 1,2-diphenylcyclobut-1-ene (**1e**; Scheme 6). After initial hydroboration, cleavage of the cyclobutene ring



Scheme 6. Synthesis of **16**.

occurred to provide the intermediate boracyclopentane **15**. After oxidation with H_2O_2 the *meso*-diol **16** was isolated in 90 % yield as a pure diastereoisomer.

In summary, we have shown that the migration of tertiary boranes constitutes a novel stereoselective method for preparing cyclic and bicyclic rings. The reaction corresponds formally to an stereoselective activation of allylic C–H bonds.

Experiment Section

Typical procedure for the amination: Preparation of (1*R**,2*R**,3*R**)-*N*-benzyl-2,3-dimethylcyclopentylamine (**12**): A $\text{BH}_3 \cdot \text{THF}$ solution (3 mL, 1.5 equiv, 3 mmol, 1.0 M) was slowly added to 1,2-dimethylcyclopentene (**1b**; 192 mg, 2 mmol) in THF (10 mL) at 25 °C. After 10 min the resulting solution was heated at 50 °C for 3 h. The solvent and excess of borane were removed under vacuum, and the residue was diluted with CH_2Cl_2 (10 mL), treated at 0 °C with a solution of BCl_3 (8 mL, 4 equiv, 8 mmol, 1.0 M) in CH_2Cl_2 , and stirred for 3 h at 25 °C. After removal of the solvent and excess of BCl_3 under vacuum, the residue was diluted with CH_2Cl_2 (10 mL) and treated at 0 °C with a solution of benzyl azide (2.4 mL, 1.2 equiv, 1.0 M) in CH_2Cl_2 . After 1 h at 25 °C the reaction was quenched with aq NaOH (10 mL, 3.0 M), extracted with ether, and dried (MgSO_4). The crude residue was purified as the hydrochloride by addition of a solution of dry HCl in ether. Analytically pure **12**·HCl was obtained after filtration (287 mg, 1.2 mmol, 60 % yield).

Typical procedure for the allylation: Preparation of (1*S**,2*S**,3*S**)-1-allyl-2,3-diphenylcyclopentane (**8**): A $\text{BH}_3 \cdot \text{THF}$ solution (3 mL, 1.5 equiv, 3 mmol, 1.0 M) was slowly added to 1,2-diphenylcyclopentene (**1a**; 440 mg, 2 mmol) in THF (10 mL) at 25 °C. After 10 min the resulting

solution was heated at 50 °C for 3 h. The solvent and excess borane were removed under vacuum, and the residue was treated with a solution of $i\text{Pr}_2\text{Zn}$ (0.8 mL, 2 equiv, 4 mmol, 5.0 M) in ether at 25 °C for 4 h. After removal of the solvent and excess of $i\text{Pr}_2\text{Zn}$ under vacuum, the residue was diluted with THF (10 mL). The black precipitate of zinc was removed by filtration, and the filtrate was slowly treated at –90 °C with a solution of $\text{CuCN} \cdot 2\text{LiCl}$ in THF (0.4 mL, 0.2 equiv, 1.0 M) and after 15 min with allyl bromide (6 mL, 3 equiv, 6 mmol, 1.0 M) in THF. The reaction was allowed to warm up to 25 °C and was quenched after 1 h with aq HCl (10 mL, 3.0 M) and extracted with ether. The crude product obtained after evaporation of the solvent was purified by chromatography (pentane) to provide analytically pure **8** (320 mg, 1.2 mmol, 61 % yield).

Received: April 16, 1998 [Z11741 IE]

German version: *Angew. Chem.* **1998**, *110*, 2597–2599

Keywords: asymmetric synthesis • hydroborations • rearrangements • zinc

- [1] J. C. W. Lohrenz, H. Jacobsen, *Angew. Chem.* **1996**, *108*, 1403; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1305, and references therein.
- [2] B. A. Arndtsen, R. G. Bergmann, *Science* **1995**, *270*, 1970; L. D. Field, A. V. George, B. A. Messerle, *J. Chem. Soc. Chem. Commun.* **1991**, 1339; N. A. Williams, Y. Uchimaru, M. Tanaka, *J. Chem. Soc. Chem. Commun.* **1995**, 1129; F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62; Y.-G. Lim, Y. H. Kim, J.-B. Kang, *J. Chem. Soc. Chem. Commun.* **1994**, 2267; P. J. Alaimo, B. A. Arndtsen, R. G. Bergman, *J. Am. Chem. Soc.* **1997**, *119*, 5269.
- [3] L. Weber in *Advances in Organometallic Chemistry*, Vol. 41 (Eds.: F. G. A. Stone, R. West), Academic Press, New York, **1997**, pp. 1–125.
- [4] R. Köster, W. Siebert, *Methoden Org. Chem. (Houben-Weyl)*, 4. ed., 1952–, Vol. 13, part 3a, **1982**, pp. 1–908.
- [5] S. E. Wood, B. Rickborn, *J. Org. Chem.* **1983**, *48*, 555.
- [6] L. D. Field, S. P. Gallagher, *Tetrahedron Lett.* **1985**, *26*, 6125.
- [7] M. T. Reetz in *Advances in Organometallic Chemistry*, Vol. 16 (Eds.: F. G. A. Stone, R. West), Academic Press, New York, **1977**, pp. 1–30.
- [8] A. Suzuki, S. Ono, H. C. Brown, M. M. Midland, *J. Am. Chem. Soc.* **1971**, *93*, 4329; P.-Y. Chavant, F. Lhermitte, M. Vaultier, *Synlett* **1993**, 519.
- [9] L. Micouin, M. Oestreich, P. Knochel, *Angew. Chem.* **1997**, *109*, 274; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 245; C. Darcel, F. Flachsmann, P. Knochel, *Chem. Commun.* **1998**, 205.
- [10] P. Knochel, R. Singer, *Chem. Rev.* **1993**, *93*, 2117.
- [11] The hydroboration of **1b** provides, after oxidation with 30 % H_2O_2 , the expected alcohol (80 %) accompanied by the epimer at the hydroxyl position (1–2 %) as well as tertiary alcohol (18 %) that did not undergo migration. However, by the amination procedure, only the product resulting from the major isomer could be detected. The boron–zinc exchange of **4b** obtained by the hydroboration of **1b** provides, after copper-catalyzed allylation, two epimeric allylated products in the ratio 92:8 and in 51 % yield upon isolation. This shows that in this case the secondary cyclopentylzinc intermediate is less configurationally stable.^[9]

Photoactivated Preparation and Patterning of Self-Assembled Monolayers with 1-Alkenes and Aldehydes on Silicon Hydride Surfaces

Franz Effenberger,* Günther Götz, Bernd Bidlingmaier, and Markus Wezstein

The preparation, investigation, and patterning of self-assembled monolayers (SAMs) for the chemical modification of surfaces is currently an intensively researched area worldwide.^[1, 2] We have already reported on the structure and properties of mono- and multilayers derived from terminally functionalized organosilanes on hydroxylated silicon surfaces.^[3] We are interested, however, in special applications of the coated silicon surfaces. In these cases the SiO₂ layers of hydroxylated silicon surfaces, which are always present, would be disturbing.^[2, 4] We have therefore investigated the formation of SAMs on silicon in such a way as to avoid the presence of an oxide layer.

Chidsey et al.^[5] have recently reported the preparation of stable SAMs of organic compounds on silicon, in which the organic layer is directly bound to silicon—without a SiO₂ interlayer. These SAMs were obtained by diacyl peroxide catalyzed reactions of 1-alkenes on hydrogen-terminated Si(111) surfaces.^[5] The disadvantages of this method are the unfavorable inclusion of acyloxy radicals in the monolayer, which are detrimental to the quality of the layer,^[1b] and the relatively low coverage.^[5] If these reactions are carried out under thermal conditions instead of using peroxide catalysts, liquid-like layers are obtained rather than solids.^[5b]

In connection with our investigations into the fundamentals of molecular electronics the incorporation of unsaturated compounds (such as polyenes and oligothiophenes) in SAMs is also of interest.^[6] We have therefore investigated alternatives to the diacyl peroxide catalyzed reactions of alkenes with silicon hydride surfaces for the formation of SAMs. The reaction of hydrogen-terminated Si(111) surfaces with 1-alkenes can also be achieved by irradiation with light. Table 1 shows a comparison of the formation of SAMs on Si(111)-H surfaces with 1-octadecene **1**, initiated by both diacyl peroxide (according to the literature procedure^[5]) and irradiation with a 150-W mercury vapor lamp.

The SiH surface was prepared by treatment of oxidized Si(111) wafers with an ammonium fluoride solution.^[7] The coverage was determined analogous to published methods^[3c] by quantitative evaluation of the IR bands of the symmetric and asymmetric methylene vibrations, $\nu_{as}(\text{CH}_2)$ and $\nu_s(\text{CH}_2)$. Table 1 shows that with respect to the coverage, photoactivation gave results comparable with those from peroxide activation without the disadvantages associated with the latter.

[*] Prof. Dr. F. Effenberger, Dr. G. Götz, Dipl.-Chem. B. Bidlingmaier, Dipl.-Chem. M. Wezstein
Institut für Organische Chemie der Universität
Pfaffenwaldring 55, D-70569 Stuttgart (Germany)
Fax: (+49) 711-685-4269
E-mail: franz.effenberger@po.uni-stuttgart.de

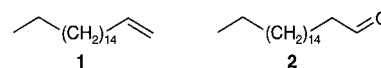


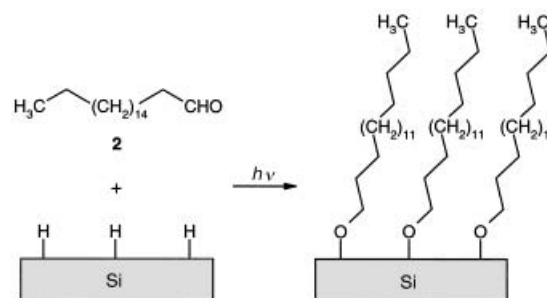
Table 1. Comparison of SAMs with octadecene **1** and octadecanal **2** on Si(111)-H surfaces.^[a]

Reactants (neat)	<i>t</i> [h]	<i>T</i> [°C]	$\nu_{as}(\text{CH}_2)$ [cm ⁻¹]	Coverage [%] ^[b]	Contact angle θ_a (H ₂ O) [°]
[C ₁₇ H ₃₅ C(O)O] ₂	1.5	100	2918.7	50	91
[C ₁₇ H ₃₅ C(O)O] ₂ : 1 (1:1)	1.0	102	2918.6	57	96
[C ₁₇ H ₃₅ C(O)O] ₂ : 1 (1:9)	1.5	101	2920.0	48	91
1	24	20–50 ^[c]	2920.5	55	95
1 ^[d]	20	20–50 ^[c]	2922.4	21	–
2	21	20–50 ^[c]	2916.8	97	105
OTS ^[e]	15	20	2917.7	100	106

[a] Initiation of layer formation by dioctadecanoyl peroxide [C₁₇H₃₅C(O)O]₂ catalysis^[5b] or by irradiation with a 150 W mercury vapor lamp. [b] Based on octadecyltrichlorosilane(OTS) films on hydroxylated Si(100) surfaces with 100% coverage. [c] Temperature increase to 50 °C during the irradiation. [d] In solution, 1:hexadecane = 9:1. [e] In solution.^[3c]

Since in the reaction of the 1-alkenes activation with H₂[PtCl₆] did not give better results,^[8] we investigated other compounds for the preparation of SAMs on Si(111)-H surfaces. Giese et al.^[9] reported that hydrosilylation of alkenes and carbonyl compounds with tris(trimethylsilyl)silane can be catalyzed not only by free-radical initiators but also by photoactivation. Based on these results we studied the mode of reaction of aldehydes with SiH surfaces. Under the conditions for the reactions with 1-octadecene (see Table 1), we obtained well-ordered monolayers with surprisingly high coverage (97% based on OTS with 100%) by the photoactivated reaction of octadecanal **2** with hydrogen-terminated Si(111) surfaces.

Scheme 1 illustrates the formation of a monolayer with the long-chain aldehyde **2** on a SiH surface. The linkage of **2** to the SiH surface was detected by X-ray photoelectron spectro-



Scheme 1. Schematic illustration of layer formation with octadecanal **2** on a SiH surface.

scopy (XPS):^[10] the signals in the spectrum at 286.3 BeV (C 1s C–O), 100.9 and 101.6 BeV (Si–O 2p_{3/2} and Si–O 2p_{1/2}, respectively) indicate covalent bonding.

In order to obtain detailed information about the scope of the application of the new method to the preparation of SAMs on silicon surfaces we investigated the dependence of the layer formation on the wavelength of the irradiating light (Figure 1) and on the reaction time (Table 2). The optimum

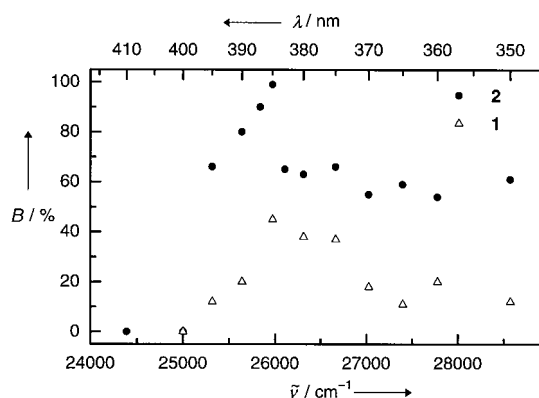


Figure 1. SAM formation with neat octadecene **1** and octadecanal **2** on a SiH surface as a function of the wavelength of the incident light. The coverages are not corrected for either the lamp spectrum or the spectral transmission of the spectrometer. B = Coverage.

Table 2. SAM formation with neat octadecanal **2** on a Si(111)-H surface as a function of the irradiation time with polychromatic light.

t [min]	$\nu_{\text{as}}(\text{CH}_2)$ [cm ⁻¹]	Area $\nu_{\text{s}}, \nu_{\text{as}}(\text{CH}_2)$	Coverage [%] ^[a]
1	2922	0.0357	39
3	2918	0.0746	82
5	2917	0.0943	103
30	2916	0.0975	106
60	2916	0.0978	107
120	2916	0.0833	91

[a] Based on OTS films with 100% coverage.

wavelength for layer formation occurs at about 385 nm. On the basis of the dissociation energy of Si–H bonds^[11] (81 kcal mol⁻¹ for tris(trimethylsilyl)silane, corresponding to 354 nm^[11a]) the energy at longer wavelengths, as expected, is indeed not sufficient to initiate the reaction (Figure 1). However, that irradiation at shorter wavelengths would lead to lower coverage was not expected. From the intensity distribution of the XBO lamp, the effectiveness of the monochromator, and the transmission behavior of the irradiation cuvette result that the relative intensity of the irradiation decreased continuously from 400 to 350 nm; the optimum layer formation at 385 nm does not depend, then, on the intensity of the irradiation. Since in the reactions of **1** optimum layer formation also occurs at 385 nm (Figure 1), photoactivation of the carbonyl or the C–C double bond can be ruled out as an explanation for the wavelength optimum for these reactions. The results of FT-IR measurements with regard to the time dependence (see Table 2; coverage, $\nu_{\text{s}}(\text{CH}_2)$ and $\nu_{\text{as}}(\text{CH}_2)$) reveal a well-ordered monolayer with a high coverage already after 5 minutes.

In all preparations of SAMs^[1–3] until now a direct lateral patterning of SAMs was not possible owing to initial chemically uniform surfaces (e.g. gold, hydroxylated or hydrogenated silicon) and the also homogeneous subsequent reaction with the self-assembling compounds. However, the light-induced preparation of SAMs described here allows, with the use of suitable masks, direct patterning of surfaces by applying the self-assembly technique. From the various materials with potential masking properties, the films used

in the manufacture of printed circuits proved to be particularly advantageous.^[10] In the reaction with **2** we could demonstrate, by means of IR spectra, that covering part of the Si(111)-H surface resulted in the formation of a SAM layer only on the light exposed part of the Si(111)-H surface. In addition we were able to show that the nonirradiated part of the SiH surface remained completely reactive.

Since the results of these experiments indicated that basically, a lateral patterning of SAMs is possible by photoactivation, we used a structured mask and carried out a light-induced coating of a SiH surface with **2**. The differing wettabilities of the coated and noncoated areas of the silicon allowed the patterned silicon surface to be observed directly under a microscope (Figure 2).^[10]

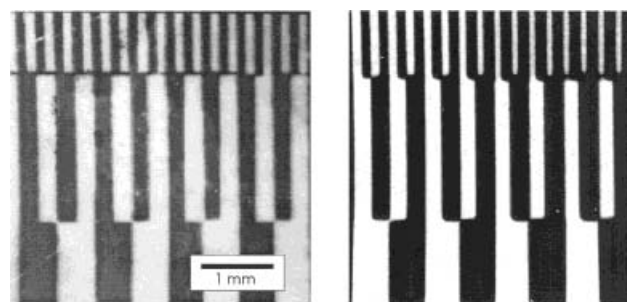


Figure 2. Microscopy images of a patterned SAM with octadecanal **2** (left) and the corresponding mask (right).

In the penultimate paragraph of a recently published review by Whitesides et al.^[2] the following comment was made on the future of “soft lithography”: “In particular, systems that form SAMs directly on semiconductors and are optimized for compatibility with current processes (especially etching with reactive ions) and materials are required”. The results presented here on the light-induced, direct lateral patterning of SAMs on SiH surfaces are certainly an interesting and important contribution to the attainment of this aim.

Experimental Section

FT-IR spectra were measured with a Bruker-IFS-66V spectrometer. All reactions were carried out in an inert gas atmosphere. Silicon wafers (Si(111), p-type, Siltronix) were used. Irradiation was carried out with an HBO-mercury vapor lamp (150 W).

Monolayer formation: The SiH substrate, prepared by etching with fluoride ions,^[7] was immersed in a melt of **1** or **2** in a glass cuvette and irradiated for 20–24 h. After removal from the cuvette the substrate was washed several times with CH₂Cl₂ and wiped with cotton.

Monolayer formation with **1 and **2** at different wavelengths:**^[10] Layer formation (see above) was carried out at 60 °C by irradiation with an XBO lamp (450 W) fitted with a double monochromator (Jarrell Ash Co., 82–440) with a half-band width of 1.3 nm. The coated substrate was cleaned as described above.

Time-dependent monolayer formation with **2:** As described above, the SiH substrate^[7] was irradiated in a melt of **2** for the times given in Table 2 and subsequently cleaned.

Preparation of the masks: The structures were drawn with the program Freehand 5.0 and printed directly with a laser photosetting system (Linotronic 530, Linotype-Hell, resolution 2540 dpi) on polymer films (Fuji Laser recorder film F 100).

Lateral patterning: The SiH substrate was covered with a mask, the aldehyde was added, and melted. For monolayer formation and cleaning see above.

Visualization of structures: The substrate with the monolayer was wetted under a microscope (Carl Zeiss, 20-fold enlargement) with a few drops of a mixture of 2-propanol and universal oil (Lubricant Consult GmbH). The pattern formed after a few seconds was photographed.

XPS measurements: XPS measurements were made with a Leybold MAX-200 spectrometer with $Mg_{K\alpha}$ radiation (300 W) under a pressure of 10^{-9} mbar. The superimposed signals were separated and assigned by calculations with the manufacturer's software (DS 100). The signals observed were O 1s (532.1 BeV), C 1s C–C (284.6 BeV), C 1s C–O (286.3 BeV), Si–O $2p_{3/2}$ (100.9 BeV), Si–O $2p_{1/2}$ (101.6 BeV).

Received: April 3, 1998

Revised version 12. June 1998 [Z11679]

German version: *Angew. Chem.* **1998**, *110*, 2651–2654

Keywords: monolayers • photochemistry • self-assembly • silicon

- [1] a) A. Ulman, *An Introduction to Ultrathin Organic Films*, Academic Press, London, **1991**; b) A. Ulman, *Chem. Rev.* **1996**, *96*, 1533–1554, and references therein.
- [2] Y. Xia, G. M. Whitesides, *Angew. Chem.* **1998**, *110*, 568–594; *Angew. Chem. Int. Ed.* **1998**, *37*, 550–575.
- [3] a) F. Effenberger, S. Heid, *Synthesis* **1995**, 1126–1130; b) K. Bierbaum, M. Kinzler, C. Wöll, M. Grunze, G. Hähner, S. Heid, F. Effenberger, *Langmuir* **1995**, *11*, 512–518; c) S. Heid, F. Effenberger, K. Bierbaum, M. Grunze, *Langmuir* **1996**, *12*, 2118–2120; d) P. Harder, K. Bierbaum, C. Wöll, M. Grunze, S. Heid, F. Effenberger, *Langmuir* **1997**, *13*, 445–454.
- [4] V. G. Lifshits, A. A. Saranin, A. V. Zotov, *Surface Phases on Silicon*, Wiley, Chichester, **1994**, pp. 319–330.
- [5] a) M. R. Linford, C. E. D. Chidsey, *J. Am. Chem. Soc.* **1993**, *115*, 12631–12632; b) M. R. Linford, P. Fenter, P. M. Eisenberger, C. E. D. Chidsey, *J. Am. Chem. Soc.* **1995**, *117*, 3145–3155.
- [6] M. Schmelzer, S. Roth, C.-P. Niesert, F. Effenberger, R. Li, *Thin Solid Films* **1993**, *235*, 210–214.
- [7] a) G. J. Pietsch, *Appl. Phys. A* **1995**, *60*, 347–363; b) G. J. Pietsch, *Struktur und Chemie technologischer Silicioberflächen*, VDI-Fortschrittsberichte, Reihe 9, *148*, VDI, Düsseldorf, **1992**.
- [8] G. Götz, B. Bidlingmaier, M. Wezstein, unpublished results.
- [9] a) B. Kopping, C. Chatgililoglu, M. Zehnder, B. Giese, *J. Org. Chem.* **1992**, *57*, 3994–4000; b) K. J. Kulicke, B. Giese, *Synlett* **1990**, *1*, 91–92.
- [10] We thank Mr. H. Aurenz for preparing the masks, Dr. B. Miehl for the microphotography, Dr. Ing. G. Bilger for the XPS measurements, and Dipl.-Phys. M. Leonhardt and Dipl.-Phys. O. Mager for their help in the irradiation experiments at different wavelengths.
- [11] a) K. Raghavachari, G. S. Higashi, Y. J. Chabal, G. W. Trucks, *Mater. Res. Soc. Symp. Proc.* **1993**, *315*, 437–446; b) Y.-D. Wu, C.-L. Wong, *J. Org. Chem.* **1995**, *60*, 821–828.

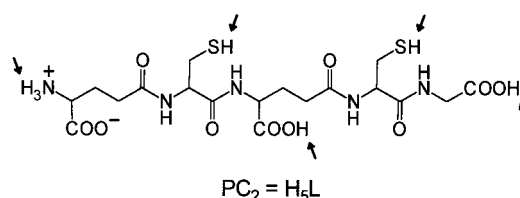
A Coordination-Chemical Basis for the Biological Function of the Phytochelatins**

Jens Johanning and Henry Strasdeit*

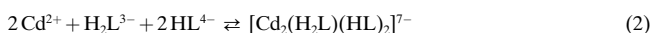
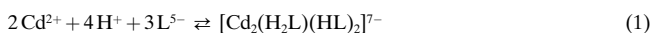
*Dedicated to Professor Bernt Krebs
on the occasion of his 60th birthday*

Organisms respond to heavy-metal stress, caused by toxic metals, with different detoxification strategies.^[1] Thus plants synthesize short peptides of the composition $(\gamma\text{-Glu-Cys})_n\text{-Gly}$ ($n = 2–11$), the phytochelatins (PC_n),^[2] which coordinate to metal ions and thereby decrease the toxicity of these ions.^[3] The best characterized phytochelatin complexes are those of cadmium.^[4] However, the bioinorganic chemist also has only a rough picture even in this case because of the heterogenic character of the native complexes. Furthermore there is a lack of data on the thermodynamic stabilities, which are essential for a better understanding of the biological function.

We have therefore examined the system $\text{Cd}^{\text{II}}/\text{PC}_2$ by potentiometric titration^[5] under exactly defined conditions (see Experimental Section) to gain information about the complexes occurring there. PC_2 , the simplest phytochelatin, is a pentabasic acid (H_5L). Starting from the fully protonated



form HPC_2^+ ($= \text{H}_6\text{L}^+$), the protonation constants $pK_1 = 2.39(5)$, $pK_2 = 3.18(3)$, $pK_3 = 4.01(7)$, $pK_4 = 8.75(9)$, $pK_5 = 9.03(3)$, and $pK_6 = 10.04(12)$ were obtained for the free ligand.^[6] The complex species that were detected are listed in Table 1. The $\lg\beta$ values given therein include the protonation equilibria of the ligands [Eq. (1)]. They are those quantities that have been directly determined in the refinements. In coordination-chemical considerations, however, $\lg K$ values calculated from them are more useful. They allow equilibria such as that given in Equation (2) to be described quantitatively.



The species models were developed and assessed on the basis of general criteria.^[5] In addition some special guidelines were available:

[*] Priv.-Doz. Dr. H. Strasdeit, Dipl.-Chem. J. Johanning
Fachbereich Chemie der Universität
Carl-von-Ossietzky-Strasse 9–11, D-26129 Oldenburg (Germany)
Fax: (+49) 441-798-3329
E-mail: strasdeit@chemie.uni-oldenburg.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. M. H. Zenk for donations of phytochelatin trifluoroacetate.

a) The pronounced tendency of Cd^{II} to bind thiolates under formation of an S_4 environment. A deficiency of thiolate results in multinuclear complexes such as $[\text{Cd}_2(\text{SR})_6]^{2-}$ and $[\text{Cd}_4(\text{SR})_{10}]^{2-}$, which contain doubly bridging ligands.^[7]

b) Cd-EXAFS results that prove an S_4 coordination for isolated $\text{Cd}^{\text{II}}/\text{PC}_n$ complexes as well as for Cd^{II} in plant cells exposed to cadmium.^[4a, b] In some cases there are indications of multinuclear complexes.^[4b] The EXAFS data also indicate an O_6 environment of cadmium in moderately acidic solutions.

c) Analyses with a cadmium-selective electrode carried out parallel to the potentiometric titrations. In this way the predictions that species models made about the pH-dependent concentration distribution of the free Cd^{II} could be experimentally checked.

In the $\text{Cd}^{\text{II}}/\text{PC}_2$ system relatively stable complexes are only formed by ligands in which at least one of the sulfhydryl functions is deprotonated. Two categories can be distinguished (Table 1): complexes that contain the same number of

Table 1. Complex species in the system $\text{Cd}^{\text{II}}/\text{PC}_2$.^[a]

Complex formula	Composition	$\lg \beta$	$\lg K^{\text{Cd}}$	$\text{PC}_2:\text{Cd}^{\text{II}}$		
				1:1	1.5:1	2:1
$[\text{Cd}(\text{H}_6\text{L})]^{3+}$	(LCdH_6)	40.3	2.9	+	+	+
$[\text{Cd}(\text{H}_3\text{L})]^{2+}$	(LCdH_3)	37.4	2.4	+	+	+
$[\text{Cd}_3(\text{H}_2\text{L})_3]^{3-}$	($\text{L}_3\text{Cd}_3\text{H}_6$)	87.0	9.9	+	+	+
$[\text{Cd}_3(\text{H}_2\text{L})_2(\text{HL})]^{4-}$	($\text{L}_3\text{Cd}_3\text{H}_5$)	82.4	11.4	+	+	
$[\text{Cd}_3(\text{H}_2\text{L})(\text{HL})_2]^{5-}$	($\text{L}_3\text{Cd}_3\text{H}_4$)	77.4	12.8	+	+	
$[\text{Cd}_3(\text{HL})_2]^{4-}$	($\text{L}_3\text{Cd}_3\text{H}_2$)	45.6	12.8	+		
$[\text{Cd}_2(\text{HL})\text{L}]^{5-}$	($\text{L}_2\text{Cd}_2\text{H}$)	36.7	13.3	+		
$[\text{CdL}]^{3-}$	(LCd)	11.7	11.7	+		
$[\text{Cd}_2(\text{H}_2\text{L})(\text{HL})]^{7-}$	($\text{L}_3\text{Cd}_2\text{H}_4$)	71.8	16.3		+	
$[\text{Cd}_2(\text{HL})_3]^{8-}$	($\text{L}_3\text{Cd}_2\text{H}_3$)	63.1	16.5		+	
$[\text{Cd}_2(\text{HL})_2\text{L}]^{9-}$	($\text{L}_3\text{Cd}_2\text{H}_2$)	53.7	16.8		+	
$[\text{Cd}_2(\text{HL})\text{L}_2]^{10-}$	($\text{L}_3\text{Cd}_2\text{H}$)	44.1	17.0		+	
$[\text{Cd}_3\text{L}_3]^{11-}$	(L_3Cd_3)	33.0	16.5		+	
$[\text{Cd}_2(\text{H}_2\text{L})_4]^{8-}$	($\text{L}_4\text{Cd}_2\text{H}_8$)	108.8	16.3			+
$[\text{Cd}_2(\text{H}_2\text{L})_3(\text{HL})]^{9-}$	($\text{L}_4\text{Cd}_2\text{H}_7$)	102.4	17.6			+
$[\text{Cd}_2(\text{H}_2\text{L})_2(\text{HL})_2]^{10-}$	($\text{L}_4\text{Cd}_2\text{H}_6$)	95.5	18.6			+
$[\text{Cd}_2(\text{H}_2\text{L})(\text{HL})_3]^{11-}$	($\text{L}_4\text{Cd}_2\text{H}_5$)	87.7	19.3			+
$[\text{Cd}(\text{HL})_2]^{6-}$	(L_2CdH_2)	37.7	17.6			+
$[\text{Cd}(\text{HL})\text{L}]^{7-}$	(L_2CdH)	28.6	18.5			+
$[\text{CdL}_2]^{8-}$	(L_2Cd)	18.0	18.0			+

[a] $\lg K^{\text{Cd}}$ gives the stability per Cd^{II} ion of a complex of nuclearity m : $\lg K^{\text{Cd}} = 1/m \lg K$. The mean estimated standard deviation of the $\lg \beta$ and the $\lg K^{\text{Cd}}$ values is ± 0.2 each. The last three columns state which complexes occur at the respective overall composition $\text{PC}_2:\text{Cd}^{\text{II}}$ of the system.

ligands and Cd^{II} ions ($\lg K^{\text{Cd}} = 9.9\text{--}13.3$) and those having more ligands than metal ions ($\lg K^{\text{Cd}} = 16.3\text{--}19.3$). The consequences resulting from that under biological pH and concentration conditions can be inferred from the species distribution diagram shown in Figure 1. The cysteinyl: Cd^{II} ratio of 3:1 given occurs in native complexes of short-chain phytochelatins ($n = 2\text{--}4$);^[4c] the total concentration of $50\text{ }\mu\text{M}$ cadmium is of the same order of magnitude as that found in highly burdened plant cells. At pH 7.3, a typical value in the cytoplasm of higher plants,^[8] $[\text{Cd}_2(\text{H}_2\text{L})(\text{HL})_2]^{7-}$ ($\text{L}_3\text{Cd}_2\text{H}_4$) is the predominant complex. It should have mainly a sulfur coordination, but perhaps not exclusively, because in H_2L^{3-} one of the two SH groups is not yet deprotonated. Thus, on the one hand a $\{\text{S}_2\text{Cd}(\mu\text{-S})_2\text{CdS}(\text{O})_x\}$ structural fragment is

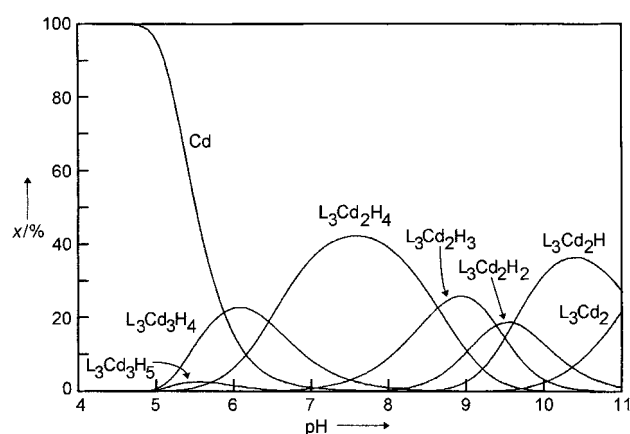


Figure 1. pH-Dependent distribution of the complex species for an overall composition of $\text{PC}_2:\text{Cd}^{\text{II}} = 1.5:1$ and a total concentration of cadmium of $50\text{ }\mu\text{M}$ (corresponding to 100%).

conceivable that does not contradict the EXAFS results (see above), which are unable to exclude a small contribution of oxygen to the coordination. On the other hand, a $\{\text{S}_2\text{Cd}(\mu\text{-S})_2\text{CdS}(\text{SH})\}$ center with thiolate and thiol coordination may be present. The coordination of thiols to Cd^{II} is rarely observed; however the complex $[\text{Cd}_3(\text{SR})_6(\text{HSR})]$ ($\text{R} = 2,4,6\text{-iPr}_3\text{C}_6\text{H}_2$), for example, has been reported, which has a mixed thiol–thiolate ligand sphere.^[9]

At pH 7.3 0.5 % of the cadmium is still uncomplexed. Even though one can expect slightly higher stabilities for the other phytochelatins ($n \geq 3$),^[10] this value nevertheless shows that the $\text{Cd}^{\text{II}}/\text{PC}_n$ complexes are by no means extremely stable. Consequently, they are not the long-term storage form of cadmium in plant cells, but they are transported from the cytosol into the vacuole, where the Cd^{II} remains in a binding state that has not been finally clarified yet.^[11]

Our stability data prove that $\text{Cd}^{\text{II}}/\text{PC}_n$ complexes dissociate considerably to entirely in the acidic environment of the vacuole. In the system $\text{Cd}^{\text{II}}/\text{PC}_2$ (Figure 1), 62 % of the cadmium is liberated at pH 5.4, a typical value in the vacuoles of higher plants.^[8] At the same pH value, this amount rises to 100 %, when the total concentration of cadmium is only $5\text{ }\mu\text{M}$ instead of $50\text{ }\mu\text{M}$. This dissociation allows the plant cell to recover the phytochelatins and should therefore be of substantial biological importance.^[12] The coordination-chemical basis for that lies in the absence of complexes with the potential carboxylate ligands H_3L^{2-} and H_4L^- as well as in the low stability of complexes with equimolar ligand and metal portions (see above). Thus, in the 1.5:1 ($\text{PC}_2:\text{Cd}^{\text{II}}$) system only the complex $[\text{Cd}_3(\text{H}_2\text{L})(\text{HL})_2]^{5-}$ ($\text{L}_3\text{Cd}_3\text{H}_4$) has a significant influence in the weakly acidic region. Its $\lg K^{\text{Cd}}$ value of 12.8, however, is far lower than that of $[\text{Cd}_2(\text{H}_2\text{L})(\text{HL})_2]^{7-}$ ($\lg K^{\text{Cd}} = 16.3$). A $\text{Cd}_3(\mu\text{-S})_3$ six-membered ring, which also occurs in the β -“cluster” of the metallothioneins,^[1] appears plausible as the central moiety of the trinuclear complexes $\text{L}_3\text{Cd}_3\text{H}_p$ ($p = 4\text{--}6$).

The results presented herein account for fundamental observations in connection with the biological function of the phytochelatins. Moreover, they can be useful for possible applications of these peptides, for example in heavy-metal biosensors.

Experimental Section

Measuring equipment: High-performance pH meter pMX 2000 (WTW, reading accuracy: 0.001 pH units) with temperature sensor, proportioning system ACCUSTEP (Tri-Continent Scientific), single-rod glass electrode 2GE1-DOKA (Jumo) with double-compartment system (salt bridge), cadmium-selective electrode Cd500 (WTW), titration cell with jacket for thermostating. Chemicals: Analytically pure $\text{HPCl}_2\text{CF}_3\text{COO}^-$ (C/H/F/N/S), $\text{Cd}(\text{NO}_3)_2 \times 4\text{H}_2\text{O}$ p. a., 0.1M aqueous solution of KOH (Aldrich, volumetric standard), 0.1M nitric acid (Aldrich, volumetric standard), KNO_3 (Fluka, MicroSelect, >99.5%). Measuring conditions: Aqueous solution, $T = 25.00 \pm 0.02^\circ\text{C}$, ionic strength $I = 1.00\text{M}$ kept constant with KNO_3 as supporting electrolyte during the entire titration, humidified N_2 protective atmosphere. The pK_w value was determined to be 13.76. Calibration of pH meter and electrode system by strong acid/strong base titration.^[13] Test system: $\text{Ni}^{II}/\text{glycine}$.^[14] Titration example: $\text{Cd}(\text{NO}_3)_2$ (67.1 μmol) and $\text{HPCl}_2\text{CF}_3\text{COO}^-$ (65.8 mg, 100.7 μmol) in supporting electrolyte solution (50.0 mL), adjusted to pH 2.5 with a known amount of nitric acid, titration with carbonate-free 0.1016M KOH solution (adjusted to $I = 1.00\text{M}$) up to pH 10.5. pK_a values: five titrations with a total of 336 experimental points ($\sigma_{\text{fit}} = 0.0039 - 0.0086$). Complex formation constants: seven titrations with different $\text{PCl}_2\text{Cd}^{II}$ ratios and a total of 677 experimental points ($\sigma_{\text{fit}} = 0.0021 - 0.0086$). Program used: BEST.^[5]

Received: April 7, 1998 [Z11694IE]

German version: *Angew. Chem.* **1998**, *110*, 2642–2644

Keywords: bioinorganic chemistry • cadmium • complex stabilities • phytochelatins • potentiometry

- [1] W. Kaim, B. Schwederski, *Bioanorganische Chemie*, 2nd ed., Teubner, Stuttgart, **1995**, pp. 336–356.
- [2] E. Grill, E.-L. Winnacker, M. H. Zenk, *Science* **1985**, *230*, 674–676.
- [3] Reviews: a) M. H. Zenk, *Gene* **1996**, *179*, 21–30; b) W. E. Rauser, *Annu. Rev. Biochem.* **1990**, *59*, 61–86.
- [4] See for example: a) H. Strasdeit, A.-K. Duhme, R. Kneer, M. H. Zenk, C. Hermes, H.-F. Nolting, *J. Chem. Soc. Chem. Commun.* **1991**, 1129–1130; b) A.-K. Duhme, Dissertation, Universität Oldenburg, **1993**; c) R. Kneer, M. H. Zenk, *Phytochemistry* **1997**, *44*, 69–74.
- [5] A. E. Martell, R. J. Motekaitis, *Determination and Use of Stability Constants*, 2nd ed., VCH, Weinheim, **1992**.
- [6] In parentheses: estimated standard deviation in units of the last place after the decimal point (for definition see for example: L. A. Currie, G. Svehla, *Pure Appl. Chem.* **1994**, *66*, 595–608).
- [7] B. Krebs, G. Henkel, *Angew. Chem.* **1991**, *103*, 785–804; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 769–788.
- [8] A. Kurkdjian, J. Guern, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1989**, *40*, 271–303.
- [9] K. Tang, X. Jin, A. Li, S. Li, Z. Li, Y. Tang, *J. Coord. Chem.* **1994**, *31*, 305–320.
- [10] Biochemical and spectroscopic studies support this assumption qualitatively.^[3]
- [11] The partial occurrence of sulfide as a ligand complicates the situation (see for example the discussion in ref. [4c]).
- [12] It has still to be studied in detail to which degree processes play a role that are coupled to the dissociation equilibrium, such as the complex formation of Cd^{II} with ligands of the vacuole.
- [13] M. Meloun, J. Havel, E. Högföldt, *Computation of Solution Equilibria*, Ellis Horwood, Chichester, **1988**, pp. 20–22.
- [14] A. Braibanti, G. Ostacoli, P. Paoletti, L. D. Pettit, S. Sammartano, *Pure Appl. Chem.* **1987**, *59*, 1721–1728.

Colloid-Bound Catalysts for Ring-Opening Metathesis Polymerization: A Combination of Homogenous and Heterogeneous Properties**

Marcus Bartz, Jörg Küther, Ram Seshadri, and Wolfgang Tremel*

The advantages and disadvantages of molecular or homogenous versus surface-bound or heterogeneous catalysts are well known. The properties of the two kinds of catalysts have been combined by attaching catalytically active species to soluble polymers, which can be bound to highly branched macromolecules.^[1] The use of transition metal ions as an intrinsic part (as “supramolecular glue”) of highly branched systems also provides potential for the construction of hybrid catalytic systems.^[2] Exploiting the fact that thiol-functionalized gold colloids behave like molecules (they are volatile, soluble, can be chromatographed) and possess a surface similar to the (111) surface of bulk gold, we have used a substituted, long-chain thiol to tether a Ru catalyst for ring-opening metathesis polymerization (ROMP) to gold colloids. The colloid-bound Ru species heterogeneously catalyzes the polymerization of norbornene in dichloromethane. At the same time, the catalyst system is readily soluble in and recoverable from acetone and therefore behaves like a molecular species. An interesting feature of the present catalytic system is the observation of much higher turnover frequencies (TOF) of the bound catalyst compared to the unbound molecular form.

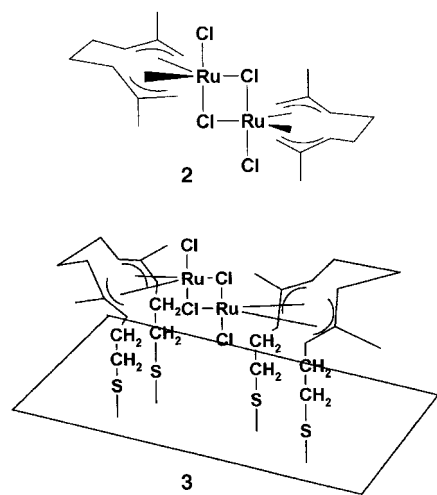
Gold salts can be reduced in toluene in the presence of long-chain thiols^[3] to give a material that almost perfectly bridges the world of molecular chemistry and the macroscopic world of extended solids and has opened up an exciting new area of nanomaterials.^[4] The thiol-coated gold colloids (usually in the 2–10 nm size range) behave like molecules in that they can be dissolved, precipitated, redissolved, sublimed, crystallized, etc. This permits the use of characterization techniques such as solution NMR and time-of-flight MS that are not normally suitable for the study of solids. On the other hand, these colloids possess a distinct solid surface, not unlike the (111) surface of gold that has been the subject of many studies.^[5,6]

We have been examining the binding of catalysts to gold (111) surfaces with ω -functionalized thiols with the intention of obtaining specific nanostructured materials, including functionalized atomic force microscopy (AFM) tips. One of the problems associated with multiple chemical modifications on a surface is the difficulty of characterizing the intermediates. This encouraged us to attempt the successive function-

[*] Prof. Dr. W. Tremel, M. Bartz, Dipl.-Chem. J. Küther, Dr. R. Seshadri
Institut für Anorganische Chemie und Analytische Chemie
der Universität
Johann-Joachim-Becher-Weg 24, D-55099 Mainz (Germany)
Fax: (+49)06131-393922

[**] We thank Professor Dr. Wolfgang Knoll for encouragement and for a generous loan of the SPS apparatus. The research group of Professor R. Zentel is thanked for the GPC measurements and Degussa, Hanau, for a gift of some chemicals. Dr. Christoph Janiak made some very helpful suggestions.

alization of gold colloids in solution. The advantages are that the reactions could be monitored very simply, for example, by FT-IR spectroscopy in the transmission mode or by NMR spectroscopy in solution. During these investigations, we prepared the thiol **1**, which has a terminal hexadiene functionality. This thiol binds to gold colloids in nonpolar solvents to give stable functionalized colloids that remain in solution unless precipitated with a polar solvent. The functionalized colloids coordinate to RuCl_3 through the hexadiene functionality to yield a known catalytically active material^[7, 8] that is acetone soluble with a high activity for the heterogeneous ROMP catalysis of norbornene in dichloromethane.^[9] For further characterization of this surface-bound catalytic system, gold-coated glass slides were treated with **1** and then with RuCl_3 . This process, which also gives the active catalyst, was investigated by surface plasmon spectroscopy (SPS). Gold colloids were functionalized with **1** in toluene. The thiol-coated colloids were precipitated with methanol and dried for recording FT-IR spectra in pressed KBr pellets. The fact that the colloidal powder redissolves in toluene confirms that the colloids are thiol-passivated. The toluene solution was stirred with $\text{RuCl}_3 \cdot 5\text{H}_2\text{O}$ for four days, during which time a precipitate formed. Washing the precipitate with methanol to remove excess RuCl_3 gave a free-flowing powder that catalyzed the heterogeneous polymerisation of norbornene in dichloromethane. The powder was sufficiently soluble in $[\text{D}_6]\text{acetone}$ for a ^1H NMR spectrum to be recorded. The FT-IR spectra were recorded on the powder in pressed KBr pellets. The spectra are consistent with the presence of the Cl-bridged dimeric catalytic species **2**^[7] and suggest the formation of the colloid-bound catalyst **3**. The FT-



IR spectra of the molecular catalyst and of the catalyst bound to gold colloids is shown in Figure 1. Blank experiments with RuCl_3 , with gold colloids, and with gold–glass substrates confirmed the specific catalytic activity of **3**.

The binding of the catalyst to the surface was monitored by recording SP spectra after successively exposing a gold-coated glass substrate to the thiol in toluene for 20 min at room

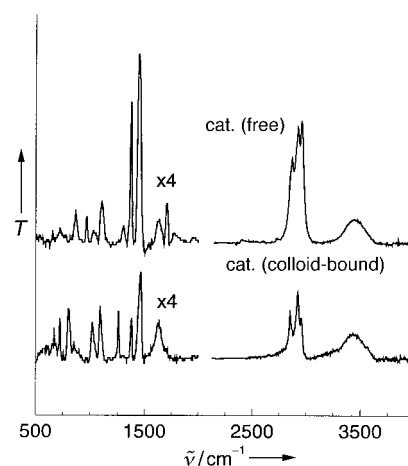


Figure 1. FT-IR spectra of the Ru ROMP catalyst unbound (A) and bound to gold colloids (B). T = transmission.

temperature and then to RuCl_3 in ethanol at 80°C for 4–5 h. The spectra (Figure 2) are consistent with the accumulation of material on the gold surface. Exposure of this coated gold

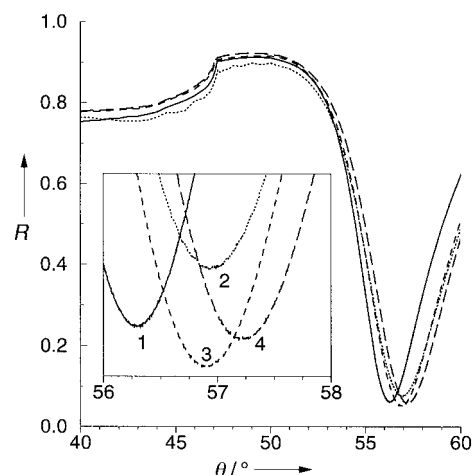


Figure 2. Surface plasmon resonance (SP) spectra of the clean gold surface (1), the surface after coverage with the thiol **1** (2), after exposure to RuCl_3 in ethanol (3), and after polymerization of norbornene (4). All spectra were acquired in water.

surface to norbornene in dichloromethane followed by work-up with methanol led to the formation of a white polymer film on the substrate. Because the SP spectra were recorded against water as the working medium, (necessary because of the refractive index), the solvent in the SP cell had to be changed after each reaction step. Thus much of the polymeric material was washed away. Hence curve 4 in Figure 2 can not be quantitatively evaluated and simply gives a qualitative indication of the increased surface thickness.

Gel-permeation chromatographic analysis (polystyrene standard, PL-Gel column combination 10^3 – 10^4 Å, trichloromethane solvent) of the polymeric material revealed that the polymer formed by catalysis on the modified gold-coated glass slides typically had a molecular weight of $M_w = 22\,000$ and a polydispersity index M_w/M_n of 2.2, whereas the colloid-bound catalyst yielded a polymer with $M_w = 17\,000$ and $M_w/M_n = 4.3$.

For the molecular (homogeneous) catalyst in dichloromethane, a TOF of 3000 h⁻¹ was determined, similar to the TOFs of catalysts in earlier investigations.^[8] For the catalyst bound to the colloid surface, the TOF was 16000 h⁻¹, and for the catalyst on the flat gold surface, it was 80000 h⁻¹. For calculating the TOF of the colloid- and surface-bound systems, the amount of catalyst was estimated by assuming full monolayer coverage in which each thiol molecule occupies an area of approximately 25 Å². Since full coverage is unlikely, the amount of catalyst is overestimated, and the TOFs of the bound catalysts represent lower limits of their activities. The dramatic increase in catalytic activity noted here is in keeping with a recent report of catalysts organized in Langmuir–Blodgett films^[10] and is probably connected with the orientation of the catalyst on the surface in a manner that favors its interaction with the monomer and the growing polymer chain.

Experimental Section

6-Chloro-3-methyl-1-hexen-3-ol **A** was prepared by the method of Kise et al.^[11] Vinyl bromide (50 g) was liquefied in a dry ice bath and was dissolved in THF (50 mL). Ethyl bromide (1 mL) and iodine (0.2 g) were added to magnesium (14.2 g) in THF (100 mL) under inert gas. The mixture was stirred at room temperature for 5 min. The solution of vinyl bromide in THF was then added slowly to the mixture. The mixture was stirred at room temperature overnight and then cooled to 10 °C. A solution of 5-chloropentanone (60 g) in THF (60 mL) was added at below 20 °C. The mixture was then allowed to warm to room temperature, stirred for an additional 2 h, and poured into 10% HCl (300 mL). The organic layer was separated, and the aqueous layer was saturated with NaCl and extracted with ether. The organic phases were combined, dried over sodium sulfate, and the solvent evaporated. The remaining crude oily product was distilled under vacuum (3 × 10⁻² mbar, b.p. 51 °C). Yield: 50%. IR $\tilde{\nu}$ = 3450 (OH), 3080 (–CH=CH₂), 2960–2870 (CH₂, CH₃), 1630 (C=C), 1470 (CH), 1311, 1105, 997, 918 cm⁻¹ (–CH=CH₂); ¹H NMR: δ = 1.26 (s, 3 H, CH₃), 1.4–2.2 (m, 4 H, ClCH₂CH₂CH₂), 3.50 (t, 2 H, ClCH₂), 4.8–5.3 (m, 2 H =CH₂), 5.68 (q, 1 H CH=CH₂).

6-Chloro-3-methyl-1,3-hexadiene **B**: P₂O₅ (40 g) was added to a solution of **A** (30 g) in toluene (150 mL) at room temperature. The mixture was stirred for 1 h, and the white precipitate filtered off. The filtrate was washed with 5% aqueous sodium hydrogencarbonate solution, saturated with NaCl, and dried over sodium sulfate. The toluene was removed under reduced pressure and the residual oil was distilled under vacuum (3 × 10⁻² mbar, b.p. 60 °C). Yield: 55%. IR: $\tilde{\nu}$ = 3090, 2960 (CH₂, CH₃), 1606 (C=C), 1442, 1375, 1303, 1085, 997, 904 cm⁻¹ (–CH=CH₂); ¹H NMR: δ = 1.70, 1.79 (s, 3 H, CH₃), 2.55 (q, 2 H, CH₂CH=), 3.45 (t, 2 H, ClCH₂), 4.92 (d, 1 H *cis*-CH=CH₂), 5.06 (d, 1 H, *trans*-CH=CH₂), 5.4 (t, 1 H, CH₂CH=), 6.25, 6.65 (2 q, 1 H CH=CH₂).

3-Methyl-6-sulfanyl-1,3-hexadiene **C**: A solution of **B** (2 g) in ethanol (20 mL) was heated to reflux, and a solution of Na₂S₂O₃ (4 g) in water (20 mL) was added dropwise. The mixture was heated at reflux under inert gas for 4–5 h. The reaction mixture was added dropwise to deoxygenated 1N HCl (100 mL), and the mixture was heated to reflux for 4 h under argon atmosphere. It was then cooled to room temperature. The product was collected by shaking the solution with CH₂Cl₂. The organic layer was dried over sodium sulfate, and the solvent removed under reduced pressure. Yield: 60%; m.p. 94 °C; IR: $\tilde{\nu}$ = 2960–2870 (CH₂, CH₃), 2688 (–SH), 1440, 1375, 1309, 1163, 1053, 848 (–CH=CH₂); EI-MS: *m/z* (%): 128.22 (36.69) (monomer), 256.41 (54.37) (dimer).

Gold colloids **D** were prepared by the method of Brust et al.^[3] by pouring 20 mL of an aqueous solution of HAuCl₄ (2 g in 100 mL H₂O) into a separating funnel. Toluene (80 mL) was added along with tetraoctylammonium bromide (0.12 g). Shaking the funnel transferred the HAuCl₄ from the aqueous into the toluene phase. Reduction at the water/toluene interface was performed with NaBH₄ (1.2 g) in water (25 mL). The organic layer became ruby red due to the formation of the colloid. Such colloids have been previously characterized by us.^[12]

1. Synthesis of [dichlorobis(μ -chloro)bis[(3,4,5- η :8,9,10- η)-4,9-dimethyl-1,12-disulfanyldodecadienediyl]ruthenium(IV)] **E** on gold colloids: **C** (100 μ L) was added to a solution of gold colloid **D** in toluene (80 mL) and the mixture stirred for 1 h. RuCl₃ · 5H₂O (0.1 g) was then added to the solution and the mixture was heated to reflux under argon for four days. The black precipitate was collected by filtration and washed with methanol to remove excess RuCl₃.

2. Synthesis of **E** on gold substrates: gold-coated glass slides were placed in a solution of **C** (100 μ L) in toluene (50 mL) and stirred for 15 h. RuCl₃ was added and the mixture was heated under reflux until the solution became green. The gold-coated glass slide was removed, washed with ethanol, and stored under argon.

Polynorbornene **F**: 2-Norbornene (1.5 g) was dissolved in CH₂Cl₂ (12 mL), and 3 mL of a 10⁻² M solution of ethyl diazoacetate in CH₂Cl₂ was added to the solution. Then 0.01 g of the colloid-bound catalyst or the catalyst-functionalized glass slide was added, and the liquid phase was stirred at 25 °C. The polymerization was stopped after different periods of time (Table 1) by adding methanol. The crude polymer was collected by

Table 1. Ring-opening metathesis polymerization of norbornene with unbound and bound catalysts

Catalyst	Yield ^[a] [%]	<i>t</i> [min]	<i>c</i> _{cat} [M]	TOF ^[b] [h ⁻¹]
unbound	30	5	8 × 10 ⁻⁶	2990
colloid-bound	90	60	9.9 × 10 ⁻⁷	15000
bound on functionalized glass slide	30	15	2.55 × 10 ⁻⁷	75000

[a] Yield refers to isolated polymer. [b] TOF = turnover frequency in mol(polynorbornene)/[mol (catalyst) · h].

filtration and purified by dissolving in toluene and reprecipitating with methanol.

Received: March 20, 1998

Revised version: June 24, 1998 [Z11617IE]

German version: *Angew. Chem.* **1998**, *110*, 2646–2649

Keywords: colloids • gold • heterogeneous catalysis • homogeneous catalysis • monolayers

- J. W. J. Knapen, A. W. van der Made, J. C. de Wilde, P. W. N. M. van Leeuwen, P. Wijkens, D. M. Grove, G. van Koten, *Nature (London)* **1994**, *372*, 659, and references therein.
- E. C. Constable, *Chem. Commun.* **1997**, 1073; S. Campagna, G. Denti, S. Serroni, A. Juris, M. Venturi, V. Ricevuto, V. Balzani, *Chem. Eur. J.* **1995**, *1*, 211.
- M. Brust, M. Walker, D. Bethell, D. J. Schiffrin, R. Whyman, *J. Chem. Soc. Commun.* **1994**, 801; M. Brust, D. Bethell, D. J. Schiffrin, C. J. Kiely, *Adv. Mater.* **1995**, *7*, 795.
- R. L. Whetten, J. T. Khoury, M. M. Alvarez, S. Murthy, I. Vezmar, Z. L. Wang, P. W. Stephens, C. L. Cleveland, W. D. Luedtke, U. Landmann, *Adv. Mater.* **1996**, *8*, 428.
- G. Schmid, *Chem. Rev.* **1992**, *92*, 1709.
- R. Terril, T. Postlethwaite, C. Chen, C. Poon, A. Terzis, A. Chen, J. Hutchinson, M. Clark, G. Wignall, J. Londono, R. Superfine, M. Falvo, C. Johnson, Jr., E. Samulski, R. Murray, *J. Am. Chem. Soc.* **1995**, *117*, 12537.
- D. N. Cox, R. Roulet, *Inorg. Chem.* **1990**, *29*, 1360.
- W. A. Herrmann, W. C. Schattenmann, O. Nuyken, S. C. Glander, *Angew. Chem.* **1996**, *108*, 1169; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1087.
- T. C. Chung, S. Ramakrishnan, M. W. Kim, *Macromolecules* **1991**, *24*, 2675.
- K. Töllner, R. Popovitz-Biro, M. Lahav, D. Milstein, *Science* **1997**, *278*, 2100.
- H. Kise, T. Sato, T. Yasuoka, M. Seno, T. Asahara, *J. Org. Chem.* **1979**, *44*, 4454.
- J. Küther, R. Seshadri, G. Nelles, H.-J. Butt, W. Knoll, W. Tremel, *Adv. Mater.* **1998**, *10*, 401.

Efficient Synthesis of a Novel Estrone-Talaromycin Hybrid Natural Product**

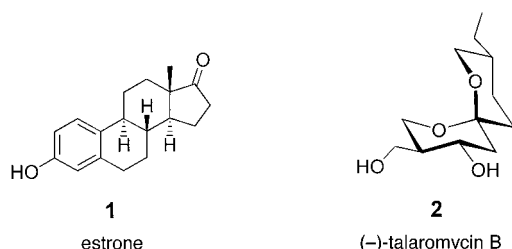
Lutz F. Tietze,* Gyula Schneider,* János Wölfling, Thomas Nöbel, Christian Wulff, Ingrid Schubert, and Angela Rübeling

Dedicated to Professor Wolfgang Steglich on the occasion of his 65th birthday

An important aim of organic chemistry is the development of new types of biologically active substances. Of particular importance are natural products that can be used in many ways, either directly or indirectly, as lead structures. Examples of this are strobilurins^[1] described by Steglich, Anke et al., and epothilones^[2] described by Höfle et al.

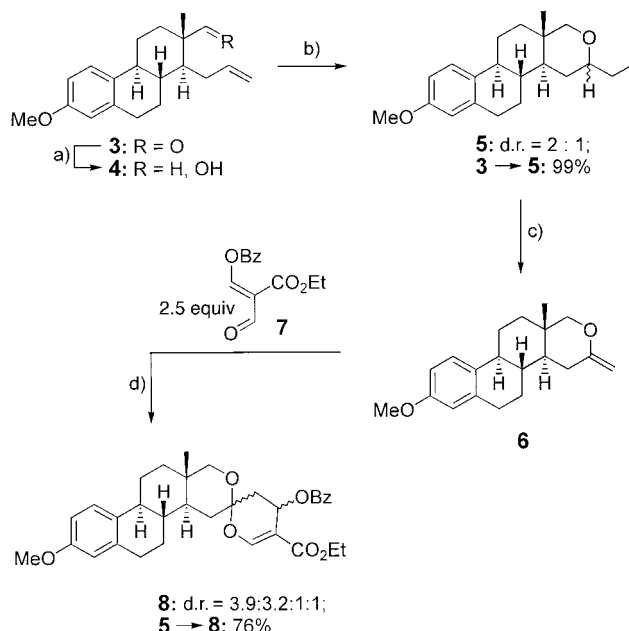
However, it should be remembered that it is not easy to find new, interesting natural products. Nevertheless an almost inexhaustible reservoir of new types of diverse structures is available from the coupling of two or more natural products to make hybrids. This route, at least in terms of the approach, is also adopted in nature, for example in the combined biosynthesis of vitamin E, which forms from a terpene and a shikimic acid.^[3] In addition, vincristin is worthy of mention, which is formed from an aspidoderma and an iboga alkaloid and which is one of the most important substances in the treatment of leukemia in children.^[4]

Although the enzymatic formation of hybrid natural products by gene manipulation is currently under intensive study,^[5] to date there have been few attempts at the chemical synthesis of such compounds.^[6] We describe here a new type of pharmacologically interesting hybrid natural product made from estrone (**1**) and the highly biologically active mycotoxin talaromycin B (**2**).^[7] The combination of a toxin with a steroid



was chosen because steroids are able to penetrate the cell membrane and bind to the cell nucleus.^[8]

For the synthesis the secoestrone derivative **3** was used which is available in four steps from **1**.^[9] Reduction of **3** with sodium borohydride in methanol at 20 °C led to the alcohol **4** from which, by reaction with iodine via an intermediate iodonium ion, iodomethyltetrahydropyran **5** was obtained as a 2:1 mixture of diastereomers (Scheme 1). The low diastereoselectivity of the reaction is insignificant since the newly formed stereogenic center is destroyed in the next step. Thus, elimination with 1,8-diazabicyclo[5.4.1]undec-7-ene (DBU) as the base yielded the exocyclic enol ether **6**. The reaction was carried out at 90 °C without solvent; in this manner isomerization of the double bond could be avoided. The enol ether is, however, not stable and was therefore converted directly in a Diels–Alder^[10] reaction with ethyl *O*-benzoyldiformylacetate (**7**) to the spiroacetal **8** which was obtained as a mixture of four diastereomers in the ratio 3.9:3.2:1:1 in 76 % yield.



Scheme 1. a) 10 Equiv NaBH₄, MeOH, RT, 30 min; b) I₂, NaHCO₃, Et₂O/H₂O, RT, 4 h; c) DBU, 90 °C, 30 min; d) toluene, CH₂Cl₂, RT, 14 h. Bz = benzoyl.

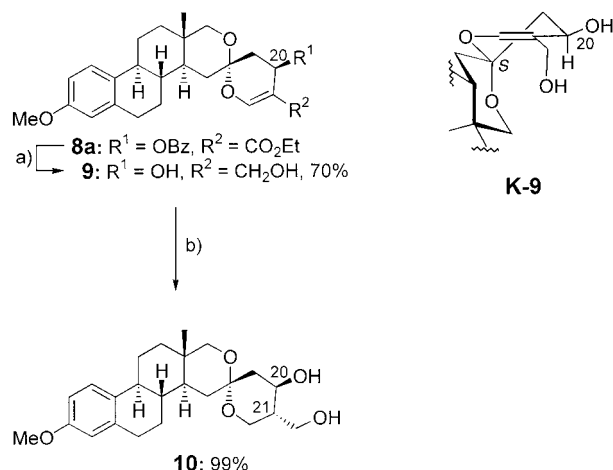
The main diastereomer **8a** was obtained in crystalline form after chromatography and its structure was elucidated by crystal structure analysis.^[11] The relative configuration of the newly formed stereogenic centers in **8a** resulted from an *exo* attack of the heterodiene **7** *anti* to the angular methyl group in **6**.

Reduction of the two ester groups in **8a** with diisobutylaluminum hydride (DIBALH) led to the diol **9** (Scheme 2) in 70 % yield. The subsequent hydrogenation of the double bond in **9** at 50 bar hydrogen pressure in methanol/ethyl acetate with platinum dioxide as catalyst afforded the desired estrone–talaromycin hybrid natural product **10** in quantitative yield.^[12] The newly formed stereogenic center in **10** resulted from β -addition of hydrogen to the olefinic double bond. The high stereoselectivity of the hydrogenation can be

[*] Prof. Dr. L. F. Tietze, Dipl.-Chem. T. Nöbel, Dipl.-Chem. C. Wulff, I. Schubert, A. Rübeling
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-399476
E-mail: ltietze@gwdg.de

Prof. Dr. G. Schneider, Dr. J. Wölfling
Department of Organic Chemistry, József Attila University
Dom tér 8, H-6720 Szeged (Hungary)
Fax: (+36) 62-454276
E-mail: schneider@chem.u-szeged.hu

[**] This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 416), by the Fonds der Chemischen Industrie, and by the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (Project No. UNG-061-96). J.W. thanks the Hungarian national Science Foundation for the award of a János Bolyai Stipendium (T016122 and F016119). C.W. thanks the Fonds der Chemischen Industrie for a doctoral stipendium.



Scheme 2. a) 12 Equiv DIBALH, THF/ CH_2Cl_2 , -78°C , 21 h; b) 10 mol % PtO_2 , 50 bar H_2 , MeOH/EtOAc, 12 h. Bz = Benzoyl.

ascribed to both stereoelectronic control and the directive effect of the β -hydroxyl group at C-21.^[13] Thus, assuming that **K-9** is the most stable reactive conformation of the transition state, hydrogenation from the β -side via an energetically favorable chair form should lead to the product obtained.^[14]

The configuration at C-20 was determined by analysis of the ^1H NMR coupling constants of the 20-H signal at $\delta = 3.81$. The coupling constants $J_1 = J_2 = 10.9$ Hz and $J_3 = 4.9$ Hz result from two axial–axial and one axial–equatorial coupling. This coupling pattern is only possible for the given diastereomer **10**.

To test the biological activities of **9** and **10** their in vitro effects on human cancer cells from the cell line A 549 were determined. For this 10^2 to 10^5 cells, in each case, were placed in 6-well multiplates and incubated with different concentrations of each substance in the culture medium DMEM, which contains 10% fetal calf serum. After 11 d cultivation at 37°C in air with a CO_2 content of 7.5% the clones were dyed with Löffler methylene blue and the relative clone formation rate was determined.^[15] The effective dosage (ED_{50}) was about $30\text{ }\mu\text{M}$, and thus lies only slightly below the cytotoxicity of aldophosphamide, the active metabolite of the well known cytostatic agent cyclophosphamide.^[16]

The efficient synthesis of **10** described, in which a hetero Diels–Alder reaction is the key step, opens the way to new types of hybrid natural products which are built up from a steroid and a mycotoxin and which show interesting biological activities. For instance, in vitro tests with **9** and **10** showed strong cytotoxic activity against human cancer cells.

Received: April 23, 1998 [Z11769IE]

German version: *Angew. Chem.* **1998**, *110*, 2644–2646

Keywords: antitumor agents • cycloadditions • mycotoxins • spiro compounds • steroids

[1] S. Zapf, A. Werle, T. Anke, D. Klostermeyer, B. Steffan, W. Steglich, *Angew. Chem.* **1995**, *107*, 255–257; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 196–198.

[2] a) G. Höfle, N. Bedorf, H. Steinmetz, P. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671–1673; *Angew. Chem.*

- Int. Ed. Engl.* **1996**, *35*, 1567–1569; b) K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120–2153; *Angew. Chem. Int. Ed.* **1998**, *37*, Nr. 15.
- [3] a) T. Netscher, *Chimia* **1996**, *50*, 563–567; b) T. Furuya, T. Yoshikawa, T. Kimura, H. Kaneko, *Phytochemistry* **1987**, *26*, 2741–2747; c) A. Stocker, H. Fretz, H. Frick, A. Rüttimann, W.-D. Woggon, *Bioorg. Med. Chem.* **1996**, *4*, 1129–1134.
- [4] a) P. Magnus, J. S. Mendoza, A. Stamford, M. Ladlow, P. Willis, *J. Am. Chem. Soc.* **1992**, *114*, 10232–10245; b) W. G. Bornmann, M. E. Kuehne, *J. Org. Chem.* **1992**, *57*, 1752–1760.
- [5] a) R. Pieper, C. Kao, C. Khosla, G. Luo, D. E. Cane, *Chem. Soc. Rev.* **1996**, *25*, 297–302; b) A. Nakagawa, S. Omura, *J. Antibiot.* **1996**, *49*, 717–741.
- [6] Examples of the combination of partial structures of natural products have been described: a) J. Wang, P. J. De Clercq, *Angew. Chem.* **1995**, *107*, 1698–1701; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1749–1752; b) I. Scherlitz-Hofmann, M. Dubs, R. Krieg, B. Schönecker, M. Kluge, D. Sicker, *Helv. Chim. Acta* **1997**, *80*, 2345–2351; c) K. M. Depew, M. Zeman, S. H. Boyer, D. J. Denhart, N. Ikemoto, D. M. Crothers, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2972–2975; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2797–2801.
- [7] a) G. D. Lynn, N. J. Phillips, W. C. Hutton, J. Shabanowitz, D. I. Fennel, R. J. Cole, *J. Am. Chem. Soc.* **1982**, *104*, 7319–7322; b) L. F. Tietze, C. Schneider, *J. Org. Chem.* **1991**, *56*, 2476–2481; c) K. Mori, M. Ikonaka, *Tetrahedron* **1987**, *43*, 45–58; d) M. M. Midland, J. Gabriel, *J. Org. Chem.* **1985**, *50*, 1143–1144.
- [8] M. Beato, P. Herrlich, G. Schütz, *Cell* **1995**, *83*, 851–857; G. F. Allan, X. Leng, S. Y. Tsai, N. L. Weigel, D. P. Edwards, B. W. O'Malley, *J. Biol. Chem.* **1992**, *267*, 19513–19520.
- [9] Gy. Schneider, S. Bottka, L. Hackler, J. Wölfling, P. Sohár, *Liebigs Ann. Chem.* **1989**, 263–267.
- [10] a) L. F. Tietze, G. Ketschau, *Top. Curr. Chem.* **1997**, *189*, 1–120; b) L. F. Tietze, G. Ketschau, J. A. Gewert, A. Schuffenhauer, *Curr. Org. Chem.* **1998**, *2*, 19–62.
- [11] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101429. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [12] **10:** M.p. 150°C (decomp); $[\alpha]_D^{25} = +109.7$ ($c = 0.3$, CHCl_3); ^1H NMR ($[\text{D}_4]\text{MeOH}$, 500 MHz): $\delta = 0.98$ (s, 3H, 18-H), 1.15–1.35 (m, 2H, 12- H_2), 1.38–1.50 (m, 3H, 14-H, 11- H_2), 1.55–1.70 (m, 3H, 19- H_b , 9-H, 8-H), 1.73 (dd, $J = 13.1$, 3.8 Hz, 1H, 7- H_b), 1.92–1.96 (m, 1H, 7- H_a), 2.00 (dd, $J = 12.6$, 5.0 Hz, 1H, 19- H_a), 2.23–2.33 (m, 2H, 15- H_2), 2.77–2.80 (m, 2H, 6- H_2), 3.08 (d, $J = 10.6$ Hz, 1H, 17- H_a), 3.29–3.31 (m, 3H, 21-H, 20-OH, 21- CH_2OH), 3.33 (d, $J = 10.6$ Hz, 1H, 17- H_b), 3.46 (t, $J = 11.3$ Hz, 1H, 22- H_b), 3.49 (dd, $J = 11.3$, 7.5 Hz, 1H, 22- H_a), 3.72 (s, 3H, 3- OCH_3), 3.76 (dd, $J = 11.2$, 4.8 Hz, 1H, 21- CH_2OH), 3.81 (td, $J = 10.9$, 4.9 Hz, 1H, 20-H), 3.83 (dd, $J = 11.2$, 3.8 Hz, 1H, 21- CH_2OH), 6.58 (d, $J = 2.6$ Hz, 1H, 4-H), 6.66 (dd, $J = 8.5$, 2.6 Hz, 1H, 2-H), 7.14 (d, $J = 8.5$ Hz, 1H, 1-H); ^{13}C NMR ($[\text{D}_4]\text{MeOH}$): $\delta = 16.34$ (C-18), 26.71 (C-11), 26.85 (C-12), 30.91 (C-13), 34.51 (C-6), 35.36 (C-7), 36.37 (C-15), 39.93 (C-14), 42.95 (C-9), 45.07 (3- OCH_3), 45.73 (C-19), 47.51 (C-8), 55.54 (C-21), 61.73 (C-22), 62.61 (21- CH_2OH), 66.29 (C-20), 73.16 (C-17), 99.84 (C-16), 112.6 (C-2), 114.4 (C-4), 127.0 (C-1), 133.8 (C-10), 138.8 (C-5), 159.0 (C-3).
- [13] a) J. M. Brown, S. A. Hall, *Tetrahedron Lett.* **1984**, *25*, 1393–1396; b) J. M. Brown, S. A. Hall, *Tetrahedron* **1985**, *41*, 4639–4646; c) R. D. Stolow, K. Sachdev, *J. Org. Chem.* **1971**, *36*, 960–966.
- [14] Force field calculations on **9** indicate that **K-9** is the most stable conformation in the ground state.
- [15] L. F. Tietze, R. Hannemann, W. Buhr, M. Loegers, P. Menningen, M. Lieb, D. Starck, T. Grote, A. Doering, I. Schuberth, *Angew. Chem.* **1996**, *108*, 2840–2842; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2674–2675.
- [16] L. F. Tietze, M. Neumann, T. Möllers, R. Fischer, K.-H. Glüsenkamp, M. F. Rajewsky, E. Jähde, *Cancer. Res.* **1989**, *49*, 4179–4184.

Novel Biocatalysts by Chemical Modification of Known Enzymes: Cross-Linked Microcrystals of the Semisynthetic Peroxidase Seleno-Subtilisin**

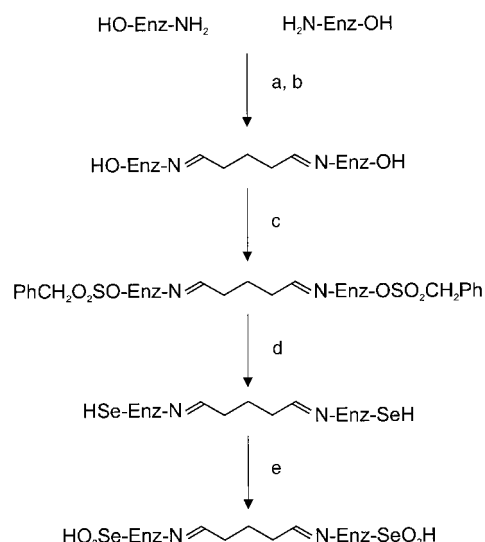
Dietmar Häring and Peter Schreier*

Dedicated to Professor Helmut Werner on the occasion of his 65th birthday

Although enzymes are widely accepted as valuable catalysts in synthetic chemistry their “natural” properties such as activity, selectivity, or stability are often insufficient. Several methodologies have been developed to overcome these problems. Genetic engineering techniques can improve the overall stability,^[1] whereas new catalytically active sites are hard to achieve. Monoclonal catalytic antibodies opened many opportunities in this field, but it is difficult to obtain useful catalysts for asymmetric synthesis.^[2] Finally, efforts were made to design synthetic enzyme mimics. However, the breakthrough in terms of catalytic efficiency and enantioselectivity still lies ahead.^[2]

The oldest techniques for enzyme tailoring are “chemical” engineering methods. For instance, specific chemical modification of the catalytically active site yielded semisynthetic enzymes with completely changed catalytic properties.^[3] Although semisynthetic enzymes open unique opportunities in enzyme design, this technique was mainly used as an analytical rather than as a synthetic tool. Here we report on a new type of chemically engineered semisynthetic enzyme for organic synthesis, which combines altered catalytic activity, reasonable substrate selectivity, and exceptional stability in one biocatalyst.

The serine proteinase subtilisin [3.4.21.62] is a well-known biocatalyst produced in several tons per year for industrial applications. Extensive substrate screenings, various genetically engineered mutants, and several X-ray studies have been described.^[4] These detailed insights into the characteristics of subtilisin provided a sound basis for rational chemical engineering studies. In order to demonstrate the potential of chemical enzyme engineering, the active site of subtilisin as well as its peptide framework were modified by simple chemical reactions. We synthesized cross-linked crystals of the semisynthetic peroxidase seleno-subtilisin according to Scheme 1. Batch crystallization of subtilisin was achieved by slow addition of saturated sodium sulfate solution to a freshly prepared acetone precipitation and yielded microscopic needles (typically 100 × 5 × 5 μm). Cross-linking of the crystals with glutardialdehyde effected that the material was insoluble in water as well as in organic solvents. Tüchsen and Ottesen^[5] found that during a reaction time of 45 min three lysine residues at the subtilisin surface had reacted with its neighbors in the crystal lattice. X-ray studies showed the same

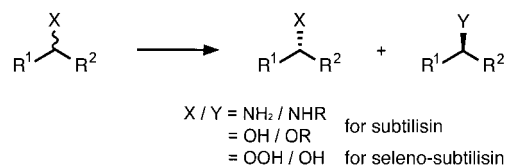


Scheme 1. Conversion of subtilisin into cross-linked microcrystals of seleno-subtilisin (see Experimental Section). a) Crystallization; b) glutardialdehyde; c) phenylmethanesulfonyl fluoride (PMSF); d) NaSeH; e) H₂O₂.

tertiary structure for cross-linked subtilisin and subtilisin in untreated crystals.^[6]

Prior to seleno-modification the active site serine 221 had to be activated by phenylmethanesulfonyl fluoride (PMSF), a typical serine proteinase inhibitor. Nucleophilic substitution of the PMSF-substituted serine by sodium hydrogen selenide required two days treatment at 45 °C. Due to the insolubility of the enzyme preparation no chromatographic purification step could be applied during the synthesis. Hence, the enzyme crystals had to be washed with aqueous sodium borohydride solution to solubilize and remove the excess precipitated selenium. The selenol group at residue 221 was subsequently oxidized with hydrogen peroxide to yield the stable seleninic acid form of cross-linked crystals (CLC) of seleno-subtilisin.

As a result of the introduction of selenium into the protease subtilisin, the semisynthetic seleno-subtilisin revealed glutathione peroxidase activity,^[7] and catalyzed the kinetic resolution of several racemic hydroperoxides^[8, 9] (Scheme 2).



Scheme 2. Comparison of the catalytic activity of the protease subtilisin with that of the semisynthetic peroxidase seleno-subtilisin. Substrate- and stereoselectivity are comparable due to identical binding sites.^[9, 14]

However, synthetic application of semisynthetic enzymes has to date been limited to 10-μmol scale and the chemically modified enzyme was not reusable. In contrast, CLC-seleno-subtilisin is insoluble in water and organic solvents and easily recovered after synthesis by centrifugation or filtration. Figure 1 summarizes the high level of activity and selectivity during ten reaction cycles. The kinetic resolution of racemic 2-hydroxy-1-phenylethyl hydroperoxide (**1**) was achieved in 25–30 min yielding 97% *ee* on average. For instance, the

[*] Prof. Dr. P. Schreier, Dipl.-Chem. D. Häring
Lehrstuhl für Lebensmittelchemie der Universität
Am Hubland, D-97074 Würzburg (Germany)
Fax: (+49) 931-888-5484
E-mail: schreier@pzc.uni-wuerzburg.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 347 “Selective reactions of metal-activated molecules”).

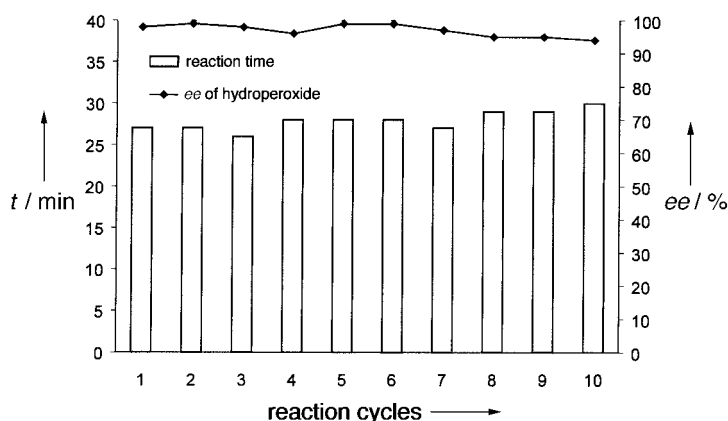


Figure 1. Enantioselective catalysis and recycling of CLC-seleno-subtilisin (see Experimental Section).

reaction of **1** or 1-phenylethyl hydroperoxide (**2**) was up-scaled to 1-mmol scale without loss of activity or selectivity.

The exceptional characteristics of cross-linked enzyme crystals were discovered by Quijcho and Richards in 1964.^[10a] They are stable towards varying pH values, high temperature, proteolytic degradation, and organic solvents, and kinetics of reactions are comparable to those of amorphous enzymes.^[10] Accordingly, semisynthetic CLC-seleno-subtilisin revealed kinetic parameters ($k_{\text{cat}} = 458 \text{ min}^{-1}$, $K_m = 17.9 \text{ mM}$ for **2**; assay see reference [8]) similar to those of amorphous peroxidase, and very high stability under denaturing conditions. Figure 2 shows a comparison of the activity of

enzyme development (e.g. genetic engineering or catalytic antibodies) only basic chemical equipment for the synthesis in gram-scale is necessary. Cross-linking of enzyme crystals yields an immobilized biocatalyst with exceptional stability. The high purity (crystalline enzyme!) together with the stability provide ideal prerequisites for further modification of the active site by chemical methods, resulting in new catalytic activity. By utilizing a well-known protein framework, details about substrate selectivity or affinity may be transferred and predicted from the template to the semi-synthetic enzyme.^[9]

Experimental Section

Subtilisin Carlsberg (Novo Nordisk, 54% (w/w) active protein) was prepurified by fractionated acetone precipitation and crystallized in 12% Na_2SO_4 in 30 mM acetate/NaOH buffer (pH 5.5; 16 °C).^[11] Treatment of subtilisin crystals with 1.5% glutaraldehyde (45 min) in 30 mM KH_2PO_4 /NaOH (pH 7.5) containing 13% Na_2SO_4 resulted in cross-linked crystals (CLC) of subtilisin (25% overall yield at gram-scale).^[12]

Prior to the introduction of selenium, CLC-subtilisin was incubated with 5 mM PMSF for 1 h in 50 mM PIPES buffer (pH 7.0) containing 20 mM CaCl_2 . Freshly prepared sodium hydrogen selenide^[13] was added under argon atmosphere and the reaction was kept at 45 °C for 45 h. Precipitated red selenium was removed by washing three times with aqueous 25 mM NaBH_4 solution. The selenol form of CLC-seleno-subtilisin was oxidized to seleninic acid by treatment with 10 mM H_2O_2 (30 min at 20 °C). After repeated washing with 50 mM citric acid/NaOH buffer (pH 5.5) containing 20 mM CaCl_2 , the enzyme crystals were stored in the same buffer and isolated for further experiments by centrifugation at 1000 g. Typically, 1.0 g CLC-subtilisin yielded 0.96 g CLC-seleno-subtilisin with 11–15 nmol active enzyme per milligram crystals (determined by active site titration with TNB^[7]).

Enantioselective catalysis and recycling of CLC-seleno-subtilisin (see Figure 1). In 325 mL 30 mM citric acid/NaOH buffer (pH 5.5) and 2 mM EDTA, CLC-seleno-subtilisin (3.8 μmol) was preincubated with 2-nitro-5-thiobenzoic acid (TNB, 0.06 mmol; 15 min). 2-Hydroxy-1-phenylethyl hydroperoxide **1** (0.33 mmol) was added and the reaction was started by slow addition of TNB (0.33 mmol). CLC-seleno-subtilisin was recovered by centrifugation (1500 g). The hydroperoxide was extracted with diethyl ether and purified on a silica gel column. The ee of **1** was determined by HPLC on a Daicel-Chiralcel OB-H. Contrary to previous studies^[8,9] the blank reaction was negligible using CLC-seleno-subtilisin. Kinetic resolution of racemic hydroperoxide **1** or **2** was carried out accordingly in preparative 1-mmol scale yielding typically 42% of the enantiomerically enriched hydroperoxides (for stereoanalytics and enantioselectivity cf.^[8,9]).

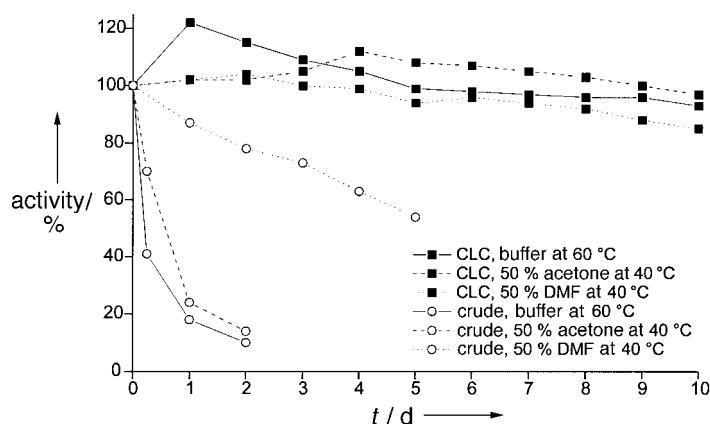


Figure 2. Stability of amorphous and cross-linked crystals of seleno-subtilisin in organic solvents or at high temperature. Peroxidase activity was measured photometrically at 410 nm with 0.2 mM cumene hydroperoxide and 0.2 mM TNB in 50 mM citric acid/NaOH buffer (pH 5.5) and 2 mM EDTA. The specific activities of crystalline (33 mU mg^{-1}) and amorphous (12 mU mg^{-1}) seleno-subtilisin were expressed as 100%.

amorphous and CLC-seleno-subtilisin in different reaction media. In every case the cross-linked crystal lattice prevented rapid denaturation by unfolding mechanisms.

In summary, the cross-linked microcrystals of seleno-subtilisin are a new type of chemically engineered enzyme. For the first time we combined the methods of chemical modification of the enzymatic framework as well as the enzymatic active site. In comparison to other methods of

Received: May 4, 1998 [Z11810IE]
German version: *Angew. Chem.* **1998**, *110*, 2628–2631

Keywords: asymmetric synthesis • enzyme catalysis • immobilization • selenium

- [1] a) D. L. Oxender, C. F. Fox, *Protein Engineering*, Alan R. Liss, New York, **1987**; b) J. Damorský, *Protein Eng.* **1998**, *11*, 21–30.
- [2] a) P. A. Brady, J. K. M. Sanders, *Chem. Soc. Rev.* **1997**, *26*, 327–336; b) A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770–790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 705–724.
- [3] a) E. T. Kaiser, *Angew. Chem.* **1988**, *100*, 945–955; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 913–922; b) E. T. Kaiser, D. S. Lawrence, *Science* **1984**, *226*, 505–511.
- [4] a) H. Takagi, *Int. J. Biochem.* **1993**, *25*, 307–312; b) J. A. Wells, D. A. Estell, *Trends Biochem. Sci.* **1988**, *13*, 291–297.
- [5] E. Tüchsen, M. Ottesen, *Carlsberg Res. Commun.* **1977**, *42*, 407–420.
- [6] P. A. Fitzpatrick, D. Ringe, A. M. Klibanov, *Biochem. Biophys. Res. Commun.* **1994**, *198*, 675–681.

- [7] Z.-P. Wu, D. Hilvert, *J. Am. Chem. Soc.* **1990**, *112*, 5647–5648.
 [8] D. Häring, M. Herderich, E. Schüler, B. Withopf, P. Schreier, *Tetrahedron: Asymmetry* **1997**, *8*, 853–856.
 [9] D. Häring, B. Hubert, E. Schüler, P. Schreier, *Arch. Biochim. Biophys.* **1998**, *354*, 263–269.
 [10] a) F. A. Quioco, F. M. Richards, *Proc. Natl. Acad. Sci. USA* **1964**, *52*, 833–839; b) T. Zelinski, H. Waldmann, *Angew. Chem.* **1997**, *109*, 746–748; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 722–724; c) N. L. St. Clair, M. A. Navia, *J. Am. Chem. Soc.* **1992**, *114*, 7314–7316.
 [11] M. Ottesen, I. Svendsen, *Methods Enzymol.* **1970**, *19*, 199–215.
 [12] The enzyme is sold as PeptiCLEC-BL (Altus Inc., USA) and shows identical behavior.
 [13] D. L. Klayman, T. S. Griffin, *J. Am. Chem. Soc.* **1973**, *95*, 197–199.
 [14] K. L. House, R. B. Dunlap, J. D. Odom, Z.-P. Wu, D. Hilvert, *J. Am. Chem. Soc.* **1992**, *114*, 8573–8579.

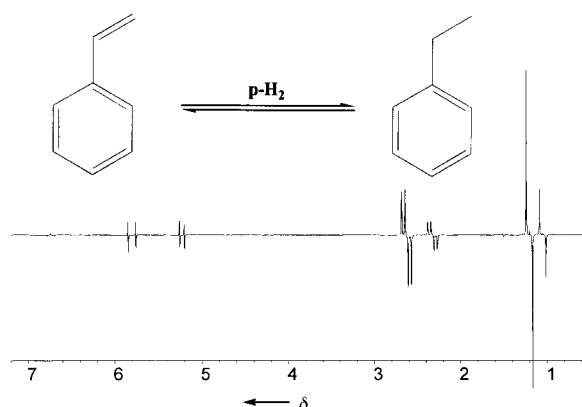


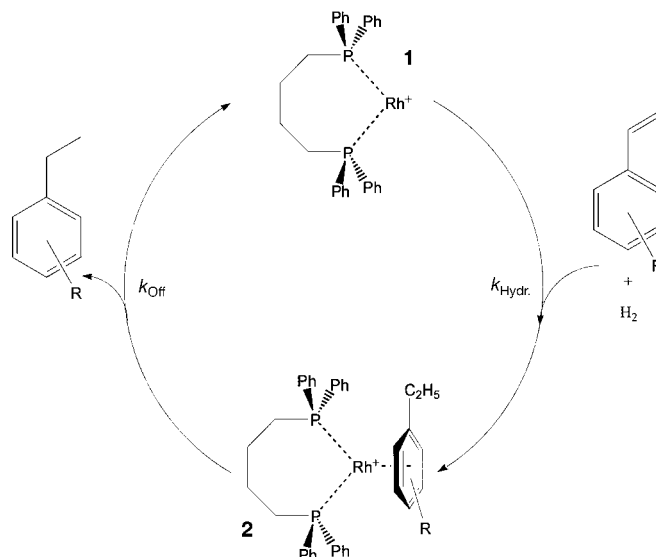
Figure 1. PHIP-NMR spectrum recorded 2 s after the end of the parahydrogen addition to styrene and $[\text{Rh}(\text{cod})(\text{dppb})]\text{BF}_4$ in $[\text{D}_6]\text{acetone}$.

Intermediate Product – Catalyst Complexes in the Homogeneous Hydrogenation of Styrene Derivatives with Parahydrogen and Cationic Rh^I Catalysts

Ralf Giernoth, Patrick Huebler, and Joachim Bargon*

PHIP-NMR spectroscopy (PHIP = *parahydrogen induced polarization*) is an analytical method that provides profound insight into the mechanisms of homogeneously catalyzed hydrogenations, presupposed that the two parahydrogen nuclei remain *J*-coupled in the product molecule.^[1–3] Recently, we have shown that PHIP-NMR spectroscopy is a suitable tool for the investigation of a pairwise hydrogen transfer into styrene, catalyzed by cationic Rh^I complexes.^[4] In contrast to former assumptions,^[5, 6] the corresponding catalytic cycle turned out to be partially reversible.^[4] Herein, we report the PHIP-NMR spectroscopic detection of hydrogenation intermediates, which remain initially coordinated to the catalyst through their arene ring and then detach from the catalyst in a slow subsequent reaction step that influences the rate of the hydrogenation.

Addition of parahydrogen to a solution of styrene and the Rh^I precatalyst $[\text{Rh}(\text{cod})(\text{dppb})]\text{BF}_4$ ^[7] in $[\text{D}_6]\text{acetone}$ gave the PHIP-NMR spectrum shown in Figure 1. The product signals of ethylbenzene appear in the range of $\delta = 1–3$ (i.e., as an antiphase quartet at $\delta = 2.65$ and an antiphase triplet at $\delta = 1.20$).^[8] In addition, high-field-shifted signals occur that show the same coupling constants as the signals of the free ethylbenzene. Evidently, they originate from product mole-



Scheme 1. Simplified scheme for the hydrogenation turnover. The kinetic parameters k_{off} and k_{hydr} determine the degree of enrichment of the intermediate complex **2**. Saturation of free coordination sites at the Rh center with solvent or substrate molecules is not considered in this scheme.

A η^6 coordination of arenes to cationic Rh^I complexes has been extensively described before in the literature.^[9a–f] For example, a slightly distorted η^6 coordination was found in the X-ray structure of $[\text{Rh}(\text{P}(\text{OMe})_3)_2]\text{BPh}_4$.^[9g] Likewise, the ^1H NMR spectrum of $[\text{Rh}(\text{nbd})(\text{C}_6\text{Me}_6)]\text{BF}_4$ ^[7] showed a singlet for the methyl protons over a wide range in temperature. The latter signal can, however, also be explained by a rapidly fluctuating η^4 coordination.^[9a]

In the PHIP-NMR spectrum, the ratio of the catalyst attached to the free ethylbenzene (deduced from Figure 1) does not correspond to the thermodynamic equilibrium. If the delay between the end of the hydrogen addition and the detection pulse is extended to more than 30 s, this ratio

[*] Prof. Dr. J. Bargon, Dipl.-Chem. R. Giernoth, Dipl.-Chem. P. Huebler
 Institut für Physikalische und Theoretische Chemie
 Wegelerstrasse 12, D-53115 Bonn (Germany)
 Fax: (+49) 0228-739424
 E-mail: bargon@uni-bonn.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Volkswagenstiftung, the Katalyse-Forschungsverbund NRW, the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (BMBF), and the Fonds der Chemischen Industrie. R. Giernoth thanks the Konrad-Adenauer-Stiftung e. V., P. Huebler thanks the Fonds der Chemischen Industrie for a graduate fellowship. We also thank Prof. Dr. A. Togni, ETH Zürich, for providing the ferrocenyl ligand (*R*)-(*S*)-JOSIPHOS.

strongly diminishes. Apparently, the production of attached species has decelerated and the detachment has now become the dominant reaction.

Consequently, conventional ^1H NMR spectroscopy of ethylbenzene and **1** (Scheme 1) in the thermodynamical equilibrium yields a much smaller ratio of intensity. Furthermore, the detection of separate and unbroadened signals leads to the conclusion that the detachment reaction is slow relative to the NMR time scale. Previous investigations of the homogeneously catalyzed hydrogenations of styrene derivatives did not take into account the consequences of an intermediate product attachment through the arene ring and the slow kinetics of the detachment process. Furthermore, the enrichment of the intermediate **2** (in contrast to the concentration in thermal equilibrium) a few seconds after the hydrogen addition is stopped suggests an important conclusion: under the assumption of the reaction scheme shown in Scheme 1, the enrichment of species **2** can only be explained, if the rate constant of its formation is at least of the same order of magnitude as the rate constant of its decomposition (or faster).

Likewise, the slow kinetics of the detachment process can be convincingly documented if the hydrogenation of $[\text{D}_8]$ styrene is investigated with the PHIP method (Figure 2). Here,

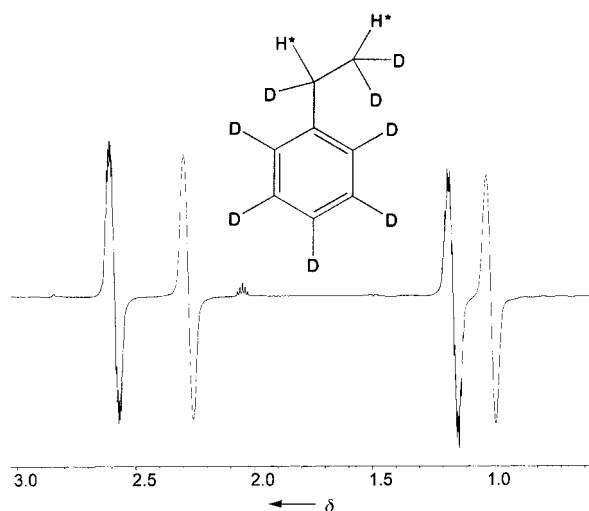


Figure 2. PHIP-NMR spectrum recorded after the parahydrogen addition to $[\text{D}_8]$ styrene and $[\text{Rh}(\text{cod})(\text{dppb})]\text{BF}_4$ in $[\text{D}_6]$ acetone.

the polarization signals of the free hydrogenation product show a fine-structure originating from the H–D couplings, whereas the corresponding signals of the bound species do not. This is due to the fact that the nonequilibrium concentration of the ethylbenzene still attached to the catalyst is diminished by the detachment process from the catalyst. Therefore, the lifetime of the bound species is shortened and the corresponding signals are broadened.^[10]

With the chiral catalyst $[(R)-(S)\text{-JOSIPHOS}]\text{Rh}(\text{cod})\text{BF}_4$ (**3**) and 3-methylstyrene as the substrate, hydrogenation with parahydrogen leads to a mixture of products, as shown in the PHIP-NMR spectrum (Figure 3). In this case, *two* high-field-shifted antiphase triplets (at $\delta = 0.93$ and 1.09) appear. They originate from two possible diastereomeric product–catalyst

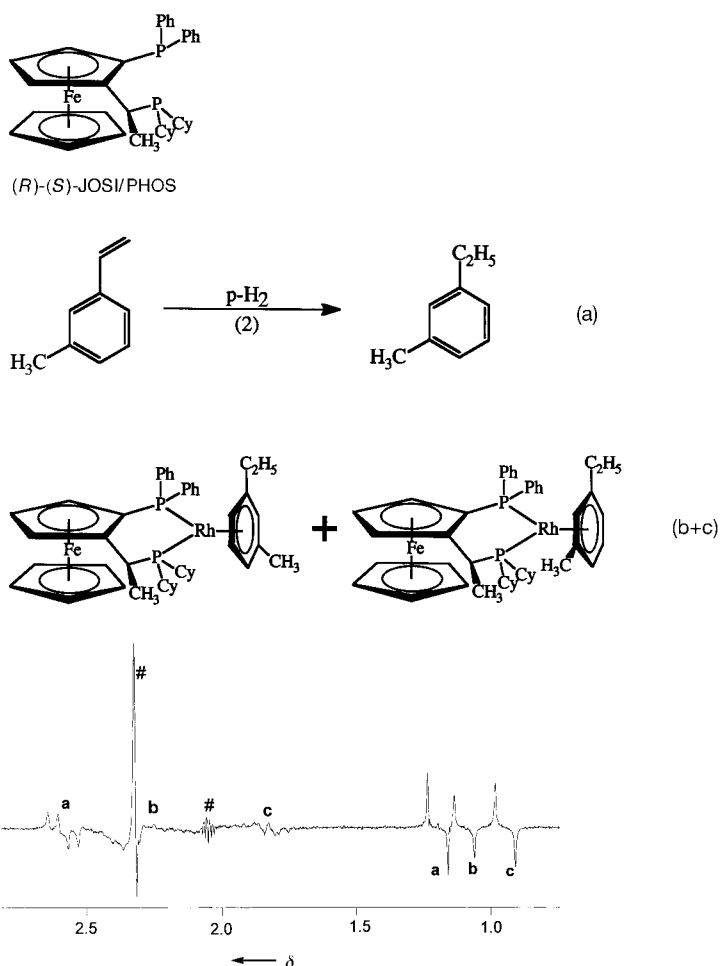


Figure 3. PHIP NMR spectrum recorded after the parahydrogen addition to 3-methylstyrene and **3** in $[\text{D}_6]$ acetone. Structural proposals are given to explain the occurrence of the signals. NMR signals marked with # result from equilibrium magnetization incompletely suppressed by the phase cycling (see Experimental Section). Cy = cyclohexyl.

complexes. The antiphase quartets corresponding to the two bound species additionally split up into two quartets as a consequence of the diastereotopy of the methylene protons. The experiment strongly indicates that, for symmetry reasons, the substrate is bound to the catalyst through the arene ring in two different fashions. Analogous to the major/minor theory of Halpern,^[11] it is possible to distinguish between two stereochemically different reaction routes for the whole time of the hydrogenation turnover. Remarkably, both routes generate identical products, whereas two stereochemically different complexes only exist as the intermediates. The corresponding intensities depend both on the rates of their formation and on the rates of their decomposition.

Experimental Section

The ^1H NMR spectra were recorded at 298 K on a Bruker AC-200 NMR spectrometer with a proton resonance frequency of 200 MHz. Hydrogen was added within 5 s. To this end, a spectrometer-controlled capillary was lowered into the probe and hydrogen was bubbled through the solution. The detection pulse was set 2–5 s after the hydrogen addition had been stopped. NMR signals originating from the magnetization in the thermo-

dynamical equilibrium^[12] were eliminated by using alternating 45° and 135° detection pulses and accumulating eight consecutive FIDs.

Received: February 16, 1998 [Z11480IE]
German version: *Angew. Chem.* **1998**, *110*, 2649–2651

Keywords: arene complexes • hydrogenations • NMR spectroscopy • parahydrogen

- [1] R. Eisenberg, *Acc. Chem. Res.* **1991**, *24*, 110–116.
- [2] C. R. Bowers, D. H. Jones, N. D. Kurur, J. A. Labinger, M. G. Prosvica, D. P. Weitekamp, *Adv. Magn. Res.* **1990**, *14*, 269–291.
- [3] J. Natterer, J. Bargon, *Prog. NMR Spectr.* **1997**, *31*, 293–315.
- [4] A. Harthun, R. Giernoth, C. J. Elsevier, J. Bargon, *Chem. Commun.* **1996**, 2483–2484.
- [5] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2134–2147.
- [6] I. Ojima, T. Kogure, N. Yoda, *J. Org. Chem.* **1980**, *45*, 4728–4739.
- [7] cod = 1,5-cyclooctadiene; dppb = 1,4-bis(diphenylphosphanyl)butane; nbd = 2,5-norbornadiene.
- [8] Due to the antiphase structure of the signals, the quartet appears with the intensities +1, +1, –1, –1, whereas the triplet appears with the intensities +1, 0, –1. The antiphase triplet, therefore, resembles a doublet with a doubled coupling constant.
- [9] a) M. Green, T. A. Kuc, *J. Chem. Soc. Dalton* **1972**, 832–839; b) J. Halpern, A. S. C. Chan, D. P. Riley, J. J. Pluth, *Adv. Chem. Ser.* **1979**, *173*, 16–25; c) J. Halpern, D. P. Riley, A. S. C. Chan, J. J. Pluth, *J. Am. Chem. Soc.* **1979**, *99*, 8055–8057; d) C. R. Landis, J. Halpern, *Organometallics* **1982**, *2*, 840–842; e) E. T. Singewald, X. Shi, C. A. Mirkin, S. J. Schofer, C. L. Stern, *Organometallics* **1996**, *15*, 3062–3069; f) M. J. Nolte, G. Gafner, L. M. Haines, *Chem. Commun.* **1969**, 1406–1407.
- [10] R. R. Ernst, G. Bodenhausen, A. Wokaun, *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Oxford University Press, New York, **1987**, pp. 211–215.
- [11] J. Halpern, *Science* **1982**, *217*, 401–407.
- [12] Magnetization in the thermal equilibrium refers to “conventional” magnetization that is determined by the Boltzmann distribution. It differs fundamentally from the magnetization resulting from a PHIP experiment: The latter is represented by the time-averaged density matrix $\sigma_{\text{PHIP}} = I_z I_z$ (for the experiments described in this paper).

Extended Calixpyrroles: *meso*-Substituted Calix[6]pyrroles**

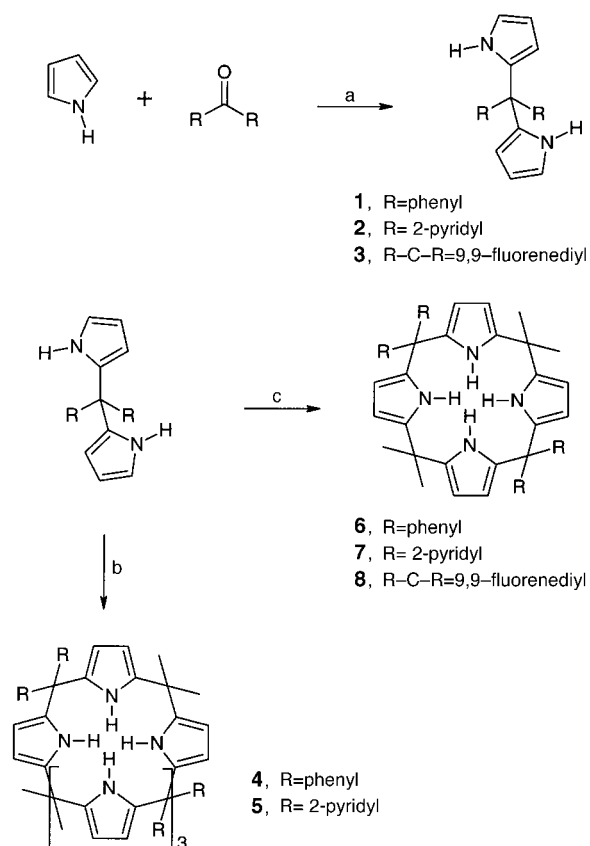
Boaz Turner, Mark Botoshansky, and Yoav Eichen*

Calix[*n*]pyrroles derived from pyrrole and simple ketones have recently become the subject of intensive research aimed at the development of novel ligands,^[1] molecular hosts for anionic species^[2–4] and for uncharged species such as simple alcohols, amines, and amides.^[5] Octaalkylcalix[4]pyrroles,

which are readily accessible, are hosts for fluoride and chloride ions both in solution and in the solid state. Some of these hosts exhibit a remarkable selectivity for binding fluorides rather than other halides even though the guest anion is bound outside the cavity.^[3]

It is anticipated that larger calix[*n*]pyrroles with larger cavities will enable selective and effective complexation of other anionic as well as uncharged species. Nevertheless, despite the rather simple synthesis of *meso*-alkylcalix[4]pyrroles, the only extended calix[*n*]pyrrole reported to date is the calix[5]pyrrole–calix[5]arene, the product of condensation of pyrrole with *p*-*tert*-butyl calix[5]arene pentamethyl ketone derivatives.^[4] Furthermore, the only calix[4]pyrroles reported to date are products of condensation between pyrrole and simple aliphatic ketones containing acidic protons at the C_α atom. Here we report on a new, two-step synthesis for the preparation of *meso*-substituted calix[6]pyrroles and some new, dissymmetric, *meso*-substituted calix[4]pyrroles.

Acid-catalyzed condensation of pyrrole with aromatic ketones such as benzophenone, di-(2-pyridyl) ketone and 9-fluorenone results in formation of the corresponding diaryl-di-(2-pyrrolyl)methanes **1–3** in moderate to good yields (reaction a in Scheme 1). The diaryl-di-(2-pyrrolyl)methane products failed to react further with the corresponding aromatic ketones to form linear polymers or cyclic products even after prolonged reaction times or at elevated temper-



Scheme 1. Synthesis of the *meso*-substituted calix[4]- and calix[6]pyrroles. a) Ketone/pyrrole = 1:2, BF₃·OEt₂, ethanol, room temperature, 7 days; b) pyrrole derivatives from reaction a) in ethanol/acetone (1/1), trifluoroacetic acid, room temperature, 7 days; c) pyrrole derivatives from reaction a) in ethanol/acetone (1/1), BF₃·OEt₂, room temperature, 7 days.

[*] Dr. Y. Eichen, B. Turner, M. Botoshansky
Department of Chemistry and Solid-State Institute
Technion – Israel Institute of Technology
Technion City, 32000 Haifa (Israel)
Fax: (+972) 4-8233735
E-mail: chryoav@technion.ac.il

[**] This work was supported by the Israel Science Foundation, administered by the Israel Academy of Sciences and Humanities and by the Fund for the Promotion of Sponsored Research at the Technion.

atures, in contrast to the reaction of pyrrole and pyrrole derivatives with most aliphatic ketones.^[6] Curiously, pyrrole failed to react with aromatic ketones bearing electron-donating or electron-withdrawing groups in the *para* position (e.g. 4,4'-dichloro-, 4,4'-dimethoxy-, or 2,7-dinitro-9-fluorenone). Table 1 summarizes some experimental results for the acid-catalyzed reaction of diaryl ketones with pyrroles.

Although diaryldi-(2-pyrrolyl)methanes fail to react further with aromatic ketones, they react readily with simple aliphatic ketones, such as acetone, in the presence of catalytic amounts of trifluoroacetic acid (reaction b in Scheme 1) to yield the corresponding *meso*-1,1,3,3,5,5-hexaaryl-*meso*-2,2,4,4,6,6-hexamethylcalix[6]pyrroles **4** and **5**. The corresponding *meso*-1,1,3,3-tetraaryl-*meso*-2,2,4,4-tetramethylcalix[4]pyrroles **6–8** were isolated as the main products when BF₃·OEt or methanesulfonic acid were used as the acid catalyst (reaction c in Scheme 1). The experimental results are summarized in Table 1.

Crystals of *meso*-1,1,3,3,5,5-hexamethyl-*meso*-2,2,4,4,6,6-hexaphenylcalix[6]pyrrole (**4**) suitable for an X-ray structure determination were obtained in the form 4·3 acetone·H₂O·CHCl₃ by slow evaporation of a chloroform/acetone solution (1:1 v/v). The macrocycle **4** forms an asymmetric, conelike structure in which all three diphenylmethylene units are situated on one side of the macrocycle, while the dimethylmethylene groups are situated on the other side (Figure 1a). One phenyl ring of each diphenylmethylene unit points perpendicular to the macrocycle plane, while the other points towards the cavity of the macrocycle. The pyrrole rings in **4** adopt a 1,3,5-*alternate* conformation, in contrast to the more abundant *cone* conformation found in calix[6]arenes^[7] or the less abundant 1,2,3-*alternate* conformation.^[8] The N–H groups of the 1,3,5 pyrrole rings point towards the side of the *meso*-dimethylene groups and are almost perpendicular to the macrocycle plane. The N–H groups of the other three pyrrole rings point towards the center of the cavity. The

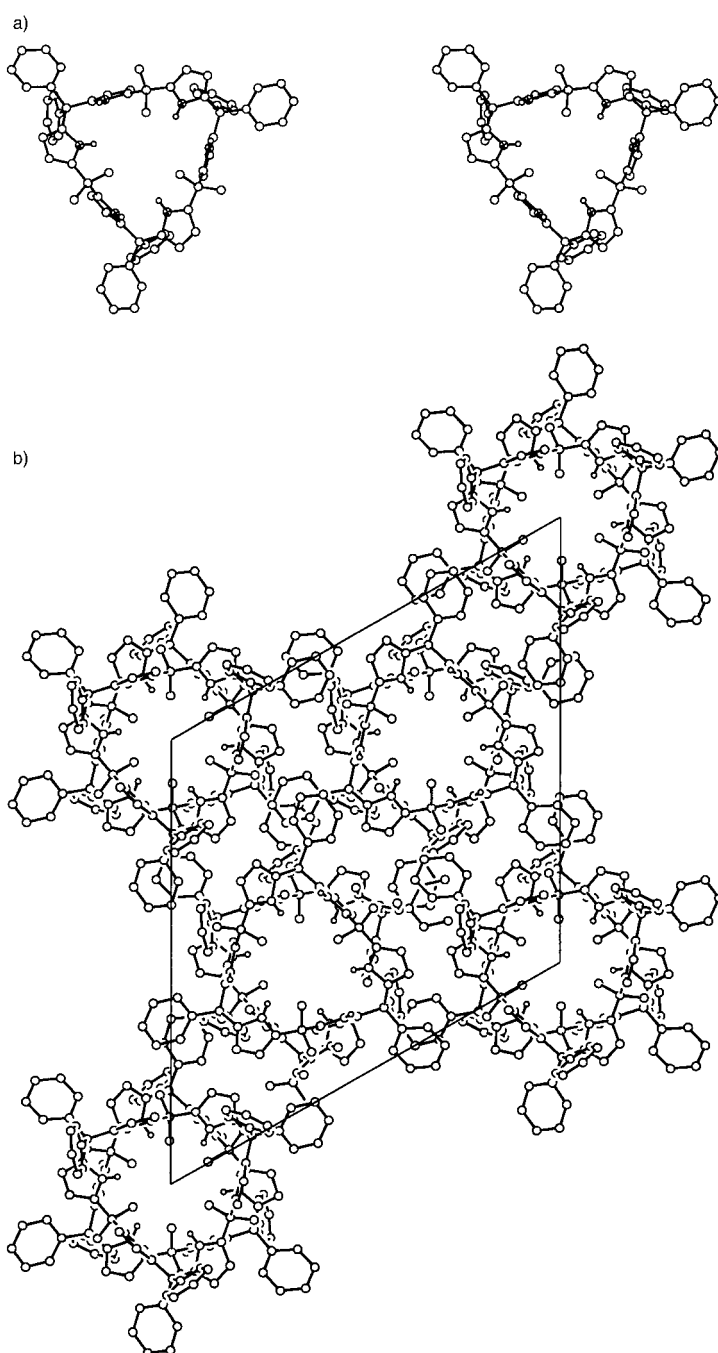


Figure 1. a) Molecular structure of **4** (stereoview). b) Axial projection of the packing of molecules of **4** in the crystal. In both figures solvent molecules and nonacidic hydrogen atoms have been omitted for clarity.

Table 1. Condensation reactions between ketones and pyrroles.

Ketone	Pyrrole	Prod.	Yield [%] uct	M.p. [°C]
benzophenone	pyrrole	1	22 ^[a] , 39 ^[b] — ^[c, d]	263–264
4,4'-dimethoxybenzophenone	pyrrole	—	— ^[a, b, c, d]	—
4,4'-dichlorobenzophenone	pyrrole	—	— ^[a, b, c, d]	—
9-fluorenone	pyrrole	3	58 ^[a] — ^[b, c, d]	238–239
2,7-dinitro-9-fluorenone	pyrrole	—	— ^[a, b, c, d]	—
di-(2-pyridyl) ketone	pyrrole	2	25 ^[a] , 35 ^[b] — ^[c, d]	165–166
dibenzosuberone	pyrrole	—	— ^[a, b, c, d]	—
acetone	1	6	20, ^[a] 56 ^[b] , 25 ^[c]	243–244
	4	9 , ^[b] 25 ^[c]	247–248	
acetone	2	—	— ^[a]	—
	7	20, ^[b] 9 ^[c]	302–303	
	5	2 ^[c]	307–308	
acetone	3	8	38 ^[a]	302–303
	—	— ^[b]	—	

[a] Methanesulfonic acid as catalyst. [b] BF₃·Et₂O as catalyst. [c] Trifluoroacetic acid as catalyst. [d] No reaction under the given conditions.

distance $d(\text{H}\cdots\text{H})$ between the protons of the latter three pyrrole rings is 4.93 Å and the cross section of the cavity measures about 60 Å². The macrocycle is composed of three different regions: a) An aromatic part formed by three phenyl rings of the *meso*-diphenylmethylene moieties. b) A central part containing three acidic protons of three pyrrole rings pointing towards the center of the cavity. c) An aliphatic part composed of three methyl groups from the *meso*-dimethylmethylene moieties with three N–H groups of three pyrrole rings pointing out of the cavity. All the solvent molecules in the crystal are situated outside the cavity, probably due to a

mismatch between their size and the size of the cavity. Figure 1b depicts the packing of the macrocycle molecules in the crystal.

The X-ray structure of crystals of the dihydrate dietherate complex of *meso*-1,1,3,3-tetramethyl-*meso*-2,2,4,4-tetraphenylcalix[4]pyrrole (**6**) is depicted in Figure 2. Crystals of $6 \cdot 2\text{H}_2\text{O} \cdot 2\text{Et}_2\text{O}$ were obtained by slow evaporation of a diethyl

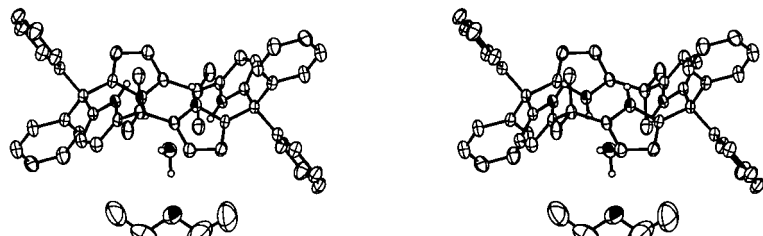


Figure 2. Molecular structure of **6** (stereoview). Nonacidic hydrogen atoms and one set of solvent molecules have been omitted for clarity.

ether/dichloromethane solution (1:1 *v/v*). Apparently, the small number of water molecules present in the crystallization solution were trapped by the macrocycle host, forming a solid-state complex. The calix[4]pyrrole receptor **6** adopts a 1,2-*alternate* conformation, the less abundant conformation of calix[4]arene^[9] and calix[4]pyrrole systems.^[4] The two water molecules are attached at the two sides of the macrocycle plane. The water molecules are attached to the macrocycle through two, almost equivalent, hydrogen bonds between the oxygen atom of the water molecule and two acidic N–H protons of adjacent pyrrole rings, ($d(\text{NH} \cdots \text{O}) = 2.170(5)$ and $2.144(4)$ Å, $\alpha(\text{N} - \text{H} \cdots \text{O}) = 161.1^\circ$ and 160.1° , respectively). One of the hydrogen atoms of each water molecule is bound to an oxygen atom of a diethyl ether molecule, ($d(\text{OH} \cdots \text{OEt}_2) = 1.753(5)$ Å, $\alpha(\text{O} - \text{H} \cdots \text{OEt}_2) = 177.9^\circ$), while the other is “sandwiched” between two adjacent electron-rich pyrrole rings, probably due to π -H interactions ($d(\text{X} \cdots \text{HO}) = 2.84$ and 2.93 Å, X = center of pyrrole ring; $\alpha(\text{O} - \text{H} \cdots \text{N}) = 127.8^\circ$ and 116.2°). The cross section of the cavity measures about $30 \text{ \AA}^2$, and is more crowded than that of its calix[6]pyrrole analogue. The two crystalline complexes **4** and **6** are monomeric and do not form hydrogen bond networks in the crystal lattice.

Preliminary studies suggest that *meso*-aryl-substituted calix[*n*]pyrroles can act as efficient hosts for neutral and charged molecules in solution and in the solid state. The investigation of the host–guest chemistry of the new systems, such as the ditopic *meso*-tetra- and *meso*-hexapyridinecalixpyrroles is currently in progress.

Experimental Section

General: NMR spectra were recorded on a Bruker AC-200F spectrometer. Mass spectra were recorded by using a triple quadrupole TSQ-70 Spectrometer (Finnigan MAT). Melting points were recorded on a PL-DSC (Polymer Laboratories) machine. Elemental analysis was performed on a CHN Analyzer (Perkin Elmer). All reagents and solvents were used as received unless stated. Anhydrous solvents were dried before use by using standard methods. Acid catalysts and pyrrole were distilled before use. General procedure for the preparation of diaryldi-(2-pyrrolyl)methanes: The ketone (2.5 mmol) and freshly distilled pyrrole (5 mmol) were dissolved in dry ethanol (45 mL). $\text{BF}_3 \cdot \text{OEt}_2$ (0.3 mL) was added to the solution, and the reaction mixture was stirred for one week at room temperature. Then solvents were removed under reduced pressure to give a

viscous residue, which was dissolved in dichloromethane and washed with aqueous ammonia solution. The aqueous phase was extracted with dichloromethane (50 mL). The organic phase was dried with anhydrous sodium sulfate, and purified by chromatography over silica (alumina for the pyridine derivatives).

General procedure for the preparation of *meso*-1,1,3,3,5,5-hexamethyl-*meso*-2,2,4,4,6,6-hexa-(2-aryl)calix[6]pyrroles and *meso*-1,1,3,3-tetramethyl-*meso*-2,2,4,4-tetraarylcalix[4]pyrroles: The di-(2-aryl)di-(2-pyrrolyl)methane (1.1 mmol) was added to a mixture of dry acetone (30 mL) and dry ethanol (30 mL). Trifluoroacetic acid (0.3 mL) (in the case of calix[6]pyrroles) or $\text{BF}_3 \cdot \text{OEt}_2$ (0.15 mL) (in the case of calix[4]pyrroles) were added to the solution and the reaction mixture was stirred at room temperature for one week. Solvents were removed under reduced pressure and the viscous residue was dissolved in dichloromethane and washed with aqueous ammonia solution. The aqueous phase was extracted with dichloromethane (50 mL). The organic phase was dried with anhydrous sodium sulfate and purified by chromatography over silica (alumina for the pyridine derivatives).

1: 40%; m.p. 263–264 °C; ^1H NMR (200 MHz, CDCl_3): $\delta = 7.93$ (br.s, 2H, NH), 7.25 (m, 6H, phenyl-H), 7.10 (m, 4H, phenyl-H), 6.73 (s, 2H, pyrrole- H_a), 6.15 (m, 2H, pyrrole- H_β), 5.94 (s, 2H, pyrrole- H_β); ^{13}C NMR (50.03 MHz, CDCl_3): $\delta = 146.0$, 135.4, 129.3, 127.9, 126.8, 117.4, 109.6, 108.1, 65.8; HR-MS: m/z : calcd for $[\text{C}_{21}\text{H}_{18}\text{N}_2]^+$: 298.1470; found for $[\text{M}]^+$ 298.1490; C, H, N analysis: calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2$: C 84.53, H 6.08, N 9.39; found: C 84.32, H 6.13, N 9.34.

2: 35%; m.p. 165–166 °C; ^1H NMR (200 MHz, CDCl_3): $\delta = 9.70$ (br.s, 2H, NH), 8.53 (d, 2H, pyridine-H), 7.60 (dt, 2H, pyridine-H), 7.14 (m, 2H, pyridine-H), 6.81 (m, 2H, pyridine-H), 6.77 (s, 2H, pyrrole- H_a), 6.18 (m, 2H, pyrrole- H_β), 5.94 (s, 2H, pyrrole- H_β); ^{13}C NMR (50.03 MHz, CDCl_3): $\delta = 165.9$, 148.3, 136.7, 133.1, 123.6, 121.5, 117.6, 109.9, 107.8, 58.2; HR-MS: m/z : calcd for $[\text{C}_{19}\text{H}_{16}\text{N}_4]^+$: 300.1375; found for $[\text{M}]^+$: 300.1374; C, H, N analysis: calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4$: C 75.98, H 5.37, N 18.65; found: C 75.63 H 5.53 N 18.48.

3: 58%; m.p. 238–239 °C; ^1H NMR (200 MHz, CDCl_3): $\delta = 7.97$ (br.s, 2H, NH), 7.74 (d, 2H, fluorene-H), 7.36 (m, 6H, fluorene-H), 6.61 (s, 2H, pyrrole- H_a), 6.09 (m, 2H, pyrrole- H_β), 6.04 (s, 2H, pyrrole- H_β); ^{13}C NMR (50.03 MHz, CDCl_3): $\delta = 149.2$, 139.6, 132.8, 128.0, 127.9, 125.3, 120.3, 117.3, 108.3, 107.2, 55.9; HR-MS: m/z : calcd for $[\text{C}_{21}\text{H}_{16}\text{N}_2]^+$: 296.1313; found for $[\text{M}]^+$: 296.1327; C, H, N analysis: calcd for $\text{C}_{21}\text{H}_{16}\text{N}_2$: C 85.11, H 5.44, N 9.45; found: C 84.83, H 5.48, N 9.36.

4: 25%; m.p. 247–248 °C; ^1H NMR (200 MHz, CDCl_3): $\delta = 7.69$ (br.s, 6H, NH), 7.20 (m, 18H, phenyl-H), 6.99 (m, 12H, phenyl-H), 5.71 (t, 6H, pyrrole- H_β), 5.58 (t, 6H, pyrrole- H_β), 1.46 (s, 18H, CH_3); ^{13}C NMR (50.03 MHz, CDCl_3): $\delta = 146.3$, 138.7, 134.1, 129.0, 127.6, 126.6, 109.5, 103.4, 55.5, 35.3, 29.6; MS (CI): m/z : 1014.6 $[\text{M}]^+$; C, H, N analysis: calcd for $\text{C}_{72}\text{H}_{66}\text{N}_6$: C 85.17, H 6.55, N 8.28; found: C 85.44, H 6.66, N 8.51.

5: 2%; m.p. 307–308 °C; ^1H NMR (200 MHz, CDCl_3): $\delta = 9.21$ (br.s, 6H, NH), 8.58 (d, 6H, pyridine-H), 7.58 (m, 6H, pyridine-H), 7.21 (m, 6H, pyridine-H), 6.64 (m, 6H, pyridine-H), 5.86 (m, 6H, pyrrole- H_β), 5.06 (m, 6H, pyrrole- H_β), 1.56 (s, 18H, CH_3); ^{13}C NMR (50.03 MHz, CDCl_3): $\delta = 164.5$, 148.4, 138.6, 136.0, 134.0, 124.1, 121.6, 107.5, 102.7, 58.2, 35.2, 28.9; MS (CI): m/z : 1021.7 $[\text{M}+\text{H}]^+$; C, H, N analysis: calcd for $\text{C}_{66}\text{H}_{60}\text{N}_{12} \cdot \text{H}_2\text{O}$: C 76.28, H 6.01, N 16.17; found: C 76.56, H 6.06, N 15.71.

6: 56%; m.p. 243–244 °C; ^1H NMR (200 MHz, CDCl_3): $\delta = 7.39$ (br.s, 4H, NH), 7.17 (m, 12H, phenyl-H), 6.97 (m, 8H, phenyl-H), 5.89 (t, 4H, pyrrole- H_β), 5.65 (t, 4H, pyrrole- H_β), 1.63 (s, 12H, CH_3); ^{13}C NMR (50.03 MHz, CDCl_3): $\delta = 146.6$, 139.3, 134.1, 128.9, 127.6, 126.3, 109.4, 102.9, 55.5, 35.3, 29.4; MS (CI): m/z : 677.0 $[\text{M}+\text{H}]^+$; C, H, N analysis: calcd for $\text{C}_{48}\text{H}_{44}\text{N}_4 \cdot 2\text{H}_2\text{O}$: C 80.87, H 6.79, N 7.86; found: C 80.50, H 6.66, N 7.88.

7: 20%; m.p. 302–303 °C; ^1H NMR (200 MHz, CDCl_3): $\delta = 9.21$ (br.s, 4H, NH), 8.58 (d, 4H, pyridine-H), 7.58 (m, 4H, pyridine-H), 7.21 (m, 4H, pyridine-H), 6.64 (m, 4H, pyridine-H), 5.86 (m, 4H, pyrrole- H_β), 5.06 (m, 4H, pyrrole- H_β), 1.56 (s, 12H, CH_3); ^{13}C NMR (50.03 MHz, CDCl_3): $\delta = 164.5$, 148.4, 138.6, 136.0, 134.0, 124.1, 121.6, 107.5, 102.7, 58.2, 35.2, 28.9; MS (CI): m/z : 681.1 $[\text{M}+\text{H}]^+$; C, H, N analysis: calcd for $\text{C}_{48}\text{H}_{40}\text{N}_8$: C 77.62, H 5.92, N 16.46; found: C 77.58, H 6.05, N 16.08.

8: 38 %; m.p. 306–307 °C; ^1H NMR (200 MHz, CDCl_3): δ = 7.90 (br.s, 4H, NH), 7.73 (d, 4H, fluorene-H), 7.38 (m, 12H, fluorene-H), 5.89 (t, 4H, pyrrole- H_β), 5.53 (t, 4H, pyrrole- H_β), 1.49 (s, 12H, CH_3); ^{13}C NMR (50.03 MHz, CDCl_3): δ = 148.4, 140.1, 139.7, 132.6, 127.8, 127.4, 124.7, 120.4, 106.3, 103.7, 55.6, 35.9, 29.8; MS (CI): m/z : 673.0 [$M+\text{H}$] $^+$; C, H, N analysis: calcd for $\text{C}_{48}\text{H}_{40}\text{N}_4 \cdot \text{H}_2\text{O}$: C 83.45, H 6.13, N 8.11; found: C 83.56, H 6.15, N 8.0.

Crystal structure determination: Crystallographic data were collected by using a Philips PW 1100 four-circle, computer-controlled, diffractometer by using graphite crystal monochromated MoK_α radiation (λ = 0.7107 Å) with $\omega/2\theta$ scan (scan width: 1.2°, scan rate: 3° min $^{-1}$). Unit cell parameters were determined by a least squares fitting of the setting angles of 25 centered reflections. The intensities of three standard reflections were measured every 120 min during the data collection. No absorption correction was performed. All non-hydrogen atoms were found by direct methods (SHELXS-86) and refined anisotropically (SHELXL-93). Hydrogen atoms were found by using a difference Fourier map and refined isotropically. The structures were solved by direct methods and refined on $|F_o|^2$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101785 (**6**) and CCDC-101786 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Crystal data for **4**: 293 K, clear crystals, crystal dimensions 0.45 × 0.35 × 0.30 mm, trigonal, $R\bar{3}$, a = 23.75(3), b = 23.75(3), c = 24.20(3) Å, V = 11822(26) Å ^{3} , Z = 18, ρ_{calcd} = 1.083 g cm $^{-3}$, μ = 0.13 mm $^{-1}$, $I > 2\sigma(I)$, $F(000)$ = 4092, 2θ range 4.3–24.08, 4329 reflections collected, 2718 independent, 289 refined parameters, $\Delta\rho_{\text{max}}$ = 0.205, wR = 0.1807, R_{obs} = 0.092.

Crystal data for **6**: 298 K, clear crystals, crystal dimensions 0.30 × 0.22 × 0.15 mm, monoclinic, $P2_1/n$ (No. 14), a = 12.080(4), b = 14.320(4), c = 14.690(4) Å, β = 102.51(3)°, V = 2480.8(13) Å ^{3} , Z = 4, ρ_{calcd} = 1.153 g cm $^{-3}$, μ = 0.072 mm $^{-1}$, $I > 2\sigma(I)$, $F(000)$ = 928, 2θ range 4.0–48.0, 3898 reflections collected, 3258 independent, 402 refined parameters, $\Delta\rho_{\text{max}}$ = 0.243, wR = 0.1912, R_{obs} = 0.068.

Received: April 1, 1998 [Z11671 IE]

German version: *Angew. Chem.* **1998**, *110*, 2633–2637

Keywords: calixpyrroles • porphyrinogens • porphyrinoids • supramolecular chemistry

- [1] a) C. Floriani, *Chem. Commun.* **1996**, 1257–1263, and references therein; b) S. Isoz, C. Floriani, K. Schenk, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1996**, *15*, 337–344; c) J. Jubb, S. Gambarotta, *Inorg. Chem.* **1994**, *33*, 2503–2504; d) C. Floriani, *Chem. Commun.* **1996**, 1257–1263, and references therein; e) U. Piarulli, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1996**, *118*, 3634–3642.
- [2] P. A. Gale, J. L. Sessler, W. E. Allen, N. A. Tvermoes, V. M. Lynch, *Chem. Commun.* **1997**, 665–666.
- [3] P. A. Gale, J. L. Sessler, V. Kral, V. M. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141.
- [4] P. A. Gale, J. L. Sessler, V. Kral, *Chem. Commun.* **1998**, 1–8.
- [5] W. E. Allen, P. A. Gale, C. T. Brown, V. M. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **1996**, *118*, 12471–12472.
- [6] B. Turner, Y. Eichen, unpublished results; cf. ref. [2–4].
- [7] a) C. D. Gutsche, *Calixarenes: Monographs in Supramolecular Chemistry* (Ed.: J. F. Stoddart), The Royal Society of Chemistry, Cambridge, **1989**, and references therein; b) P. Thuery, N. Keller, M. Lance, J.-D. Vigner, M. Nierlich, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, *20*, 373–379.
- [8] J. L. Atwood, D. L. Clark, R. K. Juneja, G. W. Orr, K. D. Robinson, R. L. Vincent, *J. Am. Chem. Soc.* **1992**, *114*, 7558–7559.
- [9] a) P. D. J. Grootenhuis, P. A. Kollman, L. C. Groenen, D. N. Reinhoudt, G. J. van Hummel, F. Ugozzoli, G. D. Andreotti, *J. Am. Chem. Soc.* **1990**, *112*, 4165–4176; b) A. Arduini, L. Domiano, A. Pochini, A. Secchi, R. Ungaro, F. Ugozzoli, O. Struck, W. Verboom, D. N. Reinhoudt, *Tetrahedron* **1997**, *53*, 3767–3776.

Mevalonate-Independent Biosynthesis of Terpenoid Volatiles in Plants: Induced and Constitutive Emission of Volatiles**

Jörn Piel, Jens Donath, Katja Bandemer, and Wilhelm Boland*

Dedicated to Professor Lothar Jaenicke on the occasion of his 75th birthday

Plants utilize volatiles to overcome constraints that result from their stationary way of life. Volatiles may serve as attractants for pollinators^[1, 2] or may attract prey to carnivorous plants^[3] over long distances. Herbivore-induced plant volatiles can even serve as cues to direct predators into the vicinity of their prey;^[4, 5] this signaling of the plant to the third trophic level is frequently interpreted as “a plant’s cry for help”.^[6] Emission of volatiles such as ethylene, methyl jasmonate, or methyl salicylate by plants under attack may even induce defense and resistance genes in undamaged neighboring plants.^[7–9] For example, in the dicotyledonous lima bean (*Phaseolus lunatus*) volatile emission can be induced by treatment with jasmonic acid or spider mite infestation.^[5, 10, 11] As shown in Figure 1, a large proportion of

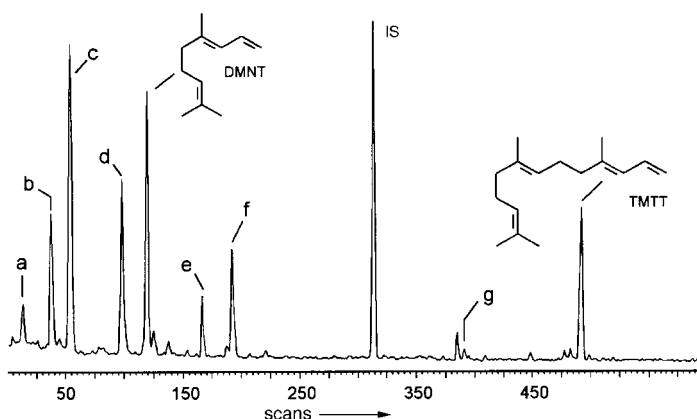


Figure 1. Profile of volatiles emitted from leaves of lima beans (*Phaseolus lunatus*) after infestation with spider mites (for details see Experimental Section). Identified compounds: a: (Z)-hex-3-enyl acetate; b: 2-ethylhexanol (contamination); c: ocimene; d: linalool; e: methyl salicylate; f: $\text{C}_{10}\text{H}_{14}\text{O}$; g: geranylacetone; DMNT, TMTT, IS: (1-bromodecane) as internal standard. After induction of lima beans with jasmonic acid (JA) a comparable blend of volatiles is released with exception of TMTT.^[10]

the emitted volatiles are terpenoids. Particularly noteworthy are the two homoterpenes 4,8-dimethylnona-1,3,7-triene (DMNT) and 4,8,12-trimethyltrideca-1,3,7,11-triene (TMTT) emitted by many higher plants in response to herbivore attack^[12, 13] and which are known to attract insectivores.^[4, 5] Both homoterpenes are synthesized de novo: mass spectro-

[*] Prof. Dr. W. Boland, Dipl.-Chem. J. Piel, Dr. J. Donath, K. Bandemer
Max-Planck-Institut für Chemische Ökologie
Tatzendpromenade 1 a, D-07745 Jena (Germany)
Fax: (+49) 3641-643670
E-mail: Boland@ice.mpg.de

[**] The project was supported by the Deutsche Forschungsgemeinschaft (SFB 284 and SPP 716).

metric studies of the volatiles emitted by cotton plants in response to herbivore feeding revealed the incorporation of ^{13}C -labeled CO_2 into several terpenoids.^[14] Differences in the extent of labeling of mono- and sesquiterpenoids were also observed after pre-treatment of freshly cut leaves of the lima bean with an aqueous solution of deuterated mevalonate ($[\text{D}_5]\text{MVA}$) followed by induction of the biosynthesis of the terpene by jasmonic acid (JA) or by infestation with spider mites.^[10, 11] Accordingly, the degree of labeling of $[\text{D}_8]\text{DMNT}$ was about 88 %, whereas monoterpenoids like $[\text{D}_4]\text{ocimene}$ and $[\text{D}_4]\text{linalool}$ exhibited a degree of labeling less than 20 % (see Figures 1 and 2).^[15]

Here we report that the differences in the extent of labeling of individual terpenoids is attributed to a different origin of their respective C_5 precursors from the long known mevalonate-dependent^[16] and the recently discovered mevalonate-independent^[17–20] pathways that both lead to isopentenyl-pyrophosphate (I-PP), the universal precursor for all terpenoids (see Scheme 1). Furthermore, we show that a parallel utilization of both pathways is possible for inducible and constitutively emitted volatiles from flowers and leaves.

Freshly cut plantlets were placed in a solution containing jasmonic acid and deuterated $[\text{D}_5]\text{MVA}$ ^[21] or deuterated deoxy-D-xylulose ($[\text{D}_2]\text{DOX}$),^[22] an intermediate^[23] of the mevalonate-independent route to I-PP, and volatiles were collected after 24 h.^[24] For the constitutive emission of volatiles from flowers and leaves no preceding induction by JA is necessary. The incorporation of the two different precursors was monitored by mass spectrometry of the trapped deuterated metabolites. In general, the extent of the labeling of the de novo synthesized compounds was high (see Figure 2). Without exception, the maximum number of isotopes present in the metabolites was in agreement with the numbers of deuterium atoms expected from the utilization of either $[\text{D}_2]\text{I-PP}$ (from $[\text{D}_2]\text{DOX}$) or $[\text{D}_4]\text{I-PP}$ (from $[\text{D}_5]\text{MVA}$). Figure 2 shows that the incorporation of $[\text{D}_2]\text{DOX}$ was particularly high in the monoterpenes $[\text{D}_4]\text{ocimene}$ (90 %) and $[\text{D}_4]\text{linalool}$ (90 %); the extent of labeling of the sesquiterpene-derived dimethylnonatriene^[25] (DMNT, see Scheme 1) was clearly lower (approximately 40 % $[\text{D}_3]\text{DMNT}$). Instead, highly labeled $[\text{D}_8]\text{DMNT}$ (up to 88 %) was obtained after preincubation with $[\text{D}_5]\text{MVA}$. On the other hand, after pretreatment with $[\text{D}_2]\text{DOX}$ and simultaneous blocking of the MVA route with inhibitors like Mevastatin^[26] or Cerivastatin^[27] the resulting $[\text{D}_3]\text{DMNT}$ also showed a high degree of labeling (approximately 70 % $[\text{D}_3]\text{DMNT}$), indicating that the biosynthesis of this important signaling compound may follow both routes. Unlike DMNT, inhibition of the MVA route could not increase the already high incorporation of $[\text{D}_2]\text{DOX}$ into the monoterpenes ocimene and linalool, thus, confirming the rather low importance of the MVA pathway for the biosynthesis of monoterpenes (Figure 2).

The incorporation of $[\text{D}_2]\text{DOX}$ into the diterpene derived TMTT^[25] was very low after elicitation with jasmonic acid.^[10] Even blocking of the MVA route with Cerivastatin did not significantly enhance the incorporation of $[\text{D}_2]\text{DOX}$ into this compound (Figure 2). However, if preincubated leaves of the

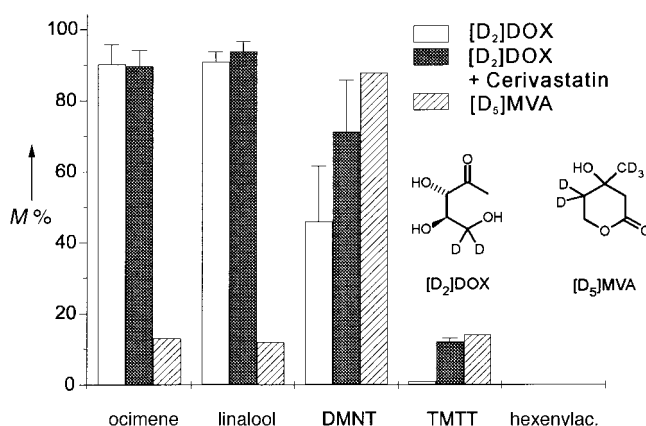
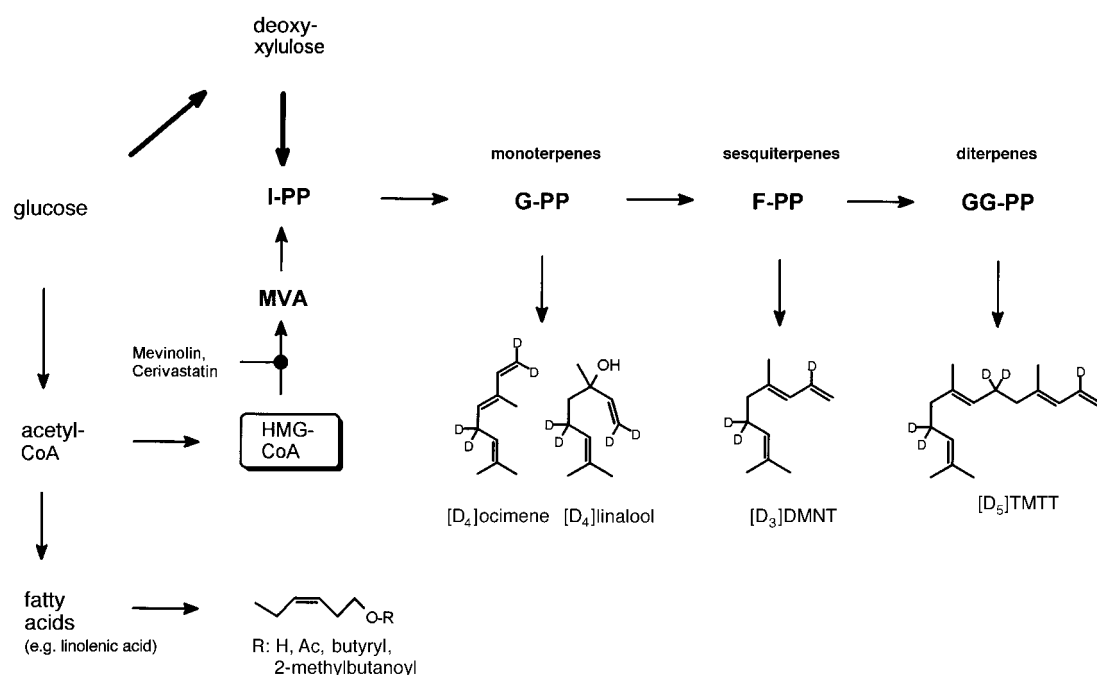


Figure 2. Degree of labeling of induced volatiles (JA treatment or spider mite infection) after preincubation of lima bean leaves (*P. lunatus*) with deuterated deoxy-D-xylulose ($[\text{D}_2]\text{DOX}$) or deuterated mevalolactone ($[\text{D}_5]\text{MVA}$). Separation and identification of compounds as described for Figure 1. Shown are relative amounts [%] of deuterium-labeled compounds of the total amounts of deuterium-labeled and unlabeled compounds. Incorporation of $[\text{D}_2]\text{DOX}$ into terpene resulted in $[\text{D}_4]\text{ocimene}$, $[\text{D}_4]\text{linalool}$, $[\text{D}_3]\text{DMNT}$, and $[\text{D}_5]\text{TMTT}$. Incorporation of $[\text{D}_5]\text{MVA}$ leads to $[\text{D}_8]\text{ocimene}$, $[\text{D}_8]\text{linalool}$, $[\text{D}_8]\text{DMNT}$, and $[\text{D}_{12}]\text{TMTT}$. The fatty acid derived hexenyl acetate showed no incorporation at all. Therefore, a random distribution of isotopes through degradation of $[\text{D}_2]\text{DOX}$ or $[\text{D}_5]\text{MVA}$ and reuse of the produced acetyl-CoA does not occur. The degree of labeling M was taken directly from the distribution of the isotopomers of the molecular ions or from the degree of labeling of the terminal prenyl fragments (M_p) (C_5H_9^+ , $m/z=69$, unlabeled; $\text{C}_5\text{H}_7\text{D}_2^+$, $m/z=71$ after incorporation of $[\text{D}_2]\text{DOX}$ or $\text{C}_5\text{H}_7\text{D}_4^+$, $m/z=73$ after incorporation of $[\text{D}_5]\text{MVA}$). Given a uniform incorporation of (labeled) I-PP into higher terpenes, the degree of labeling was extrapolated according to the equation $M_{\text{DMNT}}=2M_p-M_p^2$ and $M_{\text{TMTT}}=1-(1-M_p)^3$. After application of $[\text{D}_2]\text{DOX}$ and spider mite infection labeled $[\text{D}_5]\text{TMTT}$ (up to 94 %) was found. The figure presents only the degree of labeling after JA treatment.

lima bean were infested by spider mites, high amounts of labeled $[\text{D}_5]\text{TMTT}$ (Figure 1) were emitted (up to 92 %).

Scheme 1 illustrates the importance of the novel biosynthetic pathway (deoxyxylulose route) for the de novo synthesis of (volatile) terpenoids in lima beans. According to the above findings, $[\text{D}_2]\text{DOX}$ is preferably channeled into the mono- and diterpene biosynthesis in the plastids. The incorporation of $[\text{D}_2]\text{DOX}$ into sesquiterpenes (e.g. DMNT as a metabolite of nerolidol) that are commonly synthesized from mevalonic acid in the cytosol, is considerably lower, but not negligible (Figure 2). Apparently, a significant exchange of precursors (e.g. of isopentenyl-pyrophosphate) occurs between the cytosolic and the plastid compartments.^[28, 29] This exchange could allow stressed plants to use increasing amounts of plastidic precursors to secure the biosynthesis of sesquiterpenes as phytoalexins, if the MVA route is blocked or insufficient (Scheme 1). Whether this flexible resource management is of general importance to the plant terpene biosynthesis, or whether a deoxyxylulose route exists in the cytosol, remains to be explored.

The above findings are not limited to the dicotyledonous lima bean. High levels of incorporation of $[\text{D}_2]\text{DOX}$ in JA-induced terpenes were also observed for tobacco (*Nicotiana glauca*) and the monocotyledonous maize (*Zea mays*). After stimulation with JA, maize showed high levels of labeling of both homoterpenes ($[\text{D}_3]\text{DMNT}$, 80 %;



Scheme 1. Survey of inducible volatile production in lima beans, along the alternative pathways of biosynthesis. The mevalonate-independent route can be blocked by inhibitors of the HMGCoA-reductase (Mevinolin, Cerivastatin). The different labeling patterns of volatile terpenes after incubation with $[D_2]DOX$ are shown; the expected positions of the deuterium isotopes according to the rules for terpene biosynthesis were confirmed by mass spectrometric analysis. I-PP: isopentenyl diphosphate, G-PP: geranyl diphosphate, F-PP: farnesyl diphosphate, GG-PP: geranylgeranyl diphosphate.

Table 1. Degree of labeling M (determined mass spectrometrically from the masses of the molecular ions) of constitutively emitted leaf and flower volatiles after incubation with $[D_2]DOX$.

<i>Eucalyptus globulus</i> (leaf)		<i>Clematis vitalba</i> (flower)		<i>Hedera helix</i> (flower)		<i>Passiflora caerulea</i> (flower)		<i>Callicarpa japonica</i> (flower)	
compound	M [%]	compound	M [%]	compound	M [%]	compound	M [%]	compound	M [%]
1,8-cineole	0	β -pinene	30	sabinene	25	ocimene	83	β -pinene	74
limonene	0	limonene	24	β -myrcene	36	β -citronellal	19	linalool	20
ocimene	83	ocimene	77	limonene	20	geranylacetone	45	β -citronellol	12
DMNT	95	oxoisophorone ^[a]	0	oxoisophorone ^[a]	0	farnesene	81	nerol	37
caryophyllene	83	dihydrooxoisophorone ^[a]	0	dihydrooxoisophorone ^[a]	0	TMTT	95		
nerolidol	94	endo-borneol	15	linalool	83				
TMTT	99	nerol	33	linalooloxide	50				
		α -terpineol	11	farnesene	89				
		α -verbenone	14						
		caryophyllene	70						

[a] Compounds that will lose any incorporated deuterium during the biosynthesis of oxo- and dehydrooxoisophorone.

$[D_5]TMTT$, 96 %). Even in the evolutionary old ginkgo tree (*Ginkgo biloba*) biosynthesis of JA-inducible sesquiterpenes like linalool, copaene, caryophyllene, and farnesene mostly utilizes $[D_2]DOX$.

Similar observations were made upon treatment of flowers or leaves that constitutively emit volatiles with $[D_2]DOX$. Thus, volatile terpenoids from $[D_2]DOX$ -treated flowers of *Passiflora caerulea*, *Clematis vitalba*, *Hedera helix*, *Callicarpa japonica* and from leaves of *Eucalyptus globulus* were collected and analyzed. The results are compiled in Table 1. Depending on their different individual metabolic history (storage in vacuoles, release from conjugates, mevalonate-dependent biosynthesis) the degree of labeling of single compounds varied considerably (0 to 100 %).

The results presented here demonstrate that the recently discovered mevalonate-independent pathway (deoxyxylulose

route) is the major pathway towards volatile terpenoids in plants including the light-dependent release of isoprene from leaves (willow, poplar, etc.).^[19] However, the most important result of this work is the massive incorporation of $[D_2]DOX$ into sesquiterpenes and the flexible management of resources between cytosol and chloroplast that allows for a well-adjusted response of plants to stresses like herbivore- or pathogen infestation.

Experimental Section

For experiments with lima beans, 11–15-day-old seedlings with two fully developed primary leaves were cut and immediately placed into vials containing a solution of the deuterium-labeled precursors ($[D_5]MVA$: 3.0 mg mL⁻¹, $[D_2]DOX$: 2.0 mg mL⁻¹) in tap water; the damage caused by cutting of the stem did not induce volatile emission. After 48 h preincubation under light (270 $\mu E m^{-2} s^{-1}$), JA was added and adjusted to a final

concentration of $10.0 \mu\text{g mL}^{-1}$; alternatively pretreated leaves were infested with spider mites (*Tetranychus urticae*, approximately 50 mites per leaf; source: Neudorf, D-31860 Emmerthal, Germany) to induce volatile production. The vials with the leaves were placed into a closed system consisting of a desiccator (750 mL) equipped with a miniature circulation pump, fitted to a trap with activated charcoal (1.5 mg) for collection of the volatiles from the circulating air stream.^[24] The collection of volatiles was maintained for 24 h and then the compounds were desorbed from the carbon traps with CH_2Cl_2 ($2 \times 20 \mu\text{L}$) and immediately analyzed by GLC-MS. Inhibitor experiments with Mevastatin or Cerivastatin were conducted by sequential treatment of the plants with the inhibitor for 24 h (Mevastatin: $0.2\text{--}0.5 \text{ mg mL}^{-1}$; Cerivastatin: 0.2 mg mL^{-1}) followed by incubation with $[\text{D}_5]\text{MVA}$ or $[\text{D}_2]\text{DOX}$ and an elicitor as described above. All experiments were repeated at least twice ($n=3$) to secure reproducibility. The GC-MS analyses were performed on a Fisons MD 800 equipped with a fused silica column, coated with SE 30 ($15 \text{ m} \times 0.31 \text{ mm}$). The temperature was programmed from 50°C (2 min isothermal) to 200°C at $10^\circ\text{C min}^{-1}$; GC-interface: 270°C ; scan area $35\text{--}350 \text{ Da s}^{-1}$.

Received: November 26, 1997

Revised version: June 18, 1998 [Z11197IE]

Delayed at authors' request

German version: *Angew. Chem.* **1998**, *110*, 2622–2625

Keywords: biosynthesis • isotopic labeling • jasmonic acid • terpenoids

- [24] J. Donath, W. Boland, *Phytochemistry* **1995**, *39*, 785–790.
- [25] A. Gäbler, W. Boland, U. Preiss, H. Simon, *Helv. Chim. Acta* **1991**, *74*, 1773–1789, and references therein.
- [26] A. Endo, *Trends Biochem. Sci.* **1981**, *6*, 10–13.
- [27] H. Bischoff, R. Angerbauer, J. Bender, E. Bischoff, A. Fagiotto, D. Petzinna, J. Pfitzner, A. C. Porter, D. Schmidt, G. Thomas, *Atherosclerosis* **1997**, *135*, 119–130.
- [28] H. Kleinig, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1989**, *40*, 39–59.
- [29] J. Gershenzon, R. Croteau in *Lipid Metabolism in Plants* (Ed.: T. Moore), CRC, Boca Raton, FL, **1993**, pp. 339–388.

Catalytic Enantioselective Retro-Aldol Reactions: Kinetic Resolution of β -Hydroxyketones with Aldolase Antibodies**

Guofu Zhong, Doron Shabat, Benjamin List, James Anderson, Subhash C. Sinha, Richard A. Lerner,* and Carlos F. Barbas III*

The development of methodologies for the stereoselective synthesis of β -hydroxyketones (aldols) has long been the subject of intensive studies in organic chemistry. This challenge was initially met through the use of stoichiometric amounts of chiral auxiliaries^[1] and most recently by the design of transition metal based catalysts.^[2] An alternative to direct enantioselective synthesis is the application of the strategy of kinetic resolution.^[3, 4] Surprisingly, the application of this strategy to the aldol problem has received little, if any, attention.^[3b, 5, 6] Recently we have described the generation, broad scope, structure, high stereoselectivity, and mechanism of two aldolase antibodies 38C2 (Aldrich: Aldolase antibody 38C2, cat. no. 47,995-0 and 48,157-2) and 33F12.^[7] Since these antibodies are able to catalyze both the aldol addition and the retro-aldol reaction we envisioned that they may be useful in the kinetic resolution of aldols. A single antibody catalyst could then be used for the preparation of both aldol enantiomers (Scheme 1).

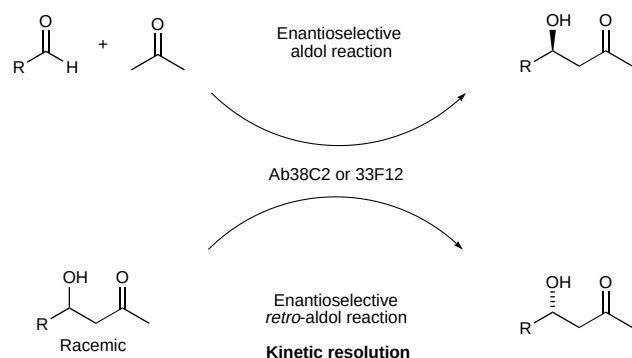
In order to address the potential of antibody-catalyzed kinetic resolution of aldols, we studied the kinetics of the retro-aldolization of (*S*)- and (*R*)-**1**. Antibody 38C2 catalyzed the retro-aldolization of (*S*)-**1** following Michaelis–Menten kinetics ($k_{\text{cat}} = 1.4 \text{ min}^{-1}$, $K_{\text{m}} = 270 \mu\text{M}$). The relative rate

- [1] J. T. Knudsen, L. Tollsten, L. G. Bergström, *Phytochemistry* **1993**, *33*, 253–280.
- [2] J. H. Langenheime, *J. Chem. Ecol.* **1994**, *20*, 1223–1280.
- [3] G. C. Kite, *Biochem. System. Ecol.* **1995**, *23*, 343–354.
- [4] M. K. Stowe, T. C. J. Turlings, J. H. Loughrin, W. J. Lewis, J. H. Tumlinson, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 23–28, and references therein.
- [5] M. Dicke, M. W. Sabelis, J. Takabayashi, J. Bruin, M. A. Posthumus, *J. Chem. Ecol.* **1990**, *16*, 3091–3118.
- [6] M. Dicke, M. Sabelis in *Insect Chemical Ecology. An Evolutionary Approach* (Eds.: B. D. Roitberg, M. B. Isman), Chapman and Hall, New York, **1992**, pp. 122–155.
- [7] E. E. Farmer, C. A. Ryan, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 7713–7716.
- [8] M. Miksch, W. Boland, *Experientia* **1996**, *52*, 739–743.
- [9] V. Shulaev, P. Silverman, I. Raskin, *Nature* **1997**, *385*, 718–721.
- [10] W. Boland, J. Hopke, J. Donath, J. Nüske, F. Bublit, *Angew. Chem.* **1995**, *107*, 1715–1717; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1600–1602.
- [11] J. Hopke, J. Donath, S. Bleichert, W. Boland, *FEBS Lett.* **1994**, *352*, 146–150.
- [12] W. Boland, Z. Feng, J. Donath, A. Gäbler, *Naturwissenschaften* **1992**, *79*, 368–371.
- [13] M. Dicke, T. A. van Beek, M. A. Posthumus, N. Ben Dom, H. van Bokhoven, A. E. de Groot, *J. Chem. Ecol.* **1990**, *16*, 381–396.
- [14] P. W. Paré, J. H. Tumlinson, *Nature* **1997**, *385*, 30–31.
- [15] J. Donath, Dissertation, Universität Karlsruhe, **1994**.
- [16] J. Chapell, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1995**, *46*, 521–527.
- [17] M. Rohmer, M. Knani, P. Simonin, B. Sutter, H. Sahn, *Biochem. J.* **1993**, *295*, 517–524.
- [18] M. Rohmer, M. Seemann, S. Horbach, S. Bringer-Meyer, H. Sahn, *J. Am. Chem. Soc.* **1996**, *118*, 2564–2566, and references therein.
- [19] J. G. Zeidler, H. K. Lichtenthaler, H. U. May, F. W. Lichtenthaler, *Z. Naturforsch. C* **1997**, *52*, 15–23, and references therein.
- [20] D. Arigoni, S. Sagner, C. Latzel, W. Eisenreich, A. Bacher, M. Zenk, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 10600–10650, and references therein.
- [21] D. E. Cane, H. J. Ha, D. B. MacIlwaine, K. O. Pascoe, *Tetrahedron Lett.* **1990**, *31*, 7553–7556.
- [22] J. Piel, W. Boland, *Tetrahedron Lett.* **1997**, *38*, 6387–6390.
- [23] T. Duval, J.-M. Bravo, C. Pale-Grosdeman, M. Rohmer, *Tetrahedron Lett.* **1997**, *27*, 4769–4772.

[*] Prof. Dr. R. A. Lerner, Prof. Dr. C. F. Barbas III, Dr. G. Zhong, Dr. D. Shabat, Dr. B. List, J. Anderson, Dr. S. C. Sinha
The Skaggs Institute for Chemical Biology and
the Department of Molecular Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 619-784-9098
E-mail: carlos@scripps.edu

[**] This study was supported in part by the National Institutes of Health [CA27489]. We thank the Sharpless group and K. R. Dress for assistance and B.L. thanks the Alexander von Humboldt Foundation, Germany, for a Feodor Lynen Fellowship.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

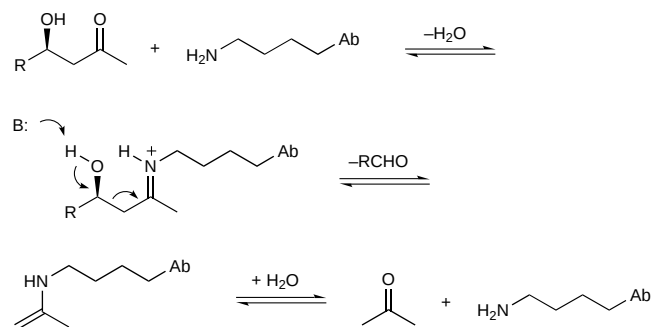


Scheme 1. Preparation of both enantiomers of β -hydroxyketones by the same antibody catalysts.

enhancement over background provided by the antibody for this reaction ($k_{\text{cat}}/k_{\text{uncat}}$) is 1.7×10^7 and the catalytic proficiency^[8] with this substrate, $(k_{\text{cat}}/K_m)/k_{\text{uncat}}$, is $6.2 \times 10^{10} \text{ M}^{-1}$ making it the most proficient catalytic antibody prepared to date.^[9]

To confirm catalysis proceeded as designed, we studied the reaction in the presence of the mechanism-based inhibitor 2,4-pentanedione. This inhibitor forms a UV-active vinylogous amide with the ϵ -amino group of the active site lysine residue of these catalysts.^[7a] Incubation of ab38C2 with a mole equivalent of 2,4-pentanedione prior to this retro-aldol reaction assay resulted in nearly complete inhibition of catalysis, indicating that the retro-aldol reaction takes place at the active site of the antibody with the essential participation of the ϵ -amino group of the active site lysine residue. In contrast, antibody catalysis of the retro-aldol reaction of *R*-**1** did not follow Michaelis–Menten kinetics and the reaction was not inhibited by 2,4-pentanedione, suggesting that catalysis occurred without the essential participation of the active site lysine residue. Treatment of the data obtained for (*R*)-**1** as a general base-catalyzed reaction allowed for the determination of a rate constant of $1.0 \times 10^{-5} \text{ min}^{-1} \mu\text{M}^{-1}$, which is similar to the value of $1.7 \times 10^{-4} \text{ min}^{-1} \mu\text{M}^{-1}$ determined for aminoacetonitrile catalyzed retro-aldolization of this substrate.^[7c] In accord with our earlier structural and kinetic studies of these catalysts the mechanism of the antibody-catalyzed retro-aldol reaction of (*S*)-aldols is shown in Scheme 2.

Given this high degree of enantioselectivity, we studied ab38C2-catalyzed kinetic resolution of *rac*-**1**. Since the K_m value for acetone is approximately 1 M in the aldol reaction and the aldol is provided at 5.0 mM in the retro-aldol reaction, the equilibrium between the aldol and its components favors retro-aldolization. Determination of the *ee* of the unconverted aldol (*R*)-**1** as a function of reaction progress allowed for the stereoselectivity factor *s* to be determined to be 228.^[10] At 52% completion of the retro-aldol reaction catalyzed by either antibody 38C2 or 33F12, the unconverted aldol (*R*)-**1** was obtained in essentially optically pure form ($>99\%$ *ee* as determined by chiral-phase high-performance liquid chromatography). We have previously reported antibodies 38C2 and 33F12 catalyzed syntheses of (*S*)-**1** with $>99\%$ *ee*. Thus, by applying antibody-catalyzed aldol and retro-aldol reactions both optical isomers of **1** were obtained in essentially



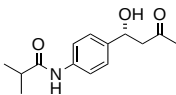
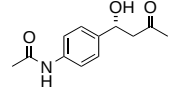
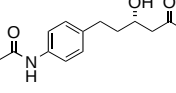
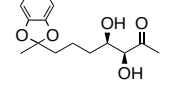
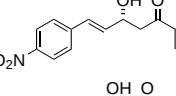
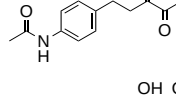
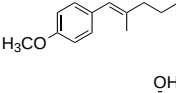
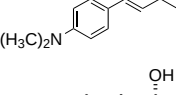
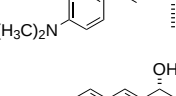
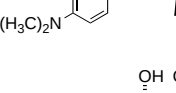
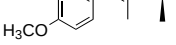
Scheme 2. The mechanism of the antibody-catalyzed retro-aldol reaction.

enantiomerically pure form. This high degree of enantioselectivity has been observed previously in antibody-catalyzed ester hydrolysis reactions but is certainly not a feature common to all such catalysts.^[9c, 11]

We studied the generality of antibody-catalyzed kinetic resolution of a variety of aldols (Table 1). Most reactions reached $\sim 50\%$ conversion after 4 h, the unconverted aldol was recovered and the *ee* value determined as described above. The antibody catalysts are very stable and could be recovered for reuse. Further, the aldehyde product could also be recovered and recycled. In most cases the unconverted aldols were recovered with very high *ee* values.

The isolation of (*S*)-**3** in $>99\%$ *ee* at 67% conversion demonstrates the power of kinetic resolution to provide high *ee* values in a case where the antibody-catalyzed synthesis of (*R*)-**3** provided only 58 or 69% *ee* for antibodies 38C2 and 33F12, respectively. Preparation of (3*S*,4*R*)-**4** in $>99\%$ *ee* demonstrates the utility of ab38C2 in the preparation of enantiomerically pure α,β -dihydroxyketones. We have subsequently used this compound and its optically pure enantiomer, (3*R*,4*S*)-**4**, prepared by antibody-catalyzed synthesis in $>99\%$ *ee* in the synthesis of members of the brevicomin family of beetle pheromones.^[12] Resolution of compounds **5** and **6** demonstrate that the scope of these catalysts is greater in the retro-aldol direction than we previously observed in the synthetic aldol addition direction. Previously we failed to observe antibody catalysis of reactions involving either 2,3-butanedione or 3-methyl-2-pentanone as aldol donor substrates, yet aldols incorporating these fragments are substrates for kinetic resolution with these catalysts.^[7c] The increased scope of the catalysts for these substrates may be explained by more favorable K_m values for these substrates in the retro-aldol reaction as compared to their constituents. Compounds **7–10** were designed to allow for a sensitive continuous UV assay to monitor retro-aldolization. Retro-aldolization of these substrates results in the production of either 4-methoxy- α -methylcinnamaldehyde ($\epsilon_{315} = 21\,722 \text{ M}^{-1} \text{ cm}^{-1}$) or 4-dimethylaminocinnamaldehyde ($\epsilon_{400} = 23\,000 \text{ M}^{-1} \text{ cm}^{-1}$), each exhibiting a new λ_{max} removed in the spectra from that of their parent aldols. These assays were applied in kinetic studies. As shown in Table 2 the efficiency with which these compounds are processed by ab38C2 is exceptional. The cinnamoyl functionality present in these aldols may be desirable for their subsequent transformation since the alkene may be oxidatively cleaved by ozonolysis to yield a ketone or aldehyde group.

Table 1. Antibody-catalyzed kinetic resolution of a variety of β -hydroxyketones (aldols).

Product	Conversion[%]	ee[%]	
	(<i>R</i>)- 1	52	> 99 ^[a]
	(<i>R</i>)- 2	52	> 99
	(<i>S</i>)- 3	67	> 99
	(3 <i>S</i> ,4 <i>R</i>)- 4	55	> 99
	(<i>R</i>)- 5 ^[b]	51	> 99
	(<i>R</i>)- 6 ^[b]	81	80
	(<i>R</i>)- 7	50	95
	(<i>R</i>)- 8	50	90
	(4 <i>R</i> ,5 <i>S</i>)- 9	59	> 99
	(4 <i>S</i> ,5 <i>S</i>)- 9 ^[b]	50	58
	(4 <i>S</i> ,5 <i>R</i>)- 10	54	98

[a] Both antibodies 38C2 and 33F12 were used. [b] Absolute configurations were assigned by analogy.

Table 2. Kinetic parameters for antibody-catalyzed retro-aldol reactions.

Substrate	$k_{\text{cat}}^{[b]}$ [min ⁻¹]	K_m [mM]	$k_{\text{cat}}/k_{\text{un}}$	$(k_{\text{cat}}/K_m)/k_{\text{un}}$ [M ⁻¹]
(S)-1	1.4	0.27	1.7×10^7	6.2×10^{10}
(±)-7	2.2	0.016	1.0×10^5	6.3×10^9
(±)-8 ^[c]	4.7	0.041	2.6×10^4	6.4×10^8
(±)-anti-9	1.5	0.017	4.4×10^4	5.3×10^8
(±)-anti-10	1.4	0.093	1.9×10^4	2.1×10^8

[a] Conditions: pH 7.0 in the presence of 2.0 μM active sites of ab38C2. [b] Per antibody active site. k_{cat} obtained by fitting experimental data to nonlinear regression analysis using Grafit software. [c] Data was determined in phosphate-buffered saline (PBS) at pH 7.4.

Resolution of compounds **9** and **10** were studied since they represent key building blocks for the synthesis of more complex polypropionates.^[13] For *syn*-**9**, 99% *ee* was obtained

at 59% conversion. We had not previously addressed in detail the stereochemistry at the α -position in reactions with an aliphatic branch at this position. The resolution of *anti*-isomers of **9** and **10** provided 58 and 98% *ee* at 50 and 54% conversion, respectively. Thus, both *syn* and *anti* stereoisomers can be obtained with high *ee* values, making this an attractive strategy for polypropionate synthesis. While all entries in Table 1 are aromatic aldols, the scope of antibodies 38C2 and 33F12 is not limited to aromatic molecules as demonstrated in earlier studies.^[7d,e] Thus, we expect that simple aliphatic aldols should also be good substrates for kinetic resolution with these catalysts.

The special ontogeny of these aldolase antibodies^[7d] has resulted in biocatalysts of unusually broad scope and as shown in Tables 1 and 2 enantioselectivities and catalytic efficiencies that are unique in the area. In the course of these studies we developed a sensitive continuous UV assay for the detection of retro-aldol activity that will facilitate the identification of new catalysts of this reaction.

Received: April 24, 1997 [Z11776IE]

German version: *Angew. Chem.* **1998**, *110*, 2609–2612

Keywords: aldol reactions • asymmetric synthesis • catalytic antibodies • enantiomeric resolution • retro-aldol reactions

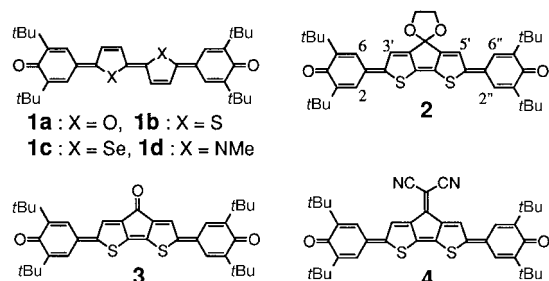
- Reviews of the aldol reaction: S. Masamune, W. Choy, J. S. Peterson, L. R. Sita, *Angew. Chem.* **1985**, *97*, 1–31; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1–30; C. H. Heathcock, *Aldrichim. Acta* **1990**, *23*, 99–111; D. A. Evans, *Science* **1988**, *240*, 420–426; C. H. Heathcock in *Comprehensive Organic Synthesis*, Vol. 2 (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 133–319; I. Peterson, *Pure Appl. Chem.* **1992**, *64*, 1821–1830.
- A. Yanagisawa, Y. Matsumoto, H. Nakashima, K. Asakawa, H. Yamamoto, *J. Am. Chem. Soc.* **1997**, *119*, 9319–9320, and references therein; E. M. Carreira, W. Lee, R. A. Singer, *J. Am. Chem. Soc.* **1995**, *117*, 3649–3650; D. A. Evans, D. W. C. MacMillan, K. R. Campos, *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860; for the only case where ketones and not pre-formed enolates are used see: Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942–1944; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871–1873.
- a) D. J. Ager, M. B. East, *Asymmetric Synthetic Methodology*, CRC Press, FL, USA, **1996**; b) C.-H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, **1994**.
- K. Faber, *Biotransformations in Organic Chemistry*, 2nd ed., Springer, Berlin, **1995**.
- For an antibody-catalyzed Henry type retro-aldol reaction see: M. E. Flanagan, J. R. Jacobsen, E. Sweet, P. G. Schultz, *J. Am. Chem. Soc.* **1996**, *118*, 6078–6079; for a retro-aldol reaction catalyzed by an antibody with an amine cofactor see: J.-L. Reymond, *Angew. Chem.* **1995**, *107*, 2471–2473; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2285–2287.
- H. J. M. Gijsen, L. Qiao, W. Fitz, C.-H. Wong, *Chem. Rev.* **1996**, *96*, 443–473; C.-H. Wong, R. L. Halcomb, Y. Ichikawa, T. Kajimoto, *Angew. Chem.* **1995**, *107*, 453–474; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 412–432.
- a) J. Wagner, R. A. Lerner, C. F. Barbas III, *Science* **1995**, *270*, 1797–1880; b) R. Björnstedt, G. Zhong, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1996**, *118*, 11720–11724; c) G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F. Barbas III, *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132; d) C. F. Barbas III, A. Heine, G. Zhong, T. Hoffmann, S. Gramatikova, R. Björnstedt, B. List, J. Anderson, E. A. Stura, E. A. Wilson, R. A. Lerner, *Science* **1997**, *278*, 2085–2092; e) T. Hoffmann, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1998**, *120*, 2768–2779.
- A. R. Radzicka, R. A. Wolfenden, *Science* **1995**, *267*, 90–93.

- [9] a) N. R. Thomas, *Nat. Prod. Rep.* **1996**, 479–511; b) J. D. Stewart, S. J. Benkovic, *Nature* **1995**, 375, 388–391; c) C.-H. L. Lo, P. Wentworth, Jr., K. W. Jung, J. Yoon, J. A. Ashley, K. D. Janda, *J. Am. Chem. Soc.* **1997**, 119, 10251–10252.
 [10] G. Balavoine, A. Moradpour, H. B. Kagan, *J. Am. Chem. Soc.* **1974**, 96, 5152–5158.
 [11] a) K. D. Janda, S. J. Benkovic, R. A. Lerner, *Science* **1989**, 244, 437–440; b) F. Tanaka, K. Kinoshita, R. Tanimura, I. Fujii, *J. Am. Chem. Soc.* **1996**, 118, 2332–2339; c) H. Wade, T. S. Scanlan, *J. Am. Chem. Soc.* **1996**, 118, 6510–6511; d) S. J. Pollack, P. Hsiun, P. G. Schultz, *J. Am. Chem. Soc.* **1989**, 111, 5961–5962.
 [12] B. List, D. Shabat, C. F. Barbas III, R. A. Lerner, *Chem. Eur. J.* **1998**, 4, 881–885.
 [13] I. Paterson, J. A. Channon, *Tetrahedron Lett.* **1992**, 33, 797–800.

The First Heterotriquinone and Dicyano-heterotriquinone Methide That Undergo a Five-Stage Amphoteric Redox Reaction**

Kazuko Takahashi,* Satoshi Fujita, Kimio Akiyama, Misao Miki, and Kazunori Yanagi

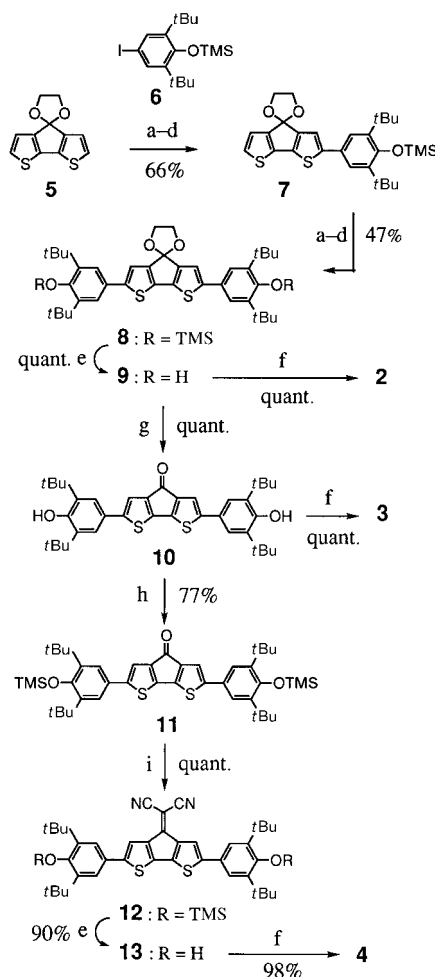
In recent years heterocycle-incorporated conjugated molecules possessing interesting electrochemical and optical properties have been widely developed in the field of fundamental molecular and supramolecular chemistry.^[1] We have recently synthesized heteroquaterphenokinones **1a–d**, which exhibit an intense absorption band in the near-IR (NIR) region and undergo amphoteric redox reactions.^[2] However, these quinones exist in a flexible conformation in solution at around room temperature, and afford unstable



anion radicals on electrochemical reduction. Furthermore, they have relatively weak electron-accepting abilities, which are sometimes unfavorable when these quinones are to be

employed as functional molecules such as electron-accepting or electron-transporting mediators, and as functional units in supramolecular electric systems that can be modulated by external electrical stimulation.^[3] To create a new type of organic redox system that does not have these disadvantages, we have now designed and synthesized the novel heterotriquinone **3** and the novel dicyanoheterotriquinone methide **4**, as the first heterotriquinone systems. On the grounds of the enhanced conjugation between the three terminal electron-withdrawing groups, each of these compounds should have a rigid conformation and thus exhibit strong electron-accepting properties, which should facilitate the formation of stable radical anions and radical trianions. Indeed, we have found that **4** exhibits very characteristic electrochemical behavior and strong electron-accepting ability; it undergoes a novel amphoteric five-stage one-electron redox reaction.

The heterotriquinone **3**, the dicyanoheterotriquinone methide **4**, and the ethylenedioxy derivative **2** (a reference compound for **3** and **4**) were synthesized according to the routes shown in Scheme 1, starting from the reaction of **5**^[4]



Scheme 1. Reagents and conditions: a) BuLi (1.0 equiv), diethyl ether, 0 °C, 1 h; b) ZnCl₂ (1.0 equiv), THF, 0 °C, 1.5 h; c) [PdCl₂(PPh₃)₂] (0.5 equiv), THF, DIBAH (0.1 equiv), room temperature, 15 min; d) **6** (1.0 equiv), THF, room temperature, 1 h; e) TBAF (2 equiv), THF, 0 °C, 2 min; f) PbO₂ (10 equiv), CH₂Cl₂, room temperature, 30 min; g) conc. HCl/THF (1/10), room temperature, 1 h; h) *N,O*-bistrimethylsilylaceta-mide (BSA) (ca. 1.2 equiv), CH₃CN, 75 °C, 1 h; i) CH₂(CN)₂ (1.2 equiv), benzene/piperidine (cat.), reflux, 22 h.

[*] Prof. Dr. K. Takahashi, S. Fujita
 Department of Chemistry, Graduate School of Science
 Tohoku University, Sendai 980-8578 (Japan)
 Fax: (+81) 22-217-6560
 E-mail: tkazuko@synchem.chem.tohoku.ac.jp
 Prof. Dr. K. Akiyama
 Institute for Chemical Reaction Science, Tohoku University
 Sendai, 980-8577 (Japan)
 Dr. K. Yanagi, M. Miki
 Biotechnology Laboratory, Sumitomo Chemical Co., Ltd.
 Takarazuka 665 (Japan)

[**] This work was supported by a Grant-in-Aid for Science Research from Ministry of Education, Science and Culture.

with **6**.^[5] Compounds **2–4**^[6] are quite stable both in the solid state and in solution in common organic solvents and possess a rigid conformation even in solution, as evident from the inequivalence of the 2/2'' protons and carbon atoms from the 6/6'' positions of the six-membered ring in ¹H and ¹³C NMR spectra. The X-ray crystallographic analysis disclosed that **4** adopts an essentially coplanar conformation (Figure 1).^[7] The

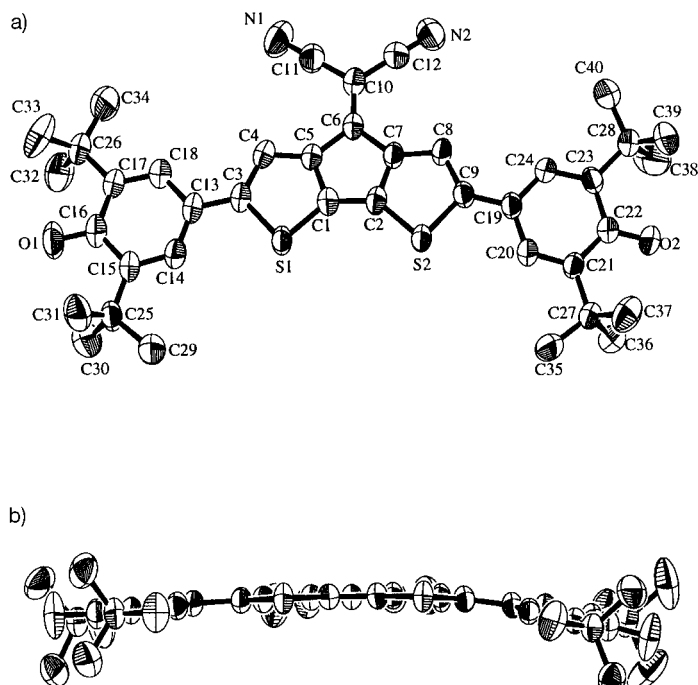


Figure 1. Molecular structure of **4** (ORTEP): a) top view, b) side view.

torsion angle between the dicyanomethylene group and the central 4*H*-cyclopentadithiophene moiety and that between the terminal six-membered rings and this moiety are 2.02° and 2.31°, respectively. Selected spectroscopic data of **2–4** are listed in Table 1. The IR frequencies of the carbonyl groups on the six-membered rings of **3** and **4** are higher by 6 and 8 cm^{−1} than that of **2**. The ¹³C NMR resonances of C-4/4'', C-1/1'', and C-3'/5' of **3** and **4** appear at lower field than the respective carbon atoms of **2**. These facts indicate that the carbonyl and the dicyanomethylene groups at the C-4' position exert a significant electron-withdrawing effect on the terminal six-membered rings and that the effect is stronger in the dicyanomethylene than in the carbonyl group. These quinones exhibit a very intense π - π^* absorption maximum at 650–700 nm, which is accompanied by a weak n - π^* absorption band at 790–890 nm due to the carbonyl groups in the six-

membered rings (Table 1). Both the π - π^* and n - π^* absorption maxima of **4** showed marked bathochromic shifts of 30 and 88 nm, respectively, from those of **2**, while the bathochromic shifts are much smaller for **3**. According to MNDO PM-3 calculations,^[8] the LUMO of **4** (−2.764 eV) lies 0.13 eV lower in energy than that of **3** (−2.631 eV) and 0.31 eV lower than that of **2** (−2.454 eV). In contrast, the HOMO of **4** is only 0.07 eV lower in energy than that of **3**. Therefore, the large bathochromic shifts of the π - π^* and n - π^* bands of **4** can be mainly ascribed to the lowering of the LUMO of **4**. This is also supported by the strong electron-accepting ability of **4** (see below).

Interestingly, the electrochemical behavior of **4** is remarkably different from that of **3**. The reduction of **4** occurs in three consecutive reversible one-electron transfer steps, as shown by cyclic voltammetry (Figure 2), affording the stable

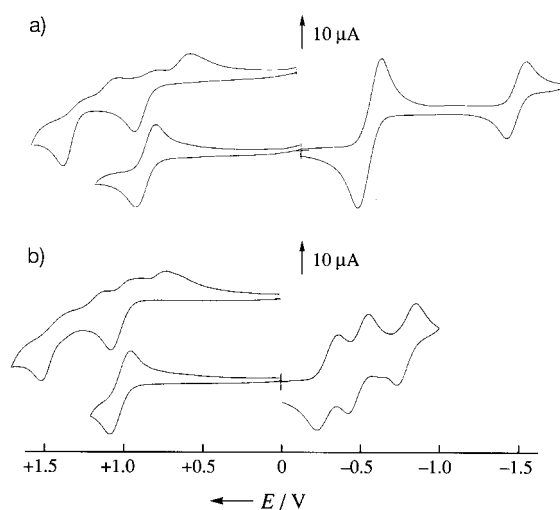


Figure 2. Cyclic voltammograms of a) **3** and b) **4**; compound (1.0 mM), electrolyte: Bu₄NClO₄ (ca. 0.1 M) in CH₂Cl₂ at room temperature, (scan rate: 50 mV s^{−1}), reference electrode: SCE.

radical anion (**4**^{•−}), dianion (**4**^{2−}), and radical trianion (**4**^{3−}). In contrast, **3** is reduced apparently in a one-step, two-electron transfer process affording the dianion (**3**^{2−}) at a half-wave reduction potential of −0.44 V vs. standard calomel electrode (SCE), and in a subsequent one-step, one-electron transfer process that affords the radical trianion (**3**^{3−}) at a half-wave reduction potential of −1.37 V vs. SCE (Table 2). By considering that **2** is also reduced apparently in a one-step, two-electron transfer process affording the dianion (**2**^{2−}) at −0.50 V vs. SCE, the one-electron transfer at −1.37 V in **3** should correspond to the reduction of the carbonyl group in the central five-membered ring. The coalescence of the first

Table 1. Spectroscopic data of **2–4**.

Compound	¹³ C NMR (CDCl ₃): δ ^[a]					IR (KBr): $\tilde{\nu}$ [cm ^{−1}]		Vis/NIR (CH ₂ Cl ₂): λ [nm] (lg ϵ)	
	C-4/4''	C-1/1''	C-3'/5'	C-4'	C-7'a/7'b	CO(6) ^[b]	CO(5) ^[c] or CN	π - π^*	n - π^* ^[d]
2	185.42	126.24	117.70	104.68	142.23	1583	—	606 (4.85), 660 (5.29), 718 sh (4.70)	790 sh (3.80)
3	185.54	128.62	120.61	179.53	144.29	1589	1714	615 (4.84), 665 (5.27)	804 br (3.61)
4	185.62	129.27	123.48	149.95	139.71	1591	2225	637 (4.96), 692 (5.15)	878 br (3.12)

[a] 150 MHz, SiMe₄. [b] The CO frequency of the six-membered ring. [c] The CO frequency of the five-membered ring. [d] This band showed a blue shift on changing the solvent from nonpolar to polar.

Table 2. Oxidation and reduction potentials^[a] of **2–4** in CH₂Cl₂.

Com- pound	E_1^{ox}	$E_{\text{p}2}^{\text{ox}}$	E_1^{red}	E_2^{red}	E_3^{red}	$\Delta E_{1-2}^{\text{red}}$	$\Delta E_{2-3}^{\text{red}}$	$E_1^{\text{sum[b]}}$
2	+0.88	+1.49	−0.50 (2e)	—	0	—	—	1.38
3	+0.98	+1.52	−0.44 (2e)	−1.37	0	0.93	1.42	
4	+1.01	+1.51	−0.30	−0.50	−0.80	0.20	0.30	1.31

[a] In V vs. SCE, obtained from the cyclic voltammogram (0.1 M TBAP, scan rate: 50 mV s^{−1}). [b] $E_1^{\text{sum}} = E_1^{\text{ox}} + (-E_1^{\text{red}})$.

and second one-electron reduction potentials in **3** reveals a short life time of **3**^{•−} and a very small Coulomb repulsion^[9] in **3**^{2−}, thus the bulk of the negative charges in **3**^{2−} should localize on the well-separated oxygen atoms at the six-membered rings, as in **2**^{2−}. On the other hand, the Coulomb repulsion in **4**^{2−} is significantly larger than that of **3**^{2−}, since the $\Delta E_{1-2}^{\text{red}}$ (= $E_2^{\text{red}} - E_1^{\text{red}}$) value of **4** is 0.2 V. This evidence indicates that the negatively charged centers in **4**^{2−} should be located much closer than in **3**^{2−}. Moreover, the Coulomb repulsions in **4**^{2−} and **4**^{3−} are not significantly different from each other: the difference between the values of $\Delta E_{1-2}^{\text{red}}$ and $\Delta E_{2-3}^{\text{red}}$ is not very large (Table 2). These facts indicate that the first one-electron transfer reaction in **4** occurs on the central dicyanomethylene group at −0.30 V (vs. SCE), followed by the stepwise second and third one-electron transfers at each of the oxygen atoms at the six-membered rings. This is remarkable if one considers that the dicyanomethylene group is bound to a cyclopentadienylidene-type unsaturated five-membered ring, which might induce an antiaromatic $4n\pi$ electronic structure and the radical anion might be highly stabilized by the contribution of the aromatic galvinoxyl unit, if the first one-electron reduction occurs at one of the oxygen atoms at the six-membered rings.

The radical anion **4**^{•−} (deep red species) and the radical trianions **4**^{3−} (deep orange species) and **3**^{3−} (yellow species) are highly stable species that exhibit well-resolved EPR spectra (Figure 3). These were obtained by electrolyses of **3** and **4** in dichloromethane with Bu₄NClO₄ as an electrolyte at room temperature, although **3**^{•−} could not be detected by the EPR spectroscopy. The hyperfine structure (hfs) constants, a^{H} (2H) = 0.065 mT and a^{N} (2N) = 0.106 mT, provided from the EPR spectrum of **4**^{•−}, can be assigned to the protons H-3' and 5' and two equivalent nitrogen atoms of the CN groups, respectively. This hfs pattern is consistent with the prominent feature of the LUMO of **4**, which bears large π -AO coefficients at the dicyanomethylene group and its adjacent C-2', C-3', C-3'a, C-4', C-4'a, C-5', and C-6' carbon atoms, as shown in Figure 3d. Thus the existence of significant spin density on the dicyanomethylene group and the adjacent carbon atoms in **4**^{•−} has been proved. The unpaired electron of **4**^{3−} mainly delocalizes on the cyclopentadithiophene carbon atoms: the EPR spectrum of **4**^{3−} (Figure 3b) gave a hfs constant a^{H} (2H) = 0.122 mT which can be assigned to H-3' and H-5', and there are relatively large π -AO coefficients at the cyclopentadithiophene carbon atoms in the NLUMO of **4** (Figure 3e). The unpaired electron of **3**^{3−} mainly delocalizes on the carbonyl group at the five-membered ring and the adjacent C-2', C-3', C-3'a, C-4', C-4'a, C-5', and C-6' carbon atoms: the hfs constant, a^{H} (2H) = 0.15 mT, assigned to H-3'

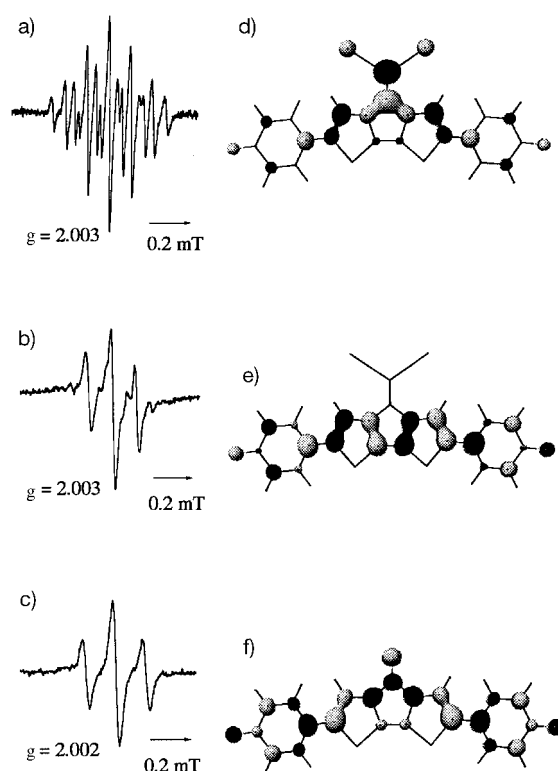
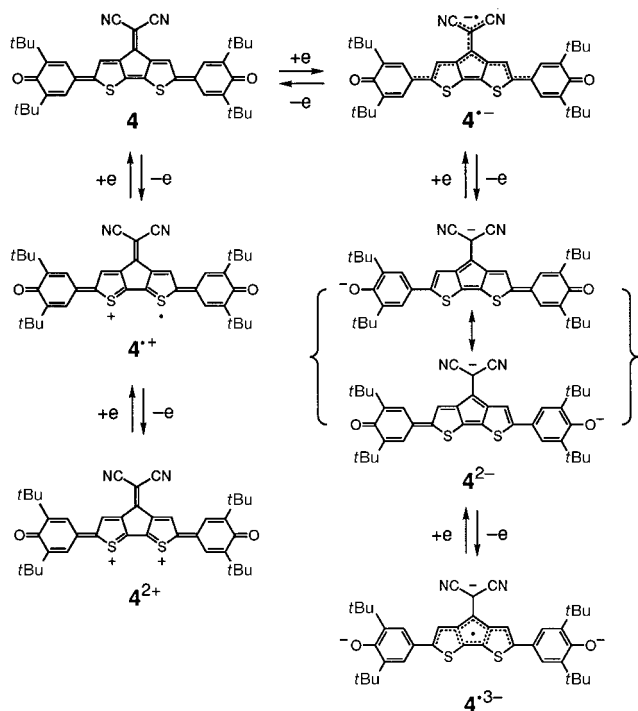


Figure 3. EPR spectra of a) **4**^{•−}, b) **4**^{3−}, and c) **3**^{3−} in CH₂Cl₂ at room temperature, and π -AO coefficients in the d) LUMO of **4**, e) NLUMO of **4**, and f) NLUMO of **3**, which were obtained from MNDO PM3 calculations. The *tert*-butyl groups of **4**, **3**, and **2** were replaced by hydrogen atoms for the calculations.

and H-5', could be deduced from the EPR spectrum of **3**^{3−} (Figure 3c) and there are large π -AO coefficients on these atoms in the NLUMO of **3** (Figure 3f). From these EPR spectroscopic analyses it is revealed that the spin density of the galvinoxyl units appears to be very small in **4**^{3−} and **3**^{3−}, although the π coefficients of the phenoxyl units are not negligibly small.^[10] These characteristic properties of **3** and **4** can be rationalized by the remarkable difference in the electron-accepting abilities between the dicyanomethylene and carbonyl groups at the C-4' position. It is also surprising that the reduction potential at the C-4' position shifted to a more positive value by 1.07 V when a carbonyl group was replaced by a dicyanomethylene group!

The E_1^{red} values become more positive in the series **2** < **3** < **4** (Table 2) in accord with the increase in the electron-accepting ability of the C-4' group. This order also coincides well with the extent of stabilization of the LUMOs of these compounds. The quinones **2–4** are amphoteric compounds: they undergo two successive one-electron oxidations in the anodic direction affording the corresponding radical cations and dication of these quinones analogous to those of **1b**.^[2] The $E_{\text{p}x}^{\text{ox}}$ values of **2–4** increase with increasing electron-accepting ability of the C-4' group, but the extent of the increase on going from **3** to **4** is fairly small. Since the E_1^{sum} (= $E_1^{\text{ox}} + (-E_1^{\text{red}})$)^[11] value, a convenient measure for evaluating the amphotericity of a specified molecule, is smallest in **4**, the amphotericity is highest in **4**.

Thus, we have clarified that the redox reaction sequence of compound **4** proceeds according to the routes shown in Scheme 2. Indeed, **4** is the first example of a redox-amphoteric compound with a closed-shell, which undergoes a reversible five-stage one-electron reaction and has a strong



Scheme 2. Five-stage one-electron redox reaction sequence for **4**.

electron-accepting ability. Compounds that undergo more than four-stage one-electron redox reactions are very rare, although one example of a redox-amphoteric compound with a closed-shell is known that undergoes a six-stage redox sequence,^[12] but with very low reduction and very high oxidation potentials. Likewise some examples of open-shell radicals that undergo six-stage redox reactions^[13] have been reported. Furthermore we have established that the hybridized functionalization of dicyanomethylene and carbonyl groups in triquinonoid systems appears to be fruitful for creating novel and unique redox systems.

Received: January 19, 1998 [Z113751E]
German version: *Angew. Chem.* **1998**, *110*, 2658–2662

Keywords: heterocycles • quinones • radical ions • redox chemistry

Chem. Int. Ed. Engl. **1996**, *35*, 648; F. Würthner, M. S. Vollmer, F. Effenberger, P. Emele, D. U. Meyer, H. Port, H. C. Wolf, *J. Am. Chem. Soc.* **1995**, *117*, 8090; J. Daub, J. Salbeck, T. Knöchel, C. Fisher, H. Kunkey, K. M. Rapp, *Angew. Chem.* **1989**, *101*, 1541; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1494; A. Knorr, J. Daub, *Angew. Chem.* **1995**, *107*, 2925; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2664.

- [4] P. Jordens, G. Rawson, H. Wynberg, *J. Chem. Soc. (C)*, **1970**, 273.
- [5] K. Takahashi, T. Suzuki, K. Akiyama, Y. Ikegami, Y. Fukazawa, *J. Am. Chem. Soc.* **1991**, *113*, 4576.
- [6] Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds. Selected physical data for **2**: metallic green powder; m.p. (decomp) >300 °C; ¹H NMR (600 MHz, CDCl₃): δ = 1.35 (36H, s, tBu), 4.42 (4H, s, OCH₂CH₂O), 7.14 (2H, s, H-3', 5'), 7.18 (2H, d, J = 2.5 Hz, H-2, 2''), 7.32 (2H, d, J = 2.5 Hz, H-6, 6''); ¹³C NMR, IR, and VIS/NIR: see Table 1; MS: *m/z* (%): 642 (100) [*M*⁺]; **3**: golden needles, m.p. (decomp) 291–292 °C; ¹H NMR (600 MHz, CDCl₃): δ = 1.34 (18H, s, tBu), 1.35 (18H, s, tBu), 7.16 (2H, d, J = 2.6 Hz, H-2, 2''), 7.31 (2H, d, J = 2.6 Hz, H-6, 6''), 7.50 (2H, s, H-3', 5'); ¹³C NMR, IR, and VIS/NIR: see Table 1; MS: *m/z* (%): 598 (100) [*M*⁺]; **4**: golden crystals, m.p. (decomp) 264–265 °C; ¹H NMR (600 MHz, CDCl₃): δ = 1.35 (36H, s, tBu), 7.12 (2H, d, J = 2.5 Hz, H-2, 2''), 7.33 (2H, d, J = 2.5 Hz, H-6, 6''), 7.92 (2H, s, H-3', 5'); ¹³C NMR, IR, and VIS/NIR: see Table 1; MS: *m/z* (%): 646 (100) [*M*⁺].
- [7] The unit cell contains two molecules of **4** which stack along the *a* axis in a face-to-face manner; the dicyanomethylene groups are directed in opposite directions. The asymmetric unit contains 1.5 benzene solvent molecules. Crystal data for **4**: C₄₀H₄₂N₂O₂S₂ · 1.5 C₆H₆, *M*_r = 764.07, triclinic space group *P* $\bar{1}$ (no. 2); *a* = 11.211(2), *b* = 20.738(3), *c* = 10.006(2) Å, α = 97.76(1), β = 106.54(1), γ = 91.04(1)°; *V* = 2211.2(6) Å³; ρ_{calcd} = 1.147 g cm⁻³; *Z* = 2; *F*(000) = 814; Cu_{Kα} radiation (λ = 1.54178 Å); *T* = 296 K. Of a total of 7029 collected reflections, 6558 were unique, and 3227 with *I* > 3σ (*I*) were observed. The structure was solved by Patterson methods by using DIRDIF92. Final *R* factor = 0.054 and *R*_w factor = 0.073. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101013. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [8] J. J. Stewart, *J. Comput. Chem.* **1989**, *10*, 211.
- [9] J. B. Torrance, *Acc. Chem. Res.* **1979**, *12*, 79.
- [10] The hfs constant for H-2/2'', 6/6'' (4H) was clearly observed in the radical anions of heteroterphenonquinones even when the spin density on the galvinoxyl unit is fairly small.^[5] The NLUMO coefficients on the galvinoxyl units become smaller when the calculation is performed on the tetra-*tert*-butyl derivatives. The *g* values of **4**^{•-}, **4**^{••-}, and **3**^{•-} are scarcely different from one another. This can be mainly ascribed to the lack of spin density on the sulfur atoms of these species.
- [11] *E*₁^{sum} expresses the span of the oxidation and reduction potentials. A small *E*₁^{sum} value thus is indicative of a compound with a high amphotericity: K. Nakasuji, K. Yoshida, I. Murata, *J. Am. Chem. Soc.* **1982**, *104*, 1432; reference [2b], and references therein.
- [12] J. Heinze, *Angew. Chem.* **1981**, *93*, 186; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 202.
- [13] J. Rieser, G. A.-Elenien, K. Wallenfels, H. Baumgärtel, *Tetrahedron Lett.* **1976**, 2363; T. Kubo, K. Yamamoto, K. Nakasuji, T. Takui, I. Murata, *Angew. Chem.* **1996**, *108*, 456; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 439.

- [1] For some recent examples see: K. Takahashi, *Pure Appl. Chem.* **1993**, *65*, 127; G. M. Tsivgoulis, J.-M. Lehn, *Angew. Chem.* **1995**, *107*, 1188; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1119; M. Munakata, L. P. Wu, T. K.-Sowa, M. Maekawa, Y. Suenaga, K. Furuichi, *J. Am. Chem. Soc.* **1996**, *118*, 3305; M. Hanazawa, R. Sumiya, Y. Horikawa, M. Irie, *J. Chem. Soc. Chem. Commun.* **1992**, 206; T. Saika, T. Iyoda, K. Honda, T. Shimidzu, *J. Chem. Soc. Chem. Commun.* **1992**, 591; S. Tarutani, T. Mori, H. Mori, S. Tanaka, K. Takahashi, *Chem. Lett.* **1997**, 627.
- [2] a) K. Takahashi, A. Gunji, K. Yanagi, M. Miki, *J. Org. Chem.* **1996**, *61*, 4784; b) K. Takahashi, T. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 5483.
- [3] For some recent examples: T. Benincori, E. Brenna, F. Sanniccolo, L. Trimarco, G. Zotti, P. Sozzani, *Angew. Chem.* **1996**, *108*, 718; *Angew.*

Electrochemical Synthesis of Polypyrrole Nanowires**

Christine Jérôme and Robert Jérôme*

Semiconductor circuitry has gone through spectacular developments in the past decades, as testified by the impressive density of electronic components and very high processing speeds. Nowadays, microelectronics and molecular electronics are fields of tremendous research activity. There is accordingly a need for molecular conductors with nanometer dimensions. As an answer to that challenge, molecular wires are being developed. Several research groups are investigating doped conducting polymers such as polyacetylene, polyaniline, polypyrrole, and other polyheterocycles and attempting their confinement in appropriate porous materials.^[1]

For example, polypyrrole, polythiophene, and polyaniline were recently grown in layered materials such as FeOCl and V₂O₅.^[2] Zeolite molecular sieves are also good candidates for inclusion chemistry owing to their structurally well defined, nanometer-size channel structures. Several studies are concerned with the confinement of molecular conductors in zeolite host channels, and molecular wires have been obtained by chemical polymerization of pyrrole in zeolite channels in the presence of iron(III) ions.^[3] Other examples include formation of filaments of conducting polymers (ca. 50–1000 nm in diameter) in the transverse pores of Nucleopore and Anopore membranes, as described by Martin,^[4] whose research group synthesized 10- μ m long polypyrrole and poly(3-methylthiophene) fibrils with diameters in the range of 0.03–1 μ m in nucleopore membranes.^[5] More recently,^[6] the electrochemical synthesis of fibrils and tubules of conducting polymers and of metal tubules and rods was carried out in similar host membranes. It is noteworthy that template-synthesized polypyrrole has higher conductivity than the bulk material; this is explained by the better packing and alignment of the polymer chains.^[7]

Here we report on a new electrochemical method for the synthesis of conducting polypyrrole nanowires. For the last few years, we have been interested in the electrodeposition of insulating polymer films onto metallic substrates (Ni, Fe).^[8] These films are designated as “grafted films”, since they have the unique property of remaining attached to the electrode surface even when they are prepared and kept in a solvent in which the polymer exhibits good solubility. This electrografting reaction was successfully achieved in appropriate solvents with some acrylic monomers, such as acrylonitrile and ethyl acrylate (EA).^[9] In this work, we used this strategy to prepare a new substrate that can act as a template for the electro-

polymerization of pyrrole to give nanowires. Figure 1 shows a typical cyclic voltammogram for the electrografting of poly-(ethyl acrylate) PEA film onto a vitreous carbon electrode in

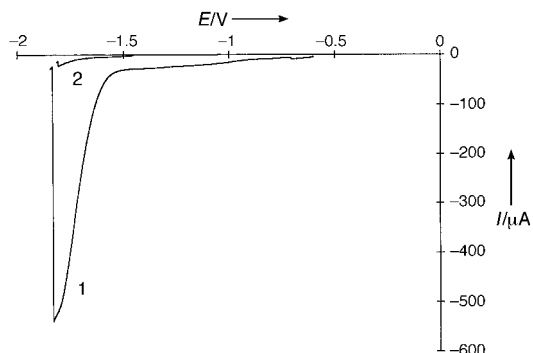


Figure 1. Cyclic voltammogram for grafting of ethyl acrylate (2.5 M in 0.05 M TEAP/DMF) onto a vitreous carbon electrode. Scanning rate = 20 mV s⁻¹; 1: first scan; 2: second scan.

a bath containing 0.05 M tetraethylammonium perchlorate (TEAP) and 2.5 M ethyl acrylate in dimethylformamide (DMF). The potential was scanned up to the top of the first reduction wave ($E = -1.8$ V (Pt electrode), scan rate = 20 mV s⁻¹, curve 1) and held until the current decreased as the result of the growth of an insulating polymer film. A second cathodic scan (curve 2) completes the passivation of the electrode. The PEA film was carefully washed with pure DMF to remove unchanged monomer and any soluble contaminants. This modified electrode was then immersed in a solution of 0.05 M TEAP and 0.005 M ferrocene in DMF to determine whether it could be used as an anode in further experiments. Figure 2 shows the corresponding voltammogram (curve B) together with that for a pure vitreous carbon

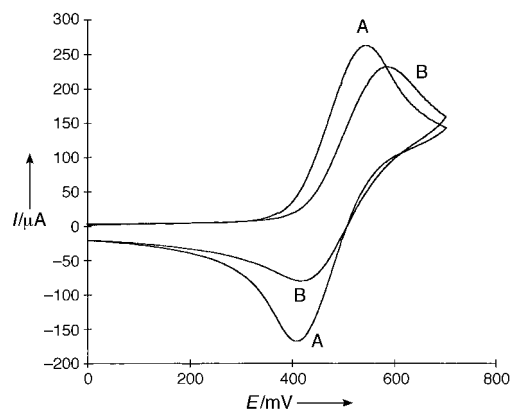


Figure 2. Cyclic voltammogram of ferrocene (0.005 M) in 0.05 M TEAP/DMF; scanning rate 20 mV s⁻¹ with a pure vitreous carbon anode (A) and with a PEA-grafted carbon anode (B).

anode (curve A). The higher potential difference between the oxidation and reduction maxima of the Fe^{II}/Fe^{III} couple for curve B indicates a small increase in resistivity for the precoated electrode due to the grafted PEA film. This coating is thus not completely insulating, most likely because swelling by DMF allows ferrocene to diffuse to the surface of the carbon electrode and to react quasireversibly.

[*] Prof. R. Jérôme, C. Jérôme
Center for Education and Research on Macromolecules
University of Liège
Sart-Tilman, B6, B-4000 Liège (Belgium)
Fax: (+32) 04-3663497
E-mail: rjerome@ulg.ac.be

[**] The authors are indebted to the Services Fédéraux des Affaires Scientifiques, Techniques et Culturelles for general support under the auspices of the Poles d'attraction Interuniversitaires: Supramolecular Catalysis and Supramolecular Chemistry. C.J. is grateful to the Fonds de la Recherche pour l'Industrie et l'Agriculture for a fellowship.

Pyrrole was electropolymerized at a constant current of 0.5 mA in a bath containing 0.05 M TEAP and 0.1 M pyrrole in DMF. The chronopotentiogram for the PEA grafted vitreous carbon anode shows a typical behavior (Figure 3, curve A): an overpotential followed by a significant decrease in potential.

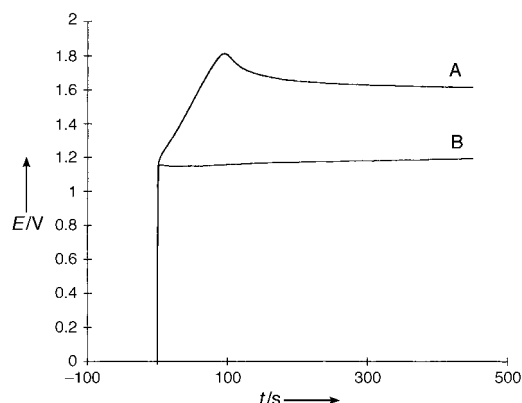


Figure 3. Chronopotentiogram of pyrrole (0.1 M in 0.05 M TEAP/DMF) with a PEA-grafted carbon anode (A) with a pure carbon anode (B). $I = 0.5$ mA.

In the case of a pure carbon anode (curve B), a monotonous curve is observed at a lower potential. Clearly, polypyrrole (PPY) can be synthesized on a PEA-coated carbon electrode, although a higher potential is required, in particular to initiate the polymerization of pyrrole. The current density is the same as that of the pure carbon anode. X-ray photoelectron spectroscopic analysis of the PEA-grafted electrode after anodic polarization gave the composition C 71, N 1.25, O 27.5, Cl 0.23 % and thus confirmed the coexistence of PEA and PPY on the electrode. A PPY/PEA weight ratio of 33 % and a PPY doping level of 0.2 were calculated.

The composite PPY/PEA electrode was investigated by scanning electron microscopy (SEM) coupled with energy dispersive analysis of X-rays (EDAX). Figure 4 clearly shows the formation of a nanowire, which grows from the electrode surface through a hole in the PEA coating. The EDAX

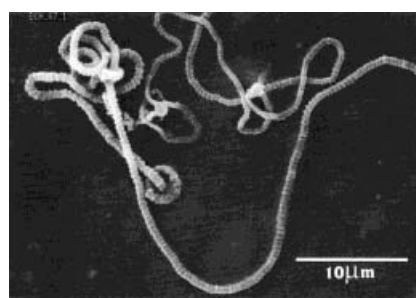


Figure 4. SEM image of a PPY wire on PEA-grafted carbon anode.

analysis shows a large amount of Cl on the wire, which is consistent with the perchlorate doping of PPY. Moreover, the PEA grafted film is very uniform with no visible defects or holes in the surface. Note, however, that the PEA film investigated by SEM was previously dried, whereas pyrrole polymerization was conducted with a PEA film that was swollen by DMF. Thus, diffusion of pyrrole through the swollen film allows electropolymerization to be initiated on

the surface of the vitreous carbon according to the usual mechanism reported by Andrieux et al.^[10] Asavapiryanont et al.^[11] studied the further stages of pyrrole polymerization, which involves an instantaneous nucleation process with three-dimensional growth on the conducting surface. Therefore, in accordance with this nucleation process, the increase in E in the first part of the chronopotentiogram would correspond to the formation and growth of nuclei, which, however, is perturbed by the grafted PEA chains. As a result, the growth of the PPY nuclei would be the rate-limiting step responsible for the increase in potential. However, since the tethered PEA chains have some mobility in DMF, they can be displaced laterally by the growing PPY, so that small channels become available and allow PPY to emerge from the PEA film with a certain diameter. Then the potential decreases until it reaches a plateau value imposed by the diffusion of the monomer through the PEA layer.

The only explanation for wire formation is that the polymerization proceeds on the surface of the electrode and thus beneath the PEA film (Figure 5). Therefore, pyrrole

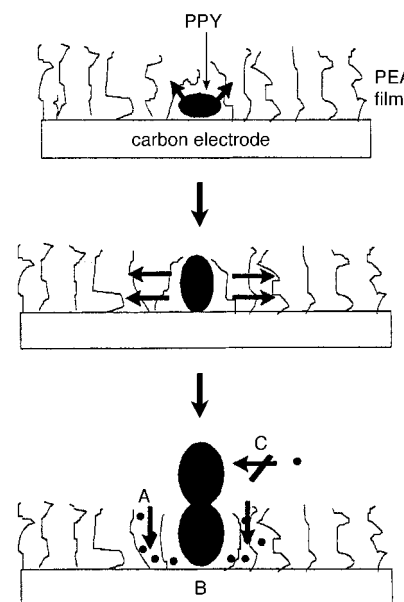


Figure 5. Schematic mechanism for PPY wire growth. 1) PPY nucleation on the C electrode in an opening in the PEA layer. 2) Channel formation in the PEA film. 3) Wire formation. A) monomer diffusion; B) PPY growth from the foot of the wire; C) No polymerization at the tip of the PPY; ● = pyrrole monomer.

molecules must diffuse between the carbon surface and the foot of the growing PPY wire, so that the already formed PPY is pushed away from the electrode for further polymerization. According to this hypothesis, no oxidation of the monomer would occur on the surface of the PPY wire, and this would preserve the horizontal dimensions imposed by the channel that is driven through the PEA coating. This explanation is consistent with fundamental considerations of the potential at the wire surface. Indeed Li et al.^[12] reported that the conductivity of PPY films electrochemically synthesized from solvents with high donor number such as DMF was as low as about 10^{-6} S cm⁻¹. As a result, the decrease in potential on the PPY wire can be estimated to be 500 V cm⁻¹. If the thickness

of the PEA layer is assumed to be 0.5 μm , the ohmic resistance through the PPY wire within this coating is 100 Ω , and the actual potential on the PPY wire emerging from PEA film may be too small for oxidation of the monomer.

Our observations in this study are completely different from the template synthesis of nanowires by electropolymerization in nanoporous membranes.^[6] In template synthesis, PPY begins to grow from the electrode surface, that is, from the foot of the pores. Then the growing PPY follows the pore wall and forms tubules, which as soon as they come out of the pores, grow as a continuous top layer. This growth mechanism is possible because the conductivity of PPY synthesized in water is sufficiently high. Moreover, the membrane is insoluble in the reaction medium, so that the monomer cannot diffuse through it to reach the electrode surface. It can only penetrate into the pores until they become completely blocked. This mechanism is thus fundamentally different from that observed in this work.

From the SEM images, the PPY wire has a diameter of approximately 600 nm and a length of about 300 μm . All the wires have an annular structure, which might be an imprint of the PEA channel through which the PPY grows. Figure 6



Figure 6. SEM image of PPY wires on PEA-grafted carbon.

shows a set of wires that have grown from the electrode surface. The PPY wires are randomly dispersed on the whole electrode surface and have diameters between 400 nm and 1 μm .

According to the proposed PPY growth mechanism, there would be no intrinsic limit to the wire length; only the polarization time would be a limiting factor. As long as the formation of channels through the PEA film remains unexplained, the wire diameter and the density of the wires on the electrode surface cannot be predicted. Wire formation is actually controlled by the complex interaction of several parameters, including PPY conductivity, current density, PPY and Py diffusion rate through the swollen layer of grafted polymer, and hence the nature, thickness, and grafting density of the insulating polymer chains.

Experimental Section

Monomers, solvent, and conducting salt were dried before use. Electrochemical experiments were carried out in a one-compartment cell with a platinum pseudoreference electrode and a platinum counterelectrode with a PAR potentiostat (EG&G, Model 273 A) in a glovebox under a dry inert atmosphere. This technique is detailed elsewhere.^[8, 9]

Received: March 19, 1998

Revised version: June 12, 1998 [Z 11608 IE]

German version: *Angew. Chem.* **1998**, *110*, 2639–2642

Keywords: conducting materials • electrochemistry • nanostructures • polymers

- [1] G. A. Ozin, *Adv. Mater.* **1992**, *4*, 612.
- [2] M. G. Kanatzidis, L. M. Tonge, T. J. Marks, H. O. Marcy, C. R. Kannewurf, *J. Am. Chem. Soc.* **1987**, *109*, 3797; M. G. Kanatzidis, C. G. Wu, H. O. Marcy, C. R. Kannewurf, *J. Am. Chem. Soc.* **1989**, *111*, 4139.
- [3] T. Bein, P. Enzel, F. Beuneu, L. Zuppiroli, *Adv. Chem. Ser.* **1990**, *226*, 433.
- [4] C. R. Martin, *Acc. Chem. Res.* **1995**, *28*, 61.
- [5] Z. Cai, C. R. Martin, *J. Am. Chem. Soc.* **1989**, *111*, 4138.
- [6] S. Demoustier-Champagne, E. Ferain, R. Legras, C. Jérôme, R. Jérôme, *Eur. Polym. J.*, in press.
- [7] R. V. Parthasarathy, C. R. Martin, *Chem. Mater.* **1994**, *6*, 1627.
- [8] R. Jérôme, M. Mertens, L. Martinot, *Adv. Mater.* **1995**, *7*, 807.
- [9] N. Baute, P. Dubois, L. Martinot, M. Mertens, P. Teyssié, R. Jérôme, *Eur. J. Inorg. Chem.*, submitted.
- [10] C. P. Andrieux, P. Audebert, P. Hapiot, J. M. Savéant, *J. Phys. Chem.* **1991**, *95*, 10158.
- [11] S. Asavapiyanont, G. K. Chandler, G. A. Gunawardena, D. Pletcher, *J. Electroanal. Chem.* **1984**, *177*, 229.
- [12] J. Ouyang, Y. Li, *Polymer* **1997**, *38*, 1971.

A Novel Class of Ruthenium Catalysts for Olefin Metathesis**

Thomas Weskamp, Wolfgang C. Schattenmann, Michael Spiegler, and Wolfgang A. Herrmann*

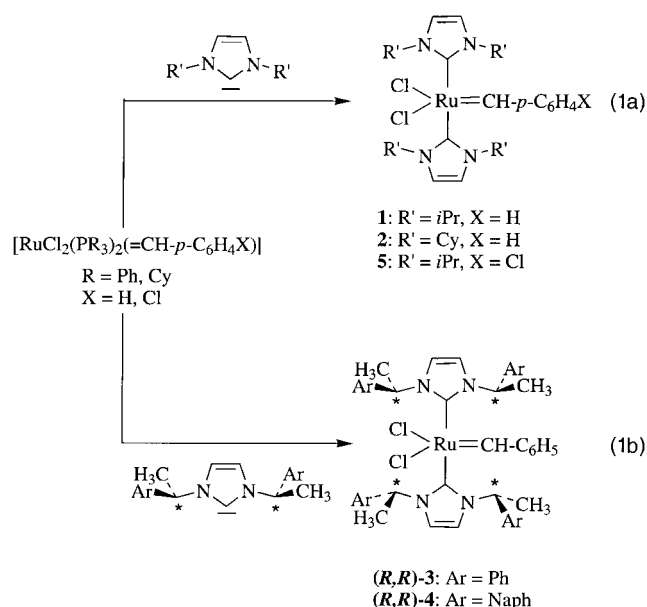
*Dedicated to Professor Heinrich Nöth
on the occasion of his 70th birthday*

Transition metal catalyzed C–C bond formation is a focal issue in both organic synthesis and polymer chemistry.^[1] One of these C–C coupling processes is olefin metathesis encompassing reactions such as ring-opening metathesis polymerization (ROMP), acyclic diene metathesis reaction (ADMET), ring-closing metathesis (RCM), and metathesis of acyclic olefins.^[2] In this area ruthenium–phosphane complexes have conveyed much progress,^[3] since they tolerate polar functional groups. Herein, we report the first ruthenium-based examples of a new class of compounds containing alkylidene groups as well as N-heterocyclic carbenes^[4–6] as ligands and their application as catalysts in olefin metathesis.

The phosphane complex $[\text{RuCl}_2(\text{PPh}_3)_2(=\text{CHPh})]$ developed by Grubbs et al.^[3d] reacts with 2.2 equivalents of the appropriate imidazolin-2-ylidene to yield compounds **1–4**

[*] Prof. Dr. W. A. Herrmann, Dipl.-Chem. T. Weskamp, Dr. W. C. Schattenmann, Dipl.-Chem. M. Spiegler
Anorganisch-chemisches Institut
der Technischen Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+49) 89-289-13473
E-mail: lit@arthur.anorg.chemie.tu-muenchen.de

[**] This work was supported by the Fonds der Chemischen Industrie (Ph.D. fellowship to T.W.), the Bayerische Forschungsförderung (Bayerischer Forschungsverbund Katalyse, FORKAT), the Deutsche Forschungsgemeinschaft, and Degussa AG (loans of RuCl_3).



(Cy = cyclohexyl, Naph = 1-naphthyl) as air-stable solids in 80–90 % yield [Eq. (1a,b)].^[7] The given complexes can also be prepared in high yields from $[RuCl_2(PCy_3)_2(=CHPh)]$, thus demonstrating the stronger Lewis basicity of N-heterocyclic carbenes as compared to that of trialkylphosphanes. Compounds $(R,R)-3$ and $(R,R)-4$ are promising extensions of the established ruthenium-based metathesis catalysts as they exhibit *chiral* imidazolin-2-ylidene ligands. A single-crystal X-ray analysis of **5** (Figure 1)^[8] reveals a lower degree of

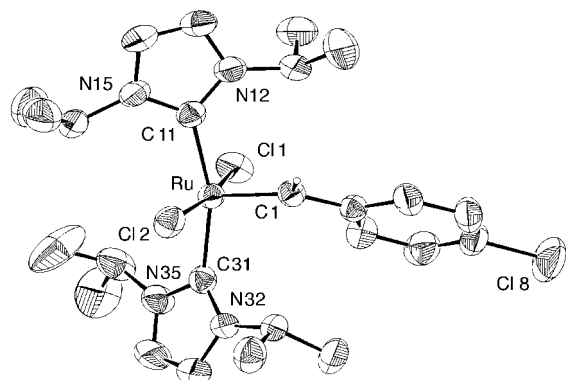


Figure 1. Platon^[9] plot of **5**. Thermal ellipsoids are at 50 % probability. All H atoms except at C1 are omitted for clarity. Selected bond lengths [Å] and angles [°]: Ru–Cl1 2.3995(9), Ru–Cl2 2.3921(8), Ru–C1 1.821(3), Ru–C11 2.107(3), Ru–C31 2.115(3); Cl1–Ru–Cl2 170.32(3), Cl1–Ru–C1 98.37(10), Cl1–Ru–C11 88.26(8), Cl1–Ru–C31 94.76(8), Cl2–Ru–C1 91.14(10), Cl2–Ru–C11 89.21(8), Cl2–Ru–C31 85.14(8), C1–Ru–C11 94.48(12), C1–Ru–C31 100.92(13), C11–Ru–C31 163.68(11).

distortion of the square-pyramidal coordination than the analogous phosphane complex $[RuCl_2(PCy_3)_2(=CH-p-C_6H_4Cl)]$.^[3d,10] The Ru–C bond lengths of the alkylidene (1.821(3) Å) and the N-heterocyclic carbene (2.107(3), 2.115(3) Å) moieties, mirror the fundamentally different nature of metal–“carbene” bonds ($\Delta d \approx 0.3$ Å).

Our new compounds show unexpected behavior in solution as demonstrated by their ¹H and ¹³C NMR spectra (Table 1).

Table 1. Selected NMR-spectroscopic data for compounds **1–5**.

1: ¹H NMR (CD₂Cl₂, 200 K): δ = 20.33 (1H, s, Ru=CH), 7.15 (2H, br, NCH), 7.03 (2H, br, NCH), 5.97 (2H, m, ³J_{HH} = 6.4 Hz, NCHMe₂), 3.73 (2H, m, ³J_{HH} = 6.4 Hz, NCHMe₂), 1.64 (12H, d, ³J_{HH} = 6.4 Hz, NCHMe₂), 1.11 (6H, d, ³J_{HH} = 6.4 Hz, NCHMe₂), 0.75 (6H, d, ³J_{HH} = 6.4 Hz, NCHMe₂); ¹³C NMR (CD₂Cl₂, 200 K): δ = 295.6 (Ru=CH), 183.5 (NCN), 118.1 and 117.2 (NCH), 52.1 and 50.1 (NCHMe₂), 24.5, 23.8, 23.8 and 22.4 (NCHMe₂). 2: ¹H NMR (CD₂Cl₂, 298 K): δ = 20.45 (1H, s, Ru=CH), 7.14 (2H, br, NCH), 7.00 (2H, br, NCH), 6.06 (2H, br, NCHMe₂), 3.82 (2H, br, NCHMe₂), 1.64 (12H, br, NCHMe₂), 0.93 (12H, br, NCHMe₂); ¹³C NMR (CD₂Cl₂, 298 K): δ = 295.6 (Ru=CH), 183.5 (NCN), 118.3 and 117.5 (br, NCH), 52.5 and 50.5 (br, NCHMe₂), 24.1 (br, NCHMe₂). (R,R)-3: ¹H NMR (CD₂Cl₂, 200 K): δ = 20.26 (1H, s, Ru=CH), 4.91 (2H, m, NCHMePh), 1.84 (3H, d, ³J_{HH} = 6.6 Hz, NCHMePh), 1.81 (3H, d, ³J_{HH} = 6.6 Hz, NCHMePh), 1.51 (3H, d, ³J_{HH} = 6.6 Hz, NCHMePh), 1.21 (3H, d, ³J_{HH} = 6.6 Hz, NCHMePh); ¹³C NMR (CD₂Cl₂, 200 K): δ = 294.7 (Ru=CH), 186.0 and 185.6 (NCN), 141.2, 140.3, 140.1 and 139.9 (<i>ipso</i>-C of NCHMePh), 120.5, 119.9, 119.2 and 118.8 (NCH), 57.6, 57.4, 56.7 and 56.1 (NCHMePh), 22.2, 20.6, 20.4 and 20.3 (NCHMePh); ¹H NMR (CD₂Cl₂, 298 K): δ = 20.43 (1H, s, Ru=CH), 5.09 (2H, br, NCHMePh), 2.02–1.20 (12H, br, NCHMePh); ¹³C NMR (CD₂Cl₂, 298 K): δ = 294.8 (Ru=CH), NCN not detected, <i>ipso</i>-C of NCHMePh not detected, 120.5 and 119.5 (br, NCH), 58.3 and 57.3 (br, NCHMePh), 21.5 (br, NCHMePh). (R,R)-4: ¹H NMR (CD₂Cl₂, 260 K): δ = 20.90 (1H, s, Ru=CH); ¹³C NMR (CD₂Cl₂, 260 K): δ = 299.9 (Ru=CH), 187.2 and 184.7 (NCN), 121.7, 121.0, 119.9 and 118.9 (NCH), 56.7, 56.1, 55.0 and 54.7 (NCHMeNaph), 24.7, 24.3, 21.0 and 20.0 (NCHMeNaph). 5: ¹H NMR (CD₂Cl₂, 200 K): δ = 20.33 (1H, s, Ru=CH), 7.15 (2H, br, NCH), 7.03 (2H, br, NCH), 5.97 (2H, m, ³J_{HH} = 6.4 Hz, NCHMe₂), 3.73 (2H, m, ³J_{HH} = 6.4 Hz, NCHMe₂), 1.64 (12H, d, ³J_{HH} = 6.4 Hz, NCHMe₂), 1.11 (6H, d, ³J_{HH} = 6.4 Hz, NCHMe₂), 0.75 (6H, d, ³J_{HH} = 6.4 Hz, NCHMe₂); ¹³C NMR (CD₂Cl₂, 200 K): δ = 295.6 (Ru=CH), 183.5 (NCN), 118.1 and 117.2 (NCH), 52.1 and 50.1 (NCHMe₂), 24.5, 23.8, 23.8 and 22.4 (NCHMe₂).

The alkylidene moiety—usually written as a “double bond” (σ donor/ π acceptor)—freely rotates around the Ru–C bond at room temperature. In contrast, the spectra reveal hindered rotation of the Ru–C linkage of the N-heterocyclic carbene ligands—usually written as a “single bond” (σ donor, virtually no π acceptor). Steric hindrance is the only reasonable explanation for this phenomenon.

Complexes **1–4** are remarkably active catalysts in ROMP and RCM; the results of selected ROMP experiments are shown in Figure 2 and Table 2. A striking feature of the catalytic cyclooctene polymerization is the pronounced dependence on the N-heterocyclic carbene ligand. While **1** (M_n = 266 kg mol^{−1}; PDI (polydispersity index): 1.76; 86 % *trans*) and **2** (M_n = 205 kg mol^{−1}; PDI: 1.71; 78 % *trans*) give polymers in near quantitative yields within one hour at room temperature, virtually no polymer is obtained under the same conditions using $(R,R)-3$, and only a modest yield with $(R,R)-4$. At elevated temperatures, however, $(R,R)-3$ and $(R,R)-4$ unfold higher catalytic activities. This indicates that subtle steric effects can be exploited to tune the catalytic performance much better than with phosphane ligands. The new

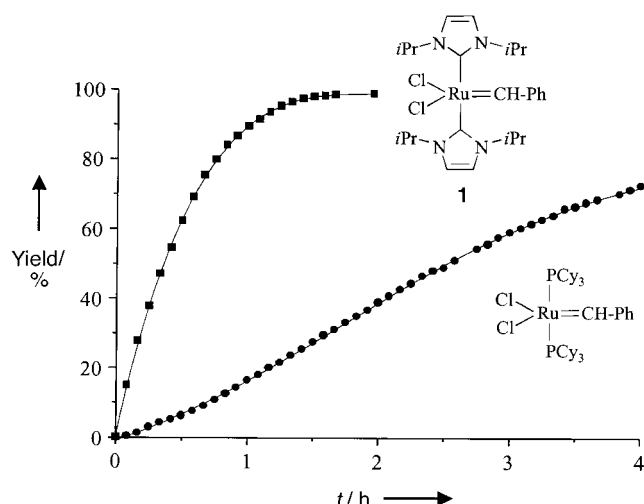


Figure 2. ROMP of cyclooctene. NMR-monitored comparison of **1** and a known ruthenium phosphane catalyst.^[3d, 10] $T = 25^\circ\text{C}$, 2.50 μmol catalyst in 0.50 mL of CD_2Cl_2 ; [cyclooctene]/[catalyst] = 250/1.

Table 2. ROMP of 2-norbornene and cyclooctene.^[a]

Catalyst	Olefin	$T [^\circ\text{C}]$	$t [\text{min}]$	Yield [%]
1	2-norbornene ^[b]	25	1	91
2	2-norbornene ^[b]	25	1	92
1	cyclooctene ^[c]	25	60	84
1	cyclooctene ^[c]	25	120	97
2	cyclooctene ^[c]	25	60	87
(<i>R,R</i>)- 3	cyclooctene ^[c]	25	60	3
(<i>R,R</i>)- 3	cyclooctene ^[c]	60	60	72
(<i>R,R</i>)- 4	cyclooctene ^[c]	25	60	54
(<i>R,R</i>)- 4	cyclooctene ^[c]	60	60	89

[a] Reactions at 25°C : Catalyst (6.30 μmol) in CH_2Cl_2 (0.50 mL); at 60°C : Catalyst (6.30 μmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.50 mL); [b] [norbornene]/[catalyst] = 100/1; [c] [cyclooctene]/[catalyst] = 500/1.

catalysts also show high resistance towards functional groups. Derivatives of norbornene with a variety of polar functionalities (e.g., aldehyde, alcohol, ketone, carboxylic acid, carboxylic ester) are readily polymerized with **1**.^[11]

Recently, a great deal of interest has been devoted to RCM in the total synthesis of natural products.^[12] The perspective of our complexes in RCM is demonstrated for 1,7-octadiene (Table 3). Once again, the activity depends on the N-heterocyclic carbene ligand. Compound **1** is more active than the chiral complex (*R,R*)-**3** at room temperature. Nevertheless, all compounds including the chiral derivatives show quantitative yields at elevated temperatures.

Table 3. RCM of 1,7-octadiene.^[a]

Catalyst	$T [^\circ\text{C}]$	$t [\text{min}]$	Yield [%]
(<i>R,R</i>)- 3	25	10	7
1	25	10	51
1	60	10	> 98
2	60	10	> 98
(<i>R,R</i>)- 3	60	10	> 98
(<i>R,R</i>)- 4	60	10	> 98

[a] Reactions at 25°C : Catalyst (6.30 μmol) in CH_2Cl_2 (0.20 mL); at 60°C : Catalyst (6.30 μmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.20 mL); [1,7-octadiene]/[catalyst] = 50/1.

Our results clearly demonstrate that alkylidene complexes of ruthenium-containing N-heterocyclic carbenes complement and extend the known phosphane systems as catalysts in olefin metathesis.^[11] The simple access to chiral metathesis catalysts appears promising for enantioselective metathesis reactions starting from prochiral olefins.^[13]

Experimental Section

General procedure for complexes **1–5**: A solution of $[\text{RuCl}_2(\text{PR}_3)_2](\text{CH-}p\text{-C}_6\text{H}_4\text{X})$ ($\text{R} = \text{Ph}$ or Cy ; $\text{X} = \text{H}$ or Cl) (1.0 mmol) in toluene (20 mL) was treated with a solution of the appropriate 1,3-dialkyl-imidazolin-2-ylidene (2.2 mmol) in toluene (5 mL) and stirred at room temperature for 45 min. The solution was filtered and then concentrated to about 2 mL. Upon addition of pentane (20 mL), a solid was precipitated which was separated from the mother liquor, dissolved in toluene (2 mL) and reprecipitated with pentane. This procedure was repeated twice. Finally, the complex was washed with pentane.

1: Yield: 86%; $\text{C}_{25}\text{H}_{38}\text{Cl}_2\text{N}_4\text{Ru}$: calcd: C 53.00, H 6.76, N 9.89; found: C 53.21, H 6.83, N 9.94.

2: Yield: 82%; $\text{C}_{37}\text{H}_{54}\text{Cl}_2\text{N}_4\text{Ru}$: calcd: C 61.14, H 7.49, N 7.71; found: C 61.23, H 7.56, N 7.87.

(*R,R*)-**3**: Yield: 83%; $\text{C}_{45}\text{H}_{66}\text{Cl}_2\text{N}_4\text{Ru}$: calcd: C 66.33, H 5.69, N 6.88; found: C 66.48, H 5.90, N 6.73.

(*R,R*)-**4**: Yield: 78%; $\text{C}_{61}\text{H}_{84}\text{Cl}_2\text{N}_4\text{Ru}$: calcd: C 72.18, H 5.36, N 5.52; found: C 72.34, H 5.46, N 5.45.

5: Crystals were obtained by slow diffusion of hexane into a solution of **5** in $\text{Et}_2\text{O}/\text{THF}$ (5:1). Yield: 89%; $\text{C}_{24}\text{H}_{38}\text{Cl}_3\text{N}_4\text{Ru}$: calcd: C 47.96, H 6.37, N 9.32; found: C 48.13, H 6.33, N 9.24.

Received: April 30, 1998 [Z11799IE]

German version: *Angew. Chem.* **1998**, *110*, 2631–2633

Keywords: alkenes • carbenes • homogeneous catalysis • metathesis • ruthenium

- [1] *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**.
- [2] For a recent review see: M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2056.
- [3] a) S. T. Nguyen, L. K. Johnson, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975; b) S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859; c) A. W. Stumpf, E. Saive, A. Demonceau, A. F. Noels, *J. Chem. Soc. Chem. Commun.* **1995**, 1127–1128; d) P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, *107*, 2179–2181; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039–2041; e) W. A. Herrmann, W. C. Schattenmann, O. Nuyken, S. C. Glander, *Angew. Chem.* **1996**, *108*, 1169–1170; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1087–1088; f) A. Demonceau, A. W. Stumpf, E. Saive, A. F. Noels, *Macromolecules* **1997**, *30*, 3127–3136.
- [4] For general reviews see: a) W. A. Herrmann, C. Köcher, *Angew. Chem.* **1997**, *109*, 2256–2282; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162–2187; b) M. Regitz, *Angew. Chem.* **1996**, *108*, 791–794; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725–728.
- [5] a) H. W. Wanzlick, H. J. Schönherr, *Angew. Chem.* **1968**, *80*, 154–155; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 141–142; b) K. Öfele, *J. Organomet. Chem.* **1968**, *12*, P42; c) A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
- [6] a) W. A. Herrmann, M. Elison, J. Fischer, C. Köcher, G. R. J. Artus, *Angew. Chem.* **1995**, *107*, 2602–2605; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2371–2374; b) W. A. Herrmann, L. J. Gooßen, C. Köcher, G. R. J. Artus, *Angew. Chem.* **1996**, *108*, 2980–2982; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2805–2807.
- [7] Compound **5** is prepared analogously starting from $[\text{RuCl}_2(\text{PPh}_3)_2](\text{CH-}p\text{-C}_6\text{H}_4\text{Cl})$.

- [8] Crystal data for **5**: $C_{25}H_{37}Cl_3N_4Ru$; $M_r = 601.02$; monoclinic; space group $P2_1/n$ (No. 14); $a = 9.8856(1)$, $b = 17.3298(4)$, $c = 16.5954(3)$ Å; $\beta = 94.3395(12)^\circ$; $V = 2834.90(9)$ Å³; $Z = 4$; $F(000) = 1240$; $\rho_{\text{calc}} = 1.408$ g cm⁻³; $\mu(\text{MoK}\alpha) = 8.6$ cm⁻¹ (crystal size: $0.15 \times 0.10 \times 0.02$ mm); $T = 193$ K; $\lambda(\text{MoK}\alpha) = 0.71073$ Å; detector: Kappa CCD (Nonius); 9603 data measured ($4.6^\circ < \theta < 25.1^\circ$), unique data = 4911; 3894 observed data [$I > 2.0\sigma(I)$]; hydrogens refined (U_{iso}); $N_{\text{ref}} = 4911$, $N_{\text{par}} = 446$; $R_1 = 0.049$, $wR_2 = 0.081$, $GOF = 1.021$; $w = 1/[\sigma^2(F_o) + (0.0379P)^2 + 1.3899P]$ with $P = (F_o^2 + 2F_c^2)/3$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101497; copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] A. L. Spek, *Acta Crystallogr. Sect. A* **1990**, *46*, C34.
- [10] P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- [11] W. A. Herrmann, W. C. Schattenmann, T. Weskamp (Hoechst R&T), DE 19815275.2, **1998**.
- [12] a) Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170–172; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166–168; b) D. Meng, D. S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y. H. Zheng, T. C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734; c) D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, *Angew. Chem.* **1997**, *109*, 543–544; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523–524; d) A. Fürstner, K. Langemann, *Synthesis* **1997**, 792–803.
- [13] a) O. Fujimura, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 2499–2500; b) J. B. Alexander, D. S. La, D. R. Cefalo, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 4041–4042.

The Stability of the Oxidation State +4 in Group 14 Compounds from Carbon to Element 114**

Michael Seth, Knut Faegri, and Peter Schwerdtfeger*

*Dedicated to Professor Warren R. Roper
on the occasion of his 60th birthday*

With the recent production of the transactinide isotopes ²⁶⁹(110), ²⁷¹(110), ²⁷³(110), ²⁷²(111), and ²⁷⁷(112),^[1, 2] the synthesis of the next superheavy elements 113 and 114 in the near future seems to be feasible.^[3] For elements with a lifetime in the second range, atom-at-a-time chemistry can give valuable

insight into their chemical behavior,^[4, 5] and very recently experiments have been carried out on element 106 (seaborgium) by Schädel et al. at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt.^[6] Macroscopic and microscopic calculations predict an island of nuclear stability near nuclear charge $Z = 114$ and neutron number $N = 180$ with an α -decay half-life of 12 h.^[7] However, it is unlikely that such a large neutron number can be achieved with current nuclear fusion techniques. Quantum-chemical calculations are therefore presently the only way to accurately predict the physical and chemical behavior of superheavy elements.^[8, 9]

Gas-phase transactinide chemistry is generally carried out in high oxidation states because the resulting volatility allows separation from the other nuclides. By comparison with the known chemistry of the Group 14 elements, the most likely oxidation states of element 114 (eka-lead) are +2 and +4. Grant and Pyper predicted heats of formation for di- and tetravalent compounds of element 114 empirically with Dirac–Fock data.^[10] This study suggests a rather low stability of the oxidation state +4, in agreement with the general trend of decreasing stability of the higher oxidation state on going to the heavier main group elements (often termed the inert pair effect).^[11] However, high-level relativistic calculations are necessary to decide whether a compound like (114)F₄ is thermodynamically stable.

We carried out spin–orbit coupled relativistic pseudopotential calculations for the hydrides, chlorides, and fluorides of element 114 [(114)X₂ and (114)X₄ (X = H, F, Cl)], as well as four-component Dirac–Fock (DF) calculations for element 114 and the hydrides (114)H₂ and (114)H₄.^[12–16] The nonrelativistic and spin–orbit coupled relativistic pseudopotentials were obtained by a multielectron fitting procedure to calculated numerical (Hartree–Fock) HF and DF data. Electron correlation was included at the coupled cluster level CCSD(T) and at the second-order Møller–Plesset level (MP2). If accurate dissociation energies were not known for the lighter Group 14 homologues Pb, Ge, and Sn, these were determined by ab initio calculations with the pseudopotentials and basis sets of Stoll et al.^[17] Optimization of the structures at the MP2 level led to T_d symmetry for (114)X₄ and C_{2v} symmetry for (114)X₂. Single-point CCSD(T) calculations were carried out with the optimized MP2 geometries. All relativistic calculations for CH₂ and CH₄ were carried out by using the nonrelativistic optimized geometry.^[18, 19]

Table 1 compares the atomic properties of element 114 calculated at the CCSD(T) level with experimental data for Pb. The ground state of element 114 is best described by jj coupling ($J = 0$). The MCDF calculations show that admixtures from $p_{3/2}$ orbitals are small. The coefficients of the configuration state wavefunctions are 0.9957 for the $p_{1/2}^2$ configuration (cf. the nonrelativistic limit of $+\sqrt{2/3}$) and -0.0929 for the $p_{3/2}^2$ configuration (nonrelativistic limit $-\sqrt{1/3}$). Hence, the ground-state configuration is a closed-shell system. However, in agreement with the other Group 14 elements, we use the term symbol $^3P_0$ in the following, even though the $^1S_0$ contribution is important in the $J = 0$ ground state of element 114. At the CCSD(T) level of theory the electron affinity of element 114 is zero (Figure 1 a), that is, element 114 cannot accommodate an extra

[*] Prof. Dr. P. Schwerdtfeger, Dr. M. Seth
Department of Chemistry, University of Auckland
Private Bag 92019, Auckland (New Zealand)
Fax: (+64) 9-3737422.
E-mail: schwerd@ccu1.auckland.ac.nz
Prof. Dr. K. Faegri
Department of Chemistry, University of Oslo
P.O. Box 1033 Blindern, N-0315 Oslo 3 (Norway)

[**] This work was supported by the European Science Foundation (REHE program), the Auckland University Research Committee, and the Marsden Fund managed by the Royal Society of New Zealand (contract number 96-UOA-PSE-0081).

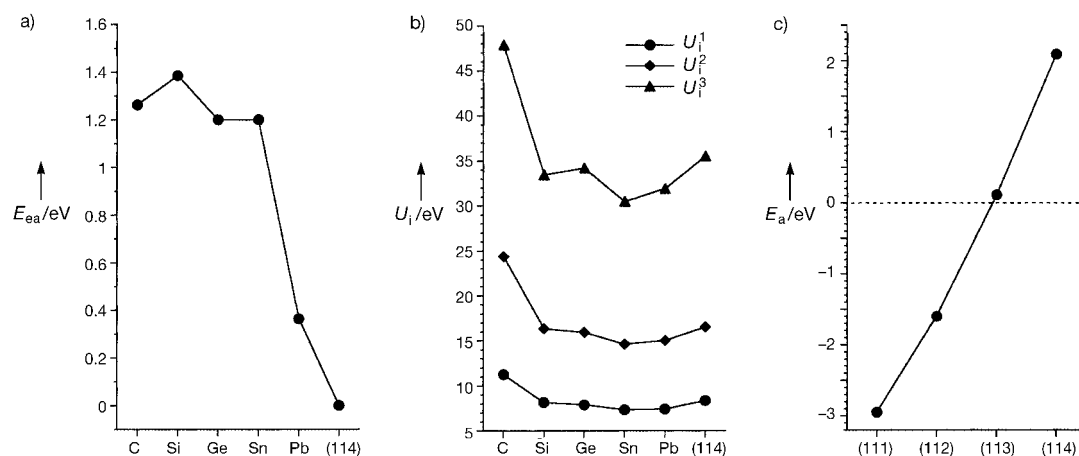


Figure 1. Trends in electron affinities E_{ea} (a) and ionization potentials U_i (b) for the Group 14 elements. c) Excitation energies E_a for the isoelectronic series (111), (112)⁺, (113)²⁺, and (114)³⁺. For C to Pb, experimental values were taken from refs. [24, 25].

Table 1. Electron affinities E_{ea} , ionization potentials U_i , and electronic excitation energies E_a for element 114 and Pb. For element 114 DFC CCSD(T) results were used, and for Pb experimental values were taken from ref. [24]. All values are given in eV.

Property	Transition	(114)	Pb
E_{ea}	$(n-1)d^{10}ns^2np_{1/2}^2(^3P_0) \rightarrow (n-1)d^{10}ns^2np_{1/2}np_{3/2}^2(^2P_{3/2})$	0.00	0.36
U_i^1	$(n-1)d^{10}ns^2np_{1/2}^2(^3P_0) \rightarrow (n-1)d^{10}ns^2np_{1/2}^2(^2P_{1/2})$	8.36	7.42
U_i^2	$(n-1)d^{10}ns^2np_{1/2}^2(^2P_{1/2}) \rightarrow (n-1)d^{10}ns^2(^1S_0)$	16.55	15.03
U_i^3	$(n-1)d^{10}ns^2(^1S_0) \rightarrow (n-1)d^{10}ns^1(^2S_{1/2})$	35.52	31.93
E_a	$(n-1)d^{10}ns^2np_{1/2}^2(^2P_{1/2}) \rightarrow (n-1)d^{10}ns^2np_{1/2}^2(^2P_{3/2})$	4.77	1.75
E_a	$(n-1)d^{10}ns^1(^2S_{1/2}) \rightarrow (n-1)d_{3/2}^4(n-1)d_{3/2}^3ns^2(^2D_{3/2})$	2.09	12.55

electron. More accurate calculations may reveal a very small positive electron affinity, but adding more diffuse p and d functions to the basis set did not change our result. The zero electron affinity is due to the large spin–orbit splitting of the 7p level, as shown by the $7p_{1/2}/7p_{3/2}$ splitting of 4.77 eV in (114)⁺ (Table 1). This results in a relativistically destabilized $7p_{3/2}$ level (diffuse $7p_{3/2}$ orbital) and a relativistically stabilized $7p_{1/2}$ level, as the comparison with the atomic data of Pb show.^[26] One can therefore conclude that element 114 is chemically inert. The first three ionization potentials for all Group 14 atoms are shown in Figure 1 b. The plot shows that element 114 has larger 7p and 7s ionization potentials than Si, Ge, Sn, and Pb but is certainly not more inert than carbon. Of the elements shown in Figure 1 b, carbon has the highest ionization potential. The suitability of ionization potentials for discussing trends in chemical reactivity along a series of elements is questionable,^[11] and accurate molecular calculations are preferable for estimating the thermodynamic stability of compounds of element 114.

The decomposition reactions (1) and (2) were used as the basis for discussing the stability of the oxidation states +4 and +2. The decomposition energies of reaction (1) for X = H is



shown in Figure 2 at the (uncorrelated) Dirac-Fock-Coulomb (DFC) and HF levels of theory. As pointed out before for the

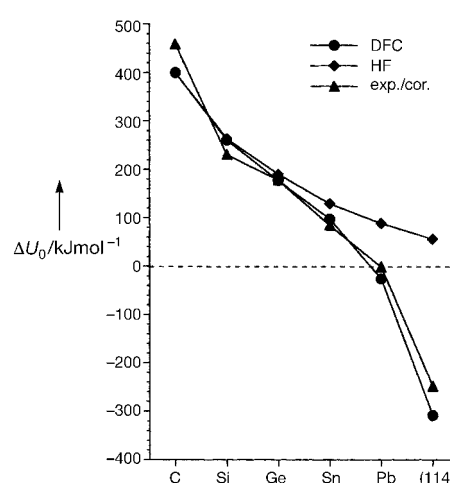


Figure 2. Decomposition energies ΔU_0 of the reaction $MH_4 \rightarrow MH_2 + H_2$ for the hydrides of Group 14. Results from relativistic DFC and non-relativistic HF calculations (see also ref. [19]). Results of electron-correlated calculations: for C and Si experimental decomposition energies were used,^[27] for Ge and Sn calculated pseudopotential MP2 values, for Pb the QCISD(T) values from ref. [11], and for element 114 DFC CCSD(T) results.

lighter Group 13 and 14 compounds,^[11, 19] the instability of the higher oxidation state +4 increases monotonically with increasing size of the Group 14 element, and for the heavier elements this effect is amplified by relativistic effects. In contrast to the ionization potentials (Figure 1 b) a pronounced zigzag trend is not observed. The inert pair effect is therefore a natural periodic trend which is intensified by relativistic effects. The DFC calculations suggest that (114) H_4 is thermodynamically highly unstable. This trend does not change significantly if electron correlation is included (Figure 2). However, more electronegative ligands such as fluorine might stabilize the oxidation state +4.

Figure 3 shows the results of relativistic spin–orbit coupled pseudopotential calculations for the hydrides, fluorides, and chlorides of lead and element 114. The fluorides and chlorides of element 114 are of interest for future radiochemical experiments. Figure 3 clearly shows a pronounced relativistic

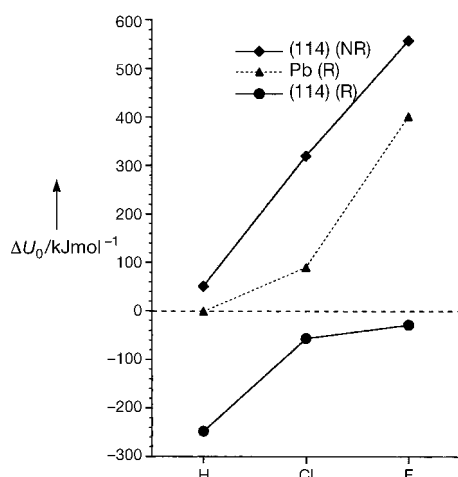


Figure 3. Nonrelativistic (NR) and relativistic (R) decomposition energies ΔU_0 for the reaction $\text{MX}_4 \rightarrow \text{MX}_2 + \text{X}_2$ for the hydrides, fluorides, and chlorides of element 114 and Pb. All results are from CCSD(T) calculations. The results for the decomposition energy of the reaction $\text{PbCl}_4 \rightarrow \text{PbCl}_2 + \text{Cl}_2$ were taken from ref. [28].

destabilization of the oxidation state +4 for element 114, and none of the compounds studied here is thermodynamically stable at this level of theory. However, the calculated structures are local minima according to frequency analyses. Hence, the $(114)\text{X}_4$ ($\text{X} = \text{H}, \text{Cl}, \text{F}$) compounds are kinetically stable. More accurate calculations on $(114)\text{F}_4$ may eventually reveal a small stability towards decomposition ($\Delta U_0 > 0$), but there is no doubt that element 114 compounds in the oxidation state +4 will have very low thermodynamic stability, and it may therefore be difficult to perform radiochemical experiments for this oxidation state.

The decrease in stability of the high oxidation state of the Group 14 elements is probably not monotonic for the fluorides. Experimental values for CF_4 and SiF_4 ^[27] and calculated MP2 values for the other fluorides give the following ΔU_0 values for the reaction $\text{MF}_4 \rightarrow \text{MF}_2 + \text{F}_2$: CF_4 : 745, SiF_4 : 1022, GeF_4 : 669, SnF_4 : 684, PbF_4 : 401, $(114)\text{F}_4$: -28 kJ mol^{-1} . The ΔU_0 values decrease from Si to element 114, and only carbon does not follow this trend. The experimental values have large errors, and more accurate correlated calculations for the Group 14 halides are necessary for discussing these trends in detail.

Concerning the stability of the oxidation state +2 [Eq. (2)], the fluoride and chloride are stable towards decomposition into element 114 and X_2 ($\Delta U_0 = 287 \text{ kJ mol}^{-1}$ for $\text{X} = \text{F}$ and 114 kJ mol^{-1} for $\text{X} = \text{Cl}$ at the CCSD(T) level). The hydride $(114)\text{H}_2$ is thermodynamically unstable ($\Delta U_0 = -320 \text{ kJ mol}^{-1}$). All compounds are relativistically destabilized. At the nonrelativistic CCSD(T) level, $\Delta U_0 = +39 \text{ kJ mol}^{-1}$ for $(114)\text{H}_2$. Hence, the most stable oxidation state for element 114 is +2 and not +4.^[10, 29]

The $(114)-\text{X}$ bonds are comparable to or slightly longer than those of the corresponding lead compounds. At the MP2 level we obtained $1.75 \text{ \AA}$ for both $(114)\text{H}_4$ and PbH_4 , in agreement with earlier predictions,^[30] and $2.14 \text{ \AA}$ for $(114)\text{F}_4$ and $1.97 \text{ \AA}$ for PbF_4 . The bond angles of the $(114)\text{X}_2$ species are very similar to those of the corresponding lead compounds.

Finally, another interesting effect is noteworthy. Figure 1c shows the $6d^{10}7s^1 \rightarrow 6d_{3/2}^4 6d_{5/2}^5 7s^2$ excitation energies for the isoelectronic series $(111), (112)^+, (113)^{2+}$, and $(114)^{3+}$.^[31–33] As observed before,^[31] element 111 (eka-gold) undergoes a relativistic change in its ground state configuration from $d^{10}s^1$ ($^2S_{1/2}$) to d^9s^2 ($^2D_{5/2}$). This is mainly due to the large direct relativistic 7s stabilization and in part due to the indirect relativistic $6d_{5/2}$ expansion. Interestingly, this effect diminishes with increasing nuclear charge along the isoelectronic series, and element 113 is the first element that again exhibits a $^2S_{1/2}$ ground state configuration. This is probably due to stabilization of the 6d orbitals with increasing nuclear charge. The relativistic effect is largest for element 111. This is well known for Group 11 elements and has been termed the Group 11 maximum.^[34]

Received: April 7, 1998

Revised version: June 8, 1998 [Z 11696 IE]

German version: *Angew. Chem.* **1998**, *110*, 2669–2672

Keywords: ab initio calculations • electronic structure • relativistic effects • transuranium elements

- a) S. Hofmann, V. Ninov, F. P. Hessberger, P. Armbruster, H. Folger, G. Münzenberger, H. J. Schött, A. G. Popeko, A. V. Yerebin, A. N. Andreyev, S. Saro, R. Janik, M. Leino, *Z. Phys. A* **1995**, *350*, 277–280; b) S. Hofmann, V. Ninov, F. P. Hessberger, P. Armbruster, H. Folger, G. Münzenberger, H. J. Schött, A. G. Popeko, A. V. Yerebin, A. N. Andreyev, S. Saro, R. Janik, M. Leino, *Z. Phys. A* **1995**, *350*, 281–282.
- S. Hofmann, V. Ninov, F. P. Hessberger, P. Armbruster, H. Folger, G. Münzenberger, H. J. Schött, A. G. Popeko, A. V. Yerebin, S. Saro, R. Janik, M. Leino, *Z. Phys. A* **1996**, *354*, 229–230.
- P. Armbruster, *Spektrum* **1996**, December 12, 54–65.
- a) D. C. Hoffman, *Chem. Eng. News* **1994**, *72*(18), 24–34; b) D. C. Hoffman, *Radiochim. Acta* **1996**, *72*, 1–6.
- M. Schädel, *Radiochim. Acta* **1995**, *70*(7), 207–223.
- M. Schädel, W. Brühle, B. Schausten, E. Schimpf, E. Jager, G. Wirth, R. Gunther, J. V. Kratz, W. Paulus, A. Seibert, P. Thorle, N. Trautmann, S. Zauner, D. Schumann, M. Andrassy, R. Misiak, K. E. Gregorich, D. C. Hoffman, D. M. Lee, E. R. Sylwester, Y. Nagame, Y. Oura, *Radiochim. Acta* **1997**, *77*, 149–159.
- P. Möller, J. R. Nix, J. V. Kratz, *At. Data Nucl. Data Tables* **1997**, *66*, 131–343.
- B. Fricke, *Struct. Bonding (Berlin)* **1975**, *21*, 89–145.
- a) V. Pershina, *Chem. Rev.* **1996**, *96*, 1977–2010; b) P. Schwerdtfeger, M. Seth in *The Encyclopedia of Computational Chemistry*, (Eds.: P. von R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. Kollman, H. F. Schaefer III), Wiley, New York, **1998**.
- I. P. Grant, N. C. Pyper, *Nature* **1977**, *265*, 715–717.
- For a detailed discussion, see P. Schwerdtfeger, G. A. Heath, M. Dolg, M. A. Bennett, *J. Am. Chem. Soc.* **1992**, *114*, 7518–7527.
- P. J. Aerts, O. Visser, L. Visscher, H. Merenga, W. A. de Jong, W. C. Nieuwpoort, MOLDIR, University of Groningen (The Netherlands), **1996**.
- M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. DeFrees, J. Baker, J. J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, GAUSSIAN 94, Revision D.1, Gaussian, Inc., Pittsburgh, PA, **1996**.
- K. Andersson, M. R. A. Blomberg, M. P. Fülscher, G. Karlström, R. Lindh, P.-Å. Malmqvist, P. Neogrády, J. Olsen, B. O. Roos, A. J. Sadlej, M. Schütz, L. Seijo, L. Serrano-Andres, P. E. M. Siegbahn, P.-O. Widmark, MOLCAS, versions 3 and 4, Lund University, Sweden,

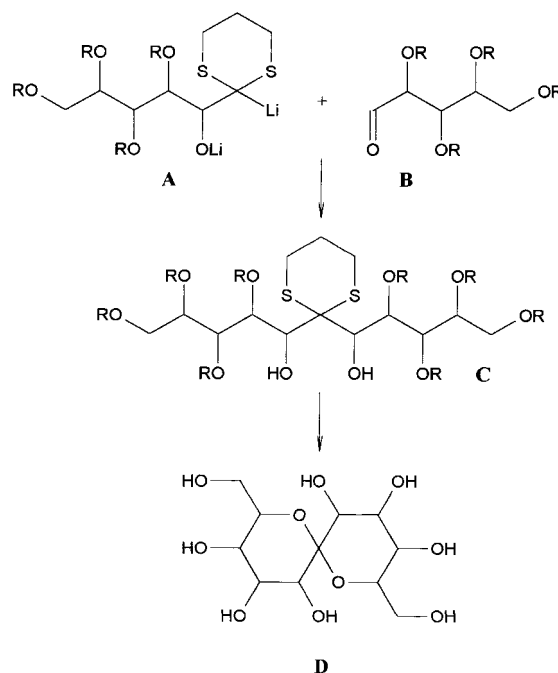
- 1997; extension to this code: a) T. J. Lee, J. E. Rice, J. A. P. Rendell, TITAN, a closed shell coupled cluster code, NASA Ames Research Center, Moffett Field, California, 1990; b) pseudopotential code by M. Pelissier, N. Komih, J. P. Daudey, *J. Comput. Chem.* **1988**, 9, 298–302.
- [15] a) R. Shepard, I. Shavitt, R. M. Pitzer, D. C. Comeau, M. Pepper, H. Lischka, P. G. Szalay, R. Ahlrichs, F. B. Brown, J. G. Zhao, *Int. J. Quantum. Chem.* **1989**, 22, 149–165; b) Spin-orbit component: R. M. Pitzer, N. W. Winter, COLUMBUS, Ohio State University, Columbus, OH, **1990**.
- [16] J. F. Stanton, J. Gauss, J. D. Watts, M. Nooijen, N. Oliphant, S. A. Perera, P. G. Szalay, W. L. Lauderdale, S. R. Gwaltney, S. Beck, A. Balková, D. E. Bernholdt, K.-K. Baek, H. Sekino, R. J. Bartlett, ACESII, University of Florida, Gainesville, FL, **1995**.
- [17] H. Stoll, M. Dolg, H. Preuss, *Pseudopotential Parameters And Basis Sets*, Universität Stuttgart, Stuttgart, **1997**.
- [18] For element 114 we used the following basis sets, which were energy optimized at the Dirac–Fock–Coulomb level (DFC): a dual large-component (LC) (26s25p18d12f)/[11s16p11d4f] and a small component (SC) (25s26p25d18f12g)/[10s15p17d11f4g] basis set for the uncorrelated calculations, and an LC (25s25p18d12f)/[10s16p11d5f] and an SC (25s25p25d18f12g)/[10s14p17d11f5g] basis set for the correlated calculations (coupled cluster CCSD(T)). In all DFC calculations the (SS|SS) integrals were neglected, and the Visscher–Coulomb correction was applied instead.^[20] The finite extension of the nucleus was described by a Gaussian distribution. For H, LC (7s2p)/[4s2p] and SC (2s7p2d)/[2s4p2d] basis sets were used in the DFC calculations^[20] and reduced to LC (5s2p)/[3s2p] and SC (2s5p2d)/[2s3p2d] for the coupled cluster calculations. Similar basis sets were used for the DFC calculations of EH_n molecules (E = C, Si, Ge, Sn, Pb; n = 2, 4) and contracted according to the atomic balance scheme. The nonrelativistic all-electron calculations were carried out with a (24s21p17d11f)/[14s13p10d5f] basis set. The nonrelativistic (NR) and relativistic Hartree–Fock (HF) geometries were optimized numerically. In the DFC correlation treatment only the 6d7s7p electrons were correlated, and all virtual orbitals with an energy of >10 au were ignored. In the all-electron HF calculations, only the 5f6s6p6d7s7p electrons were correlated, and all virtual orbitals were kept active. For the fluorides and chlorides, all-electron calculations were not feasible. The following basis sets were used in all pseudopotential calculations: for H a large (10s3p1d)/[8s3p1d] set;^[21, 22] for F and Cl a aug-cc-PVTZ basis set of Dunning.^[23] The [1s2s2p] core of the Cl atoms was kept frozen in all correlation treatments. Zero-point vibrational energy corrections were neglected. The uncorrelated HF and DF results for SiH₄, GeH₄, SnH₄ and PbH₄ are identical to those in ref. [19]. All basis sets are of HF or DF limit quality.
- [19] K. G. Dyall, *J. Chem. Phys.* **1992**, 96, 1210–1217.
- [20] L. Visscher, P. J. C. Aerts, O. Visser, W. C. Nieuwpoort, *Int. J. Quantum Chem. Symp.* **1991**, 25, 131–139.
- [21] The exponents are taken from G. C. Lie, E. Clementi, *J. Chem. Phys.* **1974**, 60, 1275–1287.
- [22] The exponents are taken from S. Huzinaga, *J. Chem. Phys.* **1965**, 42, 1293–1302.
- [23] a) T. H. Dunning, *J. Chem. Phys.* **1989**, 90, 1007–1023; b) R. A. Kendall, T. H. Dunning, R. J. Harrison, *J. Chem. Phys.* **1992**, 96, 6796–6806.
- [24] C. E. Moore, *Atomic Energy Levels*, US GPO, Washington, **1958**.
- [25] H. Hotop, W. C. Lineberger, *J. Phys. Chem. Ref. Data* **1985**, 14, 731–752.
- [26] This is also evident from a comparison of atomic DF and HF data.
- [27] D. R. Stull, H. Prophet, *JANAF Thermochemical Tables*, 2nd ed., NSRDS-NBS circular no. 37, US GPO, Washington, **1971**.
- [28] M. Kaupp, P. von R. Schleyer, *J. Am. Chem. Soc.* **1993**, 115, 1061–1073.
- [29] O. L. Keller, Jr., J. L. Burnett, T. A. Carlson, C. W. Nestor, Jr., *J. Phys. Chem.* **1970**, 74, 1127–1134.
- [30] P. Pyykkö, J. P. Desclaux, *Nature* **1977**, 266, 336–337.
- [31] E. Eliav, U. Kaldor, P. Schwerdtfeger, B. Hess, Y. Ishikawa, *Phys. Rev. Lett.* **1994**, 73, 3203–3206.
- [32] E. Eliav, U. Kaldor, Y. Ishikawa, *Phys. Rev. Lett.* **1995**, 52, 2765–2769.
- [33] E. Eliav, U. Kaldor, Y. Ishikawa, M. Seth, P. Pyykkö, *Phys. Rev. Lett.* **1996**, 53, 3926–3933.
- [34] P. Pyykkö, *Chem. Rev.* **1988**, 88, 563–594.

Perhydroxylated 1,7-Dioxaspiro[5.5]undecanes (“Spiro Sugars”): Synthesis, Stereochemistry, and Structure**

Raphael Bextermöller, Hartmut Redlich,*
Klaus Schnieders, Sven Thormählen, and
Roland Fröhlich

*Dedicated to Professor Dieter Seebach
on the occasion of his 60th birthday*

Perhydroxylated 1,7-dioxaspiro[5.5]undecanes (**D**; Scheme 1) – a class of compounds which hitherto has not been identified in nature and whose synthesis is reported herein for the first time – can be formally considered as two hexopyranoses joined together by a spiroacetal center (“spiro sugar”).^[1]



Scheme 1.

In contrast to perhydroxylated derivatives, spiroacetals are widespread in nature and exhibit a broad range of biological activities, and are found, for example, as insect pheromones, antibiotics, and toxins.^[2]

In their synthesis from open-chain precursors – the most common route^[2] – structural features such as substituents and their relative arrangement in the acyclic compound need to be taken into consideration. This is particularly evident if the relatively well known properties of monosaccharide hexopyranoses are compared to those of the perhydroxylated 1,7-dioxaspiro[5.5]undecanes (spiro sugars).

[*] Prof. Dr. H. Redlich, Dr. R. Bextermöller,
Dipl.-Chem. K. Schnieders, Dr. S. Thormählen, Dr. R. Fröhlich^[+]
Organisch-chemisches Institut der Universität
Corrensstrasse 40, D-48149 Münster (Germany)
Fax: (+49) 251-8339772
E-mail: redlich@uni-muenster.de

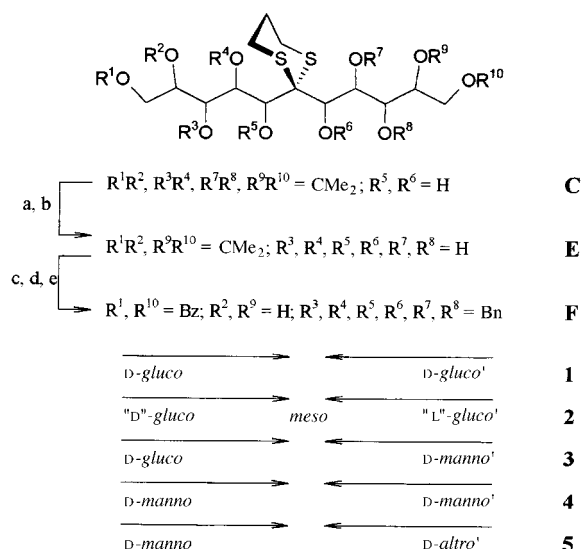
[+] Crystal structure analysis

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

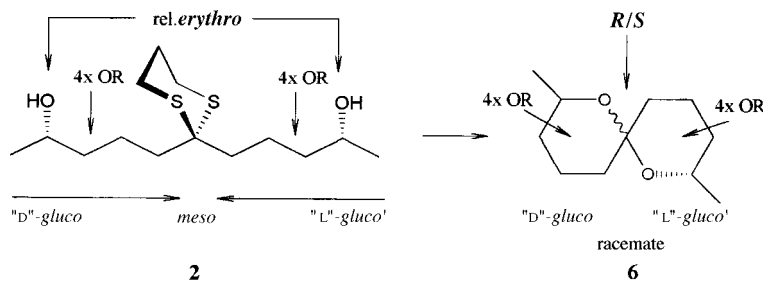
Perhydroxylated 1,7-dioxaspiro[5.5]undecanes can be synthesized efficiently by the "dithiane route"^[3] according to the Corey–Seebach procedure.^[4] In this reaction an open-chain hexose trimethylene dithioacetal **A** as dianion is coupled with an open-chain aldopentose **B** (Scheme 1). Both precursors are protected as base-stable isopropylidene derivatives,^[5] which are available in two or three synthetic steps from the respective sugars.^[6,7] Thus, the chain **C**, which is functionalized at each carbon atom and which according to carbohydrate nomenclature is designated as a substituted undec-6-ulose, is completed in the fourth synthetic step. In this study components **A** and **B** were chosen to cover all relevant combinations of configurations. With respect to the central carbonyl functions (see Table 1, footnote [b]) in the undec-6-uloses these are D-glucob-glucol', "D"-glucol/"L"-glucol', D-glucob-l-mannol', D-mannob-mannol', D-mannob-altrol' configured. The data listed in Table 1 reveal that a double stereodifferentiation is applicable to the coupling of components **A** and **B**; the carbonyl components exhibit a marked influence on the Li⁺ cation which participates in the coupling step as predicted by the "three-point chelation" model^[8] (Table 1, entry 4).

A subtly differentiated pattern of protective groups was a prerequisite for obtaining dipyrano spiroacetals from the open-chain dithianes **C**.^[9] This was achieved for all the configurations of the chain **C** studied here^[10] (Scheme 2); the simplified protective group strategy was based on fact that the kinetically controlled isopropylidenation^[6] of the completely deblocked dithianes **C** leads to the respective terminal 1,2:10,11-diisopropylidene derivatives **E**. The remaining inner free hydroxyl groups were subsequently protected (acid-stable) in the form of benzyl ethers.^[11] The cleavage of the isopropylidene groups and subsequent selective benzylation of the two primary hydroxyl groups^[12] furnished the HO-2 and HO-10 unblocked chains **F**. Cleavage of the dithioacetals in compounds **1–5** gave solely pyranoid structures.

In the intramolecular formation of the spiroacetal a new stereocenter is formed at the spiro carbon atom; thus, the *meso*-compound **2** yielded the racemate **6** (Scheme 3). In contrast, diastereomeric products can be formed for the chiral compounds **1** and **3–5**. This study, however, only focuses on those cases in which the unblocked hydroxy groups exhibit a relative *threo* configuration with respect to the central carbonyl group. If the spiroacetal center is considered as an



Scheme 2. a) 2N HCl/MeOH (1/20), 40 °C, 1 d, > 95 %; b) acetone, concentrated HCl, 25 °C, 5 min, 80 %; c) NaH (80 % in oil, 6.6 equiv), Bu₄NI (0.6 equiv), BnBr (6.6 equiv), DMF, 55 °C, 8 h, 54–75 %; d) as a), > 95 %; e) BzCl (10 equiv), pyridine, 25 °C, 30 s, 60–80 %; Bn = benzyl, benzoyl, R⁷, R⁸ = Me for **1** and **3**.



Scheme 3.

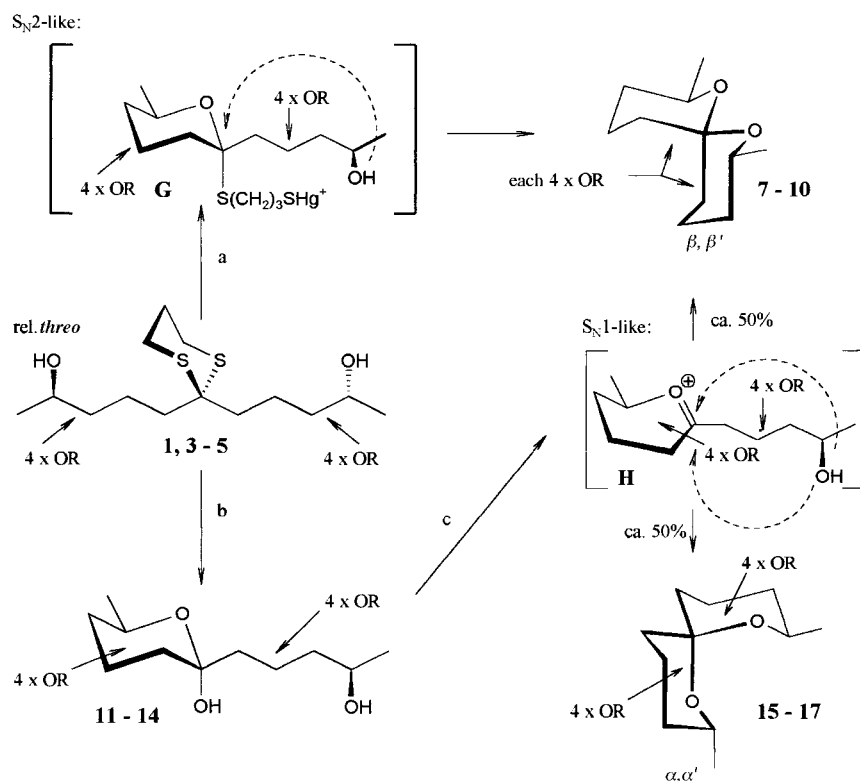
anomeric center, according to carbohydrate nomenclature only the α, α' or β, β' pairs of configurations occur. The above-mentioned *meso*-compound **2** is the prototype for an *erythro* configuration.

Based on the open-chain trimethylene dithioacetals, the two most important mechanisms of spiroacetal formation can now be verified. First the replacement of sulfur atoms in the dithioacetal by hydroxy groups at positions 2 and 10 can proceed with inversion of configuration at the spiro carbon atom in a manner similar to that in a S_N2 substitution. This evidently is the case if the conditions mentioned in Scheme 4 are applied for the dithioacetal cleavage (anhydrous acetonitrile).

Table 1. Couplings of the monosaccharides to carbohydrate chains.^[a]

Entry	Dithiane A	Aldehyde B	Chain C1 ^[b]	Chain C2 ^[b]	<i>ds</i>	Yield [%]
1	D-glucol	D-arabino	D-glucob-glucol'	D-glucob-mannol'	4:1	61
2	D-glucol	L-arabino	D-glucob-l-glucol'	D-glucob-l-mannol'	1.5:1	60
3	D-mannol	D-arabino	D-mannob-glucol'	D-mannob-mannol'	1:3	62
4	D-mannol	D-ribo	D-mannob-altrol'		1:0	65

[a] The 3,4:5,6-di-*O*-isopropylidene-hexosepropane-1,3-diyl dithioacetals were treated with 4,5-*O*-isopropylidene-2,3-di-*O*-methyl-pentose in entry 1, in entries 2–4 with the respective 2,3:4,5-di-*O*-isopropylidene-pentose. Dithiane **A** was first metalated with *n*BuLi (2.2 equiv; THF, –30 °C, 5 h), then **B** (0.7 equiv; –78 → 0 °C) was added.^[4c] Diastereomers were separated by chromatography on silica gel (cyclohexane/ethyl acetate, 8/1). The yields are based on the amount of **B** employed. [b] The nomenclature used is based on the configuration at position 6 starting from the respective termini. The initial hexose is named first.^[1] If the IUPAC rules for carbohydrates were taken into account, the here named D-glucob-glucol' case would translate to D-glucol-L-gulol'.



Scheme 4. a) HgCl_2 (3.0 equiv), HgO (4.5 equiv), acetonitrile, reflux, 2 h, 73–95%; b) HgCl_2 (3.0 equiv), HgO (4.5 equiv), acetonitrile/ H_2O (4/1), reflux, 5 h, 66%, (30–35% of them hemiacetals, 50–60% β,β' compounds, and 0–5% α,α' compounds; separation on silica gel, cyclohexane/ethyl acetate, 3/1); c) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, dichloromethane, 25 °C, 5 min, 90%, ratio of products β,β' : α,α' = 1:1 (separation on silica gel, cyclohexane/ethyl acetate, 3/1).

trile, mercury(II) chloride/mercury(II) oxide).^[13] Regardless of the symmetry of the chain (C_1 for **3** and **5**, C_2 for **1** and **4**), the relative configuration (*gluco*, *manno*, *altro*) and thus the conformation of the segments (*manno*: stretched, *gluco*, *altro*: both differently banana-shaped),^[14] only the β -configured product (according to carbohydrate nomenclature) is formed. The prerequisite for this strict preference in the reaction sequence S,S -acetal $\rightarrow$ O,S -acetal $\rightarrow$ O,O -acetal is that the α -configured “alkylthioketoside” **G** is always formed first, which in the second step reacts under repeated inversion to give the β,β' -configured spiroacetals **7–10**.

Second the formation of the O,O -acetal can proceed via a cyclic oxocarbenium ion intermediate. Experimentally this case may be understood by adding water (20%) during the cleavage of the dithioacetal (Scheme 4). Although the β,β' -spiroacetal still prevails as the major product in all the reactions (50–60% yield, based on 60–70% total yield), 30–35% of α -configured hemiacetals (**11–14**) and up to 5% of α,α' -configured spiroacetals are isolated. The hemiacetals **11–14**, regardless of the different chain structures, react spontaneously in organic solvents such as dichloromethane or acetonitrile in the presence of catalytic amounts of mineral acids and Lewis acids (HCl , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{F}_3\text{CCO}_2\text{H}$) to give 1:1 mixtures of the β,β' derivatives **7–10** and the α,α' -configured compounds **15–17**.

This result can be explained under the assumption that the tertiary hydroxy group in hemiacetals **11–14** is activated, for example, by protonation, and a cyclic oxocarbenium ion of

type **H** is formed as a result. This oxocarbenium ion undergoes extremely rapid intramolecular attack without any facial preference (i.e. as in an S_N1 substitution) by the available hydroxyl groups to furnish the mixture of diastereomeric O,O -acetals.

Overall, the stereochemical pathway of the spiroacetal formation can be fully understood—presumably because of the quasi-irreversibility present here, since hitherto, it has not been possible to convert the β,β' -configured spiroacetals to the respective α,α' isomers, for example, by proton catalysis. S_N2 -like processes govern the formation of the first intermediate, the O,S -acetal with α configuration, the “alkylthioketoside” **G**. In a second nucleophilic substitution this yields the β,β' -configured products. In contrast, S_N1 -type processes always yield mixtures of products with β,β' or α,α' configurations at the spiroacetal center, since the unusually high reactivity of the intermediate oxocarbenium ion in the intramolecular process will not allow for any facial discrimination with regard to the attack of the second hydroxy group for chains with different configurations. Since two limiting cases are apparent, the results obtained in this study may serve to generalize similar experiments in natural product syntheses—especially if the “dithiane”-route or any comparable synthetic strategies are adopted.

The assignment of the configurations at the spiroacetal centers was initially problematic, because neither the NMR-spectroscopic data nor the determinations of the amount of rotation and their correlation^[15] with well-known systems seemed to be acceptable. We assumed (wrongly) that β,β' -configured spiroacetals would not be formed because, despite the large number of similar systems occurring in nature or prepared synthetically, to our knowledge an arrangement of this kind had not been described;^[2] there are only rare reports on α,β' - or β,α' -configurations,^[2, 16] which refer to the relative *erythro*-arrangement in the above-mentioned sense and cannot be configured in another way. In addition, the NMR data in some cases gave indications for the presence of boat conformations, which are extremely unlikely for unfixed hexopyranoses. However, as can be seen in Table 2 the NMR data are clear: for all α -configurations of a hexopyranose segment normal chair conformations are present in solution,^[17] in contrast boat conformations occur for all β -*gluco*-configurations. The reason for this is the evidently very high steric demand of an equatorially orientated substituent (the OAc group) at the C2 position of one pyran ring contrasted to that at the other pyran ring, which is eased by a change in conformation (Figure 1). This change of conformation is supported by stereoelectronic effects—

Table 2. Assignment of the conformations by ^1H NMR spectroscopy.^[a]

	Spiro sugar	Ring A ^[b]		Ring B ^[b]	
		J [Hz]	conformation	J [Hz]	conformation
6		$J_{2,3} = 10.2$ $J_{3,4} = 9.2$ $J_{4,5} = 10.2$	C	$J_{2,3'} = 8.8$ $J_{3',4'} = 5.2$ $J_{4',5'} = 8.8$	B
			$\beta\text{-D-glucol}/\alpha'\text{-L-glucol}$ $\beta'\text{-L-glucol}/\alpha\text{-D-glucol}$ } racemate		
7		$J_{2,3} = 2.0$ $J_{3,4} = 8.0$ $J_{4,5} = 10.6$	${}^{1,4}B$	$J_{2,3'} = 1.6$ $J_{3',4'} = 6.8$ $J_{4',5'} = 10.8$	${}^{1,4}B$
			$\beta\text{-D-glucol}/\beta'\text{-D-glucol}$		
8		$J_{2,3} = 3.4$ $J_{3,4} = 7.6$ $J_{4,5} = 10.4$	${}^{1,4}B$	$J_{2,3'} = 3.4$ $J_{3',4'} = 8.2$ $J_{4',5'} = 8.8$	${}^4C_1$
			$\beta\text{-D-glucol}/\beta'\text{-D-manno}$		
9		$J_{2,3} = 2.8$ $J_{3,4} = 9.8$ $J_{4,5} = 9.8$	${}^4C_1$	$J_{2,3'} = 2.8$ $J_{3',4'} = 9.8$ $J_{4',5'} = 9.8$	${}^4C_1$
			$\beta\text{-D-manno}/\beta'\text{-D-manno}$		
10		$J_{2,3} = 3.6$ $J_{3,4} = 9.6$ $J_{4,5} = 9.6$	${}^4C_1$	$J_{2,3'} < 1.0$ $J_{3',4'} = 2.8$ $J_{4',5'} = 8.8$	${}^4C_1$
			$\beta\text{-D-manno}/\beta'\text{-D-altro}$		

[a] The compounds were acetylated with acetic anhydride in pyridine after cleavage of the benzoates according to Zemlén and of the benzyl ethers with H_2 , Pd/C in methanol (70–75% yield), and then measured in CDCl_3 at 300 MHz. [b] Ring A describes the first named, ring B the second named half of the respective dipyranoïd system.

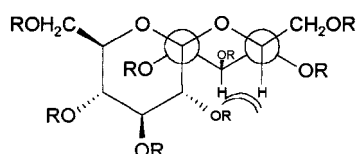


Figure 1. Steric interaction of a substituent at C-2 orientated equatorially relative to the spiroacetal center in $\beta\text{-D-glucol}/\beta'\text{-D-glucol}$ -configured spiro sugar. View along: $\text{C}_{\text{spiro}} - \text{C}-2$.

anomeric and the $\Delta 2$ effect.^[18, 19] For the “D”-gluco/“L”-gluco'-configured racemate **6** these conditions lead to the surprising result that in the case of an identical relative arrangement of the substituents, one ring adopts the chair and the other the boat conformation. On the other hand the strong 1,3-diaxial interaction between O3 of the *altro*-hexose and C2 of the *manno*-pyranose in **10** does not produce a change of the conformation.

In order to verify these interpretations three crystal structure analyses were carried out. The normal case is

represented by the $\alpha, \alpha'\text{-D-glucol}/\beta\text{-D-glucol}'$ -configured spiroacetal **15**,^[20a] in which both rings adopt the chair conformation and the $\text{C}_{\text{spiro}} - \text{O}$ distances are almost identical (1.407 and 1.414 Å), which is expected for symmetry reasons (Figure 2). The diastereomeric compound **7** with a β, β' configuration crystallizes from methanol with a molecule methanol in the crystal (Figure 3).^[20b] The pyran ring which carries the methoxy groups adopts a chair conformation, the peracetylated pyranose adopts a boat conformation. This surprising result may be explained by the slightly different patterns of the protecting groups at the two pyran rings of this otherwise C_2 symmetric compound, but in any case shows that the existence of a boat conformation is probable. Additionally, the $\text{C}_{\text{spiro}} - \text{O}$ distances are clearly different: 1.396 Å in the boat, 1.434 Å in the chair.

The crystal structure of **9** is particularly interesting (Figure 4).^[20c] This compound can almost not be distinguished from the corresponding α, α' -configured derivative **17**.^[17] The β, β' configuration for a chair conformation for both pyran rings can be seen clearly in the crystal structure. The $\text{C}_{\text{spiro}} - \text{O}$ distances differ slightly (1.389 and 1.412 Å) and indicate a distortion of the crystal. In this molecule C6', O5', C_{spiro} , O5, and C6 are

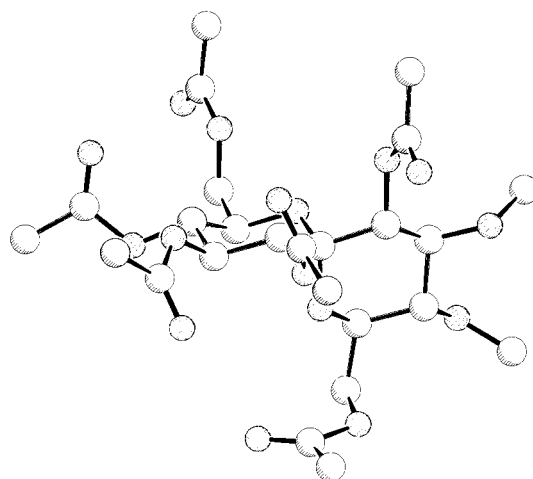


Figure 2. Crystal structure of the $\alpha\text{-D-glucol}/\alpha'\text{-D-glucol}$ system **15**.

present in the *all-trans* conformation, an arrangement which shows that this molecule is a pure oxo analogue of the associated carbocyclic compound. This arrangement (C_{2v}

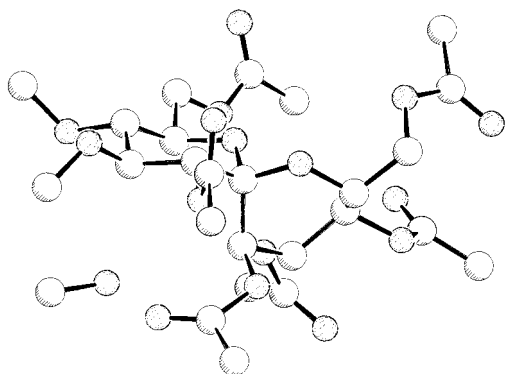


Figure 3. Crystal structure of the β -D-glucol/ β' -D-glucol system **7**.

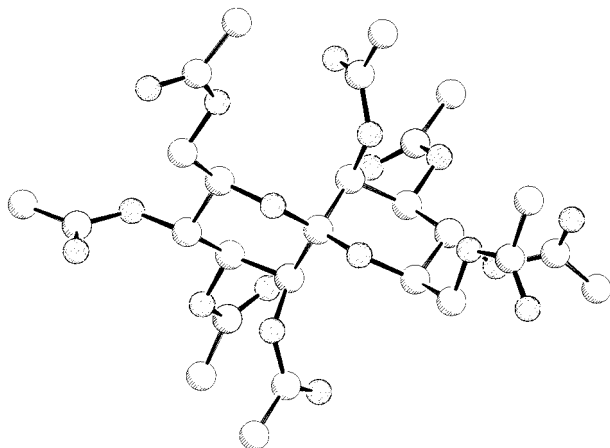


Figure 4. Crystal structure of the β -D-mannol/ β' -D-mannol system **9**.

symmetry) is the most unfavorable for an acetal segment: alone for formaldehyde hydrate the destabilization compared to an acetal segment with C_2 symmetry is about 9 kcal mol⁻¹.^[21]

Received: January 2, 1998

Revised version: June 10, 1998 [Z11309IE]

German version: *Angew. Chem.* **1998**, *110*, 2612–2616

Keywords: carbohydrates • spiro compounds • structure elucidation • synthetic methods

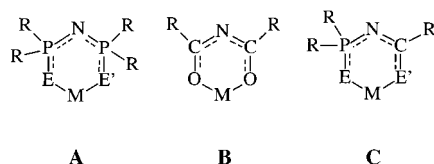
- [1] H. Redlich, J. B. Lenfers, S. Thormählen, *Synthesis* **1992**, 1112–1118.
- [2] Review: F. Perron, K. F. Albizzati, *Chem. Rev.* **1989**, *89*, 1617–1661.
- [3] D. A. Evans, C. E. Sacks, R. A. Whitney, N. G. Mandel, *Tetrahedron Lett.* **1978**, *8*, 727–730.
- [4] a) D. Seebach, *Synthesis* **1969**, 17–36; b) D. Seebach, B. T. Gröbel, *Synthesis* **1977**, 357–402; c) D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 231–237.
- [5] In the initial phase of these investigations compounds were used that were partly protected as methyl ethers.
- [6] a) H. Redlich, O. Kölln, *Synthesis* **1995**, 1376–1382; b) H. Redlich, O. Kölln, H. Frank, *Synthesis* **1995**, 1383–1388; c) H. Redlich, O. Kölln, *Synthesis* **1996**, 826–832; d) H. Redlich, O. Kölln, *Synthesis* **1996**, 963–969.
- [7] M. Fetizon, M. Jurion, *J. Chem. Soc. Chem. Commun.* **1972**, 382–383.
- [8] H. Redlich, S. Thormählen, *Tetrahedron Lett.* **1985**, *26*, 3685–3688.
- [9] The dithioacetal cleavage at the completely unprotected undeculoses resulted in mixtures of products.
- [10] Details on the synthesis and analysis of all the open-chain carbohydrates described here will be published elsewhere.

- [11] In addition to the hexabenzyl compounds in some cases also pentabenzyl products were obtained in which one OH group adjacent to the dithiane ring was not protected. As this free hydroxy function has no influence on the subsequent dithioacetal cleavage, these compounds can be used further.
- [12] A. Haines, *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11–51.
- [13] E. J. Corey, B. W. Erickson, *J. Org. Chem.* **1971**, *36*, 3553–3560.
- [14] P. L. Durette, D. Horton, *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 49–73.
- [15] K. Mori, T. Uematsu, K. Yanagi, M. Minobe, *Tetrahedron* **1985**, *41*, 2751–2758.
- [16] a) F. E. Ziegler, W. T. Cain, *J. Org. Chem.* **1989**, *54*, 3347–3353; b) M. Kobayashi, S. Aoki, I. Kitagawa, *Tetrahedron Lett.* **1994**, *35*, 1243–1246.
- [17] ¹H NMR data: **15** (α -D-glucol/ α' -D-glucol), for both rings: $J_{2,3}$ = 10.0, $J_{3,4}$ = 9.2, $J_{4,5}$ = 10.2 Hz; **16** (α -D-glucol/ α' -D-mannol), glucol ring: $J_{2,3}$ = 9.4, $J_{3,4}$ = 8.8, $J_{4,5}$ = 10.0 Hz, mannol ring: $J_{2,3}$ = 3.4, $J_{3,4}$ = 9.2, $J_{4,5}$ = 9.6 Hz; **17** (α -D-mannol/ α' -D-mannol), both rings: $J_{2,3}$ = 3.4, $J_{3,4}$ = 10.2, $J_{4,5}$ = 10.2 Hz.
- [18] a) J. T. Edward, *Chem. Ind. (London)* **1955**, 1102–1104; b) P. Deslongchamps, D. D. Rowan, N. Pothier, T. Sauvé, J. K. Saunders, *Can. J. Chem.* **1981**, *59*, 1105–1121; c) P. Deslongchamps, *Stereo-electronic Effects in Organic Chemistry*, Pergamon, New York, **1983**; d) A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, New York, **1983**; e) *The Anomeric Effect and Associated Stereoelectronic Effects* (Ed.: G. R. Thatcher), American Chemical Society, Washington, DC, **1993** (ACS Symp. Ser. **1993**, 539).
- [19] R. E. J. Reeves, *J. Am. Chem. Soc.* **1950**, *72*, 1499–1506.
- [20] a) Crystal structure data of **15** (single crystals from methanol at -10°C): $\text{C}_{25}\text{H}_{36}\text{O}_{16}$, M_r = 592.54, crystal dimensions: $0.3 \times 0.25 \times 0.2 \text{ mm}^3$, a = 10.590(1), b = 15.029(1), c = 19.076(2) Å, V = 3036.1(5) Å³, ρ_{calcd} = 1.296 g cm⁻³, μ = 9.4 cm⁻¹, Z = 4, orthorhombic, space group $P2_12_12_1$ (no. 19), 6761 measured reflections, ($-h$, $+k$, $\pm l$), $[(\sin \theta)/\lambda]_{\text{max}}$ = 0.63 Å⁻¹, 6189 independent and 5773 observed reflections with $I > 2\sigma(I)$, 379 refined parameters, R = 0.039, wR^2 = 0.108, max./min. Residual electron density 0.18/–0.19 e Å⁻³.^[20d] b) crystal structure data of **7** (single crystals from methanol at -10°C): $\text{C}_{26}\text{H}_{40}\text{O}_{17}$, M_r = 624.58, crystal dimensions: $0.35 \times 0.2 \times 0.15 \text{ mm}^3$, a = 8.1404(5), b = 8.8120(6), c = 11.7246(8) Å, α = 101.239(5), β = 107.157(6), γ = 95.688(5)°, V = 777.1(1) Å³, ρ_{calcd} = 1.334 g cm⁻³, μ = 9.7 cm⁻¹, Z = 1, triclinic, space group $P1$ (no. 1), 3562 measured reflections, ($\pm h$, $\pm k$, $\pm l$), $[(\sin \theta)/\lambda]_{\text{max}}$ = 0.62 Å⁻¹, 3520 independent and 3392 observed reflections with $I > 2\sigma(I)$, 399 refined parameters, R = 0.040, wR^2 = 0.109, max./min. Residual electron density 0.37/–0.43 e Å⁻³.^[20d] c) crystal structure data of **9** (single crystals from methanol at -10°C): $\text{C}_{27}\text{H}_{36}\text{O}_{18}$, M_r = 648.56, crystal dimensions: $0.5 \times 0.25 \times 0.1 \text{ mm}^3$, a = 8.929(2), b = 9.246(3), c = 38.281(2) Å, V = 3160.4(13) Å³, ρ_{calcd} = 1.363 g cm⁻³, μ = 10.0 cm⁻¹, Z = 4, triclinic, space group $P2_12_12_1$ (no. 19), 3671 measured reflections, ($-h$, $-k$, $-l$), $[(\sin \theta)/\lambda]_{\text{max}}$ = 0.62 Å⁻¹, 3671 independent and 2650 observed reflections with $I > 2\sigma(I)$, 414 refined parameters, R = 0.075, wR^2 = 0.194, max./min. Residual electron density 0.51/–0.36 e Å⁻³.^[20d] d) Enraf-Nonius-CAD4 diffractometer, λ = 1.54178 Å, T = 223 K, ω - 2θ scan, solution with direct methods, hydrogen atoms in calculated positions, Programs SHELXS-86, SHELXS-93, SHELXL-92. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100-729. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (Fax: (+44)1223–336–033; E-mail: deposit@ccdc.cam.ac.uk).
- [21] P. von R. Schleyer, U. Salzner, *J. Am. Chem. Soc.* **1993**, *115*, 10231–10236.

The First Six-Membered “True” Heterocycle – Hydrogen-Bond-Assisted Ladder Formation in a KOCNPS Ring System**

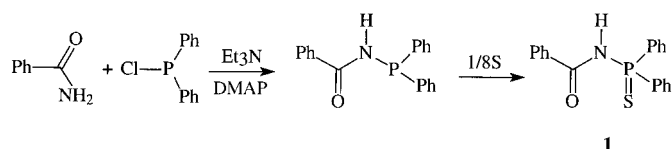
Tuan Q. Ly, Alexandra M. Z. Slawin, and J. Derek Woollins*

Recently there has been a flurry of activity in the synthesis and structural characterization of $\text{MEE}'(\text{PR})_2\text{N}$ ring systems (**A**; ($\text{E}, \text{E}' = \text{O}, \text{S}, \text{Se}$)).^[1] These metallacycles can be considered to be relatives of the more extensively studied acetylacetonato complexes but with the added ability to form nonplanar rings with more sterically demanding R groups at the phosphorus compared to the carbon substituents in β -diketonates (**B**)—this difference makes the phosphorus-containing systems useful in metal speciation and separation. The $\text{ME}_2(\text{PR})_2\text{N}$ systems have also been found to stabilize unusual



geometries at some metal centers for example square-planar Sn^{II} .^[2] Intermediate systems (**C**) are also possible (Schmidpeter and Groeger have reported^[3, 4] on the synthesis of thiourea derivatives in which $\text{E} = \text{E}' = \text{S}$) and provide the opportunity to probe ring geometries in mixed carbon/phosphorus rings as well as to develop the syntheses of “true” heterocycles, that is heterocycles in which every ring atom is different.

We synthesized $\text{Ph}_2\text{P}(\text{S})\text{NHCOPh}$ **1** by a simple P–N bond-forming reaction between benzamide and $\text{Ph}_2\text{P}(\text{Cl})$ in the presence of Et_3N and catalytic amounts of dimethylaminopyridine (DMAP), followed by oxidation of the P^{III} center using sulfur in a one-pot synthesis (Scheme 1). The use of



Scheme 1. One-pot synthesis of **1**.

DMAP as a catalyst results in better yields for reactions involving relatively nonacidic N–H protons, the yield of the reaction was also improved by using an excess of $\text{Ph}_2\text{P}(\text{Cl})$, which causes no problems during the work-up as it remains in solution.

The X-ray crystal structure analysis of **1**^[5] (Figure 1) reveals a *gauche* conformation of the P=S and C=O groups (S–P...C–O “torsion” angle of 56°) with the molecules packing into

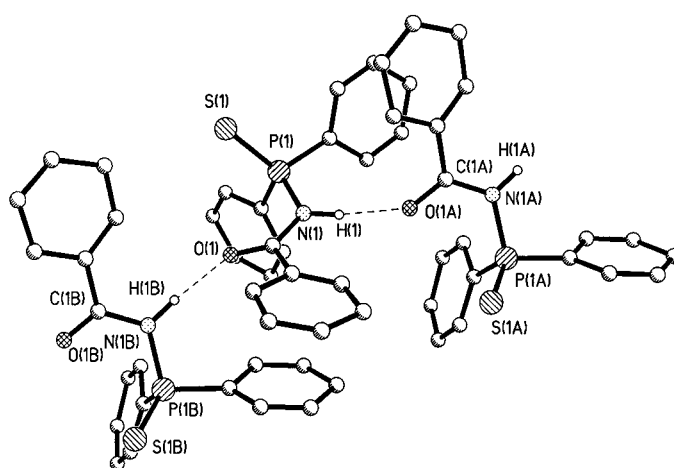


Figure 1. Structure of **1** in the crystal showing part of the hydrogen-bonded chain. Selected distances [pm] and angles $^\circ$: P(1)–S(1) 194.1(6), P(1)–N(1) 172(1), C(1)–N(1) 136(2), C(1)–O(1) 122(2); S(1)–P(1)–N(1) 115.1(4), P(1)–N(1)–C(1) 120.0(1), N(1)–C(1)–O(1) 120(2).

chains through $\text{C}=\text{O} \cdots \text{H}-\text{N}$ hydrogen bonds ($\text{N} \cdots \text{O}$ 285 pm, $\text{H} \cdots \text{O}$ 190 pm, $\text{N}-\text{H} \cdots \text{O}$ 172.5°). The conformation of the system bears a striking resemblance to that of $i\text{Pr}_2\text{P}(\text{S})\text{NH}-\text{P}(\text{S})i\text{Pr}_2$ ^[6] but is different to that observed in $\text{Ph}_2\text{P}(\text{S})\text{NHP}(\text{S})\text{Ph}_2$ ^[7] which crystallizes as dimers. The O and S atoms in **1** are well arranged for coordination with an $\text{O} \cdots \text{S}$ distance of 340 pm.

Treatment of **1** with $\text{KO}t\text{Bu}$ in THF gave $\text{K}[\text{Ph}_2\text{P}(\text{S})\text{NCOPh}]$ (**2**) as a white solid after workup. Recrystallization of **2** from methanol gave **2**·MeOH, the first example of a six-membered “true” heterocycle. The X-ray structure analysis^[8] of **2**·MeOH (Figure 2) reveals that the potassium atom is

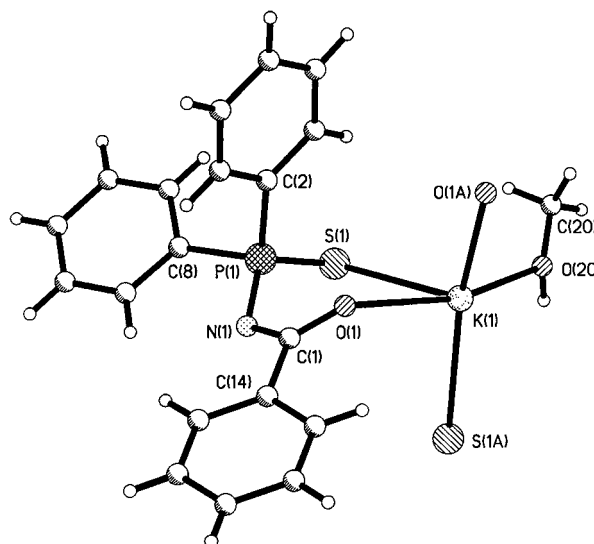


Figure 2. Structure of **2**·MeOH in the crystal showing the coordination shell. Selected distances [pm] and angles $^\circ$: K(1)–O(1) 266.9(3), K(1)–S(1) 324.4(2), K(1)–O(1A) 268.7(3), K(1)–S(1A) 328.6(2), P(1)–S(1) 195.0(2), P(1)–N(1) 161.8(4), C(1)–N(1) 133.2(6), C(1)–O(1) 124.1(5); O(1)–K(1)–O(1A) 79.1(1), O(1)–K(1)–O(20) 159.6(1), O(1)–K(1)–S(1) 75.1(1), O(1A)–K(1)–S(1) 112.6(8), O(20)–K(1)–S(1) 85.4(1), O(1)–K(1)–S(1A) 102.1(1), O(20)–K(1)–S(1A) 79.2(1), S(1)–K(1)–S(1A) 77.8(4), K(1)–S(1)–P(1) 97.1(1), S(1)–P(1)–N(1) 118.4(1), P(1)–N(1)–C(1) 119.6(3), N(1)–C(1)–O(1) 125.7(4), C(1)–O(1)–K(1) 128.7(3).

[*] Prof. J. D. Woollins, Dr. T. Q. Ly, Dr. A. M. Z. Slawin
Department of Chemistry
Loughborough University
Loughborough, LE11 3TU (UK)
Fax: (+44) 1509-223925
E-mail: j.d.woollins@lboro.ac.uk

[**] We are grateful to the JREI for an equipment grant.

coordinated by the oxygen atom of methanol, one oxygen atom and one sulfur atom of the chelate ligand as well as an oxygen atom of the ligand above and a sulfur atom of the ligand below to give a ladder structure. The six-membered KSPNCO ring adopts a pseudo-boat conformation with P(1) at the prow and O(1) at the stern of the boat (maximum deviation from the O(1)-C(1)-N(1)-P(1) mean plane is 3 pm for C(1) and maximum deviation from the P(1)-S(1)-K(1)-O(1) mean plane is 9 pm for P(1); the planes are inclined by 129°). Within **2**·MeOH the P–S and C–O bond lengths are longer than in **1**, whilst the P–N and C–N bond lengths are somewhat shorter which is entirely compatible with increased delocalization into the π system as a consequence of deprotonation. The IR spectra support this view as both $\tilde{\nu}(\text{CO})$ and $\tilde{\nu}(\text{PS})$ are observed at lower frequency in **2**. The P–N–C angles in **1** and **2**·MeOH display values that are almost perfect for a trigonal structure, whereas the P–N–P angles in $[\text{R}_2\text{P}(\text{E})\text{NP}(\text{E})\text{R}_2]^{-[1]}$ systems are generally larger than 120°. As mentioned above the S and O atoms of the anionic ligand are shared between neighboring potassium atoms to give a ladder structure made up of alternating K_2S_2 and K_2O_2 rings.

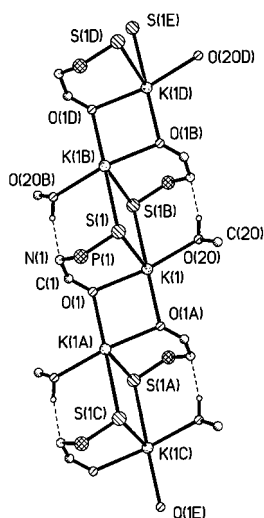


Figure 3. Structure of **2**·MeOH in the crystal showing the ladder formation in the infinite chains of alternating K_2S_2 and K_2O_2 rings. The intraring angles are: K–S–K 102.1(1), S–K–S 77.9(1), K–O–K 100.9(1), O–K–O 79.1(1)°.

The planar rings reflect the difference in the chalcogenide atom that they contain. Thus in the K_2S_2 ring the S···S distance is 410 pm and the K···K distance is 508 pm,^[9] whereas in the K_2O_2 rings the O···O and K···K distances are 340 and 413 pm, respectively. The K_2S_2 and K_2O_2 rings are twisted by 70° with respect to each other. An intrachain hydrogen-bonding system consisting of methanol···ring-N O–H···N interactions (O(20)···N(1') 295 pm, H(20)···N(1') 199 pm, O–H···N 168°) runs along the edges of the chains to aid the ladder formation (Figure 3), indeed one could speculate that this hydrogen bonding is necessary for the organization of the molecules into a chain structure. A further weak K···C interaction between one of the aryl rings and the potassium atoms is also present (K···C(3A) 347 K···C(4A) 348 pm) to increase the effective coordination number of the metal ion—a similar effect was noted in $\text{K}[\text{Ph}_2\text{P}(\text{S})\text{NP}(\text{S})\text{Ph}_2]$.^[9]

Experimental Section

PhC(O)NHP(S)Ph₂: To a solution of PhC(O)NH₂ (3.2 g, 7.7 mmol) in THF (150 mL) was added Et₃N (3.9 mL, 30 mmol), DMAP (dimethylaminopyridine; 200 mg, 20 mmol), and neat Ph₂PCl (5 mL, 27.9 mmol)—the solution was heated at reflux overnight. After the mixture had been cooled, S₈ (1.78 g, 55.7 mmol) was added and the mixture was stirred overnight at room temperature. The solution was filtered and the filtrate was reduced to dryness to give a white powder. It was then triturated with Et₂O (200 mL)

to give a yield of 6.43 g (34%). M.p. 186–190°C; ³¹P NMR (CDCl₃): δ = 56; IR (KBr): $\tilde{\nu}(\text{NH})$ 3159 m, 3060 w (CO) 1651 vs, (CN) 1454 vs, (PN) 880 w, 832 m, (PS) 636 vs cm⁻¹; FAB (*m/z*): 361 [MH+Na]⁺, 337 [MH+H]⁺; elemental analysis (%) calcd for C₁₉H₁₆NOPS: C 67.64, H 4.78, N 4.15; found: C 67.25, H 4.54, N 4.02.

K[PhC(O)NP(S)Ph₂] **2**: A solution of [PhC(O)NHP(S)Ph₂] (1 g, 2.96 mmol) and KOtBu (0.57 g, 5.12 mmol) in THF (60 mL) was stirred for 30 min. The solution was filtered through celite, and then reduced to dryness to give 1.1 g (100%) of white powder. Elemental analysis (%) calcd for C₁₉H₁₅NOPSK: C 60.78, H 4.03, N 3.73; found: C 60.34, H 4.12, N 3.45. Recrystallization of this compound from methanol gave **2**·MeOH. M.p. 286–290°C. ³¹P NMR ([D₆]DMSO): δ = 44; IR (KBr): $\tilde{\nu}(\text{CN})$ = 1588 m, (CO) 1519 vs, (PN) 895 m, 838 s, (PS) 627 s, 612 s cm⁻¹; FAB (*m/z*): 399 [MH+Na]⁺, 377 [MH+H]⁺.

Received: April 7, 1998 [Z11698IE]

German version: *Angew. Chem.* **1998**, *110*, 2605–2607

Keywords: coordination modes • heterocycles • ladder structures • potassium • structure elucidation

- [1] J. D. Woollins, *J. Chem. Soc. Dalton Trans.* **1996**, 2893–2901.
- [2] R. Cea-Olivares, J. Novosad, A. M. Z. Slawin, J. D. Woollins, V. Garcia-Montalvo, G. Espinosa-Perez, P. G. Y. Garcia, *Chem. Commun.* **1996**, 519–520.
- [3] A. Schmidpeter, H. Groeger, *Chem. Ber.* **1967**, *100*, 3052–3062.
- [4] H. Groeger, A. Schmidpeter, *Chem. Ber.* **1967**, *100*, 3216–3224.
- [5] Crystal structure analysis of **1** 0.11 × 0.11 × 0.03 mm, monoclinic, $P2_1/c$, $Z = 4$, $a = 894.2(8)$, $b = 1994(2)$, $c = 974(2)$ pm, $\beta = 100.3(1)^\circ$, $V = 1708(4) \times 10^6$ pm³, $\rho_{\text{calcd}} = 1.32$ g cm⁻³, CuK α radiation $\lambda = 154.178$ pm, ω -scan, $T = 291$ K, 2815 measured, 2634 independent, and 962 observed reflections [$I > 1.5\sigma(I)$], absorption correction ($T_{\text{min}}/T_{\text{max}}$) 0.49/1.00, structure solved by direct methods and refined against F using TeXsan, 209 refined parameters $R = 0.116$, R_w 0.085, residual electron density (max/min) 0.54/–0.48 e Å⁻³.^[8b]
- [6] D. Cupertino, R. W. Keyte, A. M. Z. Slawin, D. J. Williams, J. D. Woollins, *Inorg. Chem.* **1996**, *35*, 2695–2697.
- [7] H. Noth, *Z. Naturforsch. B* **1982**, *37*, 1491–1498.
- [8] a) Crystal structure analysis of **2**·MeOH: Crystal dimensions: 0.15 × 0.15 × 0.15 mm, monoclinic, $P2_1/c$, $Z = 4$, $a = 813.49(3)$, $b = 1202.05(4)$, $c = 2099.54(7)$ pm, $\beta = 91.705(1)^\circ$, $V = 2052(1) \times 10^6$ pm³, $\rho_{\text{calcd}} = 1.32$ g cm⁻³, MoK α radiation $\lambda = 71.069$ pm, SMART system, hemisphere data collection using 0.3° slices, $T = 291$ K, 8793 measured, 3033 independent, and 2984 observed reflections [$I > 2\sigma(I)$], semiempirical absorption correction ($T_{\text{min}}/T_{\text{max}}$) 0.62/1.00, structure solved by direct methods and refined against F^2 using SHELXTL, 239 refined parameters $R = 0.0516$, R_w 0.1198, residual electron density (max./min.) 0.63/–0.76 e Å⁻³. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101341. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] In $\text{K}[\text{Ph}_2\text{P}(\text{S})\text{NP}(\text{S})\text{Ph}_2]$ the potassium ion is formally four-coordinate and increases its coordination number to six by interaction with two phenyl rings, the K···K and S···S distances are 469 and 447 pm, respectively. A. M. Z. Slawin, J. Ward, D. J. Williams, J. D. Woollins, *J. Chem. Soc. Chem. Commun.* **1994**, 421–422.

Carbohydrates as Multifunctional Chiral Scaffolds in Combinatorial Synthesis

Tobias Wunberg, Christopher Kallus, Till Opatz, Stefan Henke, Wolfgang Schmidt, and Horst Kunz*

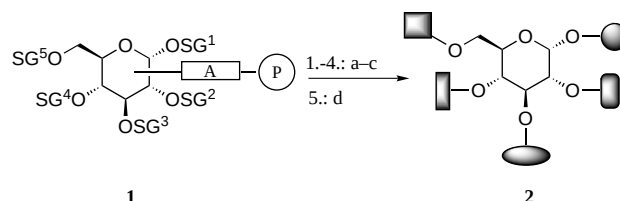
Dedicated to Professor Wolfgang Steglich on the occasion of his 65th birthday

Combinatorial chemistry has incisively changed the search for new biologically active substances in medicinal chemistry.^[1] Owing to its roots in solid-phase peptide synthesis,^[2] combinatorial reaction sequences were first carried out on solid phase to generate substance libraries (mixtures). Soon, these procedures were supplemented by one-pot reactions on nonprotected polyfunctional molecules^[3] and by multicomponent reactions in solution^[4] as well as on solid phase,^[1f] likewise yielding mixtures of compounds. The parallel synthesis of numerous single compounds is considered most desirable nowadays and can be accomplished by sequential couplings of building blocks to solid-phase-linked substrates, if suitable combinations of protecting and anchoring groups are applied.^[1] Alternatively, multiply functionalized scaffolds bound to solid phase are successively and regioselectively coupled with side chains, a procedure which also requires a tailor-made protecting and anchoring group technique.^[5]

Besides peptides and amino acid derivatives,^[1] functionalized aryl^[6] and deoxycholic acid derivatives^[7] have been applied in this sense. In comparison to these scaffolds and to the recently described squaric acid templates,^[8] carbohydrates constitute templates which not only offer more utilizable functional groups but also numerous, alternatively addressable eligible stereogenic centers. On the basis of a glucose derivative protected as the benzyl ether in 2-, 3-, and 4-position, Hirschmann et al. reported the synthesis of a biologically efficient mimetic of somatostatin.^[9]

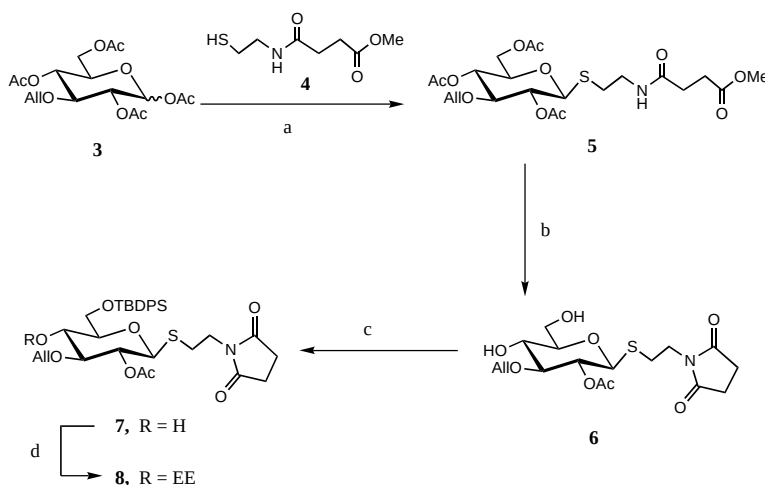
In order to apply carbohydrates as scaffolds in solid-phase combinatorial synthesis, a strategy based on orthogonally stable protecting groups must be developed which allows the selective deprotection at each hydroxylic group. Moreover, all other protecting groups must remain unaffected during the subsequent introduction of the potentially pharmacophoric side chains. Because side chains already linked to the scaffold must also be stable during these condensations, the coupling of the side chain through an ether-type linkage constitutes the most general solution. As a consequence, all protecting groups in **1** except for the one to be removed first must be

unaffected under the basic conditions of an ether synthesis. The spectrum of protecting groups, thus limited, is further reduced because benzyl ether protecting and other protecting groups cleavable under heterogeneous conditions are not applicable to solid-phase syntheses. Last but not least, an anchoring group to the solid phase must be found which remains stable during all protecting group and side-chain-introducing manipulations, however, it must also allow the detachment of the undestroyed target compound **2** from the solid phase (Scheme 1).



Scheme 1. Strategy of combinatorial synthesis with carbohydrate scaffolds: SG = protecting group, A = anchor, P = polymer (carrier); a) selective deprotection; b) functionalization; c) washing; d) cleavage of the anchor.

For D-glucopyranose as an example of a carbohydrate template, we have converted the 1,2,4,6-tetra-O-acetyl-3-O-allyl-β-D-glucopyranose^[10] **3** with succinic acid methyl ester-monomocysteamide **4** into the thioglucoside **5** (Scheme 2). Zemplén transesterification resulted in the selective deacetylation in the 4- and 6-position, whereas the 2-O-acetyl group in **6** remained unaffected because of the neighboring equa-



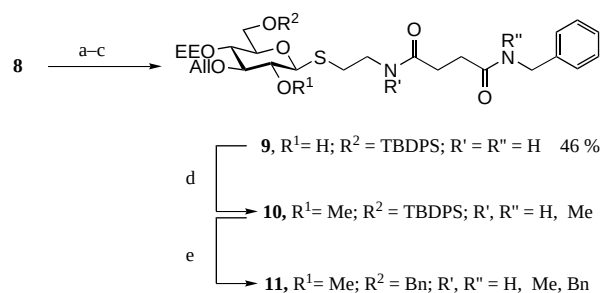
Scheme 2. Synthesis of carbohydrate scaffolds **8** equipped with orthogonally stable protecting groups: a) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 85 %; b) NaOMe/MeOH , 90 %; c) TBDPS-Cl, DMAP,^[12] CH_2Cl_2 , 90 %; d) $\text{EtOCH}=\text{CH}_2$, pyridinium-*p*-toluenesulfonate, CH_2Cl_2 , 98 %. TBDPS = *tert*-butyldiphenylsilyl; DMAP = 4-dimethylaminopyridine.

[*] Prof. Dr. H. Kunz, Dr. T. Wunberg, Dipl.-Chem. C. Kallus, Dipl.-Chem. T. Opatz
Institut für Organische Chemie der Universität
J.-J.-Becher-Weg 18–20, D-55099 Mainz (Germany)
Fax: (+49) 6131-39-4786
E-mail: hokunz@goofy.zdv.uni-mainz.de
Dr. S. Henke, Dr. W. Schmidt
Hoechst-Marion Roussel, Zentrale Pharmaforschung
Frankfurt am Main (Germany)

torial substituents.^[11] Reaction with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) gave the 6-O-silyl ether **7**, which was treated with ethyl vinyl ether to form the 1-ethoxyethyl (EE) ether group of the completely selectively deprotectable building block **8**.

In this concept, the thioglycoside anchor functionalized in the side chain is considered crucial. It must be stable during all

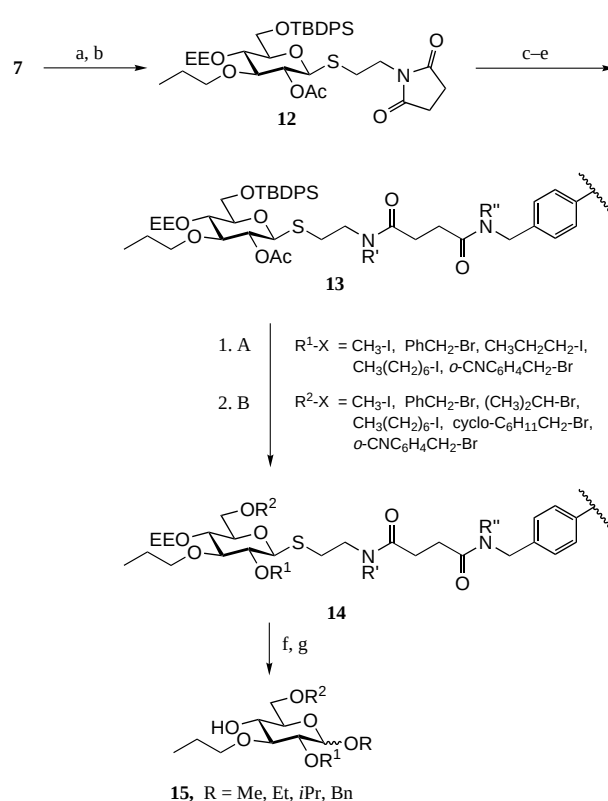
protecting group manipulations and alkylation reactions.^[13] In order to prove these prerequisites, the imide **8** was opened and the product condensed with benzylamine.^[14] Subsequent treatment with hydrazine hydrate yielded model compound **9** (Scheme 3).



Scheme 3. a) LiOH, THF, H₂O; b) Bn-NH₂, DCC, *N*-hydroxysuccinimide; c) hydrazine hydrate, DMF; d) 1. KOtBu, DMF; 2. CH₃I; 63%; e) 1. TBAF, THF, 80%; 2. KOtBu, DMF; 3. BnBr, TBAI, 57%. Bn = benzyl; DCC = dicyclohexylcarbodiimide.

Deprotonation of potassium *tert*-butylate (3 equiv) in dimethylformamide and reaction with methyl iodide (4 equiv) furnished the 2-*O*-methyl compound **10** without affecting the thioglycoside structure. In this reaction partial *N*-methylation of the amide grouping occurred. This effect as well as loss during purification are not relevant to the combinatorial synthesis on solid phase. The removal of the TBDPS group by using tetrabutylammonium fluoride (TBAF) and the subsequent formation of the 6-*O*-benzyl ether **11** were achieved again without affecting the thioglycoside. After these test reactions, the carbohydrate scaffold **8** was used for combinatorial multistep reactions. Because preliminary experiments had shown that the cleavage of allyl ethers on solid phase in contrast to the corresponding reactions in solution by treatment with [(PPh₃)₃RhCl],^[15] PdCl₂,^[16] or the zirconocene reagent^[17] were accompanied by side reactions, for example hydrogenation, the allyl ether **7** was converted into the propyl ether using diimine^[18] prior to the introduction of the 1-ethoxyethyl group to give **12** (Scheme 4). The imide group was opened and coupled to aminomethyl polystyrene (AMPS, 1.3 mmol g⁻¹) to yield the solid-phase anchored carbohydrate scaffold **13** (0.6 mmol carbohydrate per gram resin).^[19] In parallel syntheses, deprotonations were carried out using KOtBu (10 equiv) while shaking at room temperature, and alkylations were performed by using alkyl halide (30 equiv) in dimethylformamide at room temperature within 2 h. The TBDPS group was removed by using TBAF (10 equiv) in tetrahydrofuran at room temperature within 16 h. After every reaction, the resin was washed several times with dimethylformamide, toluene, and the solvent of the subsequent conversion (Scheme 4).

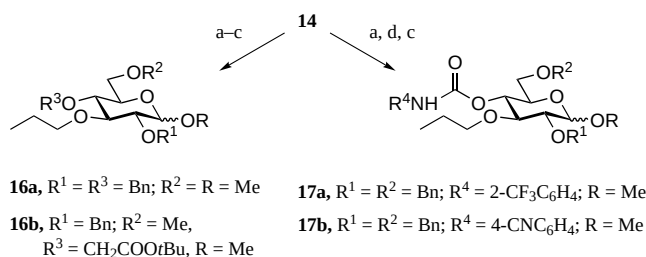
After combinatorial substitution at the 2- and 6-position, the thioglycoside anchor was cleaved by using a 1M solution of bromine in dichloromethane (3 equiv) under addition of 2,6-di-*tert*-butyl-pyridine (7.5 equiv). To this mixture, a 25% solution of the alcohol to be glycosylated (20 equiv) in dichloromethane containing tetraethylammonium bromide (1 equiv) and cyclohexene (6 equiv) were added. The prod-



Scheme 4. a) KOOCN=NCOOK, AcOH, MeCN; b) EtOCH=CH₂, TsOH; c) LiOH, THF/H₂O; d) *N,N'*-diisopropylcarbodiimide/*N*-hydroxysuccinimide/AMPS, CH₂Cl₂; e) hydrazine hydrate, DMF; A: 1. KOtBu, DMF; 2. R¹-X; B: 1. TBAF, THF; 2. KOtBu, DMF; 3. R²-X; f) 1. pyridinium-*p*-toluenesulfonate; 2. Br₂, CH₂Cl₂, 2,6-di-*tert*-butylpyridine; g) R-OH, cyclohexene, Et₄NBr. AMPS = aminomethylpolystyrene; Ts = *p*-toluenesulfonyl.

ucts were isolated after filtration, elution from a short column of silica, and evaporation of the volatile components in high vacuum. They are obtained as mixtures of anomers ($\alpha:\beta \approx 5:1$) and are identified by analytical HPLC and FAB mass spectrometry. The anomeric configuration was determined for compounds **15** (R = R¹ = Me, R² = Bn), **16a**, and **17a** from ¹H NMR spectra (400 MHz). As a rule, the purity of the mixtures of anomers according to RP-HPLC ranges from 75 to 95%; the remainder of di-*tert*-butyl-pyridine formed the major component of the impurities. Out of an array of 28 compounds **15** (Scheme 4), 25 mixtures of anomers **15** have been obtained after five reactions on solid phase and the subsequent glycosylation reaction in overall yields of 30 to 80%.

The diversity of the single compound libraries is expanded by involving the 4-position. The EE-protecting group was removed by a transacetalization reaction (Scheme 5). The fourth variable substituent can be introduced into these compound libraries not only by alkylations to give compounds of type **16**, but also by reactions with isocyanates to form **17**. The developed strategy thus provides the generation of libraries of large diversity already on the basis of the four functional groups used so far. By means of carbamate formations, branched and heterocyclic substituents can be introduced, in particular, if not only commercially available reagents are applied. The inclusion of the fifth function and



Scheme 5. a) MeOH, dioxane, pyridinium-*p*-toluenesulfonate; b) KOtBu, DMF, R³-X; c) Br₂, CH₂Cl₂, 2,6-di-*tert*-butylpyridine, ROH, Et₄NBr, CH₂Cl₂, cyclohexene; d) R⁴-NCO, DMAP, dioxane.

translation of the combinatorial synthesis to stereoisomers of the glucose scaffold (galactose, mannose) are presently under investigation.

Received: March 23, 1998

Supplemented version: June 22, 1998 [Z116221E]

German version: *Angew. Chem.* **1998**, *110*, 2620–2622

Keywords: carbohydrates • combinatorial chemistry • protecting groups • solid-phase synthesis • thioglycosides

- [1] Reviews: a) L. A. Thomson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555; b) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17; c) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288; d) A. Netzi, J. M. Ostresh, R. A. Houghten, *Chem. Rev.* **1997**, *97*, 449.
- [2] a) "Highlight of Modern Biochemistry": A. Furka, F. Sebesteyn, M. Asgedom, G. Dibo, *Proc. 14th Int. Congress Biochem.*, Utrecht (Netherlands), **1988**, 5, 47; b) H. M. Geysen, R. H. Meloen, S. J. Barteling, *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3998; c) R. A. Houghten, *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131.
- [3] a) T. Carell, E. A. Winter, A. Bashir-Hashemi, J. Rebek, Jr., *Angew. Chem.* **1994**, *106*, 2159; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2161; b) H. An, L. L. Cummins, R. H. Griffey, R. Bharadwaj, B. D. Haly, A. S. Fraser, L. Wilson-Lingardo, L. M. Risen, J. R. Wyatt, P. D. Cook, *J. Am. Chem. Soc.* **1997**, *119*, 3696.
- [4] M. Goebel, I. Ugi, *Tetrahedron Lett.* **1995**, *36*, 6043.
- [5] Siehe z. B.: M. Patek, B. Drake, M. Lebl, *Tetrahedron Lett.* **1994**, *35*, 9169.
- [6] See for example: J. Green, *J. Org. Chem.* **1995**, *60*, 4287.
- [7] a) G. Wess, K. Bock, H. Kleine, M. Kurz, W. Guba, H. Hemmerle, E. Lopez-Calle, K.-H. Baringhaus, H. Glombik, A. Ehnsen, W. Kramer, *Angew. Chem.* **1996**, *108*, 2363; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2222; b) R. Boyce, G. Li, H. P. Nestler, T. Suenaga, W. C. Still, *J. Am. Chem. Soc.* **1994**, *116*, 7955.
- [8] P. A. Tempest, R. W. Armstrong, *J. Am. Chem. Soc.* **1997**, *119*, 7607.
- [9] R. Hirschmann, K. C. Nicolaou, S. Pietramico, J. Salvino, E. M. Lealy, W. C. Shakespeare, P. S. Spengler, P. Hamley, A. B. Smith, T. Reisine, K. Raynor, C. Donaldson, W. Vale, L. Maechler, R. M. Freidinger, C. D. Strader, *J. Am. Chem. Soc.* **1993**, *115*, 12550; siehe auch: K. C. Nicolaou, J. I. Trujillo, K. Chibale, *Tetrahedron* **1997**, *53*, 8751.
- [10] K. Takeo, T. Nakaji, K. Shinmitsu, *Carbohydr. Res.* **1984**, *133*, 275.
- [11] Z. Szurmai, A. Liptak, G. Snatzke, *Carbohydr. Res.* **1990**, *200*, 201; M. Kaltenbach, Dissertation, Universität Mainz, **1994**.
- [12] G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.
- [13] This is a crucial point, because thioglycosides can be activated by electrophiles, in particular, alkylating reagents: a) H. Lönn, *Carbohydr. Res.* **1985**, *139*, 115; b) H. B. Meragata, V. R. Kulkarni, D. Ravi, G. V. Sharma, B. V. Rao, G. B. Reddy, *Tetrahedron* **1992**, *48*, 545; c) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503.
- [14] F. Weygand, D. Hoffmann, E. Wünsch, *Z. Naturforsch. B* **1966**, *21*, 426.
- [15] E. J. Corey, J. W. Suggs, *J. Org. Chem.* **1973**, *38*, 3224.
- [16] T. Ogawa, S. Nakabayashi, T. Kitajima, *Carbohydr. Res.* **1983**, *114*, 225.
- [17] Y. Hanzawa, H. Ito, T. Taguchi, *Synlett* **1995**, 299.

[18] S. Hünig, H. R. Müller, W. Thier, *Angew. Chem.* **1965**, *77*, 368; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 271.

[19] The loading was determined by elemental analysis (sulfur) and gravimetrically.

[20] For a thioglycoside anchor in oligosaccharide synthesis and an alternative cleavage: J. Rademann, R. R. Schmidt, *Tetrahedron Lett.* **1996**, *37*, 3989.

Evidence for Selective Association of Tetrahedral BO₄ Units with Na⁺ and of Trigonal BO₃ Units with H⁺ in Dehydrated Zeolite B-ZSM-5 from Solid-State NMR Spectroscopy**

Christian Fild, Hellmut Eckert, and Hubert Koller*

The study of local structure and bonding in zeolites is of fundamental interest for a better mechanistic understanding of their catalytic function. One of the unresolved questions regards the stabilization of boron in different coordination states in the zeolite framework. Typically, only boron centers tetrahedrally coordinated by O atoms (B[4]) are present in hydrothermally synthesized zeolites, some of which are transformed into trigonally coordinated centers (B[3]) when the organic structure directing agent is removed by calcination.^[1–4] The negative charge of the BO₄^{2–} groups in as-synthesized zeolites is balanced by sodium and quaternary ammonium cations, while the counterions in the calcined zeolite are Na⁺ and H⁺. Quantum-chemical calculations suggest that the bond between boron and protonated framework oxygen atoms is much weaker than the Al–O bond in Al–O(H)–Si groups; hence, the existence of three-coordinate boron centers in calcined zeolites is plausible.^[5]

Here we show that in calcined B-ZSM-5 the B[3] units selectively associate with H⁺, and the B[4] units with Na⁺ counterions. The zeolites were prepared hydrothermally with tetrapropylammonium (TPA) cations as structure-directing agent. The content of sodium cations in the zeolites was varied by changing the gel composition in the syntheses. The TPA was subsequently removed from the zeolite channels by calcination, and the samples were dehydrated in vacuum at elevated temperature. The ¹¹B MAS NMR spectra of the calcined and dehydrated samples show that the B[4]/B[3] ratio increases with increasing sodium content, and this suggests that sodium cations are associated with B[4] units (MAS = magic angle spinning; rotation of the probe in a magnetic field).

More direct evidence for this association can be obtained on the basis of the heteronuclear dipole interaction between

[*] Dr. H. Koller, C. Fild, Prof. H. Eckert
 Institut für Physikalische Chemie der Universität
 Schlossplatz 4/7, D-48149 Münster (Germany)
 Fax: (+49)251-83-29159
 E-mail: hkoller@uni-muenster.de

[**] We thank Arne Fischer for the ICP/AES analysis and Dr. Leo van Wüllen for valuable discussions. Financial support by the Fonds der Chemischen Industrie, the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie, and the Deutsche Forschungsgemeinschaft (KO 1817/1-1) is gratefully acknowledged.

NMR nuclei. Fast magic angle spinning usually averages this interaction. However, it can be reintroduced by means of the rotational echo double resonance (REDOR) experiment.^[6] A rotor-synchronized spin echo signal (pulse sequence: $\pi/2 - \tau - \pi - \tau$ - acquire) is recorded for nuclei I, and perturbation π pulses are applied to nuclei S within the echo period τ . The $\pi(S)$ pulse inverts the sign of the I–S heterodipolar coupling constant. This results in an additional decrease in the phase coherence and hence reduced echo signal intensity. Experimentally, one measures the normalized difference $\Delta S/S_0$ of the echo signal of spins I in the absence and presence of $\pi(S)$ pulses. $\Delta S/S_0$ is measured as a function of the dipolar evolution time $N \cdot T_r$, where N is the number of rotor cycles and T_r the rotor period. For an isolated I–S spin pair, the internuclear distance can be directly determined from this curve. In the case of multiple-spin interactions, the curvature of this function at short evolution times is proportional to an average dipole–dipole coupling constant.

For these REDOR studies we chose a B-ZSM-5 sample with 1.23 sodium cations and 1.32 boron atoms per unit cell (ICP/AES elemental analysis), resulting in a Si/B ratio of 72:1. This low concentration ensures isolated boron sites. A fraction of the Na^+ ions is associated with defect sites, as observed by ^{29}Si MAS NMR spectroscopy. Figure 1a shows the ^{11}B spin

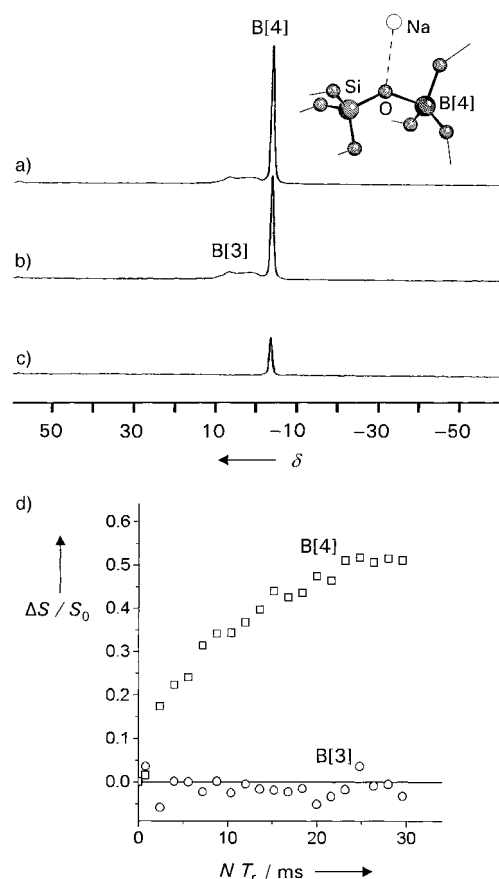


Figure 1. View of the local environment of a B[4] unit (top right) and ^{11}B spin echo MAS NMR spectra (rotation 10 kHz, relaxation delay 5 s, $\pi/2$ pulse length 3 μs) of B-ZSM-5 for 128 rotor cycles between the $\pi/2$ pulse and data acquisition. a) ^{11}B spin echo spectrum; b) $^{11}\text{B}[^{23}\text{Na}]$ REDOR spectrum, π pulse on decoupler 9.5 μs ; c) difference spectrum; d) $^{11}\text{B}[^{23}\text{Na}]$ REDOR curves for B[3] and B[4] (rotation 10 kHz, relaxation delay 5 s, $\pi/2$ pulse length 3 μs , π pulse on decoupler 7.7 μs).

echo MAS NMR spectrum of dehydrated zeolite B-ZSM-5. A sharp signal at $\delta = -3.7$ is observed for the B[4] units, while the B[3] units give rise to a MAS powder spectrum with second-order quadrupole interaction. Lineshape simulation yields a quadrupole coupling constant C_q of 2.5 MHz, an asymmetry parameter η of 0.1, and a chemical shift δ_{cs} of 9.7. Figure 1b shows the corresponding $^{11}\text{B}[^{23}\text{Na}]$ REDOR spectrum (^{11}B observed, perturbation pulses on ^{23}Na) at an evolution time of 12.8 ms. From the difference spectrum (Figure 1c) and the corresponding plot of $\Delta S/S_0$ versus $N \cdot T_r$ (Figure 1d), it is apparent that only the B[4] units exhibit a REDOR effect. These results show that the B[4] units are closely associated with sodium ions, while the B[3] units are not. That trigonal boron is located in the zeolite framework is indicated by the ^{11}B isotropic chemical shift of $\delta = 9.7 \pm 0.3$, which is typical of $\text{BO}_{3/2}$ groups connected to three silicon atoms, as in borosilicate glasses.^[7] Secondly, ^{11}B spin echo decay experiments^[8] reveal that the homodipolar $^{11}\text{B} - ^{11}\text{B}$ interactions are very weak. The resulting second moment value of $0.8 \times 10^6 \text{ rad}^{-2} \text{ s}^{-2}$ is only consistent with isolated $\text{BO}_{3/2}$ sites and the absence of B–O–B linkages.

The interaction between the H^+ counterions and the B[3] units was probed by complementary $^1\text{H}\{^{11}\text{B}\}$ and $^{11}\text{B}\{^1\text{H}\}$ REDOR experiments. Figure 2a shows the rotor-synchron-

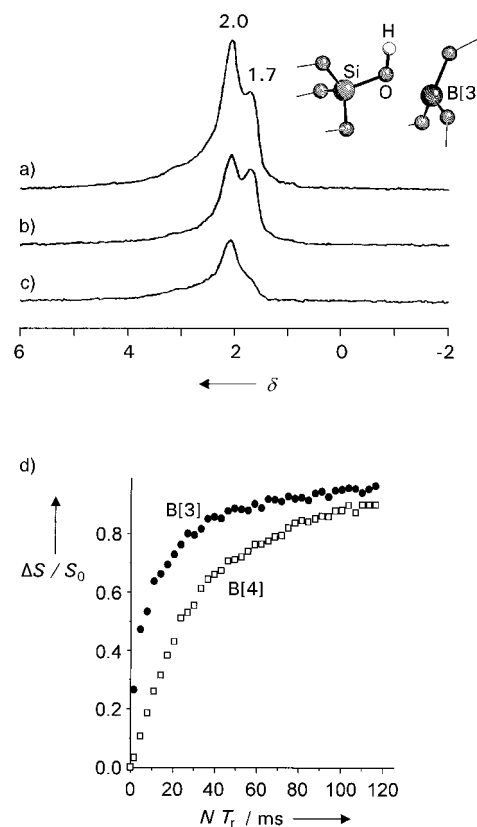


Figure 2. View of the local environment of a B[3] unit (top right) and ^1H MAS spin-echo NMR spectra of B-ZSM-5 (rotation frequency 10 kHz, relaxation delay 16 s, $\pi/2$ pulse length 5.2 μs): a) Rotor-synchronized spin echo experiment; b) $^1\text{H}\{^{11}\text{B}\}$ REDOR spectrum with 168 rotor cycles, π pulse on decoupler 8.8 μs ; c) difference spectrum; d) $^{11}\text{B}\{^1\text{H}\}$ REDOR curves for B[3] and B[4] (rotation frequency 10 kHz, relaxation delay 5 s, $\pi/2$ pulse length 3 μs , π pulse on decoupler 7.7 μs).

ized ^1H MAS spin-echo NMR spectrum of B-ZSM-5, which exhibits two maxima at $\delta = 1.7$ and 2.0 and a broad shoulder at $\delta = 3.0$. The corresponding $^1\text{H}\{^{11}\text{B}\}$ REDOR spectrum (evolution time 16.8 ms) is displayed in Figure 2b and shows a substantial decrease in the intensity of the maximum at $\delta = 2.0$ and the shoulder at $\delta = 3.0$. This is also evident in the difference spectrum (Figure 2c), in which the relatively weak change in the intensity of the signal at $\delta = 1.7$ can be seen. Although further work is necessary to clarify the detailed assignment of these three signals, it is clear that they arise from protons near to ($\delta = 3.0, 2.0$) or remote from ($\delta = 1.7$) framework boron atoms. We assign the signal at $\delta = 1.7$ to defect silanol groups, and the signals at $\delta = 3.0$ and $\delta = 2.0$ to the $\text{SiOH}\cdots\text{B}[3]$ groups in the zeolite framework. The observation of two different chemical shifts for these sites is similar to findings for analogous zeolites that contain aluminum instead of boron.^[9] The weak REDOR effect of the defect silanol groups is explained by their remoteness from boron atoms in the next nearest tetrahedral framework positions (B[3] or B[4]). Consistent with this model, we expect the B[3] units to be closely associated with the protons, since the charge of the B[4] units is balanced by sodium cations (see above). This conjecture is confirmed by the $^{11}\text{B}\{^1\text{H}\}$ REDOR curve in Figure 2d. The initial slope of the curve for B[3] is much steeper than for B[4], and this proves that the B[3] units are significantly closer to protons than the B[4] units. This suggests the formation of $\text{SiOH}\cdots\text{B}[3]$ groups, whereas the B[4] units are fairly remote from protons. Although it should be possible in principle to estimate an approximate B–H distance from such experiments, we refrain from doing so here, because the presence of long-range interactions means that no isolated spin pairs are present.

Our $^{11}\text{B}\{^{23}\text{Na}\}$, $^{11}\text{B}\{^1\text{H}\}$, and $^1\text{H}\{^{11}\text{B}\}$ REDOR results provide the first direct evidence that tetrahedral B[4] units are associated with charge-balancing sodium cations in dehydrated B-ZSM-5. Trigonal B[3] units are located in $\text{SiOH}\cdots\text{B}[3]$ groups, as predicted by the theoretical calculations of Sauer.^[5] Two proton NMR signals at $\delta = 2.0$ and 3.0 are observed for these sites. The results from experiments with other Na/H ratios are consistent with the data presented here.

Experimental Section

Zeolite B-ZSM-5 was hydrothermally crystallized at 423 K from a gel of molar composition $\text{H}_3\text{BO}_3:\text{NaOH}:\text{TPABr}:\text{TPAOH}:\text{H}_2\text{O}:\text{SiO}_2 = 0.084:0.08:0.06:0.04:36:1$. Calcination was carried out in air at 923 K, and the resulting zeolite powder was carefully dehydrated in vacuum at 623 K. The sample was initially heated to 353 K at 5 K min^{-1} and held at this temperature for 2 h. Subsequently the temperature was raised at 10 K min^{-1} to 623 K and kept at this temperature for 4 h. Solid-state double resonance NMR experiments on the dry samples were carried out on a Bruker DSX-500 spectrometer with a 4 mm triple resonance probe operating at 10 kHz spinning speed. The rotor speed was maintained by a standard automatic control unit. The resonance frequencies for ^1H , ^{11}B , and ^{23}Na are 500.11, 160.45, and 132.29 MHz, respectively.

Received: May 13, 1998 [Z11852IE]

German version: *Angew. Chem.* **1998**, *110*, 2654–2656

Keywords: boron • coordination modes • NMR spectroscopy • zeolites

- [1] G. Engelhardt, D. Michel, *High-Resolution Solid-State NMR of Silicates and Zeolites*, Wiley, Chichester, **1987**.
- [2] K. F. G. J. Scholle, W. S. Veeman, *Zeolites* **1985**, *5*, 118.
- [3] E. Brunner, D. Freude, M. Hunger, H. Pfeifer, W. Reschetilowski, B. Unger, *Chem. Phys. Lett.* **1988**, *148*, 226.
- [4] R. F. Lobo, M. E. Davis, *J. Am. Chem. Soc.* **1995**, *117*, 3766.
- [5] J. Sauer in *Modelling of Structure and Reactivity in Zeolites* (Ed.: C. R. A. Catlow), Academic Press, London, **1992**, p. 183.
- [6] a) T. Gullion, J. Schaefer, *J. Magn. Reson.* **1989**, *81*, 196; b) Y. Pan, T. Gullion, J. Schaefer, *J. Magn. Reson.* **1990**, *90*, 330; c) E. R. H. van Eck, W. S. Veeman, *Solid State NMR* **1993**, *2*, 307.
- [7] R. Martens, Dissertation, Universität Münster, **1995**.
- [8] B. Gee, H. Eckert, *Solid State NMR* **1995**, *5*, 113.
- [9] A peak at $\delta = 4.3$ and broad shoulder on the low-field side have been ascribed to different Brønsted acid sites in Al-ZSM-5: L. W. Beck, J. L. White, J. F. Haw, *J. Am. Chem. Soc.* **1994**, *116*, 9657.

An Unexpected Layered Structure in Inorganic Cyanide Clusters: $[\text{Cu}_4(\mu_3\text{-OH})_4][\text{Re}_4(\mu_3\text{-Te})_4(\text{CN})_{12}]^{**}$

Yuri V. Mironov, Alexander V. Virovets,
Sofia B. Artemkina, and Vladimir E. Fedorov*

Cyanide compounds have been known for nearly three centuries.^[1–3] New complex transition metal cyanides have been described recently that promise to have a variety of useful applications.^[4–7] Complex cyanides demonstrate unique structures, properties, and reactivity.^[1–7] The ambidentate nature of the CN^- ligand, its terminal and bridging binding modes, its wide variety of coordination number, and arrangement of metal centers favor the formation of amazing and unusual structures both for binary and for complex cyanides of transition metals. The last few years have made available the cyanide clusters.^[8–14] The availability of these compounds gave us the possibility to begin the study of their chemistry systematically.

We have recently prepared and structurally characterized caesium and potassium salts containing the new cyanide cluster anion $[\text{Re}_4(\mu_3\text{-Te})_4(\text{CN})_{12}]^{4-}$.^[13, 14] Here we report the new complex, polymeric inorganic cluster compound $[\text{Cu}_4(\mu_3\text{-OH})_4][\text{Re}_4(\mu_3\text{-Te})_4(\text{CN})_{12}]$ (**1**) built from these cluster anions.

Compound **1** was prepared by adding a solution of CuCl_2 to $\text{K}_4[\text{Re}_4\text{Te}_4(\text{CN})_{12}]$ in silica gel at about pH 7. The structure of **1** was solved by X-ray single-crystal analysis.^[15] The structure consists of layers built from the tetranuclear copper(II) cations

[*] Prof. Dr. V. E. Fedorov, Dr. Y. V. Mironov, Dr. A. V. Virovets
Institute of Inorganic Chemistry
Siberian Branch of Russian Academy of Sciences
3, Acad. Lavrentiev prospect, Novosibirsk 630090 (Russia)
Fax: (+7) 3832-344-489
E-mail: fed@che.nsk.su
S. B. Artemkina
Novosibirsk State University
2, Pirogova str., Novosibirsk 630090 (Russia)

[**] This research was supported by the Russian Foundation of Basic Research (N96-03-32955) and INTAS (N96-2705ext.). The authors thank Dr. V. N. Ikorskii for the magnetic measurements.

$[\text{Cu}_4(\mu_3\text{-OH})_4]^{4+}$ (Figure 1 a) and the cluster anions $[\text{Re}_4\text{Te}_4(\text{CN})_{12}]^{4-}$ (Figure 1 b). Eight of the twelve CN^- ligands of each anion are bonded to copper atoms in the layer (Figure 2). The remaining four CN^- ligands are directed perpendicular to the

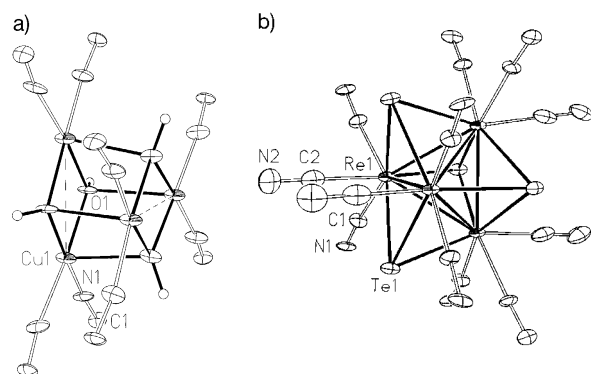


Figure 1. The structures of the $[\text{Cu}_4(\mu_3\text{-OH})_4]^{4+}$ cation (a) and the cluster anion $[\text{Re}_4\text{Te}_4(\text{CN})_{12}]^{4-}$ (b); the thermal ellipsoids are at the 50% probability level. Selected bond length [Å]: Re–Re 2.834(1) (3×), 2.857(1)(3×), Re–Te 2.632(2), 2.636(1) (2×), Re–C 2.04(2), 2.10(2) (2×), Cu–O 1.934(7) (2×), 2.31(1), Cu–N 1.96(1) (2×).

layer and form hydrogen bonds with hydroxyl groups from cations belonging to the neighboring layers (Figure 3); the N–O distances are 2.82 Å.

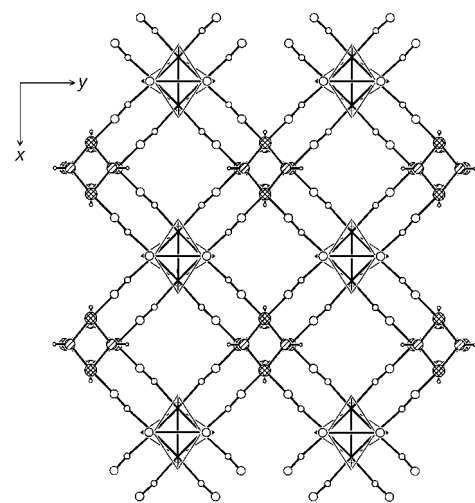


Figure 2. The covalent layer in **1** (projection along the xy plane). The Re–(μ_3 -Te) bonds are shown by thin lines.

The geometrical characteristics of the cluster anion are close to those previously reported.^[13, 14] The structure of the Re_4Te_4 core is typical of metal–chalcogen cubane clusters. In the cation $[\text{Cu}_4(\mu_3\text{-OH})_4]^{4+}$ four Cu atoms and four OH groups also form a cubane-like complex, elongated along the direction z axis, with two short and four long Cu–Cu contacts of 2.99 and 3.18 Å, respectively (Figure 1 a). The coordination polyhedron of the Cu^{2+} ions is a distorted square pyramid with two oxygen and two nitrogen atoms in the basal plane and one oxygen atom in the axial position. The cubane-like $\text{Cu}_4(\mu_3\text{-O})_4$ fragment was found previously in many Cu^{2+} complexes. But

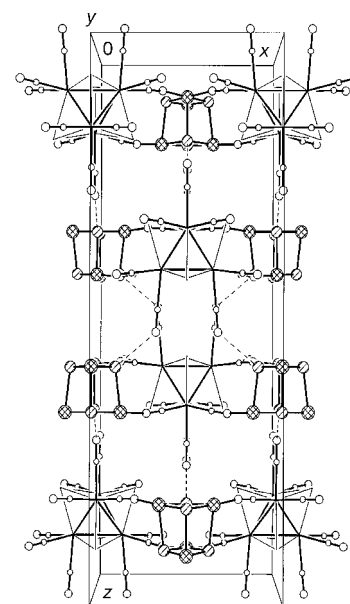


Figure 3. The packing of the layers (projection along the xz plane). The hydrogen bonds are shown by dashed lines.

there are only two known compounds with the $\{\text{Cu}_4(\mu_3\text{-OH})_4\}$ core: $[\text{Cu}_4(\text{OH})_4(\text{SO}_3\text{CF}_3)_2][\text{N}(\text{py})_3]_4 \cdot [\text{SO}_3\text{CF}_3]_2 \cdot \text{C}_3\text{H}_6\text{O}$ ^[17] (**2**, py = pyridine) and $[\text{Cu}(\text{bpy})\text{OH}]_4(\text{PF}_6)_4$ ^[18] (**3**, bpy = 2,2'-bipyridine). In many other cases the O atoms in the Cu_4O_4 fragment belong to the organic ligands. The $\text{Cu}_4(\mu_3\text{-OH})_4$ fragments in both **2** and **3** appear to be similar to that **1**. The main difference is that the copper atoms in compounds **2** and **3** are coordinated by six donor atoms, not by five as in **1**. Also, the distortions of the Cu_4 clusters from an ideal tetrahedral geometry in compounds **2** and **3** are larger than in **1** (the mean bond distances Cu–Cu are 2.970 and 3.32 Å in **2**^[17], 2.914 and 3.408 Å in **3**^[18] and 2.99 and 3.18 Å in **1**).

The layers in the structure of **1** are arranged in such a way that the classical four-layered packing ($\cdots\text{ABCD}\cdots$) is formed (Figure 3). The crystals do not have the plate shape usually expected for covalent layered structures. In our case prismatic and even cylindrically shaped crystals have been obtained. The single crystal used for structure analysis was elongated in the direction perpendicular to the layers. In the infrared spectrum^[19] the O–H stretching vibration occurs at 3360 cm^{-1} , which is close to that found for **2** (3470 cm^{-1}).^[17] Two bands at 2191 and 2145 cm^{-1} correspond to the two different CN groups, namely, the bridging and terminal ones, respectively. Preliminary magnetic measurements of the title compound between room temperature and 78 K showed a complex antiferromagnetic interaction of copper(II) ions; a maximum in χ_M occurs at about 260 K. Detailed magnetic and EPR studies are in progress.

Experimental Section

Preparation of single crystals of 1: A solution of commercial waterglass (10 mL) in water (100 mL) was titrated with acetic acid (0.5 M) to produce pH ≈ 7. After titration the mixture was placed into a U-tube, and the gel allowed to set for one day. Diffusion in the opposite direction of aqueous solutions of $\text{K}_4[\text{Re}_4\text{Te}_4(\text{CN})_{12}]$ (0.1 mmol L^{-1}) and CuCl_2 (0.5 mmol L^{-1}) through the silica gel for four weeks resulted in single crystals, some of

which were suitable for single-crystal X-ray determination. The crystals were separated from the silica gel manually. Yield: $\approx 70\%$. Our attempts to obtain the title compound by simply mixing the solutions of starting materials were unsuccessful. However, the compound can be prepared by slow diffusion of reagents through a fritted glass filter (pore size several microns).

Received: March 6, 1998 [Z11563IE]
German version: *Angew. Chem.* **1998**, *110*, 2656–2658

Keywords: clusters • copper • cyanides • layered compounds • rhenium

Reactions of Selected Bismuth Oxide Cluster Cations with Propene**

Markus Kinne, Andreas Heidenreich, and
Klaus Rademann*

Many chemical and physical properties of metal clusters have been determined over the past few years.^[1] One of the main reasons for studying these compounds—in addition to carrying out fundamental research in itself—is the hope of obtaining a deeper insight into the sequence of events involved in catalytic processes.^[2] To this end, the reactions of pure metal clusters deposited on surfaces and of free particles in the gas phase were studied.^[3] Moreover, a great number of experiments on the formation and stability of metal oxide clusters have been carried out, but very little is known about the reactions themselves.^[4] This is all the more astonishing when one considers that metal oxides in particular are widely employed as catalysts in the chemical industry. Bismuth oxide compounds are used, for example, in the oxidation of propene and butene.

We prepared bismuth oxide clusters with a modified gas aggregation source and carried out reactions with them. In order to do this, the pure metal was vaporized directly into a stream of cooled helium, whereupon clusters were formed due to oversaturation. Bismuth oxide clusters were formed by adding oxygen to the bismuth vapor. These were then ionized by using a short-pulse excimer laser (ATL, pulse length 2–4 ns, wave length 248 nm, laser energy 10 mJ) and identified by using a Wiley-McLaren mass spectrometer. The oxidation did not lead to a broad distribution of different mixed oxides, but rather to a cluster series with the general formula $\text{BiO}^+(\text{Bi}_2\text{O}_3)_n$.^[5] The structures of the Bi_3O_4^+ and Bi_5O_7^+ isomers obtained from ab initio geometry optimizations at the MP2 level are shown in Figures 1 a–c and 2 a, b.^[6] Two closed isomers were found for Bi_3O_4^+ (Figures 1 a, b). Attempts to formulate structures with terminal O atoms—in as far as any local minima on the potential hypersurface could be found for them—always led to considerably higher energies. The formation of structures with terminal O atoms can thus be excluded under experimental conditions. The open isomer (Figure 1 c) is, at 4.6 eV, higher in energy than the isomer in Figure 1 a. The ground state in all three structures is a singlet and the corresponding vertical singlet–triplet splittings are 4.6, 3.5, and 1.8 eV. Two isomer types are observed for the closed structures Bi_3O_4^+ and Bi_5O_7^+ . In type 1 (Figures 1 a and

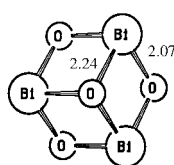
- [1] A. G. Sharp, *The Chemistry of Cyano Complexes of the Transition Metals*, Academic Press, London, **1976**.
- [2] W. P. Fehlhammer, M. Fritz, *Chem. Rev.* **1993**, *93*, 1243–1280.
- [3] K. R. Dunbar, R. A. Heintz, *Progr. Inorg. Chem.* **1997**, *45*, 283–391.
- [4] T. Mallah, S. Thiebaut, M. Verdaguer, P. Veillet, *Science* **1993**, *262*, 1554–1557.
- [5] S. Ferlay, T. Mallah, R. Ouahes, P. Veillet, M. Verdaguer, *Nature* **1995**, *378*, 701–703.
- [6] W. R. Entley, G. S. Girolami, *Science* **1995**, *268*, 397–400.
- [7] M. Verdaguer, *Science* **1996**, *272*, 698–699.
- [8] V. P. Fedin, M. R. J. Elsegood, W. Clegg, A. G. Sykes, *Polyhedron* **1996**, *15*, 485–488.
- [9] A. Slougui, Yu. V. Mironov, A. Perrin, V. E. Fedorov, *Croatica Chemica Acta* **1995**, *68*, 885–890.
- [10] V. P. Fedin, G. J. Lamprecht, T. Kohzuma, W. Clegg, M. R. J. Elsegood, A. G. Sykes, *J. Chem. Soc. Dalton Trans.* **1997**, 1747–1752.
- [11] Yu. V. Mironov, J. A. Cody, T. A. Albrecht-Schmitt, J. A. Ibers, *J. Am. Chem. Soc.* **1997**, *119*, 493–498.
- [12] V. P. Fedin, I. V. Kalinina, A. V. Virovets, N. V. Podberezskaya, A. G. Sykes, *Chem. Commun.* **1998**, 233–234.
- [13] Y. V. Mironov, T. E. Albrecht-Schmitt, J. A. Ibers, *Z. Kristallogr. New Cryst. Struct.* **1997**, *212*, 308.
- [14] Y. V. Mironov, A. V. Virovets, S. B. Artemkina, V. E. Fedorov, *Zh. Strukt. Khim.*, in press.
- [15] Crystal data for $[\text{Cu}_4(\mu_3\text{-OH})_4][\text{Re}_4(\mu_3\text{-Te})_4(\text{CN})_{12}]$: tetragonal, space group $I4_1/amd$, $Z=4$, $a=10.236(1)$, $c=28.25(1)$ Å, $V=2960(1)$ Å³, $\rho_{\text{calc}}=4.240$ g cm^{−3}, $\mu=23.006$ mm^{−1}, 1886 reflections measured, 1082 independent reflections ($R_{\text{int}}=0.0398$), min./max. transitions = 0.815/1.185, 58 parameters, $R(F)=0.0319$ and $wR(F^2)=0.0693$ for 667 reflections having $F_o^2 > 2\sigma(F_o^2)$, residual electron density 2.23 e Å^{−3}. Data were collected by a standard technique at room temperature on an Enraf-Nonius CAD-4 diffractometer ($\theta_{\text{max}}=30^\circ$), with $\text{MoK}\alpha$ radiation ($\lambda=0.71069$ Å) and ω scan mode. Data were corrected for absorption with four azimuthal scans. The structures were solved by direct methods and refined anisotropically on F^2 for all independent reflections by full-matrix least-squares method, (SHELX-97).^[16] The residual electron density peaks lie very close to heavy atoms and, therefore, do not correspond to any chemically appropriate positions. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-408291.
- [16] G. M. Sheldrick, SHELX-97, Universität Göttingen, Germany, **1997**.
- [17] P. L. Dedert, T. Sorrell, T. J. Marks, J. A. Ibers, *Inorg. Chem.* **1982**, *21*, 3506–3517.
- [18] J. Sletten, A. Sorensen, M. Julve, Y. Journaux, *Inorg. Chem.* **1990**, *29*, 5054–5058.
- [19] IR (KBr): $\tilde{\nu}=3360\text{s}$, 2191vs , 2145s , 972m , 944w , 753vw , 495s , 451s , 416s cm^{−1}.

[*] Prof. Dr. K. Rademann, Dipl.-Chem. M. Kinne
Walther-Nernst-Institut für Physikalische und
Theoretische Chemie der Universität
Bunsenstrasse 1, D-10117 Berlin (Germany)
Fax: (+49) 30-2093-5559
Dr. A. Heidenreich
School of Chemistry, Tel Aviv University
69978 Tel Aviv (Israel)
Fax: (+972) 3-6415054

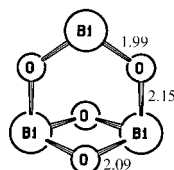
[**] This work was supported by the Humboldt-Forschungsfond and by the Fonds der Chemischen Industrie. We thank Professor Joshua Jortner for his interest and support. We also thank the Inter University Computation Center at Tel Aviv University for their assistance and for granting us computing time.



a) $C_{3v}, 1^1A_1, \Delta E \equiv 0$



b) $C_{2v}, 1^1A_1, \Delta E = 0.4 \text{ eV}$



c) $C_s, 1^1A', \Delta E = 4.6 \text{ eV}$

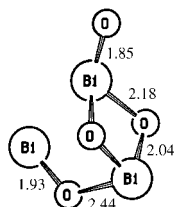
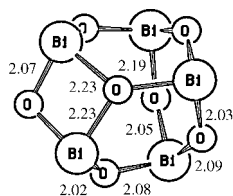


Figure 1. Optimized structures (ORTEP) of Bi_3O_4^+ isomers showing the point group, the term symbols, the energy difference ΔE relative to the isomer under a), and the bond lengths [Å].



a) $C_s, 1^1A', \Delta E \equiv 0$



b) $C_{2v}, 1^1A_1, \Delta E = 0.6 \text{ eV}$

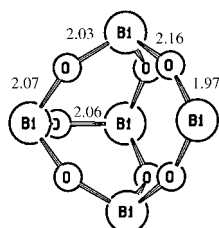


Figure 2. Optimized structures (ORTEP) of the Bi_5O_7^+ isomers.

2a), all Bi atoms have the coordination number 3. In addition, one of the O atoms is also three-coordinate. In contrast, cluster type 2 (Figures 1b and 2b) contains a two-coordinate (and therefore coordinatively unsaturated) Bi atom. The three-coordinate O atom in type 1 can be considered as the result of a donor–acceptor bond between Lewis acid and Lewis base centers within the cluster.

In order to carry out further reactions with these oxides, it was necessary to place them in a collision cell, which could be fed with various reaction gases. By operating the cell at low pressure, single collision conditions were imposed on the reactions. Figure 3a shows the change in the detected bismuth oxide cluster distribution with increasing propene partial pressure in the cell. Even with very low amounts of propene a considerable decrease was observed in the intensity of the oxide peaks. With increasing pressure the intensity of the oxide peaks decreased still further. The change in intensity of the peaks assigned to the pure metal clusters was not significant.

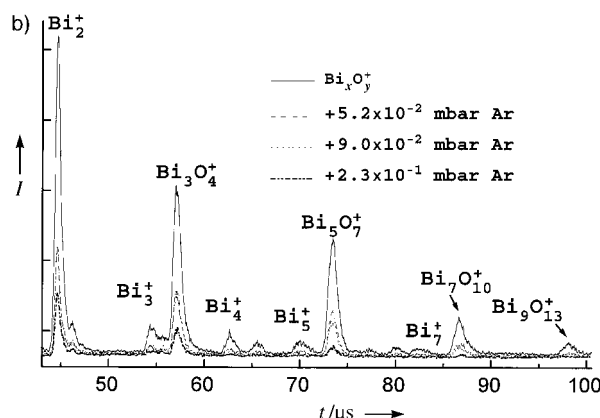
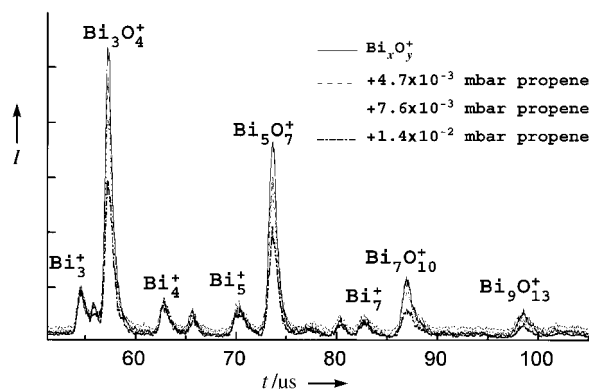


Figure 3. Mass spectra showing the change in intensity distribution of selected bismuth oxide cluster ions and bismuth cluster ions with increasing propene (a) and argon (b) partial pressures. t = time of flight.

These appeared not to react with the propene. The reaction products could not be determined due to the extremely low particle concentration. As the times of interaction were very short and only single collisions occurred, the oxidation of propene leading to CO_2 was rather improbable. In order to be certain that the observed phenomena were not just due to scattering processes, an inert gas (argon) was introduced into the cell. No effect was observed with argon at the same partial pressures used before. A significant change was first observed at higher pressures, but the intensities of all clusters and cluster oxides decreased with increasing argon partial pressure (Figure 3b). In contrast to the reactions with propene, it is highly probable that this decrease can be attributed to unreactive collisions and scattering processes.

Solid bismuth oxides employed for catalytic purposes are normally used in the form of multicomponent mixtures with other oxides (e.g. $\text{Bi}_x\text{Mo}_y\text{O}_z$).^[7] Pure bismuth oxide is usually reduced by propene to give elemental bismuth. It was shown, however, that solid bismuth oxide Bi_2O_3 can also be catalytically active under suitable reaction conditions.^[8] One of the central questions concerning these oxidations is whether only the terminal oxygen atoms take part in the reaction, or if the bridging oxygen atom also participates. It was assumed that the bridging oxygen atom is not reactive enough to participate in the oxidation process.^[9] The minimum requirement on any model substance for bismuth oxide catalysts is clearly that it reacts with propene.

As the bismuth oxide cluster ions we used have no terminal oxygen atoms, the reactions we carried out show quite clearly that bridging oxygen atoms can indeed participate in oxidation reactions. This is all the more astonishing when one considers that the bismuth oxide clusters detected should be particularly stable compounds due to their "magic" character.^[5] In addition, an analysis of the mass spectra indicated—in contrast to what was expected—that no clear size-dependent reactivity could be established for the metal oxides. Even the smallest cluster ions studied behaved similarly to solid bismuth oxide and were reduced by propene. In order to be sure that the reactions did not occur simply due to the higher energy associated with the accelerated and charged particles, the same reactions were performed with neutral bismuth oxide clusters. These experiments also resulted exclusively in a reduction of the oxides. The reduction admittedly first set in at partial propene pressures about one order of magnitude higher in the case of the nonaccelerated uncharged bismuth oxide clusters.^[10] The higher energy of the cations thus leads to an increase in the reaction cross-section, but the special selectivity of bismuth oxide clusters is independent of charge and not due to the increased kinetic energy of the cations. As further proof of the special reactivity of the bismuth oxide cluster ions in the oxidation of propene, the reaction introduced here was also carried out with antimony oxide cluster ions. These form stable polyoxides with the general formula $\text{SbO}^+(\text{Sb}_2\text{O}_3)_n$ similar to the bismuth oxide clusters.^[11] Here too, experiments were carried out both with propene and argon. In both cases, however, an increase in the partial pressure of the collision gas merely led to a decrease in the intensities of all observed peaks. These results are also a clear indication that the reactivity of the bismuth oxide cluster cations is not due to the fact that they are higher in energy than the solid because of ionization and sublimation.

The work presented here proves for the first time that mass-selected bismuth oxide cluster ions can be reduced by propene in just the same way as solid bismuth oxide. Moreover, it has been shown for the first time that supposedly unreactive bridging oxygen atoms can actively participate in oxidation reactions. Bismuth oxide clusters may possibly provide suitable model systems for bismuth oxide catalyst systems.

Received: October 28, 1997

Revised version: March 3, 1998 [Z11094]

German version: *Angew. Chem.* **1998**, *110*, 2637–2639

Keywords: ab initio calculations • alkenes • clusters • heterogeneous catalysis • oxidations

- [1] A. W. Castleman Jr., K. H. Bowen, *J. Phys. Chem.* **1996**, *101*, 12911–12944.
- [2] B. C. Gates, *Chem. Rev.* **1995**, *95*, 511–522.
- [3] a) D. J. Trevor, D. M. Cox, A. Kaldor, *J. Am. Chem. Soc.* **1990**, *112*, 3742–3749; b) P. Schnabel, K. G. Weil, M. P. Irion, *Angew. Chem.* **1992**, *104*, 633–635; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 636–638; c) D. Schröder, H. Schwarz, *Angew. Chem.* **1995**, *107*, 2126–2150; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1973–1995.
- [4] a) P. J. Ziemann, A. W. Castleman Jr., *J. Phys. Chem.* **1992**, *96*, 4271–4276; b) M. Anderson, J. L. Persson, A. Rosen, *J. Phys. Chem.* **1996**, *100*, 12222–12234.

- [5] a) M. Kinne, T. M. Bernhardt, B. Kaiser, K. Rademann, *Int. J. Mass. Ion. Proc.* **1997**, *167/168*, 161; b) M. R. France, J. W. Buchanan, J. C. Robinson, S. H. Pullins, J. L. Tucker, R. B. King, M. A. Duncan, *J. Phys. Chem. A* **1997**, *101*, 6214–6221.
- [6] A valence-double-zeta (VDZ) basis set was used for the ab initio geometry optimization to the MP2 level (Gaussian 94), in which all the inner-shell electrons were replaced by relativistic pseudo potentials.^[6a] The VDZ basis set was supplemented by sets of d functions on both bismuth and oxygen with Gauss exponentials of 0.202^[6b] and 1.33,^[6c] respectively. The harmonic vibrational frequencies were calculated for all optimized structures. a) W. J. Stevens, H. Basch, M. Krauss, *J. Chem. Phys.* **1984**, *81*, 6026; W. J. Stevens, M. Krauss, H. Basch, P. G. Jasien, *Can. J. Chem.* **1992**, *70*, 612; b) A. Höllwarth, M. Böhme, S. Dapprich, A. W. Ehlers, A. Gobbi, V. Jonas, K. F. Köhler, R. Stegmann, A. Veldkamp, G. Frenking, *Chem. Phys. Lett.* **1993**, *208*, 237; c) A. B. Alekseyev, H.-P. Liebermann, R. J. Buenker, G. Hirsch, Y. Li, *J. Chem. Phys.* **1994**, *100*, 8956.
- [7] D. Chelliah, G. W. Keulks, *J. Catal.* **1972**, *24*, 529–535.
- [8] E. Swift, J. E. Bozik, J. A. Ondrey, *J. Catal.* **1971**, *21*, 212–224.
- [9] a) B. Zhou, T. Machej, P. Ruiz, B. Delmon, *J. Catal.* **1991**, *132*, 183–199; b) B. Delmon, *Heterog. Chem. Rev.* **1994**, *1*, 219–230.
- [10] M. Kinne, K. Rademann, *Chem. Phys. Lett.*, **1998**, *284*, 363.
- [11] a) M. Kinne, T. M. Bernhardt, B. Kaiser, K. Rademann, *Z. Phys. D* **1997**, *40*, 105–107.

Self-Organization and Formation of Liquid Crystal Phases by Molecular Templates Related to Membrane Components of Archaeobacteria**

Rachel Auzély-Velty, Thierry Benvegnu, Daniel Plusquellec,* Grahame Mackenzie, Julie A. Haley, and John W. Goodby*

Molecular self-assembly and self-organization are becoming increasingly significant for the elucidation of life processes and the generation of new supramolecular structures or ensembles and molecular materials.^[1–9] Concomitantly, the most important inspirations for the conceptual development of such structures and materials are those provided by biological cells, which exemplify the assembly of a variety of microstructures of different sizes and functions. Archaeobacteria, with their resistance to extreme conditions, are one class of organisms that serve as a rich source of inspiration. This

[*] Prof. D. Plusquellec, R. Auzély-Velty, T. Benvegnu
Ecole Nationale Supérieure de Chimie de Rennes
Laboratoire de Synthèses et Activations de Biomolécules,
associé au CNRS
Avenue du Général Leclerc, F-35700 Rennes (France)
Fax: (+33)2-99-87-13-48
E-mail: daniel.plusquellec@ensc-rennes.fr

Prof. J. W. Goodby, G. Mackenzie, J. A. Haley
Department of Chemistry, Faculty of Science and the Environment
University of Hull
Hull HU6 7RX (UK)
Fax: (+44)1482-464611
E-mail: j.w.goodby@chem.hull.ac.uk

[**] We thank the following agencies for their financial support: EPSRC, the Alliance Programme of the British Council and the Ministère des Affaires Etrangères, and the CNRS Région Bretagne for a grant to R.A.V.. We also thank J. P. Rolland and D. Thomas (University de Rennes) for electron microscopic analyses.

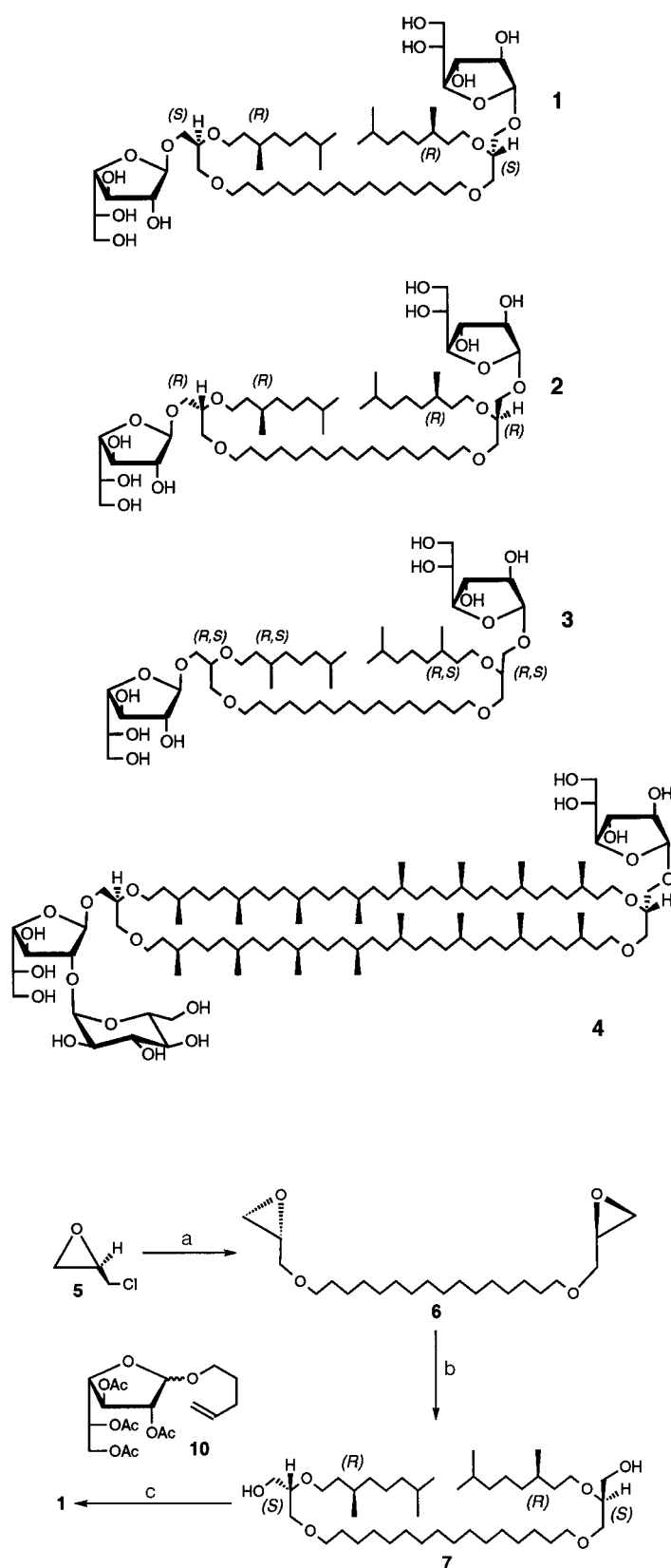
view becomes all the more poignant in the realization that mankind's increasing ability to investigate volcanoes, for example the volcano on Monseratt, has lead to the discoveries of many new strains of archaebacteria.

The Archaea domain is composed of a variety of extremophilic microorganisms and represents a third evolutive kingdom which is distinct from the well-known Eubacteria (the classical prokaryotes) and Eukarya domains.^[10–12] At a molecular level, the lipid components of Archaea membranes are strikingly different from their bacterial and eukaryotic counterparts.^[13–15] Of particular interest is the molecular topology of the lipids derived from thermophilic Archaea. These molecules are characterized by a bipolar architecture with two polar heads linked together by two C40 polyisoprenoid chains, which are thought to span the membrane and therefore determine the thickness of the lipid layer. Unique features of tetraether-based lipids are the high proportion of glycosylated lipids in the membranes of both methanogenous and sulfur-dependent thermophiles as well as the occurrence of unusual carbohydrate moieties, that is, β -D-galactofuranosyl units.^[13–15] These structural units may further stabilize the membrane structure through cooperative inter-glycosyl hydrogen bonding.^[16, 17] Nevertheless, the presence of furanosyl units in such environments remains a striking feature, as the glycofuranosides are much more rapidly hydrolyzed than their pyranosyl counterparts.^[18]

In spite of the growing attention to archaeal glycolipid structure and function, very few studies have been performed so far to elucidate relationships between the molecular structure of monomeric glycolipids and the architecture of their supramolecular aggregates. This is in part due to the difficulty of obtaining sufficient amounts of chemically pure compounds from natural sources or by synthetic methods. Here we report the total synthesis of glycosylated pseudo-tetraethers **1–3**, which were designed to mimic natural archael glycolipids; the investigation of their thermotropic and lyotropic liquid crystal properties; and the characterization of their supramolecular aggregates in aqueous media observed by electron microscopy.

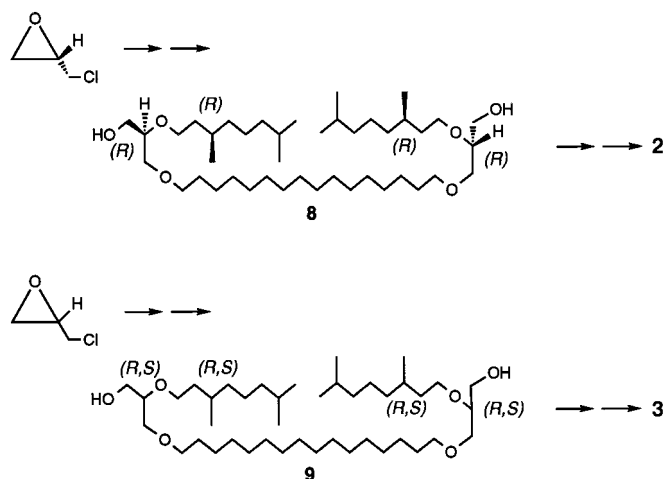
The most characteristic structural feature of our target molecules **1–3** are 1) the presence of a hexadecamethylene bridging chain attached to two glycerols at the sn3 and sn3' positions; 2) two dihydrocitronellyl chains having a combined length equal to that of the spacer, which are linked to glycerol at the sn2 and sn2' positions; and 3) two glycosyl polar head groups derived from D-galactose in its furanose form. These lipids are therefore closely related to the natural tetraether **4**, a quasi-symmetrical polar lipid obtained from the methanogen *Methanospirillum hungatei*.^[19]

The strategic plan for the synthesis of glycolipids **1–3** was based upon a suitable synthesis of pseudo-macrocylic diols **7–9** and subsequent diglycosylation with the appropriate galactofuranosyl donor. Bisalkylation of 1,16-hexadecandiol with (*R*)-epichlorhydrin afforded the diepoxide **6** with complete inversion at the sn-2 carbon atom (Scheme 1). Treatment of **6** with allyl alcohol resulted in the regiospecific opening of the epoxide rings and allowed introduction of allyl ether protecting groups at the primary positions. Alkylation at the sn2 and sn2' positions with (*R*)-citronellyl bromide



Scheme 1. Synthesis of **1**. a) 1,16-Hexadecandiol/*n*-hexane: 50% aqueous sodium hydroxide (2:1), Bu₄NBr, 55%; b) 1. allyl alcohol, NaOMe (cat.), 90%, 2. (*R*)-citronellyl bromide, NaH, 80%, 3. [RhCl(Ph₃P)₃], ethanol: toluene:water (7:3:1), 80%, 4. Raney nickel, H₂, ethanol, 95%; c) **10**, CH₂Cl₂, NIS, TESOTf, 67%, 2. MeOH, MeONa (cat.), 79%. NIS = *N*-iodosuccinimide, TESOTf = triethylsilyl trifluoromethanesulfonate, Ac = acetyl.

followed by removal of the *O*-allyl groups and reduction of the citronellyl to dihydrocitronellyl chains afforded the diol **7**. The best yield achieved for the overall sequence was 35%, with an average of 30% for repeated runs. A procedure similar to that described for the synthesis of **7** was used to synthesize the isomeric diol **8** and the racemic diol **9** starting, respectively, from (*S*)- or racemic ephchlorhydrins (Scheme 2).



Scheme 2. Syntheses of **2** and **3** (for reagents and reaction conditions, see Scheme 1).

The last crucial step involved the introduction of galactofuranose units as the polar head groups. It proved possible to introduce both β -D-galactofuranosyl residues in one step by using donor **10**, which was available in a one-pot procedure from D-galactose,^[20] thereby affording the diglycosylated lipids stereospecifically in 65–70% yield. The successful glycosylation was followed by deacetylation of the glycosyl hydroxyl groups under standard conditions. The structures of **1–3** were fully substantiated by NMR spectroscopy, mass spectrometry, and elemental analysis.

The self-assembling and self-organizing properties of **1–3** were investigated in a variety of ways. Initially, their melting and recrystallization behaviors were examined in detail by thermal polarized transmitted-light microscopy using a Zeiss Universal Polarizing Microscope in conjunction with a Mettler FP52 hot-stage and FP5 controller, and by differential scanning calorimetry using a Perkin Elmer DSC 7 PC system operating on UNIX software (scan rates 1, 5, and 10° min⁻¹). The results obtained were standardized relative to indium (onset 156.7°C, $\Delta H = 28.5 \text{ J g}^{-1}$, literature value 156.6°C, $\Delta H = 28.45 \text{ J g}^{-1}$).^[21]

All three materials exhibited similar melting behaviors; that is, upon heating they melted to give thermotropic liquid crystal phases. Identification of the resulting mesophases proved to be impossible because of the formation of paramorphotic defect textures associated with the solid state. However, on cooling from the isotropic liquid each material provided classical defect textures associated with the disordered columnar hexagonal phase (*Col*_{hd}).^[22–24] Fanlike textures were formed, but no hyperbolic or elliptical lines, associated with the lamellar smectic state, were observed.

[25, 26] Conversely, rectilinear defect lines, diagnostic of a hexagonal columnar phase, were present. The fanlike domains exhibited no banding and were completely smooth, indicating that the positions of the molecules in the phase are disordered. Polarized-light microscopy shows that the molecules in the mesophase are organized into columns, that the columns are hexagonally close-packed, and that within the columns the molecules themselves have a disordered arrangement. Figure 1 shows the defect texture of compound **3** formed

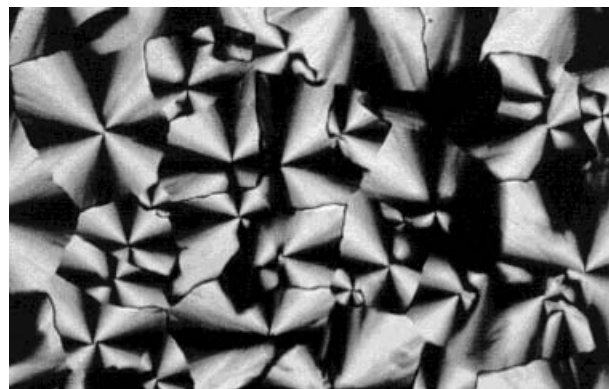


Figure 1. The fan texture of the columnar mesophase of **3** ($\times 100$).

on cooling from the isotropic liquid; the grey coloration of the observed specimens indicates the weak birefringence of the material. It is interesting to note that no homeotropic textures were observed, which would almost certainly have been expected if the phase was lamellar.

The clearing point temperature for each compound is shown in Table 1. The values found do not vary much as a function of change in stereochemistry. In fact, given the small

Table 1. Transition temperatures [°C] and enthalpies of transition [J g^{-1}] (in parentheses) for **1–3**.

Compound	Glass $\rightarrow$ columnar	Columnar $\rightarrow$ isotropic liquid	Columnar $\rightarrow$ glass
1	64.8	115.2 (1.53)	– 37.7
2	56.7	117.6 (2.93)	– 43.89
3	51.7	118.4 (1.38)	– 37.8

variations in purity and the experimental error in the measurements of the clearing temperatures, the isotropization points are effectively the same for all three compounds.

The liquid crystal phase of each compound supercooled quite substantially to temperatures well below 0°C. Recrystallization was often not observed, and instead a glassy state was formed. For this situation, the defect texture of the liquid crystal phase became frozen into the glassy specimen. Upon heating the glassy state converted smoothly back into the liquid crystal with virtually no changes occurring in the defect texture; therefore, well-defined glass transitions could not be observed by microscopy. Glass transitions, however, were determined by differential scanning calorimetry (see Table 1).

These results show that the mesophase has a columnar structure. As a consequence we can postulate two structures for the phase, one where the aliphatic chains are on the exterior and the sugar moieties are in the inside of the columns, and one where the aliphatic chains are in the interior and the sugar moieties are on the outside. However, the controlled addition of water to the neat phase shows that the thermotropic columnar phase is not continuously miscible with water. This indicates that the aliphatic chains must be located towards the exterior of the columnar structure. Thus, the columnar structure shown in Figure 2 is preferred where

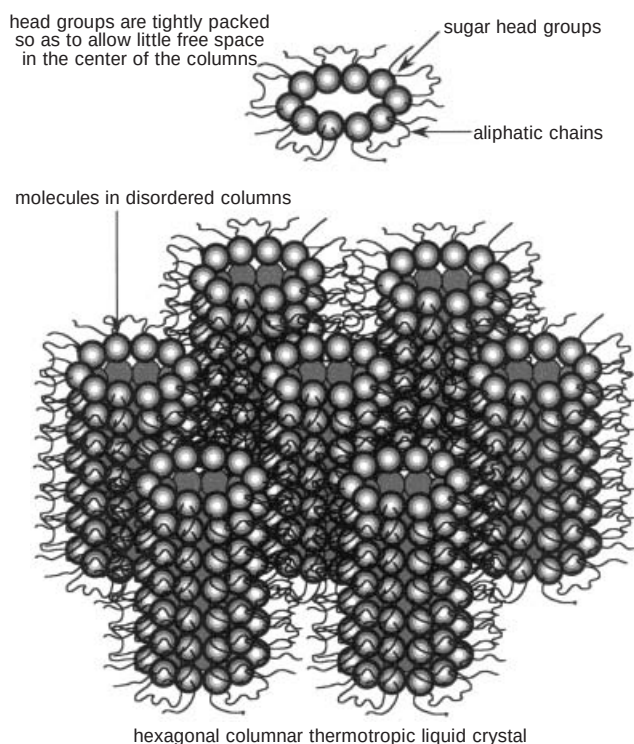


Figure 2. The disordered columnar structure of the thermotropic phase exhibited by **1–3**.

the molecules are bent and have hairpinlike conformations. This molecular folding allows the chains to be located towards the exterior of the columnar structure and the sugar units to be in the interior. This conclusion is supported to some degree by the results recently reported by Taguchi et al.^[27] on dotriacontan-1,32-diylphosphate (C32P) and the nearly isomeric double-chain phosphate 2C16P. The alkyl chain in C32P has mostly a *trans* structure with some *gauche* conformers present; the molecule therefore has a hairpin structure with a bend at the center of the chain. In the resulting columnar structure, in which the molecules are disordered along the column axis and are in a relatively fluid state, the liquidlike columns are packed into a hexagonal array to give a disordered hexagonal columnar thermotropic liquid crystal.

Lyotropic studies show that the three compounds exhibit hexagonal phases. However, as the thermotropic columnar phases are not continuously miscible with water, the hexagonal lyotropic phases are more likely to have structures based on ensembles where the polar head groups are on the outside of the columns. The fact that some of the materials are capable

of forming tubules in aqueous media suggests that a double-layer structure, as in a membrane, is the more likely self-assembled configuration as the basis of the structure of the hexagonal lyotropic phase.

The supramolecular aggregates formed by the materials in aqueous media were observed under electron microscopy. Compounds **1** and **3** provided tubules, whereas **2** did not (Figure 3). Thus, unlike the self-assembling properties which

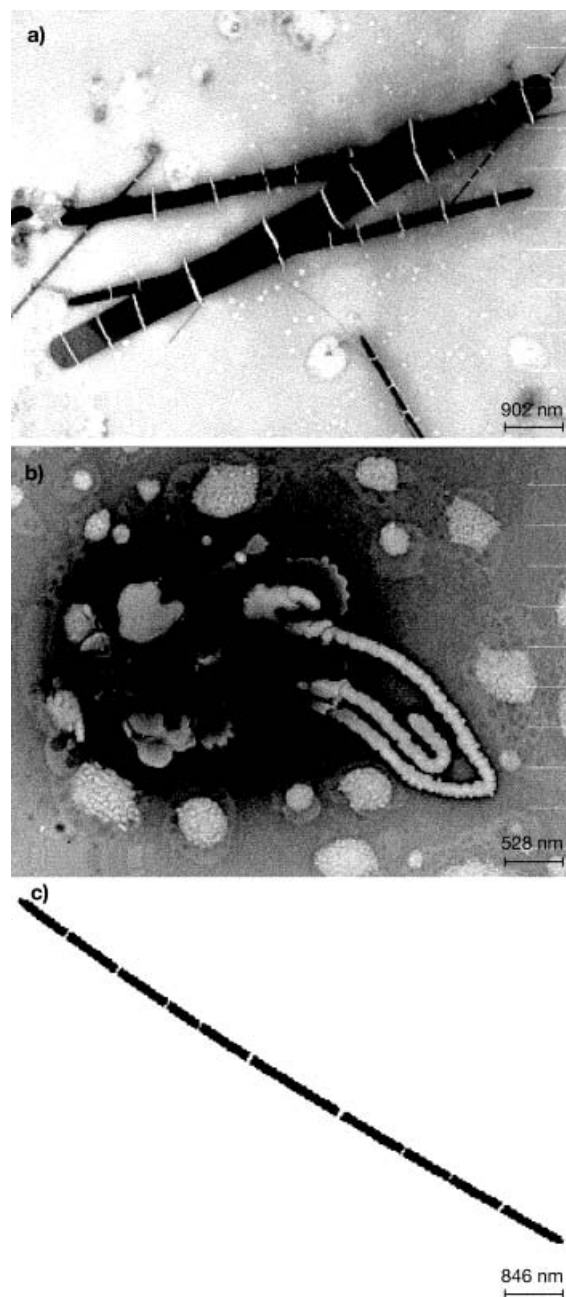


Figure 3. Electron microscopy micrographs of typical supramolecular aggregates formed by glycolipids **1–3** (a–c) in aqueous media (negative staining with uranyl acetate).

lead to the formation of liquid crystal phases, this self-organization to tubules is sensitive to the stereochemistry of the material in question. Interestingly, the tubules resulting from **1** and **3** appear to have almost equidistantly separated

parallel defect lines running across the long axes of the tubules (Figure 3a and c). Lines of this nature are usually associated with chirality, and in particular helicity which results from the way the chiral molecules pack together. These results suggest that the tubules either have a helical multilayer structure composed of several hundred molecular layers, or else they have a periodic defect structure that is based on some form of helicity. Periodic defect structures are well known for thermotropic liquid crystals, and are often manifested when the need for the molecules to form a twisted macrostructure is confronted with some structural or spatial limitation (e.g., Blue Phases, TGB Phases). This competition results in a frustration which is relieved by the creation of defects.

In the case of **1** and **3**, the lines running across the tubules could be related to defects produced by a localization of the twist, in a similar way to how twist is localized in the structure of the twist grain boundary phase.^[28] Conversely, **2** does not exhibit tubules. This may be because it has a different stereochemical structure to **1** and **3**, and as a result may not experience the same competition in the packing of the asymmetric moieties of its molecules. Detailed studies and explanations of these self-assembled structures are, however, complex, and a more comprehensive explanation of their properties will be given elsewhere.

Received: March 11, 1998 [Z11574IE]
German version: *Angew. Chem.* **1998**, *110*, 2665–2668

Keywords: amphiphiles • carbohydrates • lipids • liquid crystals

- [1] J. M. Lehn, *Angew. Chem.* **1990**, *102*, 1347; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304.
- [2] P. Ball, *Nature* **1994**, *371*, 202.
- [3] M. T. Krejchi, E. D. T. Atkins, A. J. Waddon, M. J. Fournier, T. L. Mason, D. A. Tirrell, *Science* **1994**, *265*, 1427.
- [4] R. S. Lokey, B. L. Iverson, *Nature* **1995**, *375*, 303.
- [5] D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1155.
- [6] R. H. Berg, S. Hvilsted, P. S. Ramanujam, *Nature* **1996**, *383*, 505.
- [7] A. Muller, C. Bengholt, *Nature* **1996**, *383*, 296.
- [8] D. Me Rosa, A. Morana in *Neural Networks and Biomolecular Engineering to Bioelectronics* (Ed.: C. Nicolini), Plenum, New York, **1995**.
- [9] C. M. Niemeyer, *Angew. Chem.* **1997**, *109*, 603; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 585.
- [10] C. R. Woese, G. E. Fox, *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 5088.
- [11] F. J. Auhman, K. McCallum, A. A. Davis, *Nature* **1992**, *356*, 148.
- [12] E. F. Delong, K. Y. Wu, B. B. Prezelin, R. V. M. Javine, *Nature* **1994**, *371*, 695.
- [13] G. D. Sprott, *J. Bioenerg. Biomembr.* **1992**, *24*, 555.
- [14] M. Kates in *The Biochemistry of Archaea (Archaeobacteria)* (Eds.: M. Kates, D. J. Kushner, A. T. Matheson), Elsevier, Amsterdam, **1993**.
- [15] A. Gambacorta, A. Gliozzi, M. De Rosa, *World J. Microbiol. Biotech.* **1995**, *11*, 115.
- [16] M. De Rosa, *Thin Solid Films* **1996**, *284–285*, 13.
- [17] K. Yamauchi, M. Kinoshita, *Prog. Polym. Sci.* **1993**, *18*, 763.
- [18] J. W. Green, *Adv. Carbohydr. Chem.* **1966**, *21*, 95.
- [19] G. Ferrante, I. Ekiel, G. D. Sprott, *Biochim. Biophys. Acta.* **1987**, *921*, 281.
- [20] R. Velly, T. Benvenugu, M. Gelin, E. Privat, D. Plusquellec, *Carbohydr. Res.* **1997**, *299*, 7.
- [21] *CRC Handbook of Physics and Chemistry* (Ed.: R. C. Priest), 68th ed., CRC, Boca Raton (FL), **1988**, D62.

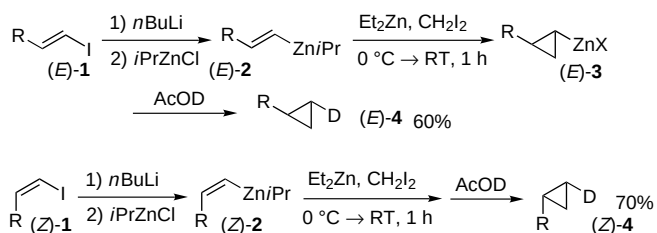
- [22] Y. Bouligand, *J. Phys. (Paris)* **1980**, *41*, 1297.
- [23] Y. Bouligand, *J. Phys. (Paris)* **1980**, *41*, 1307.
- [24] S. Chandrasekhar, G. S. Ranganath, *Rec. Prog. Phys.* **1990**, *53*, 57.
- [25] G. Friedel, *Ann. Phys.* **1922**, *18*, 273.
- [26] G. W. Gray, J. W. Goodby, *Smectic Liquid Crystals: Textures and Structures*, Leonard Hill, Philadelphia, **1984**.
- [27] K. Taguchi, K. Arakawa, T. Eguchi, K. Katinuma, Y. Nakatani, G. Ourisson, *New J. Chem.* **1998**, *22*, 63.
- [28] J. W. Goodby, M. A. Waugh, S. M. Stein, E. Chin, R. Pindak, J. S. Patel, *Nature* **1989**, *337*, 449.

A Facile Generation of a Cyclopropylzinc Compound from an Alkenylzinc Derivative and Its Reaction with Electrophiles**

Kentaro Yachi, Hiroshi Shinokubo, and Koichiro Oshima*

Cyclopropylmetal compounds are useful reagents for the construction of cyclopropane derivatives. The most common method for the preparation of these reagents is metalation of halocyclopropane derivatives with metals or organometallic compounds such as lithium, magnesium, or butyllithium.^[1, 2] However, present synthetic approaches to the halocyclopropanes^[3] are very lengthy and rather inefficient. Thus, development of a more convenient and direct access to cyclopropylmetal derivatives should expand their synthetic utility. Although the direct cyclopropanation of some 1-alkenylmetal compounds^[4] (B, Al, Si, Sn) by the Simmons–Smith reaction^[5] has been reported, the resulting cyclopropylmetal compounds have low reactivities with respect to electrophiles; there are no examples of their direct reaction with carbon electrophiles. Here we report the first example of the preparation of a cyclopropylzinc derivative from a 1-alkenylzinc compound and its synthetic use for further reaction with electrophiles in a one-pot procedure.

The 1-alkenylzinc compound was prepared from isopropylzinc chloride^[6] and a 1-alkenyllithium reagent, which was generated from a 1-iodo-1-alkene upon treatment with butyllithium in hexane (Scheme 1).^[7] Diethylzinc and CH₂I₂ were



Scheme 1. Stereospecific cyclopropanation of alkenylzinc compounds. R = n-C₁₀H₂₁; X = I, iPr.

[*] Prof. Dr. K. Oshima, K. Yachi, Dr. H. Shinokubo
Department of Material Chemistry
Graduate School of Engineering, Kyoto University
Kyoto 606-8501 (Japan)
Fax: (+81) 75-761-8846

[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

- M. Arai, E. Nakamura, *J. Am. Chem. Soc.* **1995**, *117*, 1179–1180; E. Nakamura, *Pure Appl. Chem.* **1996**, *68*, 123–130.
- [3] J. R. A. Dulayymi, M. S. Baird, I. G. Bolesov, V. Tveresovsky, M. Rubin, *Tetrahedron Lett.* **1996**, *37*, 8933–8936; J. T. Groves, K. W. Ma, *J. Am. Chem. Soc.* **1974**, *96*, 6527–6529; C. W. Jefford, D. Kirkpatrick, F. Delay, *J. Am. Chem. Soc.* **1972**, *94*, 8905–8907.
- [4] Boron: a) T. Imai, H. Mineta, S. Nishida, *J. Org. Chem.* **1990**, *55*, 4986–4988; b) P. Fontani, B. Carboni, M. Vaultier, G. Maas, *Synthesis* **1991**, 605–609; c) X.-Z. Wang, M.-Z. Deng, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2663–2664; d) J. P. Hildebrand, S. P. Marsden, *Synlett* **1996**, 893–894; e) J. Pietruszka, M. Widenmeyer, *Synlett* **1997**, 977–979; f) J. E. A. Luihthle, J. Pietruszka, *Liebigs Ann.* **1997**, 2297–2302; aluminum: G. Zweifel, G. M. Clark, C. C. Whitney, *J. Am. Chem. Soc.* **1971**, *93*, 1305–1307; silicon: K. Hirabayashi, A. Mori, T. Hiyama, *Tetrahedron Lett.* **1997**, *38*, 461–464; tin: D. Seyferth, H. M. Cohen, *Inorg. Chem.* **1962**, *1*, 913–916.
- [5] a) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, C. M. Hoiness, *Org. React.* **1973**, *20*, 1–131; b) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53–58.
- [6] The use of ZnCl_2 in the place of $i\text{PrZnCl}$ afforded (*E*)-**4** in 37% yield.
- [7] H. Shinokubo, H. Miki, T. Yokoo, K. Oshima, K. Utimoto, *Tetrahedron* **1995**, *51*, 11681–11692.
- [8] A. Sidduri, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1993**, *58*, 2694–2713; A. Sidduri, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 7579–7581.
- [9] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390–2392; L. Micouin, P. Knochel, *Synlett* **1997**, 327–328; P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117–2188; P. Knochel, *Synlett* **1995**, 393–403.
- [10] Compound (*E*)-**3** was also coupled with acetyl chloride under Pd^0 catalysis (30% yield).^[14]
- [11] P. Wipf, W. Xu, *Tetrahedron Lett.* **1994**, *35*, 5197–5200.
- [12] A. Vaupel, P. Knochel, *J. Org. Chem.* **1996**, *61*, 5743–5753.
- [13] J. Schwartz, J. A. Labinger, *Angew. Chem.* **1976**, *88*, 402–409; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333–340; J. A. Labinger in *Comprehensive Organic Synthesis*, Vol. 8 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 667–702.
- [14] T. Harada, T. Katsuhira, K. Hattori, A. Oku, *J. Org. Chem.* **1993**, *58*, 2958–2965.

Magnesium Complexes Bearing η^2 -Pyrazolato Ligands**

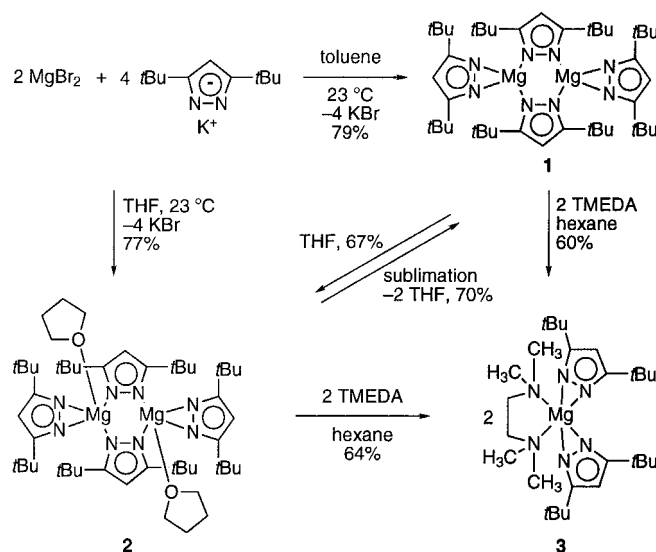
Dirk Pfeiffer, Mary Jane Heeg, and Charles H. Winter*

Pyrazolato ligands are commonly employed in complexes of the middle to late d-block metals, and either exhibit η^1 bonding to a single metal ion or bridge two metal centers.^[1] η^2 -Pyrazolato bonding is generally observed in lanthanide(III) complexes as a consequence of the more ionic bonding and larger size of the metal centers, relative to the d-block metals.^[2] We have described several titanium(IV) and tantalum(V) complexes that contain η^2 -pyrazolato ligands, and demonstrated that this binding mode is significantly favored over η^1 binding unless the coordination sphere is sterically congested.^[3–5] Very recently, we reported the crystal structure

of a hexameric potassium pyrazolato complex that contains bridging η^2 -pyrazolato ligands.^[6] Since the η^2 coordination mode was observed in the potassium complex it seemed very likely that this coordination mode would be observed in other main group metal complexes.

Our motivation for exploring pyrazolato complexes concerns the development of improved source compounds for chemical vapor deposition (CVD) applications. Volatile metal complexes composed of Group 2 or lanthanide metals with 1,3-diketonate ligands are widely used in CVD processes.^[7] However, the presence of oxygen makes diketonate-based precursors inappropriate for the deposition of non-oxide materials, such as magnesium-doped gallium nitride.^[8] With these considerations in mind, we report the synthesis, structure, and reactivity of several magnesium pyrazolato complexes. Surprisingly, η^2 -pyrazolato coordination is observed in these complexes, despite the small size of the magnesium ion. This study gives the first structural documentation of terminal η^2 -pyrazolato ligands with the main group metals and offers new insight into the design of volatile Group 2 compounds for use in film depositions through CVD methods.

Treatment of magnesium bromide with potassium 3,5-di-*tert*-butylpyrazolate^[6] (2 equiv) in toluene led to the formation of bis[bis(3,5-di-*tert*-butylpyrazolato)magnesium] (**1**, 79%; Scheme 1) as colorless crystals after workup. If the



Scheme 1. Synthesis and reactions of the pyrazatomagnesium complexes **1**–**3**.

reaction of magnesium bromide with potassium 3,5-di-*tert*-butylpyrazolate was carried out in tetrahydrofuran (THF), workup afforded bis[bis(3,5-di-*tert*-butylpyrazolato)(tetrahydrofuran)magnesium] (**2**, 77%) as colorless crystals. Treatment of **1** or **2** with *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 1 equiv per magnesium) led to the formation of bis(3,5-di-*tert*-butylpyrazolato)(*N,N,N',N'*-tetramethylethylenediamine)magnesium (**3**, 60–64%). Dissolution of **1** in THF followed by workup, afforded **2** (67%), while sublimation of **2** at 150 °C (0.1 torr) afforded **1** (70%) with loss of the

[*] Prof. Dr. C. H. Winter, D. Pfeiffer, Dr. M. J. Heeg
Department of Chemistry, Wayne State University
Detroit, MI 48202 (USA)
Fax: + (1) 313-577-1377
E-mail: cwinter@sun.science.wayne.edu

[**] We thank the US Army Research Office for support of this research.

coordinated THF ligand. Sublimation of **3** (ca. 150 °C, 0.1 torr) afforded variable mixtures of **1** and **3** (3:1–4:1). The structures of **1–3** were established by spectroscopic and analytical techniques as well as by X-ray crystal structure determinations. In the ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of **1** in $[\text{D}_8]\text{toluene}$ signals were observed for only one type of pyrazolato ligand between -80 and 20°C , suggesting fast exchange between the terminal and bridging pyrazolato ligands in this temperature range.

To establish the solid-state structure, the X-ray crystal structures of **1–3** were determined.^[9] The structure of **2** was of lower precision than **1** and **3**, because of disorder of the THF ligands and the *tert*-butyl groups. However, the gross structure of **2** was unambiguously established from the X-ray data. Perspective views of **1** and **3** are presented in Figures 1 and 2, respectively.

Complex **1** exists as a dimeric complex with two η^2 -pyrazolato ligands and two bridging pyrazolato ligands (Figure 1). Each binuclear molecule occupies a crystallographic inversion center. The plane containing the η^2 -pyrazolato ligands is approximately perpendicular to the plane containing the bridging ligands. The η^2 -pyrazolato ligands are characterized by Mg–N bond lengths of 1.987(4) and 2.050(4) Å, while the corresponding values for the bridging pyrazolato ligands are 2.001(3) and 2.047(3) Å. The bonding

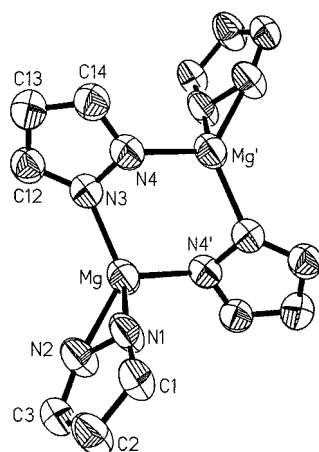


Figure 1. Structure of **1** in the solid state. The *tert*-butyl groups are omitted for clarity. Selected bond lengths [Å] and angles [°]: Mg–N1 1.987(4), Mg–N2 2.050(4), Mg–N3 2.001(3), Mg–N4' 2.047(3), Mg–N4 2.690(4), Mg–Mg' 3.322(2), N1–N2 1.397(4), N3–N4 1.397(4); N1–Mg–N2 40.47(11), Mg–N1–N2 72.2(2), Mg–N2–N1 67.3(2), N1–Mg–N3 124.04(13), N1–Mg–N4' 112.03(13), N2–Mg–N3 125.10(14), N2–Mg–N4' 128.31(14), Mg–N3–N4 103.3(2), N3–Mg–N4' 106.56(13).

of the η^2 -pyrazolato ligand is unsymmetrical, with a difference in the Mg–N bond lengths of 0.06 Å. We have previously documented similar “slipped” η^2 -pyrazolato coordination in a tantalum complex.^[4] The coordination geometry about each magnesium atom can be envisioned as distorted trigonal planar if the center of the η^2 -pyrazolato ligand is considered to be a monodentate donor (N1–Mg–N3 124.04(13), N1–Mg–N4' 112.03(13), N2–Mg–N3 125.10(14), N2–Mg–N4' 128.31(14), N3–Mg–N4' 106.56°). The dihedral angle between the planes described by N1–Mg1–N2 and Mg1–N3–N4 is 52.95°.

Complex **3** exists as a six-coordinate monomeric complex with two η^2 -pyrazolato ligands and one TMEDA ligand (Figure 2). The bonding of the pyrazolato ligands to magnesium is asymmetric with one short and one long Mg–N bond

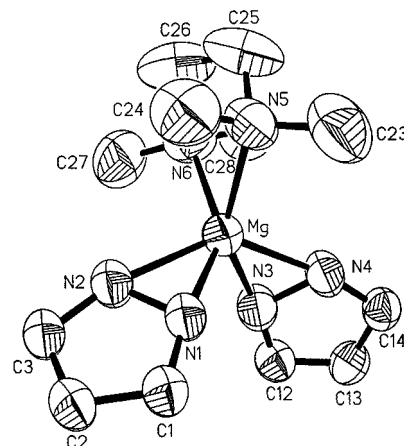


Figure 2. Perspective view of one independent molecule of **3**. The *tert*-butyl groups are omitted for clarity. Selected bond lengths [Å] and angles [°]: Mg–N1 2.047(3), Mg–N2 2.140(3), Mg–N3 2.054(3), Mg–N4 2.144(3), Mg–N5 2.235(3), Mg–N6 2.221(3), N1–N2 1.390(4), N3–N4 1.397(4); N1–Mg–N2 38.70(10), N3–Mg–N4 38.78(11), N5–Mg–N6 80.65(14), N1–Mg–N3 103.55(13), N1–Mg–N4 112.76(12), N2–Mg–N3 110.05(13), N2–Mg–N4 140.75(12), N1–Mg–N5 95.06(12), N1–Mg–N6 146.75(13), N2–Mg–N5 99.76(12), N2–Mg–N6 109.14(13), N3–Mg–N5 149.32(14), N3–Mg–N6 95.81(13), N4–Mg–N5 111.32(13), N4–Mg–N6 99.31(13).

(Mg–N1 2.047(3), Mg–N2 2.140(3), Mg–N3 2.054(3), Mg–N4 2.144(3) Å). The pyrazolato Mg–N bond lengths in **3** are longer than those in **1**, probably as a consequence of the increased coordination number about the magnesium center. The asymmetry associated with the pyrazolato ligands in **3** is more pronounced than in **1**, again probably because of the increased steric interactions present in **3**. The Mg–N bond lengths associated with the TMEDA ligand are 2.235(3) and 2.221(3) Å. The coordination geometry about the magnesium atom can be described as distorted tetrahedral if the center of each pyrazolato ligand is considered as a monodentate donor.

Complexes **1–3** are the first main group metal complexes with terminal η^2 -pyrazolato ligands. The η^2 -pyrazolato coordination is markedly asymmetric in **1** and **3**, with differences in Mg–N bond length of 0.06–0.09 Å within each pyrazolato ligand. The “slipped” η^2 bonding may originate from steric interactions between the bulky 3,5-di-*tert*-butylpyrazolato ligands, since the differences were larger for the six-coordinate metal center in **3** than for the four-coordinate magnesium center in **1**. The observation of η^2 -pyrazolato bonding in **1–3** is surprising in view of the small size of Mg^{2+} (ionic radius of 0.72 Å^[10] for a six-coordinate Mg^{2+} ion) and the rarity of this coordination mode among metals in general.^[3–5] We have recently reported that potassium (3,5-diphenylpyrazolato)(tetrahydrofuran) exists as a hexamer in which each potassium atom is bonded to the nitrogen atoms of one diphenylpyrazolato ligand in an η^2 fashion and to the nitrogen atoms of two adjacent diphenylpyrazolato ligands with η^1 interactions.^[6] This precedent, coupled with the results of the present work, implies that η^2 -pyrazolato ligand coordination should

be common in many main group metal complexes. Such a prediction is important because of the structural similarities between η^2 -pyrazolato and 1,3-diketonate complexes. Since 1,3-diketonate complexes are employed as precursors for film depositions by CVD techniques,^[8] it is likely that pyrazolato complexes can be used in applications where oxygen contamination is detrimental. To this end, we are studying the use of **1** (sublimes at 150 °C, 0.1 torr without decomposition) as a CVD precursor for the fabrication of magnesium-doped Group 13 semiconductors.^[11]

Experimental Section

1: A 200-mL Schlenk flask was charged with magnesium bromide (0.500 g, 2.71 mmol), potassium 3,5-di-*tert*-butylpyrazolate (1.18 g, 5.42 mmol), and toluene (50 mL). The resultant mixture was stirred at ambient temperature for 72 h, during which time a fine white precipitate formed. The volatile components were removed under reduced pressure to afford a colorless, sticky solid. This solid was extracted with hexane (60 mL), and the resultant solution filtered through a 2-cm pad of Celite on a coarse glass frit. The resultant clear, colorless solution was concentrated under vacuum to approximately 20 mL and then stored at –20 °C for 18 h to afford **1** as colorless crystals (0.82 g, 79%): m.p. 148–152 °C; IR (Nujol) $\tilde{\nu}$ = 1531 (m), 1508 (s), 1412 (m), 1360 (s), 1317 (s), 1254 (vs), 1226 (m), 1202 (m), 1059 (m), 1040 (s), 1016 (s), 987 (s), 786 cm^{–1} (s); ¹H NMR ([D₆]benzene, 23 °C): δ = 6.09 (s, 2H, pyrazolato C–H), 1.26 (s, 36H, C(CH₃)₃); ¹³C{¹H} NMR ([D₆]benzene, 23 °C): δ = 165.66 (s, C–C(CH₃)₃), 100.34 (s, pyrazolato C–H), 31.91 (s, C(CH₃)₃), 30.75 (s, C(CH₃)₃); elemental analysis calcd for C₄₄H₇₆Mg₂N₈: C 69.02, H 10.00, N 14.63; found: C 69.05, H 10.17, N 14.65.

2: In a similar fashion to the preparation of **1**, magnesium bromide (0.500 g, 2.71 mmol) and potassium 3,5-di-*tert*-butylpyrazolate (1.18 g, 5.42 mmol) were allowed to react in THF (40 mL) to afford **2** as colorless crystals (0.95 g, 77%): m.p. 114–122 °C (decomp.); IR (Nujol) $\tilde{\nu}$ = 1501 (s), 1410 (m), 1359 (vs), 1308 (s), 1249 (s), 1225 (s), 1205 (s), 1052 (s), 1034 (s), 1015 (s), 997 (s), 896 (m), 784 cm^{–1} (s); ¹H NMR ([D₆]benzene, 23 °C): δ = 6.04 (s, 2H, pyrazolato C–H), 3.48 (m, 4H, OCH₂CH₂), 1.40 (s, 36H, C(CH₃)₃), 1.31 (m, 4H, OCH₂CH₂); ¹³C{¹H} NMR ([D₆]benzene, 23 °C): δ = 161.88 (s, C–C(CH₃)₃), 97.08 (s, pyrazolato C–H), 67.99 (s, OCH₂CH₂), 31.91 (s, C(CH₃)₃), 30.38 (s, C(CH₃)₃), 25.18 (s, OCH₂CH₂); elemental analysis calcd for C₅₂H₉₂Mg₂N₈O₂: C 68.64, H 10.19, N 12.31; found: C 68.78, H 10.21, N 12.54.

3: A 200-mL Schlenk flask was charged with **1** (0.500 g, 0.654 mmol), TMEDA (0.152 g, 1.31 mmol), and hexane (40 mL). The reaction was stirred for 18 h at ambient temperature and then filtered through a 2-cm pad of Celite on a coarse glass frit. The clear, colorless hexane solution was concentrated to about 20 mL and then stored at –20 °C for 18 h to afford **3** as colorless crystals (0.39 g, 60%): m.p. 163–165 °C; IR (Nujol) $\tilde{\nu}$ = 3110 (m), 2799 (s), 1514 (vs), 1494 (vs), 1413 (m), 1355 (vs), 1325 (s), 1287 (s), 1248 (vs), 1226 (s), 1205 (s), 1189 (m), 1163 (m), 1123 (m), 1058 (m), 1014 (vs), 996 (vs), 949 (s), 797 (s), 770 cm^{–1} (vs); ¹H NMR ([D₆]benzene, 23 °C): δ = 6.07 (s, 2H, pyrazolato C–H), 2.03 (s, 12H, N–CH₃), 1.86 (s, 4H, N–CH₂), 1.39 (s, 36H, C(CH₃)₃); ¹³C{¹H} NMR ([D₆]benzene, 23 °C): δ = 159.65 (s, C–C(CH₃)₃), 96.05 (s, pyrazolato C–H), 55.84 (s, N–CH₂), 46.31 (s, N–CH₃), 31.79 (s, C(CH₃)₃), 31.54 (s, C(CH₃)₃); elemental analysis calcd for C₂₈H₅₄MgN₆: C 67.39, H 10.91, N 16.84; found: C 66.77, H 10.62, N 16.52.

Received: March 30, 1998 [Z11654IE]
German version: *Angew. Chem.* **1998**, *110*, 2674–2676

Keywords: chemical vapor deposition • magnesium • pyrazoles • semiconductors

- Ed. Engl.* **1993**, *32*, 874–875; G. B. Deacon, B. M. Gatehouse, S. Nickel, S. M. Platts, *Aust. J. Chem.* **1991**, *44*, 613–621; J. E. Cosgriff, G. B. Deacon, B. M. Gatehouse, *Aust. J. Chem.* **1993**, *46*, 1881–1896; J. E. Cosgriff, G. B. Deacon, B. M. Gatehouse, H. Hemling, H. Schumann, *Aust. J. Chem.* **1994**, *47*, 1223–1235.
- [3] I. A. Guzei, A. G. Baboul, G. P. A. Yap, A. L. Rheingold, H. B. Schlegel, C. H. Winter, *J. Am. Chem. Soc.* **1996**, *118*, 3387–3388.
- [4] I. A. Guzei, G. P. A. Yap, C. H. Winter, *Inorg. Chem.* **1997**, *36*, 1738–1739.
- [5] See also: J. E. Cosgriff, G. B. Deacon, *Angew. Chem.* **1998**, *110*, 298–299; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 286–287.
- [6] C. Yélamos, M. J. Heeg, C. H. Winter, *Inorg. Chem.* **1998**, *37*, 3892–3894.
- [7] Selected recent reviews: W. A. Wojtczak, P. F. Fleig, M. J. Hampden-Smith, *Adv. Organomet. Chem.* **1996**, *40*, 215–340; B. W. Wessels, *Annu. Rev. Mater. Sci.* **1995**, *25*, 525–546. T. J. Marks, *Pure Appl. Chem.* **1995**, *67*, 313–318; D. L. Schulz, T. J. Marks, *Adv. Mater.* **1994**, *6*, 719–730; C. H. Winter, *Strem Chem.* **1994**, *15*, 1–9; A. R. Barron, W. S. Rees, Jr., *Adv. Mater. Opt. Elec.* **1993**, *2*, 271–288; M. Schieber, *J. Cryst. Growth* **1991**, *109*, 401–417.
- [8] Recent overviews: S. N. Mohamad, A. A. Salvador, H. Morkoc, *Proc. IEEE* **1995**, *83*, 1306–1355; H. Morkoc, S. N. Mohamad, *Science* **1995**, *267*, 51–55; R. L. Gunshor, A. V. Nurmikko, *MRS Bulletin* **1995**, *20*, 15–19.
- [9] X-ray crystal data for **1**: C₄₄H₇₆Mg₂N₈, *M*_r = 765.75, monoclinic, *P*₂₁/*c*, *a* = 12.0348(14), *b* = 11.7684(12), *c* = 18.159(2) Å, β = 101.661(2)°, *V* = 2518.8(5) Å³, *Z* = 2, ρ_{calcd} = 1.010 g cm^{–3}, μ = 0.083 mm^{–1}, 5278 independent reflections harvested from 1390 frames of data containing 13076 integrated intensities, *R*_{int} = 0.12. All data were included in the refinement. For *I* ≥ 2σ(*I*), *R*₁ = 0.0721 and *wR*₂ = 0.1507; including weak data *R*₁ = 0.2709 and *wR*₂ = 0.2114. Siemens/Bruker P4-CCD, MoK α radiation (λ = 0.71073 Å), graphite monochromator, $2\theta_{\text{max}}$ = 56.6°, *T* = 295(2) K. X-ray crystal data for **3**: C₂₈H₅₄MgN₆, *M*_r = 499.08, triclinic, *P*₁, *a* = 9.5463(7) Å, *b* = 10.3431(9) Å, *c* = 19.471(2) Å, α = 98.200(2)°, β = 97.488(2)°, γ = 116.013(2)°, *V* = 1669.5(2) Å³, *Z* = 2, ρ_{calcd} = 0.993 g cm^{–3}, μ = 0.076 mm^{–1}, 6418 independent reflections were harvested from 1470 frames of data containing 9490 integrated intensities, *R*_{int} = 0.035. All data were included in the refinement. For *I* ≥ 2σ(*I*), *R*₁ = 0.082 and *wR*₂ = 0.242; including weak data, *R*₁ = 0.165 and *wR*₂ = 0.287. Siemens/Bruker P4-CCD, MoK α radiation (λ = 0.71073 Å), graphite monochromator, $2\theta_{\text{max}}$ = 56.5°, *T* = 295(2) K. Suitable crystals for single-crystal X-ray analysis were selected and mounted inside thin-walled capillaries in a dry box under a nitrogen atmosphere. Data collection and integration used the Bruker SMART and SAINT software. Empirical absorption corrections were calculated using the program SADABS.^[12] Solution and refinement used the programs SHELXS^[12] and SHELXL-93.^[12] All non-hydrogen atoms were described anisotropically. Hydrogen atoms were placed in calculated positions. The 3,5-di-*tert*-butylpyrazolato ligands typically show severe disorder in the *tert*-butyl groups, which results in modeling difficulties and high *R* values. However, other criteria of chemical and crystallographic reasonableness show these to be acceptable structural models. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-101335. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + (44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [10] N. N. Greenwood, A. Earnshaw, *Chemistry of the Elements*, Pergamon Press, Oxford, **1984**, p. 122.
- [11] J. G. Cederberg, D. Pfeiffer, C. H. Winter, T. F. Kuech, unpublished results.
- [12] G. Sheldrick, Universität Göttingen, Germany.

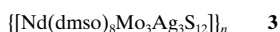
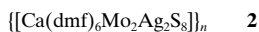
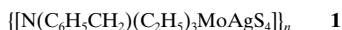
[1] Recent reviews: G. La Monica, G. A. Ardizzone, *Progr. Inorg. Chem.* **1997**, *46*, 151–238; A. P. Sadimenko, S. S. Basson, *Coord. Chem. Rev.* **1996**, *147*, 247–297.

[2] J. E. Cosgriff, G. B. Deacon, B. M. Gatehouse, H. Hemling, H. Schumann, *Angew. Chem.* **1993**, *105*, 906–907. *Angew. Chem. Int.*

Three New Structural Types of Mo/Ag/S Polymeric Complexes**

Heng Yu, Wenjian Zhang, Xintao Wu,* Tianlu Sheng, Quanming Wang, and Ping Lin

Transition metal sulfur complexes are of important biological and industrial significance.^[1] The pioneering work of Müller and co-workers^[2] has largely promoted research on Mo(W)/Cu(Ag)/S systems. Since the first characterization of $[\text{PPh}_4]_n[\text{MoAgS}_4]_n$ by resonance Raman spectroscopy,^[3] a series of one-dimensional W/Ag/S polymeric compounds have been synthesized. It was found that their configurations are controlled by the valence states and the dimensions of the cations; a variety of structures exist, for example, single linear chains,^[4a] double chains,^[5] zigzag chains,^[6] one-dimensional chains in which the square units were linked by Ag atoms,^[7] and helical chains.^[8] Only few polymeric Mo/Ag/S complexes have been characterized by X-ray crystallography.^[4] We have reported on the self-assembly of $[\text{NH}_4]_2[\text{WS}_4]$ and AgNO_3 to form a variety of polymeric chains.^[5–8] After the failure to achieve the analogous self-assembly of $[\text{MoS}_4]^{2-}$ and AgNO_3 , we recently developed a new procedure: When AgNO_3 was substituted by Ag_2S as the starting material, reactions of $[\text{MoS}_4]^{2-}$ and Ag_2S provided three new types of polymeric complexes with unprecedented configurations. Compounds **1–3** (DMF = dimethylformamide, DMSO = dimethyl sulfoxide) have wavelike, zigzag, and helical polymeric anions, respectively.



Compound **1** was synthesized by the reaction of $[\text{NH}_4]_2[\text{MoS}_4]$, Ag_2S , and $[\text{N}(\text{C}_6\text{H}_5\text{CH}_2)(\text{C}_2\text{H}_5)_3\text{Cl}]$ in DMF, and its crystal structure was determined^[9] (Figure 1). The

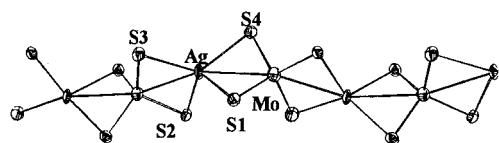


Figure 1. The structure of the polymeric anion of **1**. Selected bond lengths [Å] and angles [°]: Mo–Ag 2.893(1), 2.916(1); Mo–S 2.918(3), 2.216(4), 2.200(3), 2.193(3); Ag–S 2.601(3), 2.560(3), 2.460(4), 2.559(3); Mo–Ag–Mo 156.47(5), Ag–Mo–Ag 157.14(5).

[*] Prof. X. Wu, H. Yu, W. Zhang, T. Sheng, Q. Wang, P. Lin
State Key Laboratory of Structural Chemistry and
Fujian Institute of Research on the Structure of Matter
Chinese Academy of Sciences
Fuzhou 350002 (China)
Fax: (+86) 591-371-4946
E-mail: wxt@ms.fjirsm.ac.cn

[**] This research was supported by grants from the State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, and the Science Foundations of the Nation, CAS and Fujian Province.

polymeric anion has a wavelike chain structure with a Ag–Mo–Ag bond angle of 157.14(5)° and a Mo–Ag–Mo bond angle of 156.47(5)°. This is in contrast to the nearly linear anion chains of $[\text{AgMoS}_4(\gamma\text{-MePyH})]_n$ and $[\text{AgMoS}_4(\alpha\text{-MePyH})]_n$ ^[4a] (Py = pyridine), in which the Ag–Mo–Ag and Mo–Ag–Mo angles are 179.3(2)–180.0(1)°, and the linear $[\text{WAgS}_4]_n$ chain with Ag–W–Ag and W–Ag–W angles of 176.4(5) and 176.4(3)°, respectively;^[5] in the case of the latter the large cation $\text{H}_3\text{NC}(\text{CH}_2\text{CH}_2\text{OH})_3^+$ induces the linear structure. Therefore, the wavelike chain of **1** that deviates highly from linearity is unexpected. Within the cluster, all Ag atoms are bonded to four μ_2 -S atoms, which also form bonds to Mo atoms; in this way each Ag atom interacts with two Mo atoms. All the Mo and Ag atoms are almost in the same plane. The chains have two orientations: one type runs parallel to the crystallographic *b* axis, whereas the other parallel to the *a* axis.

When Ca^{2+} was used as the complementary cation in place of $[\text{N}(\text{C}_6\text{H}_5\text{CH}_2)(\text{C}_2\text{H}_5)_3]^+$, the reaction of $[\text{NH}_4]_2[\text{MoS}_4]$ and Ag_2S yields **2**, which displays zigzag polymeric anions (Figure 2).^[10] As in the case of **1**, all the Mo and Ag atoms

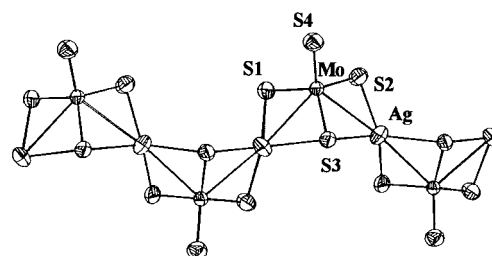


Figure 2. The structure of the polymeric anion of **2**. Selected bond lengths [Å] and angles [°]: Ag–Mo 2.9603(5), 2.9611(5); Ag– μ_2 -S 2.5098(3), 2.5503(13); Ag– μ_3 -S 2.5591(12), 2.5920(12); Mo–S_{terminal} 2.1447(12); Mo– μ_2 -S 2.150(5), 2.223(12); Mo– μ_3 -S 2.2551(12); Mo–Ag–Mo 173.30(2), Ag–Mo–Ag 96.964(10).

are almost in the same plane. Every Mo atom is linked to two Ag atoms through three μ_2 -S atoms, and a highly distorted tetrahedral AgS_4 moiety (tetrahedral angle 93.6–118.8°) is formed. The whole chain looks like a string of “butterflies”, and all the Mo and Ag atoms of one chain form an equilateral zigzag arrangement. Although a W/Ag/S polymeric compound with the same cation is not available for comparison, $[\text{Ca}(\text{dmsO})_6]_2(\text{W}_4\text{Ag}_4\text{S}_{16})_n$ ^[6] which has the similar cation $[\text{Ca}(\text{dmsO})_6]^{2+}$, has an uneven zigzag chain structure in which W–Ag–W units are perpendicular to W–Ag–W–Ag–W–Ag units. Compared with the linear M/Ag/S (M = W, Mo) chains induced by the univalent cations, this anionic structure indicates that use of cations with a higher valence state will result in more compact structures of the anionic chains.

Compound **3** was synthesized by the reaction of $[\text{NH}_4]_2[\text{MoS}_4]$ and Ag_2S with the complementary cation $[\text{Nd}(\text{dmsO})_8]^{3+}$ (Figure 3).^[10] It has different structural features than the polymeric $[\text{Nd}(\text{dmsO})_8\text{W}_3\text{Ag}_3\text{S}_{12}]_n$ (**4**), which was self-assembled from $[\text{NH}_4]_2[\text{WS}_4]$ and AgNO_3 .^[8] Both **3** and **4** have helical chains consisting of SMS_3Ag_2 (M = Mo, W) butterfly-type units. Every chain in **3** is made up of two sets of helices which alternatively propagate along the chain (this

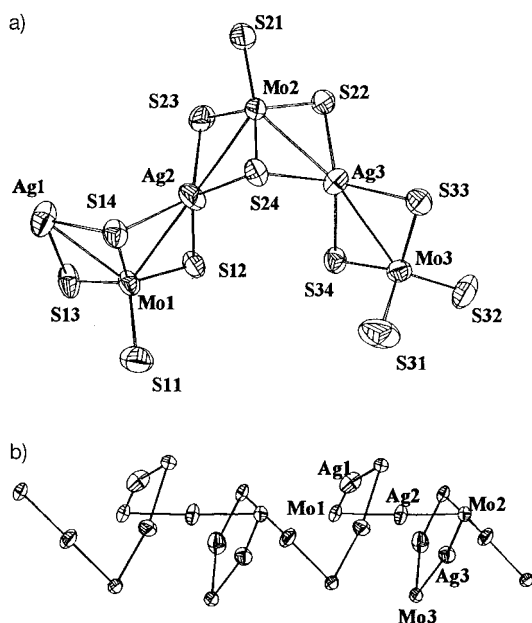


Figure 3. a) The framework of the polymeric anion of **3** (ORTEP representation, 50% displacement ellipsoids). b) The structure of the polymeric anion of **3**. Selected bond lengths [Å] and angles [°]: Ag–Mo 2.9220(13)–2.9625(12); Ag– μ_2 -S 2.463(3)–2.617(4); Ag– μ_3 -S 2.546(3)–2.592(3); Mo–S_{terminal} 2.139(4), 2.154(3), 2.157(4); Mo– μ_2 -S 2.193(3)–2.212(3); Mo– μ_3 -S 2.237(3), 2.244(3), 2.249(3); Ag–Mo–Ag 82.53(4), 86.18(4), 88.08(4); Mo–Ag–Mo 177.43(5), 162.69(5), 166.04(5); dihedral angle Mo2–S24–Ag2/Mo2–S24–Ag3 60.12°.

remarkable structure is shown Figure 3a), while **4** has a relatively unruly helical structure. These differences may arise from the different spreading of the “wings” of the butterfly. The smaller dihedral angle Ag2–Mo2–S24/Ag3–Mo2–S24 of 60.12° in **3** (69.45° in **4**) results in a much more compact anionic partial structure in **3** (Figure 3b). The topological structure of **3** is the same as that of **2**, which further reflects the steric constraints imposed by the cations on Mo/Ag/S polymeric compounds. Furthermore, the structures of **3** and **4** demonstrate the different ways in which their anionic parts are adopted to suit a certain kind of cation.

As is well known, Ag ions have a higher affinity for the [MoS₄]^{2−} ion than for the [WS₄]^{2−} ion. As a result, it is more difficult to control the self-assembly of [MoS₄]^{2−} and AgNO₃ than that of [WS₄]^{2−} and AgNO₃. The scarce Ag⁺ ion in solution released by Ag₂S is very beneficial for the control of the reaction.

Experimental Section

1: A mixture of [N(C₆H₅CH₂)(C₂H₅)₃]Cl (2 mmol), [NH₄]₂[MoS₄] (2 mmol), and Ag₂S (2 mmol) in DMF (10 mL) was stirred for 30 h, and then filtered. The dark filtrate was allowed to stand for several days at ambient temperature in the air, and dark red crystals of **1** were produced (0.30 g, 50% yield). IR (KBr): $\tilde{\nu}$ (Mo–S) [cm^{−1}] = 459.0 (vs), 439.7 (sh).

2: The synthesis of **2** was similar to that of **1**, except for the use of Ca(NO₃)₂ · 4H₂O instead of [N(C₆H₅CH₂)(C₂H₅)₃]Cl in DMF (10 mL). The procedure gave dark red crystals of **2** (30% yield). IR (KBr): $\tilde{\nu}$ (Mo–S) [cm^{−1}] = 501.4 (m), 455.1 (s), 416.6 (w).

3: The synthesis of **3** was similar to that of **1**, except for the use of Nd(NO₃)₃ · nH₂O in DMSO. The yield was about 50%. IR (KBr): $\tilde{\nu}$ (Mo–S) [cm^{−1}] = 495.6 (s), 453.29 (vs), 405.5 (s), $\tilde{\nu}$ (S=O) = 1004.7, 954.6, 935.3.

Received: March 11, 1998 [Z11573IE]
German version: *Angew. Chem.* **1998**, *110*, 2662–2664

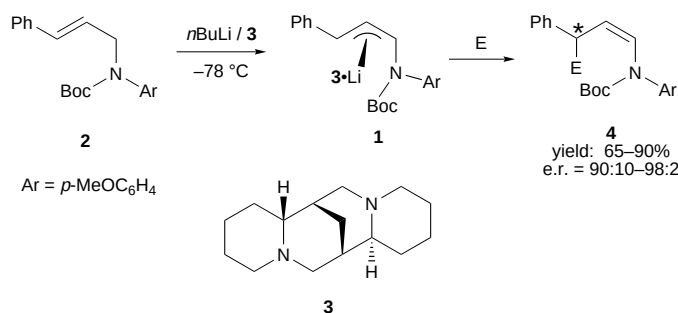
Keywords: clusters • inorganic polymers • molybdenum • silver • sulfur

- [1] “Transition Metal Sulfur Chemistry: Biological and Industrial Significances”: *ACS Symp. Ser.* **1996**, 653.
- [2] a) A. Müller, E. Diemann, R. Jostes, H. Bögge, *Angew. Chem.* **1981**, *93*, 957; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 934, and references therein; b) A. Müller, H. Bögge, U. Schimanski, M. Penk, K. Nieradzik, M. Dartman, E. Krickemeyer, J. Schimanski, C. Römer, H. Dornfeld, U. Wienböcker, W. Hellmann, M. Zimmermann, *Monatsh. Chem.* **1989**, *120*, 367, and references therein.
- [3] a) A. Müller, W. Jaegemann, W. Hellmann, *J. Mol. Struct.* **1983**, *100*, 559. b) A. Müller, W. Hellmann, *Spectrochim. Acta A* **1985**, *41*, 359.
- [4] a) J.-P. Lang, J.-G. Li, S.-A. Bao, X.-Q. Xin, *Polyhedron* **1993**, *12*, 801; b) [PPh₄]_n[MoAgS₄]_n: A. Müller, unpublished results.
- [5] Q. Huang, X.-T. Wu, T.-L. Sheng, Q.-M. Wang, *Inorg. Chem.* **1995**, *34*, 4931.
- [6] Q. Huang, X.-T. Wu, J.-X. Lu, *Inorg. Chem.* **1996**, *35*, 7445.
- [7] Q. Huang, X.-T. Wu, Q.-M. Wang, T.-L. Sheng, J.-X. Lu, *Angew. Chem.* **1996**, *108*, 985; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 868.
- [8] Q. Huang, X.-T. Wu, J.-X. Lu, *Chem. Commun.* **1997**, 703.
- [9] a) Crystal structure analysis of **1**: Data were collected on an Enraf-Nonius CAD4 diffractometer with $\lambda(\text{MoK}\alpha) = 0.71073$ Å. A red crystal of dimensions 0.25 × 0.12 × 0.12 mm was used; tetragonal, space group *P*₄/2₁2, *a* = 11.15(9), *c* = 29.84(3) Å, *V* = 3711.1(7) Å³, *Z* = 4, $\rho_{\text{calcd}} = 1.5$ g cm^{−3}, $\mu = 9.4$ cm^{−1}, $2\theta_{\text{max}} = 50^\circ$, *T* = 296 K; of 3719 reflections collected, 3719 were independent and 2887 observed (*I* > 3σ(*I*)). The structure was solved by direct methods with the MolEN/PC program. Data were corrected for Lorentz and polarization effects. No absorption correction was applied. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were not included (181 parameters). Final *R* = 0.055 and *R*_w = 0.067. Largest difference peak and hole: 1.53 and −0.62 e Å^{−3}. b) Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102085 (**1**), -102086 (**2**), and -102087 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [10] Crystal structure analyses of **2** and **3**: Data were collected on a Siemens Smart CCD area diffractometer with $\lambda(\text{MoK}\alpha) = 0.71073$ Å. **2**: A red prism of dimensions 0.10 × 0.12 × 0.15 mm was used, monoclinic, space group *P*₂/c, *a* = 9.4600(1), *b* = 24.6284(4), *c* = 8.8526(2) Å, $\beta = 95.1230(10)^\circ$, *V* = 2054.28(6) Å³, *Z* = 2, $\rho_{\text{calcd}} = 1.847$ g cm^{−3}, $\mu = 2.104$ cm^{−1}, $2\theta_{\text{max}} = 46.48^\circ$, *T* = 293 K; of 7994 reflections collected, 2943 were independent and 2639 observed (*I* > 2σ(*I*)). The structure was solved by direct methods with the SHELXTL-93 program. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were not included (196 parameters). The final cycle of full-matrix least-square refinement converged with $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o| = 0.0287$ and $R_w = \{\Sigma w[(F_o^2 - F_c^2)^2]/\Sigma w[(F_o^2)^2]\}^{0.5} = 0.0750$, $w = [\sigma^2 F_o^2 + (0.0346 P)^2 + 3.7068 P]^{-1}$, $P = F_o^2 + 2 F_c^2/3$. Largest difference peak and hole: 0.396 and −0.661 e Å^{−3}. **3**: A red crystal of dimensions 0.25 × 0.15 × 0.20 mm was used, monoclinic, space group *P*₂/n, *a* = 12.4879(3), *b* = 23.7262(4), *c* = 19.2383(2) Å, $\beta = 103.7040(10)^\circ$, *V* = 5537.9(2) Å³, *Z* = 4, $\rho_{\text{calcd}} = 2.111$ g cm^{−3}, $\mu = 3.235$ cm^{−3}, $2\theta_{\text{max}} = 50.06^\circ$, *T* = 296 K; of 1625 reflections collected, 9378 were independent and 6908 observed (*I* > 2σ(*I*)). The structure was solved by direct methods with the SHELXTL-93 program. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were not included (460 parameters). The final cycle of full-matrix least-square refinement converged with $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o| = 0.0589$ and $R_w = \{\Sigma w[(F_o^2 - F_c^2)^2]/\Sigma w[(F_o^2)^2]\}^{0.5} = 0.1561$, $w = [\sigma^2 F_o^2 + (0.0947 P)^2 + 17.2245 P]^{-1}$, $P = F_o^2 + 2 F_c^2/3$. Largest difference

Solid-State Structural Investigation of an Organolithium (–)-Sparteine Complex: η^3 -*N*-Boc-*N*-(*p*-methoxyphenyl)-3-phenylallyllithium · (–)-Sparteine**

Daniel J. Pippel, Gerald A. Weisenburger, Scott R. Wilson, and Peter Beak*

A number of organolithium compounds have been found to be of remarkable value for the enantioselective formation of carbon–carbon bonds under the influence of (–)-sparteine.^[1] Definitive information about the structure of the lithiated species that are involved in these reactions is needed to understand and improve the methodology. Herein we report the isolation and X-ray crystallographic analysis of η^3 -*N*-Boc-*N*-(*p*-methoxyphenyl)-3-phenylallyllithium · (–)-sparteine (**1**). This configurationally stable complex, which results from the asymmetric deprotonation of *N*-Boc-*N*-(*p*-methoxyphenyl)-cinnamylamine (**2**) by *n*BuLi in the presence of (–)-sparteine (**3**), undergoes reactions with alkylating and acylating reagents and 1,4-additions to afford products **4** with high enantioenrichments.^[2] The determination of the structure of this key intermediate allows definitive conclusions about the stereochemical course of the conversions of **1** into **4**.



The organolithium species **1** crystallizes in the triclinic space group *P*1.^[3] The unit cell contains two nearly identical complexes along with four molecules of uncoordinated diethyl ether.^[6] The crystal structure for one of the complexes of **1** is shown in Figure 1. It is interesting that Li1 in **1** is associated in a η^3 fashion to the allyl unit (Li1–C7 258.2(1.3), Li1–C8 244.2(1.3), Li1–C9 274.0(1.4) pm). This is in contrast to an analogous carbamoyloxy-3-trimethylsilyllithium (–)-sparteine complex in which the Li cation is coordinated in an η^1 manner.^[7a] Dimeric, 3-metalated (3*S*)-3-lithio-1-[(*S*)-2-(methoxymethyl)pyrrolidino]-1,3-diphenylpropene has also

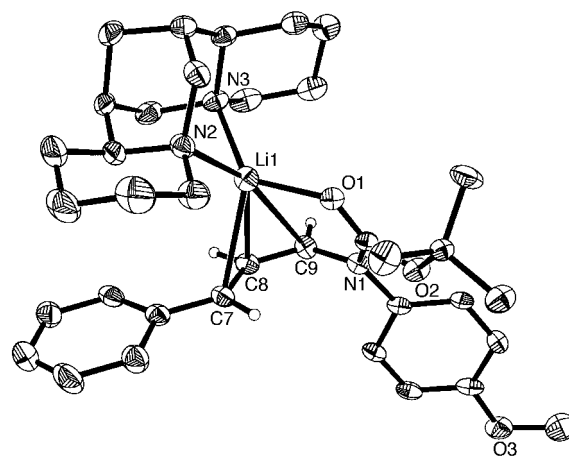


Figure 1. Molecular structure of **1** in the crystal.^[3, 6] Important distances [pm] as well as bond and torsional angles [°]: C7–C8 141.0(0.9), C8–C9 137.5(0.9), Li1–C7 258.2(1.3), Li1–C8 244.2(1.3), Li1–C9 274.0(1.4), Li1–N2 212.3(1.3), Li1–N3 212.3(1.2), Li1–O1 191.7(1.2), C9–N1 142.6(0.8), N1–C17 137.4(0.8), O1–C17 123.4(0.7), C17–O2 134.2(0.7); C7–C8–C9 129.3(0.6), Li1–C7–C8–C9 77.1(0.7).

been characterized as an unbridged structure in the solid state.^[7b] The 1-butyindenidelithium · (–)-sparteine complex characterized by Boche and Hoppe is similar to **1** but with a closer association between the lithium cation and the η^3 -allyl carbon atoms.^[7c]

Another significant feature of the structure is the 68° angle between the planes formed by the allyl unit (C7–C8–C9) and the amide functionality (O1–C17–N1). This twist allows bonding of the carbonyl group to the bridging lithium atom and relieves the repulsive pair–pair interactions between the electrons in the HOMOs of the amide π bond and the sp^2 carbanion.^[8]

To verify that the isolated intermediate is the same as the major species present in solution during the standard reaction sequence, isolated crystalline **1** was dissolved in diethyl ether at –78 °C, and benzyl bromide was added. The reaction yielded (*S*)-**4a** with an enantiomeric ratio (e.r.) of 99:1. The absolute configuration of the major enantiomer was identical to that observed from the normal lithiation/substitution sequence as determined by the elution order from HPLC on a chiral stationary phase. Thus, the crystallization also provides an opportunity for increased enantioenrichment.^[9]

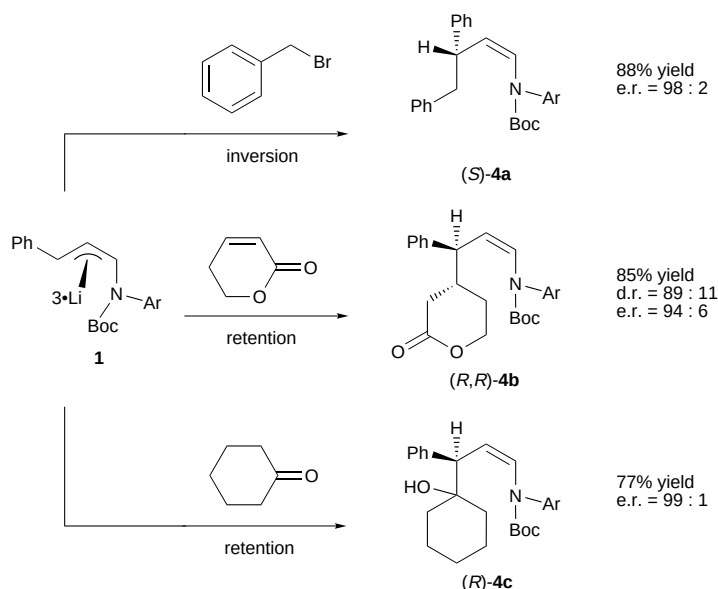
From the configuration of **1**, which has the lithium · (–)-sparteine complex on the *re* face of the allyl unit, the stereochemical course of substitution with different types of electrophiles is evident. Reaction with the alkyl halide benzyl bromide proceeds with inversion of configuration to give product (*S*)-**4a**. In contrast, reactions with the Michael acceptor 5,6-dihydro-2*H*-pyran-2-one and the carbonyl electrophile cyclohexanone proceed with retention of configuration to give (*R,R*)-**4b** and (*R*)-**4c**. The latter cases are considered to involve precomplexation between the carbonyl group and lithium cation; this type of interaction is not favorable in the trigonal-bipyramidal transition structure for the reaction of **1** with an alkyl halide electrophile.^[10]

We have reported a transmetalation sequence with trimethyltin chloride which provides access to the enantiomers with the opposite configuration to the reaction products **4**.^[2]

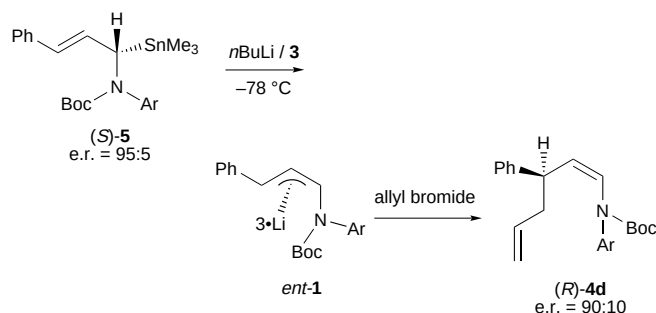
[*] P. Beak, D. J. Pippel, G. A. Weisenburger, S. R. Wilson
Department of Chemistry
University of Illinois at Urbana-Champaign
Fax: (+1) 217-244-8068
E-mail: beak@aries.scs.uiuc.edu

[**] Financial support, which has been provided by the National Institutes of Health (GM 18874) and the National Science Foundation (NSF-95-26355), is appreciated. We are especially grateful to Professor Greg Girolami and Julia Brumaghim for assistance in growing air- and temperature-sensitive crystals. Boc = *tert*-butoxycarbonyl.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



We have established now by X-ray crystallographic analysis of **(S)-5** that trimethyltin chloride reacts with inversion of configuration.^[3, 11] Transmetalation of **(S)-5** with *n*BuLi and subsequent reaction with allyl bromide gives **(R)-4d**, with the



configuration of the major enantiomer opposite to that observed in the normal lithiation/substitution protocol. This result establishes that the tin–lithium transmetalation proceeds with retention of configuration.^[12]

In summary, we have isolated and crystallographically characterized the important η^3 -allyllithium·(–)-sparteine complex **1**. This structural determination allows assignment of the stereochemical course for carbon–carbon bond forming reactions which proceed with high enantioselectivity. We believe these definitive structural assignments will aid in further developing the synthetic potential of these species.

Experimental Section

1: Single crystals of **1** were prepared in an oven-dried Schlenk flask under dry argon. *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine (**2**) (187 mg, 0.551 mmol) was dissolved in diethyl ether (13 mL, freshly distilled from sodium/benzophenone). (–)-Sparteine (**3**, 0.127 mL, 0.551 mmol) was added to the clear solution at room temperature. The reaction mixture was then cooled to -78°C , and *n*BuLi (0.404 mL, 1.5 M, 0.606 mmol) was added. After 1 h under argon, the yellow homogenous solution was placed under vacuum (0.04 torr) with continued stirring at -78°C for 1.5 h. The flask was then back-filled with argon, and the homogenous yellow solution

was allowed to sit undisturbed at -78°C for 36 h. During this period, brilliant yellow crystals of **1** formed. In a test reaction, the crystals were separated by filtration and redissolved in pre-cooled diethyl ether (10 mL). Treatment of the solution with benzyl bromide (4 equiv) for 1.5 h at -78°C gave **(S)-4a** (33% yield based on **2**, e.r. = 99:1). The supernatant was also allowed to react with benzyl bromide (1.8 equiv) for 1.5 h at -78°C , to give **(S)-4a** (35% yield based on **2**, e.r. = 89:11).

Received: March 26, 1998 [Z11649 IE]
German version: *Angew. Chem.* **1998**, *110*, 2600–2602

Keywords: asymmetric synthesis • lithium • metalations • (–)-sparteine • structure–activity relationships

- a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560; b) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316 and references therein.
- a) G. A. Weisenburger, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 12218–12219; b) Y. S. Park, G. A. Weisenburger, P. Beak, *J. Am. Chem. Soc.* **1997**, *119*, 10537–10538.
- X-ray data were collected with 0.3° steps in the ω scan mode on a Siemens SMART system equipped with a CCD detector ($\text{MoK}\alpha$ radiation, $\lambda = 71.073$ pm). The structures were solved by direct methods and refined with full-matrix least squares on all reflections, based on F_o^2 with SHELXTL.^[4] Crystallographic data for **1**·2Et₂O ($\text{C}_{36}\text{H}_{50}\text{LiN}_1\text{O}_3 \cdot 2\text{C}_4\text{H}_{10}\text{O}$, $M_r = 727.97$): A yellow crystal with the dimensions $0.30 \times 0.44 \times 1.10$ mm was mounted on a 0.7-mm cryoloop at 163(2) K. Triclinic space group *P1*, $a = 946.57(7)$, $b = 1395.39(10)$, $c = 1796.55(12)$ pm, $\alpha = 111.6920(10)$, $\beta = 96.5740(10)$, $\gamma = 92.4160(10)^{\circ}$, $V = 2181.2(3) \times 10^6$ pm³; $Z = 2$, $\rho_{\text{calc}} = 1.108$ g cm^{–3}; $\mu = 0.071$ mm^{–1} (no absorption correction was applied); 10258 data, 8549 unique ($R_{\text{int}} = 0.0361$), $2\theta < 50.8^{\circ}$, 973 free parameters; $R_1 = 0.075$, $wR_2 = 0.178$ for 7309 data observed ($I > 2\sigma(I)$); max./min. residual electron density $+0.357/-0.349$ e Å^{–3}. Allylic H atoms were independently refined; the remaining H atoms were included as fixed idealized contributors. Crystallographic data for **5** ($\text{C}_{24}\text{H}_{33}\text{N}_1\text{O}_3\text{Sn}$, $M_r = 502.21$): A colorless crystal with the dimensions $0.10 \times 0.20 \times 0.30$ mm was mounted in paratone oil at 198(2) K. Monoclinic space group *P2*₁, $a = 1040.63(6)$, $b = 682.02(4)$, $c = 1748.85(11)$ pm, $\beta = 101.690(2)$, $V = 1215.47(13) \times 10^6$ pm³; $Z = 2$, $\rho_{\text{calc}} = 1.372$ g cm^{–3}; $\mu = 1.073$ mm^{–1} (an empirical absorption correction was applied, transmission 0.4830–0.9369); 7723 data, 5242 unique ($R_{\text{int}} = 0.0840$), $2\theta < 56.8^{\circ}$, 269 free parameters; $R_1 = 0.083$, $wR_2 = 0.192$ for 4314 data observed ($I > 2\sigma(I)$), Flack parameter $-0.08(7)$; min./max. residual electron density $+1.592/-1.699$ e Å^{–3}. All H atoms were included as fixed idealized contributors.^[5]
- The Siemens X-ray structure refinement package consists of SAINT Version 4, SHELXTL Version 5, and SMART Version 4 and is marketed by Siemens Industrial Automation, Inc., Madison, WI.
- Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101316. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- The greatest difference in bond lengths between **1** and **2** is 3.5 pm for an aromatic C–C bond on the *p*-OMeC₆H₄ ring. Bond lengths and angles reported here are for complex **1**.
- a) M. Marsch, K. Harms, O. Zschage, D. Hoppe, G. Boche, *Angew. Chem.* **1991**, *103*, 338–339; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 321–323; b) H. Ahlbrecht, G. Boche, K. Harms, M. Marsch, H. Sommer, *Chem. Ber.* **1990**, *123*, 1853–1858; c) I. Hoppe, M. Marsch, K. Harms, G. Boche, D. Hoppe, *Angew. Chem.* **1995**, *107*, 2328–2330; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2158–2160.
- a) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356–363; b) P. Beak, W. K. Lee, *J. Org. Chem.* **1993**, *58*, 1109–1117 and references therein.
- D. Hoppe, O. Zschage, *Angew. Chem.* **1989**, *101*, 67–69; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 69–71.

- [10] a) P. Beak, J. E. Hunter, Y. M. Jun, A. P. Wallin, *J. Am. Chem. Soc.* **1987**, *109*, 5403–5412; b) A. Carstens, D. Hoppe, *Tetrahedron* **1994**, *50*, 6097–6108.
 [11] The absolute configurations of **4b** and **5** are opposite to our earlier provisional assignments.^[2a] The determination of the absolute configuration for **4b** is detailed in the supporting information.
 [12] H. J. Reich, J. P. Borst, M. B. Coplien, N. H. Phillips, *J. Am. Chem. Soc.* **1992**, *114*, 6577–6579.

Generation of a Silylene Complex by the 1,2-Migration of Hydrogen from Silicon to Platinum**

Gregory P. Mitchell and T. Don Tilley*

Intramolecular migrations in transition metal silicon compounds have attracted considerable attention in recent years.^[1] Many of the catalytic cycles and the most interesting transformations for metal–silicon systems appear to feature such migrations,^[1,2] but discrete examples of these steps have proven difficult to observe and characterize. Silylene complexes of the type $[L_nM=SiR_2]$ are commonly featured as key intermediates in mechanistic speculations on 1,2- and 1,3-migrations.^[1–3] Silylene complexes have only recently been isolated,^[4] but despite great effort the formation of a silylene ligand through an intramolecular migration has not yet been observed. We recently described a reversible 1,2-hydrogen migration which interconverts *cis*- $[(PEt_3)_2Pt(H)Si(SiBu)_2][OTf]$ and *cis*- $[(PEt_3)_2Pt(NCMe)SiH(SiBu)_2][OTf]$ ($Tf = SO_2CF_3$), probably via an intermediate silylene complex.^[5] Here we report the first observation of a facile 1,2-hydride migration which generates an observable platinum silylene complex.

In the search for a 1,2-migration that might produce a silylene ligand, we targeted the synthesis of an alkylsilyl complex of the type $[L_2PtR(SiHR'_2)]$. It was thought that migration of a hydrogen atom to a platinum center to produce the alkyl hydride $[L_2Pt(R)(H)(=SiR'_2)]$ might result in elimination of alkane^[6] to produce a silylene complex of the type $[L_2Pt=SiR'_2]$. Thus, the reaction of $[(dippe)PtMeCl]$ (*dippe* = $iPr_2PCH_2CH_2P(iPr)_2$) with $[(thf)_2LiSiHMe_2]$ ^[7] (*Mes* = 2,4,6- $Me_3C_6H_2$) in diethyl ether yielded a light brown solution, from which the platinum silyl complex $[(dippe)Pt(Me)-SiHMe_2]$ (**1**) was isolated in a 79% yield as colorless crystals that were suitable for an X-ray diffraction study (Figure 1).^[8] The Pt–Si distance of 2.388(3) Å is similar to that observed for *cis*- $[(MePh_2P)_2PtMe(SiPh_3)]$ (2.381(2) Å),^[9] and the silicon-bound hydrogen atom was located and refined at a distance of 1.36(3) Å from the silicon atom.

[*] Prof. Dr. T. D. Tilley, G. P. Mitchell
 Department of Chemistry
 University of California, Berkeley
 Berkeley, CA 94720–1460 (USA)
 Fax: (+1) 510-642-8940
 E-mail: tdttilley@socrates.berkeley.edu

[**] This research was supported by the National Science Foundation.

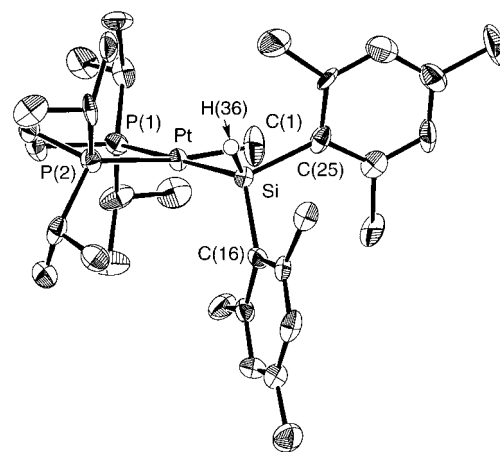
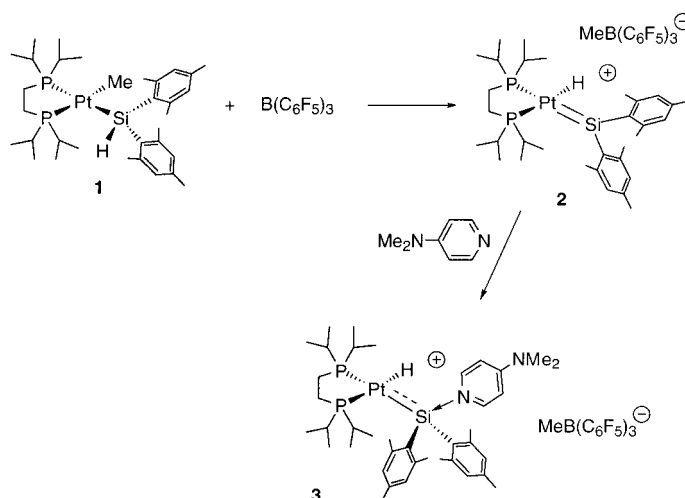


Figure 1. Molecular structure of **1**. Selected interatomic distances [Å] and angles [°]: Pt–Si 2.388 (3), Pt–P(1) 2.329 (3), Pt–P(2) 2.285 (3), Pt–C(1) 2.09 (1), Si–H(36) 1.46 (3), Si–C(16) 1.93 (1), Si–C(25) 1.91 (1); P(1)–Pt–P(2) 86.1 (1), P(1)–Pt–Si 177.7 (1), P(1)–Pt–C(1) 91.0 (4), P(2)–Pt–Si 96.1 (1), P(2)–Pt–C(1) 172.0 (4), Si–Pt–C(1) 86.8 (4), Pt–Si–C(16) 119.3 (4), Pt–Si–C(25) 117.7(4).

Compound **1** is remarkably stable. Heating a solution of **1** in $[D_8]$ toluene at 110 °C for two weeks resulted in no detectable decomposition (^1H and ^{31}P NMR spectroscopy). Also, no reaction was observed between **1** and diphenylacetylene or 2-butyne after heating at 100 °C in $[D_8]$ toluene for three days. However, **1** does react with H_2 at 110 °C over a period of one month to give $MeSi(H)Me_2$ ^[7] (GC/MS and ^1H NMR spectroscopy), presumably by reductive elimination and formation of a Si–C bond. These results suggest that a 1,2-hydrogen migration from the silicon atom to produce a five-coordinate platinum silylene species might be disfavored.

The reaction of **1** with $B(C_6F_5)_3$ in $[D_2]$ dichloromethane resulted in the rapid generation of a clear yellow solution and formation of primarily (> 95%) one new compound (^1H and ^{31}P NMR spectroscopy). The Si–H resonance of **1** ($\delta = 6.21$) was replaced by a Pt–H signal at $\delta = -1.50$ ($J(H,Pt) = 743$ Hz), suggesting that a 1,2-hydride shift had taken place to generate the silylene complex $[(dippe)(H)Pt=SiMe_2][MeB(C_6F_5)_3]$ (**2**, Scheme 1). This was confirmed by observa-



Scheme 1. Generation of the platinum silylene complex **2** and its conversion into **3**.

tion of the ^{29}Si NMR chemical shift at $\delta = 338.5$ (Figure 2), which is indicative of the presence of a three-coordinate silicon atom,^[4c,d] and by the ^{19}F NMR spectrum, which is consistent with formation of $[\text{MeB}(\text{C}_6\text{F}_5)_3]^-$.^[10] The ^1H NMR spectrum of **2** also contains a broad signal at $\delta = 1.37$, which is

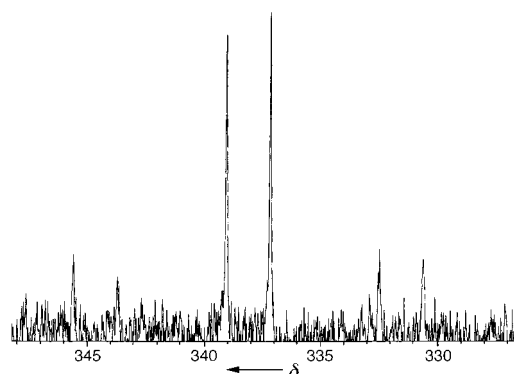


Figure 2. $^{29}\text{Si}\{^1\text{H}\}$ NMR spectrum of **2** (99.3 MHz): $\delta = 338.1$ ($^1J(\text{Si},\text{Pt}) = 1305$, $^2J(\text{Si},\text{Pt})_{\text{trans}} = 187.8$ Hz; $^2J(\text{Si},\text{P})_{\text{cis}}$ coupling was not observed).

assigned to the BCH_3 group. This ^1H NMR chemical shift is noticeably downfield from that of free $[\text{MeB}(\text{C}_6\text{F}_5)_3]^-$ ($\delta \approx 0.5$ (br) in $[\text{D}_2]$ dichloromethane^[10,11]), and may therefore indicate the presence of a tight ion pair. A similar downfield chemical shift ($\delta = 1.67$) for $[\text{MeB}(\text{C}_6\text{F}_5)_3]^-$, was observed by Jordan and Coles for an aluminum amidinate system and was attributed to an $\text{Al} \cdots \text{MeB}(\text{C}_6\text{F}_5)_3$ interaction.^[12] However, the exceptional downfield-shifted ^{29}Si NMR resonance for **2** strongly indicates that any $\text{Si} \cdots \text{MeB}(\text{C}_6\text{F}_5)_3$ interaction must be extremely weak or nonexistent. The value of $^1J(\text{Si},\text{Pt})$ for **2** (1305 Hz) is moderately smaller than the analogous value for **1** (1315 Hz), possibly reflecting the weaker σ donating ability of the $-\text{SiMe}_2$ ligand relative to $-\text{SiHMe}_2$. However, a much larger drop in the value of $^1J(\text{Si},\text{Pt})$ was observed when *trans*- $[(\text{Cy}_3\text{P})_2(\text{H})\text{PtSi}(\text{SEt})_2][\text{OTf}]$ (1825 Hz) was converted into *trans*- $[(\text{Cy}_3\text{P})_2(\text{H})\text{PtSi}(\text{SEt})_2][\text{BPh}_4]$ (1558 Hz).^[4c] Initial attempts to isolate **2** indicate that it is an oil at room temperature. It is somewhat thermally sensitive, and decomposes at room temperature with a half-life of approximately 12 h in $[\text{D}_2]$ dichloromethane.

As with a similar silylene complex,^[4c] the reaction of **2** with *p*-dimethylaminopyridine (DMAP) generates the base-stabilized silylene complex $[(\text{dippe})(\text{H})\text{PtSiMe}_2(\text{DMAP})][\text{MeB}(\text{C}_6\text{F}_5)_3]$ (**3**), which was isolated in a 47% yield as a light yellow solid (Scheme 1). The ^1H NMR chemical shift of $\delta = 0.47$ ($[\text{D}_2]$ dichloromethane) for $[\text{MeB}(\text{C}_6\text{F}_5)_3]^-$ is consistent with formation of the free anion, which has presumably been completely displaced from the complex by the much more basic DMAP ligand. Not surprisingly, compound **3** is considerably more stable than **2**, and undergoes less than 10% decomposition over one week in $[\text{D}_2]$ dichloromethane at room temperature.

Monitoring the formation of **2** at -70°C by ^{31}P NMR spectroscopy provided no evidence of reaction intermediates, such as the three-coordinate platinum species $[(\text{dippe})\text{PtSiHMe}_2][\text{MeB}(\text{C}_6\text{F}_5)_3]$. Addition of H_2SiPh_2 and HClSiPh_2 to **2** resulted in the rapid formation of H_2SiMe_2 (^1H NMR

spectroscopy) and multiple platinum-containing products, but no products with silicon–silicon bonds were observed. Similarly, treatment of **2** with H_2 generated H_2SiMe_2 as the major species containing a mesityl group as well as several uncharacterized platinum products.

This work represents the first direct detection of a 1,2-migration from silicon to a metal atom to generate an observable transition metal silylene complex. Of particular interest is the fact that the four-coordinate platinum complex **1** is remarkably inert, while facile migration occurs when a coordination site on the metal is vacated. In reactions of square planar, four-coordinate platinum silyl complexes, therefore, it seems that α -hydrogen migration (without prior ligand dissociation) is an unlikely mechanistic step. Thus, for example, the previously observed elimination of MeSiH_3 from $[(\text{dmpe})\text{Pt}(\text{SiH}_2\text{Mes})_2]$ ($\text{dmpe} = \text{Me}_2\text{PCH}_2\text{CH}_2\text{PMe}_2$), to form the “dimerized” platinum silylene complex $[(\text{dmpe})\text{Pt}(\mu\text{-SiHMe})_2\text{Pt}(\text{dmpe})]$, probably proceeds through oxidative addition/reductive elimination cycles rather than via the silylene intermediates $[(\text{dmpe})\text{Pt}(\text{SiHMe})(\text{H})(\text{SiH}_2\text{Mes})]$ and $[(\text{dmpe})\text{Pt}=\text{SiHMe}]$.^[13]

Despite abundant circumstantial evidence, the relevance of intramolecular 1,2- and 1,3-migrations in silane polymerization, hydrosilation, and silane redistribution mechanisms is still largely a matter of speculation. Nevertheless, such migrations are viable and may even be prevalent in transformations of transition metal silicon complexes.

Experimental Section

General procedures: All reactions were carried out under nitrogen using standard Schlenk techniques. Benzene, pentane, and diethyl ether were distilled from Na/benzophenone prior to use and stored under nitrogen. Dichloromethane was distilled from CaH_2 and degassed with two freeze-pump-thaw cycles prior to use. The compounds $[(\text{cod})\text{PtMeCl}]$ ($\text{cod} = 1,5$ -cyclooctadiene),^[14] *dippe*,^[15] $[(\text{thf})_2\text{LiSiHMe}_2]$,^[7] and $\text{B}(\text{C}_6\text{F}_5)_3$ ^[16] were prepared according to known procedures. NMR spectra were recorded in $[\text{D}_6]$ benzene at room temperature unless otherwise noted. Elemental analyses were performed by the microanalytical facility at the University of California, Berkeley. All IR samples were prepared as KBr pellets.

$[(\text{dippe})\text{PtMeCl}]$: A procedure analogous to the preparation of $[(\text{dppe})\text{PtMeCl}]$ ($\text{dppe} = 1,2$ -bis(diphenylphosphanyl)ethane) was used,^[17] but starting from $[(\text{cod})\text{PtMeCl}]$ and *dippe* in benzene. Thus, $[(\text{dippe})\text{PtMeCl}]$ was crystallized from dichloromethane at -40°C . ^1H NMR (400 MHz): $\delta = 0.66$ (dd, $^3J(\text{H},\text{H}) = 7.2$, $^3J(\text{H},\text{P}) = 14.4$ Hz, 6H, *iPr*), 0.70 (m, PtMe), 0.81 (dd, $^3J(\text{H},\text{H}) = 7.2$, $^3J(\text{H},\text{P}) = 13.6$ Hz, 6H, *iPr*), 0.92 (dd, $^3J(\text{H},\text{H}) = 7.2$, $^3J(\text{H},\text{P}) = 16.4$ Hz, 6H, *iPr*), 1.17 (m, CH_2), 1.28 (dd, $^3J(\text{H},\text{H}) = 7.2$, $^3J(\text{H},\text{P}) = 15.6$ Hz, 6H, *iPr*), 1.83 (m, 2H, *P*Pr), 2.25 (m, 2H, *iPr*); $^{31}\text{P}\{^1\text{H}\}$ NMR (161.98 MHz): $\delta = 63.19$ (s with ^{195}Pt satellites, $^1J(\text{P},\text{Pt}) = 4013$ Hz), 72.49 (s with ^{195}Pt satellites, $^1J(\text{P},\text{Pt}) = 1760$ Hz).

1: Et_2O (15 mL) was added to a mixture of $[(\text{dippe})\text{PtMeCl}]$ (0.411 g, 0.810 mmol) and $[(\text{thf})_2\text{LiSiHMe}_2]$ (0.339 g, 0.810 mmol). The mixture was stirred for 12 hours, and then the volatile compounds were removed under reduced pressure. Extraction of the residue with pentane (5×20 mL), followed by concentration to approximately half its volume and cooling to -78°C , resulted in crystallization of pure **1**. Yield 79% (0.473 g). Elemental analysis calcd for $\text{C}_{35}\text{H}_{38}\text{P}_2\text{PtSi}$: C 53.57, H 7.90; found: C 53.23, H 8.12; m.p. 195 – 198°C (decomp); ^1H NMR (400 MHz): $\delta = 0.76$ (m, 12H, *iPr*), 0.91 (m, 12H, *iPr*), 1.05 (dd, $^3J(\text{Si},\text{P}) = 9.6$, $^3J(\text{H},\text{P}) = 6.4$ Hz, PtMe), 1.13 (m, CH_2 and *iPr*), 1.96 (m, 2H, CH_2), 2.23 (s, 6H, *p*-Me), 2.78 (s, 12H, *o*-Me), 6.21 (m, 1H, SiH), 6.93 (s, 4H, ArH); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz): $\delta = 5.6$ (m, *iPr*), 8.6 (m, *iPr*), 13.1 (m, PtMe), 16.4 (s, Mes), 18.2 (s, Mes), 17.1 (m, CH_2), 18.2 (m, CH_2), 25.2 (m, *iPr*), 27.4 (m, *iPr*), 118.8 (s, Ar), 122.1 (s, Ar), 125.3 (s, Ar), 131.1 (s, Ar), 132.3 (s, Ar), 138.8 (s, Ar); $^{31}\text{P}\{^1\text{H}\}$ NMR (161.98 MHz): $\delta = 66.54$ (s with ^{195}Pt satellites, $^1J(\text{P},\text{Pt}) =$

1784 Hz), 76.00 (s with ^{195}Pt satellites, $^1\text{J}(\text{P},\text{Pt}) = 1378\text{ Hz}$); $^{29}\text{Si}\{^1\text{H}\}$ NMR (99.3 MHz): $\delta = -28.70$ (dd with ^{195}Pt satellites, $^1\text{J}(\text{P},\text{Pt}) = 1315$, $^2\text{J}(\text{Si},\text{Pt})_{\text{trans}} = 192$, $^2\text{J}(\text{Si},\text{Pt})_{\text{cis}} = 13.3\text{ Hz}$); IR: 2956s, 2913s, 2051m (SiH), 1600w, 1542w, 1459s, 1405m 1384w, 1253w, 1226w, 1035m, 836s, 698m, 657m, 632m, 594m, 549w, 424 cm^{-1} m.

2: A mixture of **1** (0.050 g, 0.067 mmol) and $\text{B}(\text{C}_6\text{F}_5)_3$ (0.035 g, 0.068 mmol) was dissolved in $[\text{D}_2]$ dichloromethane (0.700 mL), generating a bright yellow solution of **2**. ^1H NMR (400 MHz): $\delta = -1.50$ (dd, $^2\text{J}(\text{H},\text{P})_{\text{cis}} = 7.1$, $^2\text{J}(\text{H},\text{P})_{\text{trans}} = 105$, $^1\text{J}(\text{H},\text{Pt}) = 743\text{ Hz}$, 1H, PtH), 0.63 (m, 12H, *i*Pr), 0.85 (m, 12H, *i*Pr), 1.25 (m, CH_2 and *i*Pr), 1.36 (brs, 3H, $\text{MeB}(\text{C}_6\text{F}_5)_3$), 1.62 (m, 2H, CH_2), 2.00(s, 6H, *p*-Me), 2.23 (s, 12H, *o*-Me), 6.62 (s, 4H, ArH); $^{31}\text{P}\{^1\text{H}\}$ NMR (161.98 MHz): $\delta = 77.2$ (s with ^{195}Pt satellites, $^1\text{J}(\text{P},\text{Pt}) = 1726\text{ Hz}$), 81.4 (s with ^{195}Pt satellites, $^1\text{J}(\text{P},\text{Pt}) = 2523\text{ Hz}$); ^{19}F NMR (376.4 MHz): $\delta = -132.2$ (brs, 2F), -165.1 (brs, 1F), -167.2 (brs, 2F); $^{29}\text{Si}\{^1\text{H}\}$ NMR (99.38 MHz): $\delta = 338.1$ (d with ^{195}Pt satellites, $^2\text{J}(\text{Si},\text{P}) = 187.8$, $^1\text{J}(\text{Si},\text{Pt}) = 1305\text{ Hz}$).

3: Dichloromethane (10 mL) was added to a mixture of **1** (0.300 g, 0.405 mmol) and $\text{B}(\text{C}_6\text{F}_5)_3$ (0.207 g, 0.405 mmol) to generate **2**. After all of the reactants had dissolved, a solution of DMAP (0.049 g, 0.405 mmol) in dichloromethane (5 mL) was added by cannula. This resulted in the immediate formation of a colorless solution. Removal of the volatile material under reduced pressure gave a light yellow oil, to which Et_2O (5 mL) was added. Cooling the mixture to -78°C for 12 h resulted in precipitation of **3** as a light yellow powder. Yield 47% (0.225 g). Elemental analysis calcd for $\text{C}_{38}\text{H}_{68}\text{BF}_{15}\text{N}_3\text{P}_2\text{Si}$: C 58.83, H 5.79; found: C 58.53, H 5.56; m.p. $105-107^\circ\text{C}$ (dec). ^1H NMR (400 MHz, $[\text{D}_2]$ dichloromethane): $\delta = -3.57$ (dd with ^{195}Pt satellites, $^2\text{J}(\text{H},\text{P})_{\text{cis}} =$, $^2\text{J}(\text{H},\text{P})_{\text{trans}} = 148$, $^1\text{J}(\text{H},\text{Pt}) = 918\text{ Hz}$, 1H, PtH), 0.47 (brs, $\text{MeB}(\text{C}_6\text{F}_5)_3$), 0.65 (m, 12H, *i*Pr), 0.94 (m, 12H, *i*Pr), 1.13 (m, CH_2 and *i*Pr), 1.96 (m, 2H, CH_2), 2.32 (s, 6H, *p*-Me), 2.36 (s, 12H, *o*-Me), 3.09 (s, 6H, NMe_2), 6.56 (d, $^3\text{J}(\text{HH}) = 7.6\text{ Hz}$), 6.81 (s, 1H, ArH), 8.32 (d); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $[\text{D}_2]$ dichloromethane): $\delta = 7.1$ (m, *i*Pr), 8.2 (m, *i*Pr), 10.1 (br s, MeBAr_3), 19.1 (s, Mes), 19.9 (s, Mes), 23.3 (m, CH_2), 28.4 (m, CH_2), 32.1 (s, NMe_2), 117.5 (s, Ar), 119.1 (s, Ar), 121.3 (s, Ar), 124.1 (s, Ar), 127.1 (s, Ar), 130.1 (s, Ar), 131.6 (s, Ar), not all of the aryl carbon atoms were observed; $^{31}\text{P}\{^1\text{H}\}$ NMR (161.98 MHz, $[\text{D}_2]$ dichloromethane): $\delta = 71.87$ (d with ^{195}Pt satellites, $^2\text{J}(\text{P},\text{P}) = 3.4$, $^1\text{J}(\text{P},\text{Pt}) = 2075\text{ Hz}$), 92.37 (d with ^{195}Pt satellites, $^1\text{J}(\text{P},\text{Pt}) = 1636\text{ Hz}$); IR: 2971s, 2916s, 2072m (PtH), 1572w, 1489s, 1426m 1401w, 1319w, 1251w, 1092m, 913s, 852m, 741m, 695m, 525 cm^{-1} m.

Received: March 24, 1998 [Z 11632IE]
German version: *Angew. Chem.* **1998**, *110*, 2602–2605

Keywords: platinum • silicon • silylene • rearrangements

- [1] a) K. H. Pannell, J. Cervantes, C. Hernandez, J. Cassias, S. Vincenti, *Organometallics* **1986**, *5*, 1056; b) K. H. Pannell, J. M. Rozell Jr., C. Hernandez, *J. Am. Chem. Soc.* **1989**, *111*, 4482; c) K. H. Pannell, L.-J. Wang, J. M. Rozell, *Organometallics* **1989**, *8*, 550; d) K. H. Pannell, H. Sharma, *Organometallics* **1991**, *10*, 954; e) K. L. Jones, K. H. Pannell, *J. Am. Chem. Soc.* **1993**, *115*, 11336; f) C. Hernandez, H. K. Sharma, K. H. Pannell, *J. Organomet. Chem.* **1993**, *462*, 259; g) K. H. Pannell, M.-C. Brun, H. Sharma, K. Jones, S. Sharma, *Organometallics* **1994**, *13*, 1075; h) H. Tobita, K. Ueno, H. Ogino, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2797; i) K. Ueno, H. Tobita, H. Ogino, *Chem. Lett.* **1990**, 369; j) K. Ueno, K. Kakano, H. Ogino, *Chem. Lett.* **1996**, 459; k) M. Okazaki, H. Tobita, H. Ogino, *J. Chem. Soc. Dalton Trans.* **1997**, 3531; l) A. Haynes, M. W. George, M. T. Haward, M. Poliakkoff, J. J. Turner, N. M. Boag, M. Green, *J. Am. Chem. Soc.* **1991**, *113*, 2011; m) S. Nlate, E. Herdtweck, R. A. Fischer, *Angew. Chem.* **1996**, *108*, 1957; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1861; n) D. C. Pestana, T. S. Koloski, D. H. Berry, *Organometallics* **1994**, *13*, 4173.
- [2] a) M. D. Curtis, P. S. Epstein, *Adv. Organomet. Chem.* **1981**, *19*, 213; b) T. Kobayashi, T. Hayashi, H. Yamashita, M. Tanaka, *Chem. Lett.* **1988**, 1411; c) T. D. Tilley, *Comments Inorg. Chem.* **1990**, *10*, 37; d) M. Ishikawa, H. Sakamoto, F. Kanetani, *Organometallics* **1989**, *8*, 2767; e) J. A. Reichl, C. M. Popoff, L. A. Gallagher, E. E. Remsen, D. H. Berry, *J. Am. Chem. Soc.* **1996**, *118*, 9430; f) W. S. Palmer, K. A. Woerpel, *Organometallics* **1997**, *16*, 4824; g) D. Seyferth, M. L. Shannon, S. C. Vick, T. F. O. Lim, *Organometallics* **1985**, *4*, 57; h) H. Yamashita, M. Tanaka, M. Goto, *Organometallics* **1992**, *11*, 3227; i) Y. Tanaka, H. Yamashita, M. Tanaka, *Organometallics* **1995**, *14*, 530; j) K. Tamao, G.-R. Sun, A. Kawachi, *J. Am. Chem. Soc.* **1995**, *117*, 8043.
- [3] a) T. D. Tilley in *The Silicon-Heteroatom Bond* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1991**, chap 9, 10, pp. 245, 309; b) T. D. Tilley in *The Chemistry of Organic Silicon Compounds* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1989**, chap 24, P. 1415; c) J. Corey in *Advances in Silicon Chemistry, Vol. 1* (Ed.: G. Larson), JAI, Greenwich, CT, **1991**, p. 327; d) K. H. Pannell, H. K. Sharma, *Chem. Rev.* **1995**, *95*, 1351; e) C. Zybail, *Top. Curr. Chem.* **1991**, *160*, 1; f) P. D. Lickiss, *Chem. Soc. Rev.* **1992**, 271.
- [4] Silylene complexes with sp^2 silicon atoms: a) D. A. Straus, S. D. Grumbine, T. D. Tilley, *J. Am. Chem. Soc.* **1990**, *112*, 7801; b) S. D. Grumbine, T. D. Tilley, A. L. Rheingold, *J. Am. Chem. Soc.* **1993**, *115*, 358; c) S. D. Grumbine, T. D. Tilley, F. P. Arnold, A. L. Rheingold, *J. Am. Chem. Soc.* **1993**, *115*, 7884; d) S. K. Grumbine, T. D. Tilley, F. P. Arnold, A. L. Rheingold, *J. Am. Chem. Soc.* **1994**, *116*, 5495; e) M. Denk, R. K. Hayashi, R. West, *J. Chem. Soc. Chem. Commun.* **1994**, 33.
- [5] G. P. Mitchell, T. D. Tilley, *J. Am. Chem. Soc.*, in press.
- [6] J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science, Mill Valley, CA, **1987**, Ch. 5.
- [7] D. M. Roddick, R. H. Heyn, T. D. Tilley, *Organometallics* **1989**, *8*, 324.
- [8] Crystal data for **1**: $\text{C}_{33}\text{H}_{57}\text{PtP}_2\text{Si}$, $0.10 \times 0.15 \times 0.10\text{ mm}$, tetragonal, space group $P2_1c$, $a = 22.0264(3)$, $c = 14.2660(2)\text{ \AA}$, $V = 6947.3(1)\text{ \AA}^3$, $Z = 8$; $\mu(\text{MoK}\alpha) = 41.69\text{ cm}^{-1}$, $T = 158\text{ K}$. Of 28993 data collected ($2\theta < 46.5^\circ$), 3551 were independent and used in the refinement of 334 variables. The data were corrected for Lorentz and polarization effects, but no absorption correction was applied. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were treated as idealized contributions, except H(36), which was located and refined isotropically. $R(F) = 0.029$; $R(wF) = 0.029$. Max./min. peaks in final difference map: $0.55/-0.57\text{ e}^{-\text{\AA}^{-3}}$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102839. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] F. Ozawa, T. Hikida, T. Hayashi, *J. Am. Chem. Soc.* **1994**, *116*, 2844.
- [10] X. Yang, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1994**, *116*, 10015.
- [11] C. L. Gillis, M.-J. Tudoret, M. C. Baird, *J. Am. Chem. Soc.* **1993**, *115*, 2543.
- [12] M. P. Coles, R. F. Jordan, *J. Am. Chem. Soc.* **1997**, *119*, 8125.
- [13] a) R. H. Heyn, T. D. Tilley, *J. Am. Chem. Soc.* **1992**, *114*, 1917; b) R. H. Heyn, Dissertation, University of California, San Diego (USA), **1992**.
- [14] H. C. Clark, L. E. Manzer, *J. Organomet. Chem.* **1973**, *59*, 411.
- [15] a) M. D. Fryzuk, T. Jones, F. W. B. Einstein, *Organometallics*, **1984**, *3*, 185; b) R. J. Burt, J. Chatt, W. Hussain, G. J. Leigh, *J. Organomet. Chem.* **1979**, *182*, 203.
- [16] A. G. Massey, A. J. Park, *J. Organomet. Chem.* **1964**, *2*, 245.
- [17] T. G. Appleton, M. A. Bennett, I. B. Tomkins, *J. Chem. Soc. Dalton Trans.* **1976**, 439.

Silicon Boron Nitrides: Hypothetical Polymorphs of $\text{Si}_3\text{B}_3\text{N}_7$ **

Peter Kroll and Roald Hoffmann*

Materials based on silicon boron carbon nitrides (Si-B-(C)-N) are intriguing potential “ultra high temperature materials”, combining thermal stability at temperatures of 1700 °C and above^[1, 2] with remarkable resistance to oxidation.^[3, 4] Recent reviews on their synthesis by polymer-to-ceramic transformations are given by Riedel et al. and by Baldus and Jansen.^[5, 6] In particular, Baldus and Jansen concentrated on the synthesis of two stoichiometric compounds, $\text{Si}_3\text{B}_3\text{N}_7$ and SiBCN_3 . As a consequence of the synthesis from single source precursors, these ternary and quaternary Si-B-(C)-N compounds are homogeneous down to the length scale of current high-resolution transmission electron microscopy (ca. 10 Å). What impedes structural investigations is the fact that these compounds are amorphous.

We do know something of the local environment of the atoms. In $\text{Si}_3\text{B}_3\text{N}_7$ the boron atoms are locally coordinated as in hexagonal BN, that is, approximately threefold planar coordinated by nitrogen atoms.^[6] The local environment of silicon is similar to that in Si_3N_4 (α or β phase), approximately tetrahedrally coordinated by four nitrogen atoms. The local environment of nitrogen is threefold (planar), and appears to consist of a mixture of N–B and N–Si bonds. Given the structure of the molecular precursor^[7] and the synthetic method, Si–Si, B–B, N–N as well as Si–B bonds appear unlikely.

Since the properties of compounds depend ultimately on their geometrical and electronic structure, we set out in search of translationally periodic three-dimensional covalent inorganic networks which would satisfy the experimentally found bonding topology and thus serve as models for amorphous $\text{Si}_3\text{B}_3\text{N}_7$ and SiBCN_3 . Here, we restrict ourselves to $\text{Si}_3\text{B}_3\text{N}_7$ models. One such structure has been suggested by Schön and Jansen.^[8] We show that hypothetical structures for $\text{Si}_3\text{B}_3\text{N}_7$ can be derived in principle from any alternating 3/4-connected net of stoichiometry A_3B_4 .^[9]

To illustrate our approach, consider the structure of α - Si_3N_4 (**1**, Figure 1), which is composed of tetrahedral silicon atoms and almost trigonal-planar nitrogen atoms. Imagine removing one nitrogen atom. This will leave three silicon atoms, each with one “dangling bond” (**2**). If we replace these silicon atoms with boron, each boron atom will be bonded to three nitrogen atoms (**3**). Of course, the boron atom is initially

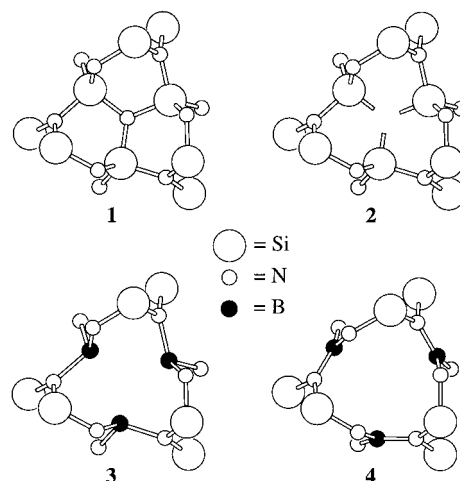


Figure 1. Illustration of the discarding/replacing procedure; the cluster model shown is an example taken from α - Si_3N_4 (**1**) in which a nitrogen atom is removed (**2**), and three silicon atoms are replaced by boron (**3**). Relaxation of **3** leads to **4**.

pyramidal, but this will change during a subsequent relaxation of the structural parameters (**4**).

Let us see how the stoichiometry is affected by this construction. Every time we discard one nitrogen atom, we replace three silicon atoms with boron.^[10] If we start with a composition $\text{Si}_{3Z}\text{N}_{4Z}$, where Z is the number of formula units in the repeated cell, after the n th repetition of the protocol described we reach a stoichiometry $\text{Si}_{3Z-3n}\text{B}_{3n}\text{N}_{4Z-n}$. Therefore, if we want to create a Si-B-N network with a ratio of silicon to boron atoms of $k_{\text{Si}}/k_{\text{B}}$, the parent 3/4-connected network should have $Z = n((k_{\text{Si}}/k_{\text{B}}) + 1)$ units of Si_3N_4 . The value of n has to be chosen to make Z an integer. Clearly a complete range of Si/B ratios is accessible with this procedure, and the amount of nitrogen in an Si-B-N phase depends explicitly on this ratio.

Our search for possible parent networks for the generation of $\text{Si}_3\text{B}_3\text{N}_7$ structures began with both silicon nitride structures. Since we limited ourselves to structures with 13 or 26 atoms in the unit cell ($Z \leq 2$), we could derive 3 candidates from β - Si_3N_4 (one with $Z = 1$) and 14 candidates from α - Si_3N_4 (all with $Z = 2$). Enlarging the basis of parent networks to further alternating 3/4-connected nets increases the number of distinct $\text{Si}_3\text{B}_3\text{N}_7$ structures with $Z \leq 2$ to more than 100.^[11, 12] We analyzed all nets through their coordination sequences and extended Schläfli symbol^[13] and found that each parent network generates $\text{Si}_3\text{B}_3\text{N}_7$ networks distinct from those derived from other parent structures. In our calculations we also included the one structure suggested for $\text{Si}_3\text{B}_3\text{N}_7$ that has been published previously.^[8]

A detailed description of all the nets is not possible here, but we mention the extensive variety of boron–nitrogen substructures observed. Common zero-dimensional motifs are the BN_3 or $\text{N}(\text{BN}_2)_3$ molecular units as well as 6- and 12-membered BN rings. A prevalent one-dimensional motif is a BN chain, which is more or less distorted from an ideal, polyacetylene-like configuration. Structures with two-dimensional BN subnets are also found. Moreover, the reduced mean connectivity ($42/13 = 3.23$) in comparison to a four-

[*] R. Hoffmann, P. Kroll
Cornell University
Chemistry Department, Baker Laboratory
Ithaca, NY 14853–1301 (USA)
Fax: (+1) 607-255-5707
E-mail: rh34@cornell.edu

[**] The authors gratefully acknowledge the generous support by the National Science Foundation (grant no. CHE 94–08455) and the Center for Materials Science at Cornell University. We also thank the Deutsche Forschungsgemeinschaft for granting a research fellowship (contract Kr 1805/1–1). For computer time we thank the Cornell Theory Center, and the theory group at the Fritz-Haber-Institut in Berlin (Germany) for making their programs publicly available.

connected net even allows the construction of two-dimensional $\text{Si}_3\text{B}_3\text{N}_7$ structures.

With over 100 structures for $\text{Si}_3\text{B}_3\text{N}_7$ derived by our construction principle, we faced the problem of identifying those with lowest energy. First we concentrated on the structures derived from α - and β - Si_3N_4 . To broaden our investigation we also viewed structures derived from willemitte-II,^[14] sphalerite, γ -Si, the boron subnet in CrB_4 , and MAPO-39 structures.^[15] The ground-state properties of the structures were calculated with use of standard density functional theory methods with full geometry optimization.^[16] Table 1 gives a summary of the results for selected $\text{Si}_3\text{B}_3\text{N}_7$ structures. Many other structures are more than 1.9 eV per formula unit less stable than the lowest energy structure. The two $\text{Si}_3\text{B}_3\text{N}_7$ structures lowest in total energy, α -1- $\text{Si}_3\text{B}_3\text{N}_7$ and β -2- $\text{Si}_3\text{B}_3\text{N}_7$, are derived from α - Si_3N_4 and β - Si_3N_4 .

Note that all computed $\text{Si}_3\text{B}_3\text{N}_7$ structures (except a high-pressure phase γ -hp) are less dense than Si_3N_4 , having only 85–90 % of the density of the parent structure. For example, the density of α - and β - Si_3N_4 is about 3.3 g cm^{-3} , whereas $\text{Si}_3\text{B}_3\text{N}_7$ structures derived from these structures have a density between 2.8 and 2.9 g cm^{-3} (Table 1). The reason for this is the protocol in which nitrogen is removed and silicon is substituted by boron, which is only partially compensated by a decrease in the volume of the unit cell. The $\text{Si}_3\text{B}_3\text{N}_7$ phase with lowest density (ca. 2.5 g cm^{-3}), but high energy, was derived from the zeolite net MAPO-39.^[17]

Looking at the structural details (not reported here) we find the following: 1) Boron always relaxes to be approximately planar. The sum of angles at boron deviates less than 3.5° from 360° (the ideal planar configuration). The bond angles at boron are close to 120° with a maximum deviation of 6° . 2) Nitrogen also tends to be planar, although the preference is less expressed than for boron. For structures derived from α - or β - Si_3N_4 the minimum sum of angles at the nitrogen site is 340° (in α -3), which indicates somewhat pyramidal coordination. For structures derived from other parent 3/4-connected nets the deviation from planarity is even higher. Bond angles at nitrogen scatter in the range between 100 and 140° .

The structure of β -2- $\text{Si}_3\text{B}_3\text{N}_7$, which has a clear resemblance to that of β - Si_3N_4 , is shown in a ball-and-stick model in Figure 2. The boron atoms relax towards the center of the big channels as they become planar; the channels are built from stacked $[(\text{Si}_6\text{N}_6)(\text{B}_6\text{N}_6)]$ sequences and are connected through the silicon atoms by additional nitrogen atoms. In molecular

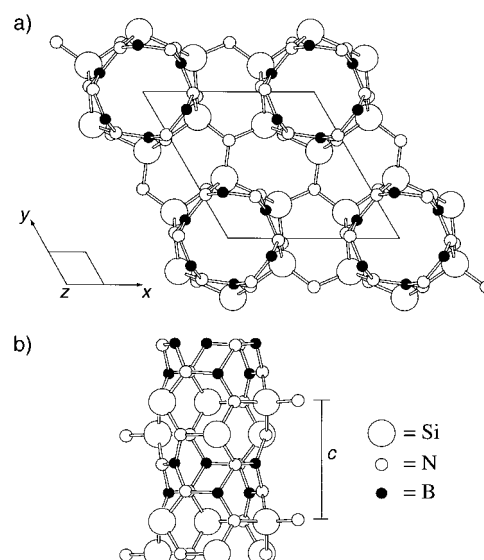


Figure 2. Ball-and-stick model of the structure of β -2- $\text{Si}_3\text{B}_3\text{N}_7$. a) Projection on to the xy plane, which makes the resemblance to β - Si_3N_4 clear. b) View perpendicular to the z axis. Columnar $\text{Si}_3\text{B}_3\text{N}_6$ tubes are linked by additional nitrogen atoms.

chemistry the large 12-membered B_6N_6 ring is known only as part of a macrocycle.^[18] In the 12-membered B_6N_6 ring of β -2- $\text{Si}_3\text{B}_3\text{N}_7$ the calculated B–N distances are 1.43 and $1.47 \text{ \AA}$.^[19] The computed bond angles N–B–N and B–N–B are 117.1 and 114.6° , respectively; the dihedral angles N–B–N–B and B–N–B–N are 14.5 and 112.2° , respectively.

In Figure 3 we show the structure of α -1- $\text{Si}_3\text{B}_3\text{N}_7$. Intriguing here is the motif of one-dimensional chains of B and N atoms, an inorganic analogue of polyacetylene. The B–N distances inside the chains are 1.486 and $1.492 \text{ \AA}$. The chains are slightly deformed and twisted relative to an idealized geometry; the N–B–N and B–N–B angles are 126.1 and 123.2° , respectively; and the dihedral angles N–B–N–B and B–N–B–N are 160.7 and 159.5° , respectively.^[20]

How hard might these materials be? We calculated the bulk modulus for various structures.^[21] It turned out that α -1- $\text{Si}_3\text{B}_3\text{N}_7$ is the phase with the highest bulk modulus (Table 1). It is also the only phase where the bulk modulus (2.4 Mbar) is comparable to that of silicon nitride (α - Si_3N_4 : 2.4, β - Si_3N_4 : 2.55 Mbar). Our calculations furthermore revealed a high-pressure phase γ -hp, which should be energetically more favorable at pressures of about 20 GPa. This γ -hp phase is about 20 % more dense than β -2- $\text{Si}_3\text{B}_3\text{N}_7$. As in the cubic

Table 1. Space group, number of formula units in the unit cell (Z), volume (per formula unit $\text{Si}_3\text{B}_3\text{N}_7$; V_0), density (ρ), relative energy (ΔE_0), and bulk modulus (B_0) for selected hypothetical phases of $\text{Si}_3\text{B}_3\text{N}_7$. The α and β structures are derived from α - Si_3N_4 and β - Si_3N_4 , respectively. The numerals after the structure abbreviation are from an arbitrary numbering of structures in the class; sj is the $\text{Si}_3\text{B}_3\text{N}_7$ structure given in reference [8]. γ -hp is a high-pressure phase of $\text{Si}_3\text{B}_3\text{N}_7$ with a different bonding topology (see text). The total energy is given per $\text{Si}_3\text{B}_3\text{N}_7$ formula unit and relative to that of β -2- $\text{Si}_3\text{B}_3\text{N}_7$ (-2468.0 eV).

Phase	β -1	β -2	α -1	α -3	α -4	sj	γ -hp
space group	$P\bar{6}$ (176)	$P\bar{3}$ (147)	$P31c$ (159)	$P3$ (143)	$P3$ (143)	$P1$ (1)	$R3$ (146)
Z	1	2	2	2	2	1	1
$V_0 [\text{\AA}^3]$	126.5	127.8	123.9	126.5	124.4	128.7	101.3
$\rho [\text{g cm}^{-3}]$	2.82	2.79	2.88	2.82	2.87	2.77	3.52
$\Delta E_0 [\text{eV}]$	1.0	[0]	0.2	1.1	0.4	1.2	2.3
$B_0 [\text{MBar}]$	1.9	2.0	2.4	2.1	2.3		2.7

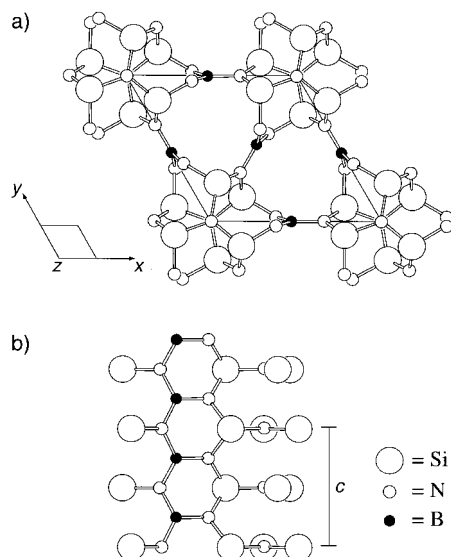


Figure 3. Ball-and-stick model of the structure of α -1- $\text{Si}_3\text{B}_3\text{N}_7$. a) Projection on to the xy plane. b) View perpendicular to the z axis showing one-dimensional chains formed by B and N atoms.

phase of boron nitride, we can find four-connected boron and nitrogen atoms in γ -hp. Since the number of tetrahedral sites in this structure is higher than in the others we considered for $\text{Si}_3\text{B}_3\text{N}_7$, we expect this structure to be more rigid. And indeed we found the bulk modulus to be 2.7 MBar, which is 10% higher than that computed for α -1- $\text{Si}_3\text{B}_3\text{N}_7$.

All structures we calculated are semiconductors with wide band gaps (typical band gap: 4–6 eV (local density approximation, LDA)), as expected from the network topology and the difference in electronegativity of the elements. A crystal orbital overlap population^[22] analysis of Si–N and B–N bonds in α -1- and β -2- $\text{Si}_3\text{B}_3\text{N}_7$ revealed that these bonds are quite similar, as expected, to those in the corresponding binary compounds Si_3N_4 and h-BN.

Our final result concerns the energetics of decomposition of $\text{Si}_3\text{B}_3\text{N}_7$. We calculated the total energies for β - Si_3N_4 and h-BN to obtain the energy for the reaction $\text{Si}_3\text{B}_3\text{N}_7 \rightarrow \beta\text{-Si}_3\text{N}_4 + 3\text{BN}$. The resulting $\Delta E \approx -1.7$ eV (approximately 0.1 eV per atom) suggests that $\text{Si}_3\text{B}_3\text{N}_7$ is not thermodynamically stable at low temperatures. At elevated temperatures the entropy contribution to the free energy might lower this difference or even change the sign of ΔE . The energetically most favorable structures, β -2- $\text{Si}_3\text{B}_3\text{N}_7$ and α -1- $\text{Si}_3\text{B}_3\text{N}_7$, are at least mechanically stable.^[23] If they are synthesized, they will encounter a substantial kinetic barrier to their decomposition.

In summary, we have illustrated a construction principle for structures of the formula $\text{Si}_{3Z-3n}\text{B}_{3n}\text{N}_{4Z-n}$ and examined the structure and energetics of many candidate structures for ordered $\text{Si}_3\text{B}_3\text{N}_7$. Full geometrical optimization of the structures reveals that boron atoms with planar coordination and nitrogen atoms with nearly planar coordination are characteristic of the low-energy structures. The two lowest energy structures are about 15% less dense than Si_3N_4 , but exhibit comparable mechanical properties. Although none of the hypothetical ordered phases we showed has been synthesized so far, we are convinced that the covalent network of

amorphous $\text{Si}_3\text{B}_3\text{N}_7$ and one or more of the more stable hypothetical phases described here will resemble one another.

Received: February 19, 1998 [Z11494IE]
German version: *Angew. Chem.* **1998**, *110*, 2616–2620

Keywords: ceramics • density functional calculations • inorganic networks • materials science • solid-state structures

- [1] H.-P. Baldus, O. Wagner, M. Jansen, *Mater. Res. Soc. Symp. Proc.* **1992**, *271*, 821–826.
- [2] R. Riedel, A. Kienzle, W. Dressler, L. Ruwisch, J. Bill, F. Aldinger, *Nature* **1996**, *382*, 796–798.
- [3] H.-P. Baldus, G. Passing, *Mater. Res. Soc. Symp. Proc.* **1994**, *346*, 617–622.
- [4] M. A. Rooke, P. M. A. Sherwood, *Chem. Mater.* **1997**, *9*, 285–296.
- [5] R. Riedel, J. Bill, A. Kienzle, *Organomet. Chem.* **1996**, *10*, 241–256.
- [6] H.-P. Baldus, M. Jansen, *Angew. Chem.* **1997**, *109*, 338–354; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 328–343.
- [7] M. Mühlhäuser, M. Gastreich, C. M. Marian, H. Jüngermann, M. Jansen, *J. Phys. Chem.* **1996**, *100*, 16551–16554.
- [8] J. C. Schön, M. Jansen, *Angew. Chem.* **1996**, *108*, 1358–1377; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1286–1304; this structure contains chains of borazine rings (B_3N_3).
- [9] In an alternating 3/4-connected net every four-connected vertex is linked to four three-connected vertices and every three-connected vertex is linked to three four-connected vertices. Rings with an odd number of atoms are thus excluded. Since silicon will be tetrahedrally coordinated, we rule out parent nets with a square-planar four-connected vertex, such as that proposed for Pt_4O_4 .
- [10] The nitrogen atom which is to be discarded must not be already bonded to a boron atom.
- [11] A more rigorous approach to the search for $\text{Si}_3\text{B}_3\text{N}_7$ polymorphs is provided by a graph theoretical approach (see e.g.: M. Bader, W. E. Klee, G. Thimm, *Z. Kristallogr.* **1997**, *212*, 553–558). This procedure may be rather cumbersome to apply here, since the stoichiometry $\text{Si}_3\text{B}_3\text{N}_7$ requires at least 13 vertices in the unit cell, and a huge number of labeled graphs would result (a combinatorial explosion: M. M. Treacy, K. H. Randall, S. Rao, J. A. Perry, D. J. Chadi, *Z. Kristall.* **1997**, *212*, 768–791).
- [12] Our method may be incomplete! We may miss some genuine $\text{Si}_3\text{B}_3\text{N}_7$ structures, those which cannot be derived by the construction principle described.
- [13] M. O’Keeffe, B. G. Hyde, *Crystal Structures, I. Patterns and Symmetry*, Mineralogical Society of America, Washington, **1996**.
- [14] F. Marumo, Y. Syono, *Acta Crystallogr. Sect. B* **1971**, *27*, 1868–1870.
- [15] These structures can be found in reference [13]. A useful compendium for open framework structures such as MAPO-39 is the *Atlas of Zeolite Structure Types*: W. M. Meier, D. H. Olson, *Zeolites* **1992**, *12*, 449–654.
- [16] Our calculations of the total energy and atomic structure were performed within the density functional theory (see e.g. R. M. Dreizler, E. K. U. Gross, *Density Functional Theory*, Springer, Berlin, **1990**). We used the local-density approximation with soft, separable, norm-conserving, nonlocal pseudopotentials (N. Troullier, J. L. Martins, *Phys. Rev. B* **1991**, *43*, 1993–2006; M. Fuchs, M. Scheffler, unpublished results). The electronic wave functions are expanded in terms of plane waves with an energy cut-off $E_{\text{cut}}^{\text{PW}}$ of 70 Ry. Integration over the Brillouin zone was done using special points. All calculations were carried out with the program fhi96md (M. Bockstedte, A. Kley, J. Neugebauer, M. Scheffler, *Comp. Phys. Comm.* **1997**, *107*, 187–222). We optimized fully all structural parameters (atomic coordinates and cell constants) using a Car–Parinello scheme with damped Newton dynamics. A more complete description of the computational procedure will be given in a full paper.
- [17] To our knowledge the density of amorphous $\text{Si}_3\text{B}_3\text{N}_7$ has not been reported so far. The density of SiBCN_3 is about $1.8\text{--}2\text{ g cm}^{-3}$.^[6]
- [18] a) I. Haiduc, R. B. King in *Large Ring Molecules*, (Ed.: J. A. Semlyen), Wiley, **1996**, pp. 525–597; b) A. Meller, H.-J. Füllgrabe, *Angew. Chem.* **1975**, *87*, 382–383; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 359–360.

- [19] For comparison: We computed the B–N bond length in hexagonal boron nitride as 1.436 Å, in cubic boron nitride as 1.547 Å. The experimental values are 1.446 and 1.565 Å, respectively (K.-H. Hellwege, A. M. Hellwege in *Landolt-Börnstein, New Series, Group III, Vol. 7, Crystal Structure Data of Inorganic Compounds, Part C*, Springer, Berlin, 1978).
- [20] For both structures, β -2-Si₃B₃N₇ and α -1-Si₃B₃N₇, the mean Si–N bond distance is 1.715 Å, with very small deviations. This is nearly exactly the same as computed for α -Si₃N₄ and β -Si₃N₄, 1.713 and 1.716 Å, respectively (experimental values: 1.738 Å (I. Kohatsu, J. W. McCauley, *Mat. Res. Bull.* 1974, 9, 917–920) and 1.732 Å (R. Grün, *Acta Crystallogr. Sect. B* 1979, 35, 800–804), respectively).
- [21] There is no a priori correlation between bulk modulus and hardness. Nevertheless, for an isotropic material both values are found empirically to be proportional to each other, as long as no plastic deformations occur: R. G. Pearson, *Chemical Hardness*, WILEY-VCH, Weinheim, 1997, chap. 6.
- [22] R. Hoffmann, *Solids and Surfaces: A Chemist's View of Bonding in Extended Structures*, VCH, New York, 1988.
- [23] The calculation of the elastic constants for both structures revealed that they meet the Born criteria for mechanical stability (positive definite stiffness matrix). Thus, the structures are stable against strain. The actual values will be given in a full paper; they are comparable to those of β -Si₃N₄.

Modeling of Benzene Adsorption in Metal-Exchanged Zeolites by Calculation of ⁷Li Chemical Shifts**

Dewey H. Barich, Teng Xu, Jinhua Zhang, and James F. Haw*

Metal-exchanged zeolites are important adsorbents and catalysts, and NMR spectroscopy is commonly used to determine the structure and dynamics of complexes formed between adsorbates and metal cations in zeolites, but such studies usually focus on ²H or ¹³C nuclei in the organic species. Adsorbate-induced changes in the chemical shifts have been observed for ¹³³Cs nuclei in zeolites,^[1] but ¹³³Cs has an exceptionally large chemical-shift range and may not be representative. At the other extreme is lithium, which has a very modest chemical-shift range. If the ⁷Li or ⁶Li chemical shift were sensitive to adsorbate complexation, the effect might be generally useful, especially when quadrupolar effects can either be ignored (as for the central transition of ⁷Li at moderate fields) or separated from the chemical shift.^[2]

Magic angle spinning (MAS) ⁷Li NMR spectra of zeolite LiZSM-5 suggest almost quantitative titration of the ⁷Li resonance with 0.9 equivalents of benzene (Figure 1). The ⁷Li isotropic chemical shift of the evacuated zeolite is $\delta = -0.2$ at 298 K, and adsorption of benzene results in discontinuous

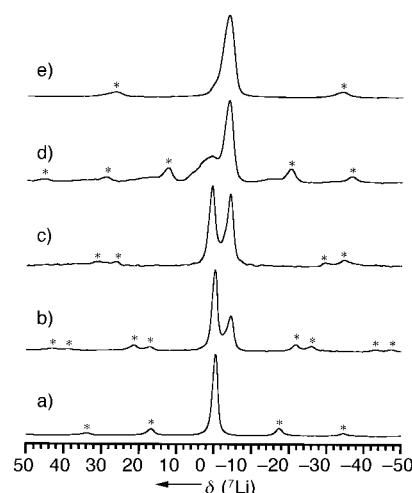


Figure 1. ⁷Li MAS NMR spectra (116.5 MHz) of LiZSM-5 with the following benzene loadings: a) 0.0, b) 0.4, c) 0.6, d) 0.9, e) 2.0 equiv. Spinning sidebands are indicated by an asterisk.

movement of the ⁷Li signal to $\delta = -3.5$ ($\Delta\delta = -3.3$). The spectra appear to be in the slow-exchange regime of benzene hopping between cation sites. The ⁷Li MAS NMR spectrum of the sample with 0.6 equivalents of benzene was recorded as a function of temperature. Coalescence of the two isotropic signals was observed in the vicinity of 493 K (not shown).

Aromatic adsorbates such as *p*-xylene produce changes in the ²⁹Si chemical shifts of ZSM-5 zeolites by inducing a phase transition between polymorphs.^[3] Here we present theoretical calculations which confirm that the changes in the ⁷Li chemical shift above are indeed the result of 1:1 complexation between Li⁺ and benzene, and not other effects.

Cation– π interactions have been studied both experimentally and theoretically, and have been recently reviewed.^[4] In gas-phase calculations, Li⁺ forms both 1:1 and 1:2 complexes with benzene. These are more strongly bound than analogous complexes of the other alkali metal cations. Cation– π interactions in aqueous solution have also been studied theoretically to model their roles in biochemical processes (e.g., ion-channel selectivity).^[5]

We used ab initio methods to quantitatively model the experimental observations of Figure 1. We used the GIAO-MP2 method^[6–8] to explore how the ⁷Li chemical shift changes when Li⁺ ions are π -complexed by benzene or when they are coordinated to various other ligands. Full geometry optimizations were performed at the MP2/6-311 + G* level (Figure 2). We used Li⁺, LiH, Li⁺·H₂O, and Li⁺·2H₂O as simplified models of the uncomplexed site. Additionally, we optimized a complex of Li⁺ with two benzene molecules. Because of computational costs, we did not include larger, more realistic models of Li sites, such as Li⁺·3H₂O.

The chemical shifts of the structures in Figure 2 were calculated at the GIAO-MP2 level (Table 1). The ⁷Li chemical shift is relatively insensitive to the basis set on C; in each case the ⁷Li shift moved downfield (more positive) by 0.2 ppm when the basis on C was reduced from tzp to dzp (see Experimental Section). The isotropic ¹³C shift moved downfield by only $\Delta\delta = 3.7$ when benzene was complexed with Li⁺, which is in agreement with experiment. Smaller effects were

[*] Prof. J. F. Haw, D. H. Barich, Dr. T. Xu, J. Zhang
Department of Chemistry
Texas A&M University
P.O. Box 300012, College Station, TX 77842–3012 (USA)
Fax: (+1) 409-845-7638
E-mail: haw@chemvx.tamu.edu

[**] This work was supported by the National Science Foundation (CHE-9528959).

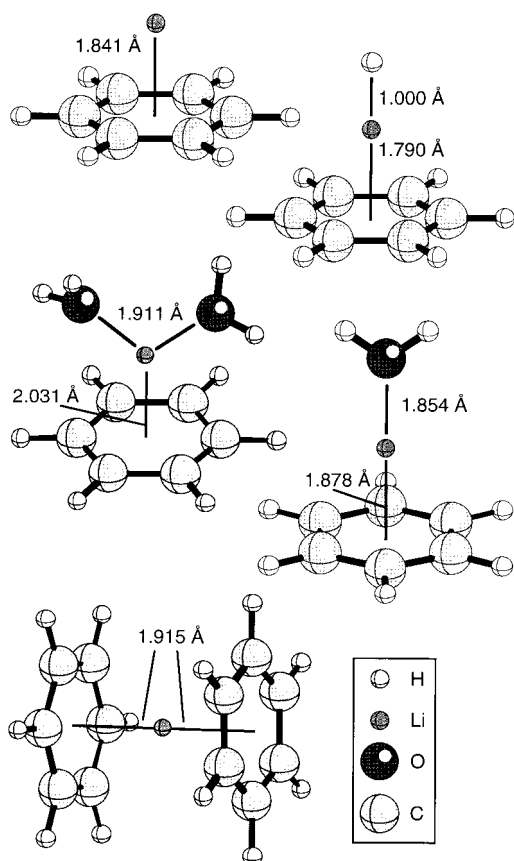


Figure 2. Theoretical structures of model compounds. All structures were optimized at the MP2/6-311 + G* level.

Table 1. Calculated ${}^7\text{Li}$ chemical shifts^[a] of lithium–benzene model compounds.

System	C Basis	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	CSA ^[b]	η
$\text{Li}^+ \cdot \text{C}_6\text{H}_6$	tzp	–7.3	–0.5	–0.5	–21.0	–20.4	0.00
$\text{LiH} \cdot \text{C}_6\text{H}_6$	tzp	–6.5	2.1	2.1	–23.8	–25.9	0.00
$\text{Li}^+ \cdot \text{H}_2\text{O} \cdot \text{C}_6\text{H}_6$	tzp	–6.5	3.9	3.2	–26.5	–30.1	0.04
$\text{Li}^+ \cdot 2\text{H}_2\text{O} \cdot \text{C}_6\text{H}_6$	tzp	–4.9	6.2	–3.0	–17.9	–19.5	0.71
$\text{C}_6\text{H}_6 \cdot \text{Li}^+ \cdot \text{C}_6\text{H}_6$	dzp	–12.4	0.9	0.9	–39.1	–40.0	0.00
LiH		–0.4	2.6	2.6	–6.2	–8.8	0.00
$\text{Li}^+ \cdot \text{H}_2\text{O}$		0.5	4.2	3.7	–6.4	–10.3	0.06
$\text{Li}^+ \cdot 2\text{H}_2\text{O}$		0.9	7.5	7.5	–12.2	–19.7	0.00

[a] Chemical shifts were calculated at the GIAO-MP2 level and are reported relative to that of Li^+ . The absolute shielding of Li^+ is 95.4 ppm.

[b] CSA = chemical shift anisotropy.

predicted by the other models. In each case complexation shifted δ_{22} of the ${}^{13}\text{C}$ tensor downfield, but this was partially offset by upfield shifts in δ_{33} .

For the complexation of Li^+ by a single benzene molecule, $\Delta\delta({}^7\text{Li})$ ranged between –5.8 for $\text{Li}^+ \cdot 2\text{H}_2\text{O}$ and –7.3 for Li^+ (Table 1). For $\text{Li}^+ \cdot 2\text{C}_6\text{H}_6$ $\Delta\delta$ is –12.4. Not surprisingly, complexation to benzene has the most pronounced effect on δ_{33} , which lies along the axis joining the cation and the center of the benzene ring(s). The experimental $\Delta\delta({}^7\text{Li})$ value for benzene complexation in LiZSM-5 zeolite of –3.3 is several times smaller than that calculated for the 1:2 complex but only slightly smaller than that calculated for $\text{Li}^+ \cdot 2\text{H}_2\text{O}$. We conclude that the change in the ${}^7\text{Li}$ chemical shift reflects

formation of a 1:1 complex, and the slightly smaller magnitude of the experimental $\Delta\delta$ value suggests that the zeolite channel prevents benzene from approaching Li^+ as closely as it does in the structures in Figure 2. Thus, the alkali metal nucleus is a potential source not only of dynamical but also of structural information.

Experimental Section

${}^7\text{Li}$ NMR spectra were recorded at 116.5 MHz on a Chemagnetics CMX-300 spectrometer with magic angle spinning, and shifts are reported relative to that for 1.0 M aqueous LiCl. Zeolite HZSM-5 (Si/Al = 19) was obtained from UOP and converted into the lithium form by repeated ion exchange. [${}^{13}\text{C}_6$]Benzene was adsorbed into the zeolite by quantitative manometry and procedures described elsewhere.^[9]

All geometries were optimized at the MP2/6-311 + G* level with Gaussian 94.^[10] We used ACES II for all chemical shift calculations.^[11] The following basis sets^[12] were employed: Li: tzp {51111/1/1}; O: tzp {51111/311/1}; H: dz {31}. For C we used tzp {51111/311/1} and dzp {5111/31/1} basis sets for each structure, except for $\text{Li}^+ \cdot 2\text{C}_6\text{H}_6$, for which only the dzp calculation was tractable.

Received: April 2, 1998 [Z11674IE]

German version: *Angew. Chem.* **1998**, *110*, 2607–2609

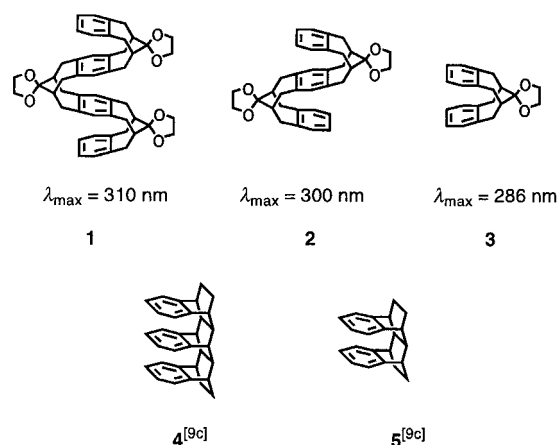
Keywords: ab initio calculations • alkali metals • NMR spectroscopy • pi interactions • zeolites

- [1] D. K. Murray, J.-W. Chang, J. F. Haw, *J. Am. Chem. Soc.* **1993**, *115*, 4731–4741.
- [2] L. Frydman, J. S. Hardwood, *J. Am. Chem. Soc.* **1995**, *117*, 5367–5368.
- [3] C. A. Fyfe, H. Strobl, G. T. Kokotailo, G. J. Kennedy, G. E. Barlow, *J. Am. Chem. Soc.* **1988**, *110*, 3373–3380.
- [4] J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, *97*, 1303–1324.
- [5] R. A. Kumpf, D. A. Dougherty, *Science* **1993**, *261*, 1708–1710.
- [6] K. Wolinski, J. F. Hinton, P. Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260.
- [7] J. Gauss, *Chem. Phys. Lett.* **1992**, *191*, 614–620.
- [8] S. Sieber, P. von R. Schleyer, J. Gauss, *J. Am. Chem. Soc.* **1993**, *115*, 6987–6988.
- [9] J. F. Haw, J. B. Nicholas, T. Xu, L. W. Beck, D. B. Ferguson, *Acc. Chem. Res.* **1996**, *29*, 259–267.
- [10] Gaussian 94, Revision E.2, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople.
- [11] ACES II, an ab initio quantum chemical program system, J. F. Stanton, J. Gauss, J. D. Watts, W. J. Lauderdale, R. J. Bartlett.
- [12] A. Schafer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571–2577.

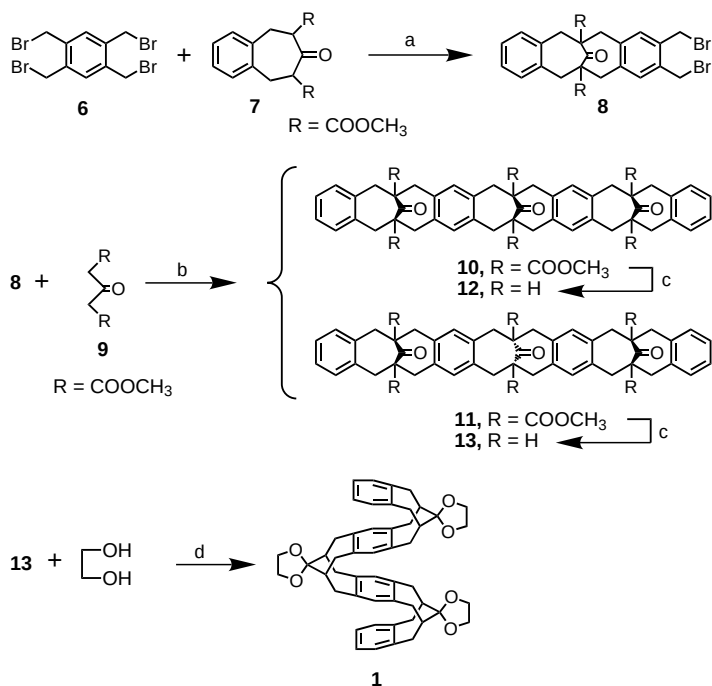
Quadruple Decker [3.3][3.3][3.3]Ortho-cyclophane Acetal—An Orthocyclophane Ladder

Shuntaro Mataka,* Kouichiro Shigaki, Tsuyoshi Sawada, Yoshihara Mitoma, Masahiko Taniguchi, Thies Thiemann, Kazuya Ohga, and Naoyoshi Egashira

Nonbonding interactions between aromatic units play a fundamental role in the behavior of many molecules, with some of them being important to natural processes.^[1] Of these, π – π interactions between closely layered π systems have been a subject of ongoing interest.^[2] For benzene, the difference in the energy of a stacked dimer with a face-to-face geometry to that with an offset geometry or that with an edge-on geometry is well known.^[3] A variety of compounds have been synthesized in which aromatic rings are held rigidly at a short distance in a face-to-face geometry. Typically, ring-substituted or complexed cyclophanes with small ring-sizes^[4] have been used to demonstrate the effects arising from the through-space interaction of π orbitals. The π systems in smaller meta- and paracyclophanes, however, often suffer high distortion.^[5] Thus, it is not always easy to differentiate effects^[6, 7] from a through-space π – π interaction from any effects caused by the distortion of the π system. For the most part, the aromatic units of orthocyclophanes are nondistorted or at most slightly distorted. Orthocyclophanes are often flexible structures and exhibit a less interesting topology.^[8] Through clever bridging, however, rigid orthocyclophanes may be formed with layered π systems, which have only a slight degree of distortion.^[9] One such class of molecules^[10] is made up of [3.3]orthocyclophanes, in which arene units are linked by a bicyclo[4.4.1]undecane group. The introduction of bulky substituents onto the central bridge in these molecules^[11] forces the arene units into a facing position. In this way, starting from the flexible orthocyclophane ketones, rigid, layered [3.3]orthocyclophanes (for example **1**–**5**) can be synthesized. In principle, because of the possibility of a “saw-tooth” or byobulike stacking mode (a byobu is a traditional Japanese folding screen), it is possible to build orthocyclophane ladders in which π – π interactions over longer distances can be expected.



The strategy used for the preparation of quadruple layered **1** is shown in Scheme 1. Dibromide **8** was prepared by treating 1,2,4,5-tetrakis(bromomethyl)benzene (**6**) with dimethyl 1,2-benzo-1-cyclohepten-5-one-4,6-dicarboxylate **7**. The reaction



Scheme 1. a) 5% NaOH/CH₂Cl₂, TBABr, room temperature, 6 h, 80%; b) 20% NaOH/CH₂Cl₂, TBABr, room temperature, 24 h; separation by column chromatography (**10** (R = COOCH₃): 16%; **11** (R = COOCH₃): 44%); c) 1. 10% KOH/EtOH (70 mL), reflux, 4 h, (**10** (R = COOH): 88%; **11** (R = COOH): 91%); 2. 320 °C, (**12**: 56%; **13**: 70%); d) benzene/nitrobenzene (6 mL, 1/1), *p*-toluenesulfonic acid, reflux, 48 h, 68%.

of **8** with dimethyl acetonedicarboxylate (**9**) afforded a 1:4 mixture of diastereoisomeric hexacarboxylates **10** and **11**, which could be separated by column chromatography. The compounds were transformed separately to their corresponding triketones **12** and **13** through a sequence of hydrolysis and thermally induced decarboxylation. The X-ray structure of **12**^[13] showed it to have its three carbonyl groups on the same side of the molecular plane. However, diastereoisomeric **13**

[*] Prof. Dr. S. Mataka, Dr. T. Sawada, Dr. T. Thiemann
Institute of Advanced Material Study
Kyushu University
6-1, Kasuga-koh-en, Kasuga 816–8580 (Japan)
Fax: (+81)92-583-7811
E-mail: mataka@cm.kyushu-u.ac.jp
K. Shigaki, Dr. Y. Mitoma, M. Taniguchi
Department of Molecular Science and Technology
Graduate School of Engineering Sciences
Kyushu University
6-1, Kasuga-koh-en, Kasuga 816–8580 (Japan)
Prof. Dr. K. Ohga, Dr. N. Egashira
Department of Applied Chemistry
Faculty of Engineering
Oita University
Oita Dannoharu 700, Oita 870–1192 (Japan)

could be acetalized easily to yield the quadruple layered [3.3][3.3][3.3]orthocyclophane tris(acetal) **1**.

The symmetric structure of **1** is reflected in its ^1H NMR spectrum. An upfield shift of the aromatic protons in the two middle stacks of the structure ($\delta = 5.77$ in CDCl_3) is more pronounced than those of the two outer stacks ($\delta = 6.40$ – 6.62). Interestingly, however, this upfield shift cannot be explained sufficiently by a simple addition of effects arising from the anisotropy of two isolated facing benzene units, as evidenced by a comparison with the shift of the aromatic protons of the inner stack of the triple layered analogue **2** ($\delta = 5.90$ in CDCl_3).

The UV/Vis spectroscopic data gives the first evidence for a π – π interaction in **1**. The rigid layered orthocyclophane acetal **1** ($\lambda_{\text{max}} = 310$ nm) shows an absorption at a much longer wavelength than the corresponding flexible orthocyclophane ketone **13** (280 nm, which corresponds exactly to the λ_{max} value of 1,2,4,5-tetramethylbenzene). A comparison of the electronic spectra of the corresponding double-layered [3.3]orthocyclophane **3** ($\lambda_{\text{max}} = 286$ nm) and the triple-layered [3.3]orthocyclophane **2** ($\lambda_{\text{max}} = 300$ nm) with that of **1** shows a progressive, albeit small bathochromic shift in the absorption maxima. This is in contrast to the sesqui- and sesterbicyclo[2.2.2]octanes **4** and **5**, where the stacking of an additional benzene unit leads to no further shift of the absorption maximum.^[9c] Multilayered paracyclophanes, however, do show more pronounced bathochromic shifts.^[6]

A very intriguing feature of **1** which arises from the π – π through-space interaction in **1** can be found in its cyclic voltammogram. Thus, at -40°C , it can be oxidized reversibly to its monocation radical ($E_1 = 0.80$ V versus $[\text{Ag}|\text{AgNO}_3, 10^{-2}\text{M}$ in CH_3CN ^[14]]) followed by the reversible formation of its dication ($E_2 = 1.29$ V) (Figure 1). Under the conditions

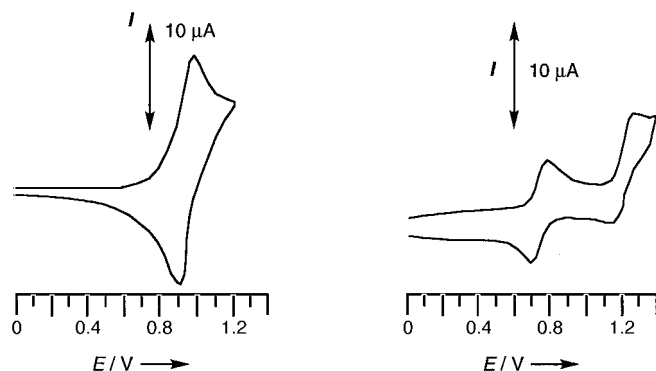


Figure 1. Cyclic voltammogram of orthocyclophanes **1** and **2**. Conditions: $c = 5 \times 10^{-5}\text{M}$ for **1** and $1 \times 10^{-4}\text{M}$ for **2** in $\text{CH}_2\text{Cl}_2/0.1\text{M}$ Bu_4NPF_6 , glassy carbon anode, $T = -40^\circ\text{C}$, $V = 100\text{ mV s}^{-1}$, E versus $[\text{Ag}|\text{AgNO}_3, 10^{-2}\text{M}$ in CH_3CN].^[14]

used ($c = 5 \times 10^{-5}\text{M}$ in CH_2Cl_2 , 0.1M Bu_4NPF_6 , $V = 100\text{ mV s}^{-1}$), the monocation radical is also formed reversibly at room temperature. Benzene itself cannot be oxidized reversibly, but instead undergoes polymerization upon oxidation.^[15] In fact, only with the oxidation of the sesterbenzobicyclo[2.2.2]octane **4** was the first reversible oxidation of a hydrocarbon consisting of only benzene π systems observed.^[9c] Both the radical cation as well as the dication of **1** were generated at similar

potentials to the corresponding cations of **4**. Moreover, consecutive stacking of benzene units in [3.3]orthocyclophanes leads to the stabilization of cationic charges, with the higher stacked systems undergoing oxidation more readily. Thus, triple-layered [3.3][3.3]orthocyclophane **2** shows a reversible oxidation wave at 1.02 V and a nonreversible oxidation to an unstable dication at 1.66 V. Double-layered [3.3]orthocyclophane **3** only shows one nonreversible oxidation wave at 1.52 V, which corresponds to the monocation radical.

The physical and chemical properties of the quadruple-layered [3.3]orthocyclophane **1** indicate that for this “saw-tooth” mode of stacking benzene units, the upper limit of exploiting π – π interaction in these molecules has not yet been reached. Further stacking of π systems in [3.3]orthocyclophane ladders of this type may well lead to stable cations of higher electronic charge.

Experimental Section

8: A mixture of **6** (810 mg, 1.8 mmol) and **7** (165 mg, 0.6 mmol) was added dropwise to a well stirred mixture of tetrabutylammonium bromide (TBABr; 97 mg, 0.3 mmol) in 5% aqueous NaOH (200 mL) and CH_2Cl_2 (25 mL). The resulting mixture was stirred for 6 h at room temperature, and then it was extracted with water (2×50 mL). The separated organic phase was dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 4/1) to yield **8** (270 mg, 80%) as colorless crystals; m.p. 225 – 228°C ; IR (KBr): $\tilde{\nu} = 1740$ (C=O), 1700 cm^{-1} (C=O); ^1H NMR (270 MHz, CD_2Cl_2): $\delta = 1.05$ – 1.90 (br, 4H), 2.60 – 3.20 (br, 4H, CH_2), 3.60 – 3.95 (br, 6H, COOCH_3), 4.40 – 4.70 (br, 4H), 7.08 – 7.35 (br, 6H, aryl); EI-MS (70 eV): m/z (%): 566 (26) $[[^{81}\text{Br}_2]\text{M}]^+$, 564 (52) $[[^{79}\text{Br}^{81}\text{Br}]\text{M}]^+$, 562 (27) $[[^{79}\text{Br}_2]\text{M}]^+$; elemental analysis calcd for $\text{C}_{25}\text{H}_{24}\text{Br}_2\text{O}_5$ (564.27): C 53.25, H 4.25; found: C 53.50, H 4.37.

10 and **11:** A solution of **8** (282 mg, 0.5 mmol) and **9** (140 mg, 0.8 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a well-stirred mixture of TBABr (64 mg, 0.2 mmol) in 20% aqueous NaOH (100 mL) and CH_2Cl_2 (50 mL). The resulting mixture was stirred for 24 h at room temperature. Water (2×50 mL) was then added, and the organic phase dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was separated by column chromatography on silica gel (CH_2Cl_2 /ethyl acetate, 4/1) to give hexamethyl *syn*-triketohexacarboxylate (**10**; 40 mg, 16%) and hexamethyl *anti*-triketohexacarboxylate (**11**; 110 mg, 44%).

10: M.p. 241 – 244°C ; IR (KBr) 1740 (C=O), 1700 cm^{-1} (C=O); ^1H NMR (270 MHz, CDCl_3): $\delta = 2.68$ – 3.58 (br, 24H, CH_2), 3.65 (brs, 18H, COOCH_3), 7.22 – 7.36 (br, 12H, aryl); EI-MS (70 eV): m/z (%): 978 (97) $[\text{M}]^+$; elemental analysis calcd for $\text{C}_{57}\text{H}_{54}\text{O}_{15} \cdot \text{H}_2\text{O}$ (997.05): C 68.69, H 5.42; found: C 68.86, H 5.94.

11: M.p. 300 – 320°C ; IR (KBr): $\tilde{\nu} = 1742$ (C=O), 1699 cm^{-1} (C=O); ^1H NMR (270 MHz, CDCl_3): $\delta = 2.78$ – 3.69 (br, 42H), 7.15 – 7.25 (br, 12H, aryl); EI-MS (70 eV): m/z (%): 978 (16) $[\text{M}]^+$; elemental analysis calcd for $\text{C}_{57}\text{H}_{54}\text{O}_{15}$ (979.04): C 69.96, H 5.52; found: C 69.74, H 5.59.

12: A mixture of **10** (50 mg, $5.1 \times 10^{-2}\text{ mmol}$) in ethanolic 10% KOH (70 mL, 1:1) was refluxed for 4 h. The reaction mixture was cooled, and then water (70 mL) and 3N HCl (140 mL) were added sequentially. The resulting mixture was left at 4°C for 12 h. The precipitate formed was filtered off and washed carefully with water to give the corresponding hexacarboxylic acid **10** ($\text{R} = \text{COOH}$, 40 mg, 88%). This diacid was heated in a pyrex tube at 320°C to give **12** (15 mg, 56%) as colorless crystals; m.p. 198 – 223°C ; IR (KBr): $\tilde{\nu} = 1700\text{ cm}^{-1}$ (C=O); ^1H NMR (270 MHz, CDCl_3): $\delta = 2.60$ – 2.95 (br, 24H, CH_2), 2.95 – 3.16 (br, 6H, CH), 6.95 – 7.15 (br, 12H, aryl); EI-MS (70 eV): m/z (%): 630 (100) $[\text{M}]^+$; elemental analysis calcd for $\text{C}_{48}\text{H}_{42}\text{O}_3$ (630.82): C 85.72, H 6.66; found: C 85.40, H 6.70.

13: Compound **11** (50 mg, $5.1 \times 10^{-2}\text{ mmol}$) was treated using the same procedure as for **12** to give **13** (21 mg, 64% yield for the two steps); m.p. 214 – 216°C ; IR (KBr): $\tilde{\nu} = 1700$ (C=O), 1490 , 1444 cm^{-1} ; ^1H NMR

(270 MHz, CDCl_3): δ = 2.60–3.11 (br, 30 H), 7.00 (brs, 4 H, aryl), 7.17 (brs, 8 H, aryl); EI-MS (70 eV): m/z (%): 630 (100) $[M]^+$; elemental analysis calcd for $\text{C}_{45}\text{H}_{42}\text{O}_3 \cdot 0.5\text{H}_2\text{O}$ (639.83): C 84.52, H 6.57; found: C 84.68, H 6.66.

1: A mixture of **13** (50 mg, $8.0 \cdot 10^{-2}$ mmol), *p*-toluenesulfonic acid (5 mg), and ethylene glycol (31 mg, 0.5 mmol) in a mixture of benzene/nitrobenzene (6 mL, 1/1) were refluxed for 48 h. The reaction mixture was then cooled, and the resulting precipitate was collected and washed carefully with hexane to give **1** (42 mg, 68%); m.p. 345–347 °C; IR (KBr): $\tilde{\nu}$ = 1103 cm^{-1} (C–O); ^1H NMR (270 MHz, CDCl_3): δ = 1.91–2.56 (m, 18 H), 2.83–3.31 (m, 8 H), 3.93–4.09 (m, 12 H, OCH_2), 5.77 (s, 4 H, aryl), 6.40–6.62 (m, 8 H, aryl); EI-MS (70 eV): m/z (%): 762 (17) $[M]^+$; elemental analysis calcd for $\text{C}_{51}\text{H}_{54}\text{O}_6 \times \text{H}_2\text{O}$ (781.00): C 78.48, H 6.92; found: C 78.46, H 7.02.

Received: February 24, 1998 [Z11512IE]
German version: *Angew. Chem.* **1998**, *110*, 2626–2628

Keywords: cations • cyclic voltammetry • cyclophanes • stacking interactions

and the reduction of the spirocyclopropane substituted compound^[12] to a bis-*gem*-dimethyl bridged compound (**14**, X = Y = CH_3) both lead to rigid layered [3.3]orthocyclophanes.



14

- [12] S. Mataka, M. Taniguchi, Y. Mitoma, T. Sawada, M. Tashiro, *J. Chem. Res. Synop.* **1997** 48–49; *J. Chem. Res. Miniprint* **1997**, 437–452.
- [13] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101215. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [14] $E^0[\text{Ag}|\text{AgNO}_3, (10^{-2} \text{ M in } \text{CH}_3\text{CN})] = +0.53 \text{ V}$ versus normal hydrogen electrode (NHE); see also: C. K. Mann, “Nonaqueous Solvents for Electrochemical Use” in *Electroanalytical Chemistry*, Vol. 3, (Ed.: A. J. Bard), Marcel Dekker, New York, **1969**, p. 64.
- [15] M. Dietrich, J. Mortensen, J. Heinze, *J. Chem. Soc. Chem. Commun.* **1986**, 1131–1132, and references therein.

- [1] T. Benzing, T. Tjivikua, J. Wolfe, J. Rebek, *Science* **1988**, *242*, 266; S. K. Burley, G. A. Petsko, *Science* **1985**, *229*, 23; S. Mataka, J. Ma, T. Thiemann, J. M. Rudziński, H. Tsuzuki, T. Sawada, M. Tashiro, *Tetrahedron* **1997**, *53*, 885–902; D. A. Evans, K. T. Chapman, D. Tan Hung, A. T. Kawaguchi, *Angew. Chem.* **1987**, *99*, 1197–1199; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1184–1186, and references therein.
- [2] A. V. Muehldorf, D. van Engen, J. C. Warner, A. D. Hamilton, *J. Am. Chem. Soc.* **1988**, *110*, 6561–6562; T. Ishi-i, T. Sawada, S. Mataka, M. Tashiro, T. Thiemann, *Chem. Ber.* **1996**, *129*, 289–296.
- [3] W. L. Jorgensen, D. L. Severance, *J. Am. Chem. Soc.* **1990**, *112*, 4768–4774, and references therein.
- [4] See D. J. Cram, R. H. Bauer, *J. Am. Chem. Soc.* **1959**, *81*, 5971–5977; L. A. Singer, D. J. Cram, *J. Am. Chem. Soc.* **1963**, *85*, 1080–1084.
- [5] Review: S. M. Rosenfeld, K. A. Choe in *Cyclophanes* (Eds.: P. M. Keehn, S. M. Rosenfeld), Academic Press, New York, **1983**.
- [6] Paracyclophanes show a bathochromic shift in their UV/Vis spectra relative to similarly substituted open-chain arenes. This effect is partly the result of the deformation of the aromatic system. D. Cram has shown that by shortening the ansachain of $[n]$ paracyclophanes a bathochromic shift can be observed as a consequence of the deformation of the aromatic ring: D. J. Cram, C. S. Montgomery, G. R. Knox, *J. Am. Chem. Soc.* **1966**, *88*, 515–525.
- [7] Nevertheless, the absorption spectra in multilayered [2.2]paracyclophanes show both a bathochromic and a hyperchromic shift with an increasing number of layers. This effect can be quite large relative to that seen in double-layered [2.2]paracyclophanes, and can only result from transannular π – π electronic interactions: T. Otsubo, S. Mizogami, J. Otsubo, Z. Tozuka, A. Sakagami, Y. Sakata, S. Misumi, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3519–3530; S. Misumi, *Multilayered Cyclophanes* in reference [5].
- [8] See also: F. Vögtle, *Cyclophane Chemistry—Synthesis, Structures and Reactions*, Wiley, Chichester, **1993**, pp. 57–58.
- [9] a) S. J. Cristol, D. C. Lewis, *J. Am. Chem. Soc.* **1967**, *89*, 1467–1487; b) H. Prinzbach, G. Sedelmeier, C. Krüger, R. Goddard, H.-D. Martin, R. Gleiter, *Angew. Chem.* **1978**, *90*, 297–305; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 271; c) W. Grimme, H. T. Kämmerling, J. Lex, R. Gleiter, J. Heinze, M. Dietrich, *Angew. Chem.* **1991**, *25*, 215–217; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 205–207; d) S. Mataka, K. Takahashi, T. Hirota, K. Takuma, H. Kobayashi, M. Tashiro, *J. Chem. Soc. Chem. Commun.* **1985**, 973–973.
- [10] a) S. Mataka, K. Takahashi, T. Mimura, T. Hirota, K. Takuma, H. Kobayashi, M. Yashiro, K. Imada, M. Kuniyoshi, *J. Org. Chem.* **1987**, *52*, 2653–2656; b) S. Mataka, Y. Mitoma, T. Sawada, M. Tashiro, *Tetrahedron Lett.* **1996**, *37*, 65–68; c) S. Mataka, Y. Mitoma, T. Thiemann, T. Sawada, M. Taniguchi, M. Kobuchi, M. Tashiro, *Tetrahedron* **1997**, *53*, 3015–3026.
- [11] Apart from the acetalization of the keto group, a 1,2-addition of a Grignard reagent to the keto group (**14**, X = OH, Y = CH_3 , C_6H_5)^[10a]

Solid-Phase Synthesis of Macrocyclic Systems by a Cyclorelease Strategy: Application of the Stille Coupling to a Synthesis of (*S*)-Zearalenone

K. C. Nicolaou,* Nicolas Winssinger, Joaquin Pastor, Fiona Murphy

In recent years combinatorial chemistry and solid-phase synthesis have emerged as powerful tools for the drug discovery process.^[1] Solid-phase synthesis is particularly useful for the construction of combinatorial libraries by virtue of the opportunity to adopt the powerful and elegant encoded split-pool methods^[2] as well as convenient purification procedures. Considering the importance of natural products to chemistry, biology, and medicine, we initiated a program directed at the development of solid-phase technologies suitable for the total synthesis of such molecules and of directed libraries of their analogues.^[3] Herein, we report a new solid-phase method for the construction of macrocycles by a novel cyclorelease mechanism^[4] that employs the Stille coupling,^[5] and its application to the total synthesis of (*S*)-zearalenone,^[6,7] a biologically active natural product.^[8] Currently, most solid-

[*] Prof. Dr. K. C. Nicolaou, N. Winssinger, Dr. J. Pastor, Dr. F. Murphy
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 619-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

[**] We thank Dr. D. H. Huang and Dr. G. Suizdak for assistance with the NMR spectroscopy and mass spectrometry, respectively. This work was supported by The Skaggs Institute for Chemical Biology, the National Institutes of Health USA, a fellowship from the Ministerio de Educación y Ciencia (Spain) (to J.P.), and grants from Merck, DuPont-Merck, and Schering Plough.

phase methods incorporate a heteroatom such as oxygen, sulfur, or nitrogen within a suitably designed protecting device that links the substrate to the polymer support.^[9] Release from the polymer is achieved by deprotecting the heteroatom which, however, remains as a vestigial stub in every library member (see Figure 1 A).

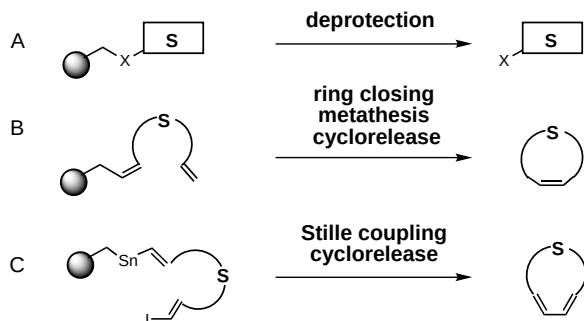
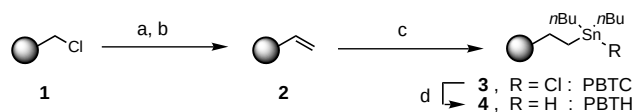


Figure 1. Release of substrate **S** from polymer.

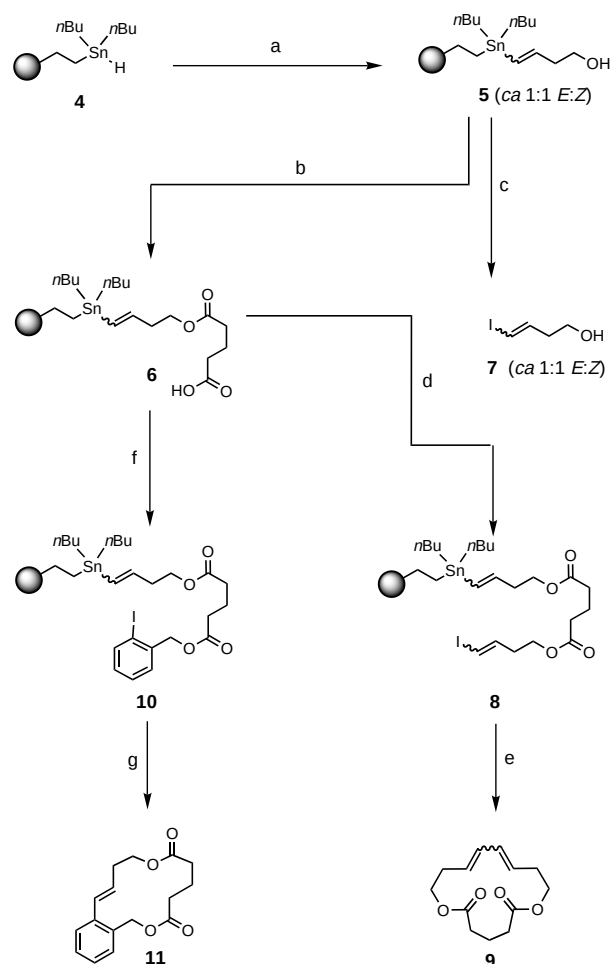
Recently, we applied the ring-closing metathesis in a cyclorelease mode to prepare an epothilone library (Figure 1 B).^[10] Applying the Stille coupling to cyclorelease reveals the strategy shown in Figure 1 C for which polymer-supported tin reagents are required. To this end, we prepared^[11] resin **3** (polystyrene-di-*n*-butyltin chloride, PBTC) and **4** (polystyrene-di-*n*-butyltin hydride, PBTH) as shown in Scheme 1.



Scheme 1. Synthesis of polymer-supported PBTC (**3**) and PBTH (**4**). Reagents and conditions: a) K_2CO_3 (10.0 equiv), DMSO, 145 °C, 15 h; b) $CH_2=PPh_3$ (2.0 equiv), THF, 23 °C, 8 h; c) nBu_2SnCl_2 (2.0 equiv), nBu_2SnH_2 (2.0 equiv), AIBN (0.05 equiv), hv, toluene, 0 °C, 4 h (90 % from **1**); d) $LiBH_4$ (4.0 equiv), THF, 23 °C, 4 h. AIBN = 2,2'-azobisisobutyronitrile.

Oxidation of Merrifield resin^[12] (**1**, Scheme 1) with K_2CO_3 in DMSO at 145 °C, followed by olefination of the resulting aldehyde gave polystyrene vinyl resin **2**, which was allowed to react with nBu_2SnHCl ^[13] (formed in situ from equimolar amounts of nBu_2SnH_2 and nBu_2SnCl_2) in the presence of AIBN (toluene, 0 °C) to afford PBTC (**3**) in 90 % overall yield.^[14] Reduction of **3** with $LiBH_4$ furnished the polymer-supported tin hydride **4** (PBTH).

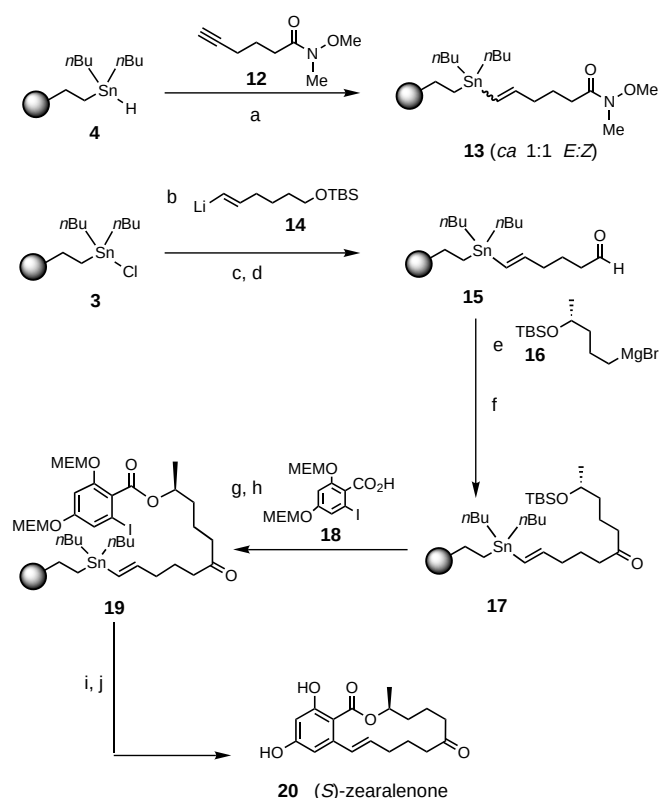
The utilization of PBTH (**4**) in solid-phase synthesis and the proof of concept for the present strategy is demonstrated in Scheme 2. Thus, tin hydride **4** added across the acetylenic bond of 3-butynol (AIBN, 100 °C) to afford a mixture of **5** (*E*:*Z* ca. 1:1),^[15] from which vinyl iodide **7** (*E*:*Z* ca. 1:1) was generated by addition of I_2 .^[16] Coupling of **5** with glutaric anhydride in the presence of 4-DMAP and Et_3N resulted in the formation of **6** to which was attached the vinyl iodide **7** or 2-iodobenzyl alcohol by DCC coupling, furnishing conjugates **8** and **10**, respectively. Finally, cyclorelease was induced by the action of $[Pd(PPh_3)_4]$ catalyst, leading to macrocyclic systems



Scheme 2. Solid-phase synthesis of model macrocyclic systems **9** and **11** by a cyclorelease mechanism that employs the Stille coupling strategy. Reagents and conditions: a) 3-butynol (4.0 equiv), AIBN (0.05 equiv), toluene, 100 °C, 8 h, (94 % from **3**); b) glutaric anhydride (4.0 equiv), 4-DMAP (0.1 equiv), Et_3N (5.0 equiv), CH_2Cl_2 , 23 °C, 15 h (96 %). c) I_2 (1.1 equiv), THF, 23 °C, 2 h (quant.); d) **7** (4.0 equiv), DCC (4.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2 , 23 °C, 18 h (93 %); e) $Pd(PPh_3)_4$ (0.10 equiv), toluene, 100 °C, 48 h (56 % as a 1:1:2 *EE*:*ZZ*:*EZ* mixture); f) 2-iodobenzyl alcohol (4.0 equiv), DCC (4.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2 , 23 °C, 15 h (95 %); g) $Pd(PPh_3)_4$ (0.10 equiv), toluene, 100 °C (51 % based on loading of *E* isomer). 4-DMAP = 4-dimethylaminopyridine; DCC = 1,3-dicyclohexylcarbodiimide.

9 (56 % from **8**) and **11** (51 % from **10** based on the loading of the *E* isomer). Notable was the absence of the *Z* isomer of **11** from the cyclorelease of **10**, and the isolation of a dimer (7 %) corresponding to **11** possessing one *Z* and one *E* double bond.

The use of the polymer-supported tin reagents **3** and **4** and the demonstration of the power of the method in natural product synthesis is shown in Scheme 3 with the total synthesis of (*S*)-zearelenone (**20**). The adopted strategy (Figure 2) was demonstrated in solution by Stille and Hegedus in 1991.^[6] While the addition of PBTH (**4**) to the acetylenic Weinreb amide **12** gave a stoichiometric mixture of *Z*:*E* vinyltin conjugates **13**, the displacement of the chloride from PHTC (**3**) by lithium reagent **14**^[17] led, after deprotection and oxidation, exclusively to the *E*-vinyltin polymer **15**. Addition of Grignard reagent **16**^[17] to the Weinreb amide **13** or to aldehyde **15** followed by Corey–Kim oxidation gave **17**,



Scheme 3. Solid-phase total synthesis of (S)-zearealene (20) by a cyclorelease mechanism that employs the Stille coupling strategy. Reagents and conditions: a) **12** (4.0 equiv), AIBN (0.05 equiv), toluene, 100 °C, 4 h (90 % from **3**); b) **14** (3.0 equiv), THF, −78 → 23 °C, 4 h (87 %); c) TBAF (10.0 equiv), THF, 23 °C, 5 h (94 %); d) NCS (4.0 equiv), Me₂S (5.0 equiv), 0 °C, 15 min; then add resin, 0 °C, 1 h; Et₃N (6.0 equiv) 0 → 23 °C, 0.5 h; e) **16** (2.0 equiv), THF, 0 → 23 °C, 4 h (92 %, 2 steps); f) NCS (4.0 equiv), Me₂S (5.0 equiv), 0 °C, 15 min; then add resin, −40 °C, 1.5 h; Et₃N (6.0 equiv), −40 → 23 °C, 0.5 h (97 %). g) TBAF (10.0 equiv), THF, 23 °C, 13 h; h) **18** (3.0 equiv), PPh₃ (3.0 equiv), DEAD (4.0 equiv), 0 → 23 °C, 6 h (76 %, two steps); i) Pd(PPh₃)₄ (0.10 equiv), toluene, 100 °C, 48 h (54 %); j) 2:1 THF/HCl aq. (5 %), 23 °C, 5 days (80 %). TBAF = tetra-*n*-butylammonium fluoride; NCS = *N*-chlorosuccinimide; DIAD = diisopropyl azodicarboxylate.

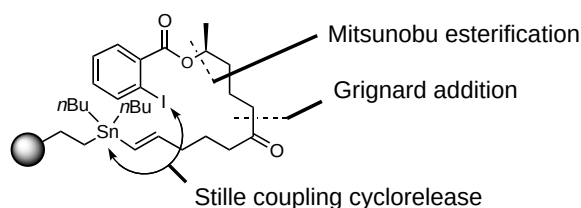


Figure 2. Bond disconnections for the solid-phase synthesis of (S)-zearealene (20) by a cyclorelease mechanism that employs the Stille coupling strategy.

which was desilylated and coupled to carboxylic acid **18**^[17] to afford the desired precursor **19**. As expected, cyclorelease took place smoothly upon exposure of **19** to [Pd(PPh₃)₄] catalyst to afford, after acid-induced deprotection,^[6] (S)-zearealene (**20**). Similarly to the previous case (**10** → **11**), the cyclorelease of the *Z* isomer of zearealene was not observed. Selected physical properties of several of the compounds synthesized here are given in Table 1.

The described solid-phase chemistry extends the utility of the cyclorelease strategy to the synthesis of complex macrocycles, including natural products, by adding the Stille coupling to the repertoire of applicable reactions. This efficient method should facilitate the construction of compound libraries of such systems for biological screening and other uses.

Received: April 14, 1998 [Z11732IE]

German version: *Angew. Chem.* **1998**, *110*, 2677–2680

Keywords: cyclizations • natural products • solid-phase synthesis • Stille coupling • synthetic methods

- [1] For reviews, see: a) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436–2487; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288–2337; b) L. A. Thompson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555–617; c) M. A. Gallop, R. W. Barret, W. J. Dower, S. P. Foder, E. M. Gorden, *J. Med. Chem.* **1994**, *37*, 1233–1281; d) E. M. Gorden, R. M. Barret, W. J. Dower, S. P. Foder, M. A. Gallop, *ibid.* **1994**, *37*, 1385–1405; e) W. H. Moos, G. D. Green, M. R. Pavia, *Annu. Rep. Med. Chem.* **1993**, *28*, 315–324.
- [2] For general references, see: a) J. J. Baldwin, I. Henderson in *Synthesis of Encoded Small Molecule Combinatorial Libraries* (Ed.: J. P. Delvin), Dekker, New York, NY, **1997**; b) A. W. Czarnick, *Curr. Opin. Chem. Biol.* **1997**, *1*, 60–66; c) X. Y. Xiao, C. Zhao, H. Potash, M. P. Nova, *Angew. Chem.* **1997**, *109*, 799–801; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 780–782.
- [3] For references relating to non-oligomeric natural product synthesis on solid phase, see: a) K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarbia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268–272; b) S. Chen, K. D. Janda, *J. Am. Chem. Soc.* **1997**, *119*, 8724–8725.
- [4] For previous examples of cyclorelease, see: a) X. Beebe, N. E. Schore, M. J. Kurth, *J. Am. Chem. Soc.* **1992**, *114*, 10061–10062; b) S. H. Dewitt, J. S. Kiely, C. J. Stankovic, M. C. Schroeder, D. M. R. Cody, M. R. Pavia, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909–6913. For carbon–carbon bond cyclorelease, see: c) J. H. van Maarseveen, J. A. J. den Hartog, V. Engelen, E. Finner, G. Visser, C. G. Kruse, *Tetrahedron Lett.* **1996**, *37*, 8249–8252; d) A. D. Piscopio, J. F. Miller, K. Koch, *ibid.* **1997**, *38*, 7143–7146; reference [3a]; e) M. R. Gowravaram, M. A. Gallop, *ibid.* **1997**, *38*, 6973–6976.
- [5] a) J. K. Stille, *Pure Appl. Chem.* **1985**, *57*, 1771–1780; b) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–520; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; c) V. Farina, V. Krishnamurthy, W. Scott, *Org. React. (N.Y.)* **1995**, *50*, 1–676.
- [6] K. Kalivretanos, J. K. Stille, L. S. Hegedus, *J. Org. Chem.* **1991**, *56*, 2883–2894.
- [7] See the following references and the references therein: a) M. T. Shipchandler, *Heterocycles* **1975**, *3*, 471–476; b) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, N. L. Weber, *Tetrahedron*, **1968**, *24*, 2443–2454; c) E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616; d) S. Masamune, S. Kamata, W. Schilling, *ibid.* **1975**, *97*, 3515–3516; e) T. Takahashi, K. Kasuga, M. Takahashi, J. Tsuji, *ibid.* **1979**, *101*, 5072–5073.
- [8] S. Omura, *Macrolide Antibiotics*, Academic Press, New York, **1984**.
- [9] B. J. Backes, J. A. Ellman, *Curr. Opin. Chem. Biol.* **1997**, *1*, 86–93.
- [10] K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, N. P. King, R. M. V. Finlay, P. Giannakakou, P. Verdier-Pinard, E. Hamel, *Angew. Chem.* **1997**, *109*, 2181–2187; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097–2103.
- [11] While the preparation of polymer-supported organotin reagents **3** and **4** have been reported on a macroporous resin by Neumann et al., the authors were unsuccessful in their attempts to prepare it on a 2 % cross-linked resin: a) M. Peterseim, W. P. Neumann, *React. Polym.* **1993**, *20*, 189–205; b) U. Gerigk, M. Gerlach, W. P. Neumann, R. Vieler, V. Weintritt, *Synthesis* **1990**, 448–452. For some applications of

Table 1. Selected physical properties of compounds **4**, **7**, **9**, **11**, **13**, and **20**.

4: Infrared analysis of the resin revealed an intense Sn–H stretching absorption at 1802 cm^{−1}.

7: R_f = 0.28 (silica gel, EtOAc/hexane, 1:3); FT-IR (neat) $\tilde{\nu}_{\max}$ = 3332, 2942, 2878, 1606, 1422, 1216, 1045, 944 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 6.54 (dt, J = 14.5, 7.0 Hz, 1H, CH=CHI, *E* isomer), 6.37 (dt, J = 7.5, 1.0 Hz, 1H, CH=CHI, *Z* isomer), 6.28 (dt, J = 7.5, 7.0 Hz, 1H, CH=CHI, *Z* isomer), 6.17 (dt, J = 14.5, 7.0 Hz, 1H, CH=CHI, *E* isomer), 3.75 (t, J = 6.5 Hz, 2H, CH₂O, *Z* isomer), 3.68 (t, J = 6.5 Hz, 2H, CH₂O, *E* isomer), 2.44 (dtd, J = 7.0, 6.5, 1.0 Hz, 2H, CH₂CH=CHI, *Z* isomer), 2.33 (dtd, J = 7.0, 6.5, 1.0 Hz, 2H, CH₂CH=CHI, *E* isomer); ¹³C NMR (125 MHz, CDCl₃): δ = 142.7, 137.6, 84.8, 77.3, 60.9, 60.8, 39.1, 38.1.

9: Compound **9** was obtained as a 1:1:2 mixture of *EE*:*ZZ*:*EZ* isomers. (*EE*)-**9**: R_f = 0.51 (silica gel, EtOAc/hexane, 1:3); FT-IR (neat) $\tilde{\nu}_{\max}$ = 2991, 2961, 2931, 1736, 1412, 1378, 1210, 1159, 1092, 1022, 1000, 863, 802 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 5.94–5.86 (m, 2H, CH=CH–CH=CH), 5.41–5.29 (m, 2H, CH=CH–CH=CH), 4.22 (t, J = 5.5 Hz, 4H, CH₂O), 2.37 (t, J = 6.0 Hz, 4H, CH₂COO), 2.25 (dt, J = 6.0, 5.5 Hz, 4H, CH₂CH=CH), 1.75 (qt, J = 6.0 Hz, 2H, CH₂CH₂COO); ¹³C NMR (125 MHz, CDCl₃): δ = 173.0, 133.5, 128.0, 60.8, 33.9, 31.3, 18.8; HRMS (FAB) calcd for C₁₃H₁₈O₄ [M⁺Na⁺]: 239.1283; found: 239.1279.

(*ZZ*)-**9**: R_f = 0.42 (silica gel, EtOAc/hexane, 1:3); FT-IR (neat) $\tilde{\nu}_{\max}$ = 2918, 1732, 1697, 1650, 1556, 1536, 1519, 1452, 1241, 1150 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 6.45–6.39 (m, 2H, CH=CH–CH=CH), 5.46–5.40 (m, 2H, CH=CH–CH=CH), 4.22 (m, 2H, CH₂O), 4.09 (m, 2H, CH₂O), 2.39–2.31 (m, 8H, CH₂CH=CH, CH₂COO), 1.84 (qt, J = 6.5 Hz, 2H, CH₂CH₂COO); ¹³C NMR (125 MHz, CDCl₃): δ = 172.9, 127.8, 126.6, 62.2, 32.0, 31.6, 27.7, 22.6, 14.1; HRMS (FAB) calcd for C₁₃H₁₈O₄ [M⁺Na⁺]: 261.1103; found: 261.1110.

(*EZ*)-**9**: R_f = 0.40 (silica gel, EtOAc/hexane, 1:3); FT-IR (neat) $\tilde{\nu}_{\max}$ = 2955, 1732, 1454, 1382, 1248, 1150, 1063 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 6.33 (ddd, J = 15.0, 10.5, 2.5 Hz, 1H, CH=CH–CH=CH), 6.11 (dd, J = 10.5, 10.5 Hz, 1H, CH=CH–CH=CH), 5.62 (dt, J = 15.0, 7.5 Hz, 1H, CH=CH–CH=CH), 5.34 (dt, J = 10.5, 7.5 Hz, 1H, CH=CH–CH=CH), 4.20–4.17 (m, 4H, CH₂O), 2.47–2.43 (m, 2H, CH₂CH=CH), 2.42–2.37 (m, 2H, CH₂CH=CH), 2.37 (t, J = 7.5 Hz, CH₂COO), 2.34 (t, J = 7.5 Hz, CH₂COO), 1.93–1.87 (m, 2H, CH₂CH₂COO); ¹³C NMR (125 MHz, CDCl₃): δ = 172.6, 172.5, 131.7, 130.6, 128.8, 126.0, 62.6, 62.5, 33.5, 33.3, 32.7, 27.5, 20.5, 14.1; HRMS (FAB) calcd for C₁₃H₁₈O₄ [M⁺Na⁺]: 261.1103; found: 261.1109.

11: R_f = 0.30 (silica gel, EtOAc/hexane, 1:3); FT-IR (neat) $\tilde{\nu}_{\max}$ = 2947, 1731, 1242, 1146, 964, 752 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 7.42 (d, J = 8.0 Hz, 1H, ArH), 7.33 (ddd, J = 8.0, 8.0, 2.5 Hz, 1H, ArH), 7.27–7.21 (m, 2H, ArH), 6.64 (d, J = 15.5 Hz, 1H, ArCH=CHCH₂), 6.05 (dt, J = 15.5, 7.0 Hz, 1H, ArCH=CHCH₂), 5.13 (s, 2H, PhCH₂O), 4.22 (m, 2H, CH₂CH₂O), 2.53 (dt, J = 7.0, 5.0 Hz, 2H, CH=CHCH₂), 2.44 (dd, J = 6.5, 6.0 Hz, 2H, CH₂COO), 2.37 (dd, J = 6.5, 6.0 Hz, 2H, CH₂COO), 2.03–1.96 (m, 2H, COCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃): δ = 173.2, 172.6, 138.6, 132.2, 130.7, 130.1, 129.3, 129.1, 127.2, 127.1, 65.7, 62.9, 32.9, 32.4, 31.4, 20.0; HRMS (FAB) calcd for C₁₆H₁₈O₄ [M⁺Na⁺]: 297.1103; found: 297.1109.

13: Iodonolysis of resin **13** afforded an inseparable *E*:*Z* (1:1) mixture of the corresponding vinyl iodide. R_f = 0.22 (silica gel, EtOAc-hexane, 1:3); FT-IR (neat) $\tilde{\nu}_{\max}$ = 2934, 1666, 1416, 1385, 1178, 996 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 6.45 (dt, J = 14.5, 7.0 Hz, 1H, CH=CHI, *E* isomer), 6.21 (m, 1H, CH=CHI, *Z* isomer), 6.16 (dt, J = 7.5, 7.0 Hz, 1H, CH=CHI, *Z* isomer), 6.00 (dt, J = 14.5, 1.5 Hz, 1H, CH=CHI, *E* isomer), 3.66 (s, 3H, OCH₃), 3.65 (s, 3H, OCH₃), 3.16 (s, 3H, NCH₃), 3.15 (s, 3H, NCH₃), 2.45 (t, J = 7.0 Hz, 2H, CH₂CON), 2.40 (m, 2H, CH₂CON), 2.18 (dt, J = 7.0, 7.0 Hz, 2H, CH₂CH=CHI, *Z* isomer), 2.03 (dtd, J = 7.0, 7.0, 1.5 Hz, 2H, CH₂CH=CHI, *E* isomer), 1.76 (qt, J = 7.0 Hz, 2H, CH₂CH₂CH₂), 1.72 (qt, J = 7.0 Hz, 2H, CH₂CH₂CH₂); ¹³C NMR (125 MHz, CDCl₃): δ = 145.7, 140.6, 83.1, 75.2, 61.2, 35.4, 34.2, 23.0, 22.8; HRMS (FAB) calcd for C₈H₁₄INO₂ [M⁺]: 284.0148; found: 284.0158.

(*S*)-Zearalenone (**20**): R_f = 0.45 (silica gel, EtOAc/hexane, 1:1); $[\alpha]_D^{25}$ = −124.2 (c = 0.5, MeOH)^[7a] $[\alpha]_D^{24}$ = −134 (c = 1.0, MeOH); FT-IR (neat) $\tilde{\nu}$ = 3421, 2938, 1700, 1648, 1611, 1577, 1452, 1355, 1314, 1260, 1201, 1170, 1124, 1018, 970 cm^{−1}; ¹H NMR (500 MHz, CDCl₃): δ = 10.10 (s, 1H, ArOH), 7.00 (dd, J = 15.5, 1.5 Hz, 1H, CH=CHAr), 6.41 (d, J = 2.5 Hz, 1H, ArH), 6.35 (d, J = 2.5 Hz, 1H, ArH), 5.67 (ddd, J = 15.5, 10.5, 3.5 Hz, 1H, CH=CHAr), 4.98 (m, 1H, CHOCOAr), 2.86 (ddd, J = 18.5, 12.0, 1.0 Hz, 1H), 2.60 (m, 1H), 2.36 (m, 1H), 2.21–2.10 (m, 4H), 1.80–1.70 (m, 2H), 1.67–1.61 (m, 2H), 1.49 (m, 1H), 1.36 (d, J = 6.5 Hz, 3H, C(CH₃)OCOAr); ¹³C NMR (125 MHz, CDCl₃): δ = 211.8, 171.3, 165.4, 160.6, 144.0, 133.2, 132.4, 108.4, 102.4, 73.4, 42.9, 36.7, 34.7, 31.0, 22.3, 21.0, 20.9, 20.8; HRMS (FAB) calcd for C₁₈H₂₂O₅ [M⁺]: 319.1545; found: 319.1555. The synthetic zearalenone **20** was identical (¹H, ¹³C, TLC) to an authentic sample purchased from Aldrich.

polymer supported organotin reagents, see: H. Kuhn, W. P. Neumann, *Synlett* **1994**, 123–124; and M. Gerlach, F. Jordens, H. Kuhn, W. P. Neumann, M. Peterseim, *J. Org. Chem.* **1991**, 56, 5971–5972.

[12] J. M. Frechet, C. Schuerch, *J. Am. Chem. Soc.* **1971**, 93, 492–496. The reported procedure employed NaHCO₃ rather than K₂CO₃.

[13] W. P. Neumann, J. Pedain, *Tetrahedron Lett.* **1964**, 2461–2465.

[14] The yield was calculated based on the mass gain of the polymer. All subsequent yields are based on the amount of compound recovered upon iodolysis from the resin.

[15] The ratios of polymer bound vinyl tin isomers were extrapolated from the ratio of vinyl iodide isomers obtained upon iodolysis.

[16] The preparation of spectroscopically homogeneous vinyl iodide **7** was carried out on a 1–10-mmol scale by a) titrating vinyl tin resin **5** with a THF iodine solution slightly beyond the end point (ca. 1.1 equiv) and b) diluting with Et₂O and washing with saturated aqueous Na₂S₂O₃.

[17] The spectroscopic characteristics of compounds **14**, **16**, and **18** were identical to those previously reported.^[6]