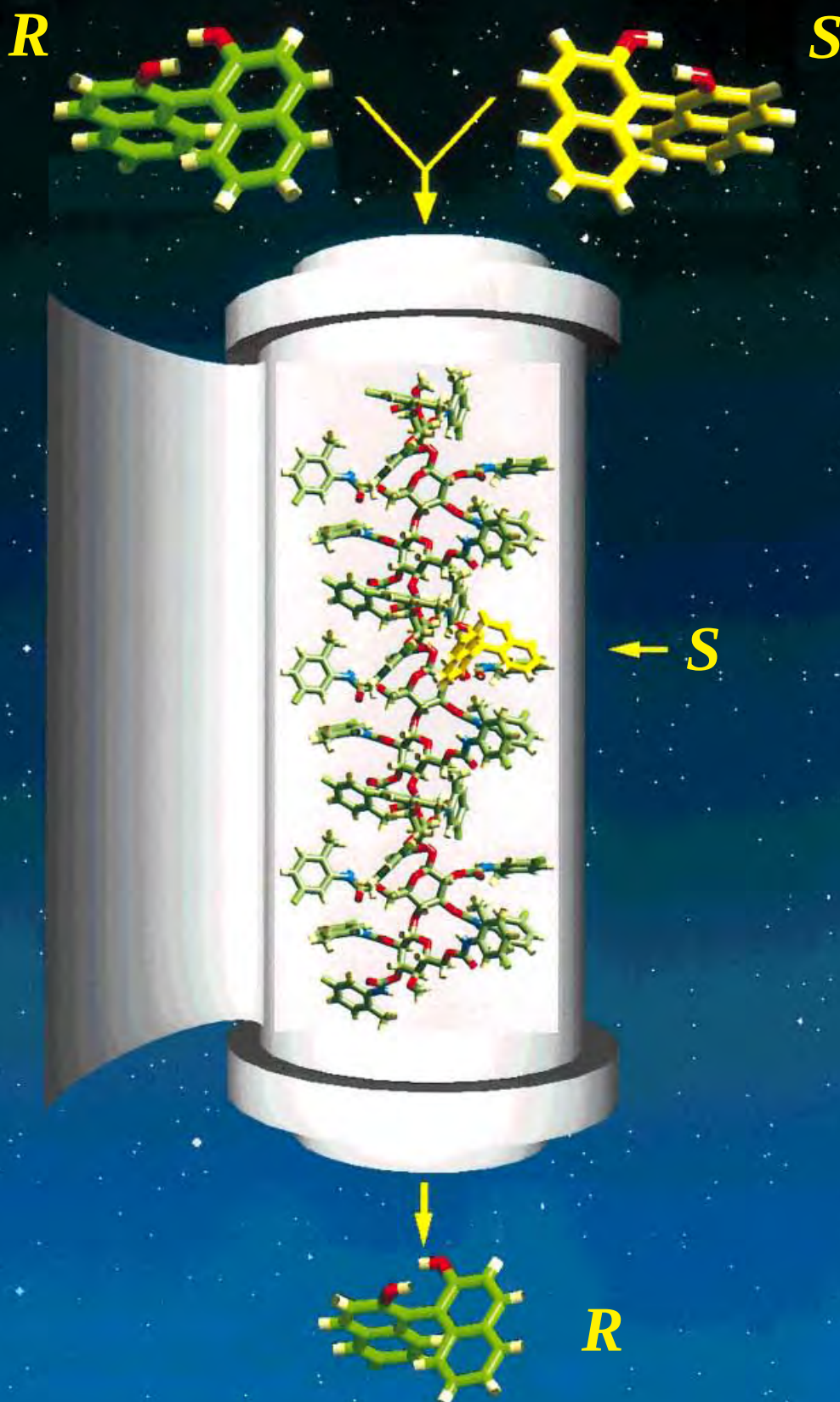




**Insight into the separation of enantiomers
by HPLC on polysaccharide derivatives**

Polysaccharide Derivatives for Chromatographic Separation of Enantiomers

Yoshio Okamoto* and Eiji Yashima

In living systems, chirality is a critical factor. However, this fact had frequently been ignored because enantiomer separations were very difficult and laborious, and most synthetic chiral drugs were therefore commercialized as racemates. In the past two decades, this situation has significantly changed because chromatographic enantioseparations, particularly by high-performance liquid chromatography (HPLC), have been markedly improved. This resolution procedure has already been recognized in many fields as one of the most useful methods for the analysis and separation of enantiomers. Now, most racemates appear to be resolved by liquid chro-

matography with commercially available chiral stationary phases. Among them, polysaccharide-based phases such as cellulose esters as well as phenylcarbamates of cellulose and amylose are some of the most popular ones. These can be used to resolve a wide range of racemates including aliphatic and aromatic compounds with or without functional groups and many drugs from an analytical to a preparative scale. These polysaccharide phases offer a great chance to resolve enantiomers of interest. Although the mechanism for discrimination between enantiomers on polysaccharide phases has not yet been satisfactorily elucidated, some interesting

approaches have been performed by chromatographic, computational, and spectroscopic studies. Mechanistic studies at a molecular level are of great importance and interest from the viewpoint of molecular recognition, which will provide a chance to develop a more efficient polysaccharide-based chiral stationary phase. This review focuses on the direct separation of enantiomers on polysaccharide derivatives after providing a brief historical background.

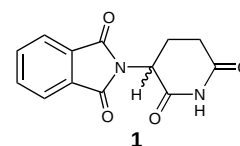
Keywords: chirality • enantiomeric resolution • liquid chromatography • molecular recognition • polysaccharides

1. Introduction

In 1980 G. Blaschke reported the first comprehensive review of chromatographic enantioseparation entitled "Chromatographic Resolution of Racemates" in this journal.^[1] At that time there was no chiral stationary phase (CSP) for high-performance liquid chromatography (HPLC) commercially available, and liquid chromatography (LC) was mostly used to resolve enantiomers for preparative, but not for analytical, purposes. The chirality of drugs was frequently neglected, and most chiral drugs were used as racemates. Nevertheless, Blaschke et al. succeeded in resolving many drugs using optically active polyacrylamide gels on a preparative scale and evaluated the different pharmacological behaviors between the enantiomers.^[1] For the first time, they resolved ($\pm$)-thalidomide (**1**), which had been used as a hypnotic drug and sedative under the name Contergan and induced a tragedy owing to its potent teratogenicity. They reported that the

teratogenic action may be caused only by the *S* isomer, whereas the *R* isomer may not show any teratogenic behavior, even at high doses.^[2] Although this conclusion remains controversial, because each enantiomer racemizes at physiological pH or after injection into rabbits,^[3] this is one of the key studies through which people recognized the importance of evaluating the difference in the pharmacological behaviors of both enantiomers of a drug.

As Blaschke predicted in 1980, chromatographic enantioseparations, and in particular resolution by HPLC, have significantly advanced in the past two decades, and are now generally recognized in many fields of science dealing with chiral compounds as one of the most powerful methods available for obtaining both pure enantiomers and for determining enantiomer composition.^[4] The determination of enantiomeric excess (*ee*) or optical purity was a laborious task before 1980, and there existed only three practical methods: polarimetric, NMR spectroscopic, and chromatographic (by HPLC or GC).^[5] The latter requires prior conversion of the enantiomers into diastereomeric derivatives. These methods could be used to estimate the enantiomeric excess for a limited number



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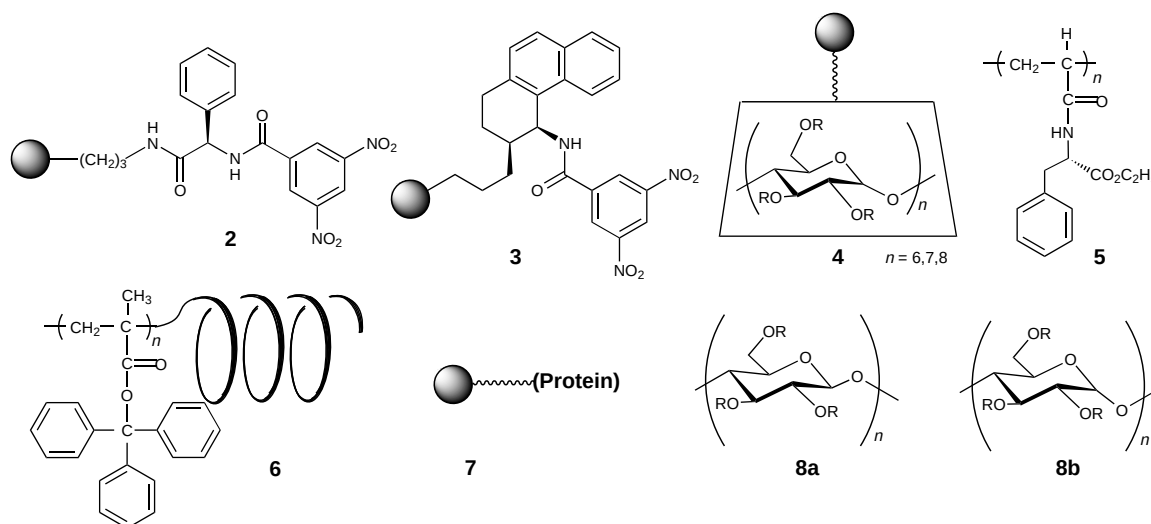


Figure 1. Typical chiral stationary phases for HPLC. The gray spheres represent silica gel.

of chiral compounds with a relatively low accuracy. However, most racemates now appear to be resolved by HPLC.^[6]

Particularly in the pharmaceutical industry, enantiomer separations by HPLC have become essential for the research and development of chiral drugs,^[3b, 7] since enantiomers of chiral drugs often exhibit marked differences in their biological activity in living systems.^[8] This forces regulatory agencies to issue the guidelines for the development of chiral drugs, which requires the submission of data on pharmacokinetics as well as physiological, toxicological, and metabolic activities of the drug enantiomers.^[9] As a result of these trends, marketing of chiral drugs as a single enantiomer is increasing.^[3b, 10] The annual sales of enantiomerically pure drugs reached 45 billion dollars in 1994 and will certainly increase in the future.^[3b, 10] The recent significant development of instruments coupled with sensitive detectors and high-resolution columns packed with efficient CSPs have made a major contribution to the advancement of HPLC as an effective technique for the separation of enantiomers.

The design and preparation of a CSP capable of effectively recognizing chirality is the key point in developing this chromatographic enantioseparation technique. Therefore, many CSPs have been prepared for HPLC, and more than 100 CSPs have been introduced on the market since 1981.

There are basically two types of CSPs (Figure 1): One type consists of small chiral molecules (e.g. **2–4**) which are usually immobilized on a support silica gel (“brush-” or “Pirkle-type” CSPs), and the other is derived from an optically active polymer (e.g. **5–8**) which can be used as a porous gel or with silica gel. A large number of brush-type CSPs have been prepared^[4, 11] since Pirkle developed the first commercially available CSP **2** in 1981.^[12] Typical examples of the latter CSPs are polyacrylamides (**5**) developed by Blaschke,^[1, 13] one-handed helical polymethacrylates (**6**),^[14] proteins (**7**),^[4b] and polysaccharide derivatives (**8**),^[15] which have been reviewed in detail elsewhere. Besides the CSPs described above, the cross-linked polymer gels with chiral cavities generated with a chiral molecule as a template by the molecular-imprinting

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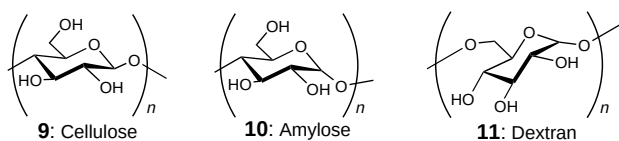
Eiji Yashima was born in Kyoto, Japan, in 1958. He received his Ph.D. from Osaka University. After spending five years at Kagoshima University, he joined Okamoto's group at Nagoya University in 1991 and was appointed Associate Professor in 1995 and Professor in 1998. His current research concerns synthesis of helical polymers with optical activity, enantioseparation by HPLC, and computational studies in the recognition of chirality.

technique are also interesting materials as CSPs and biometric sensors.^[16]

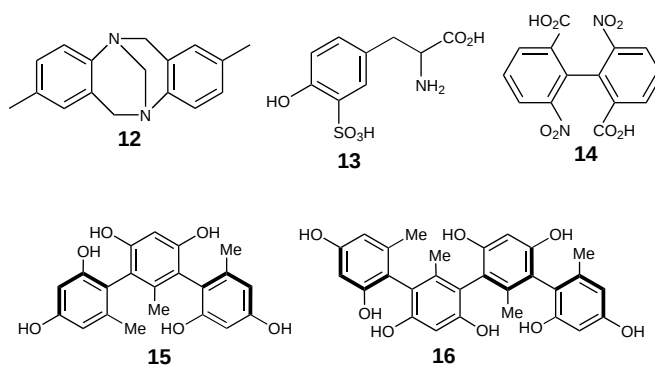
HPLC is also recognized as a valuable technique for the isolation and purification of chiral drugs and natural products on a large scale,^[17] and competes with other synthetic and separation methods such as asymmetric synthesis and kinetic resolution with biocatalysts.^[10b] This review focuses on the direct separation of enantiomers on polysaccharide-based CSPs, which appear to be among the most popular CSPs. The wide applicability and usefulness of the polysaccharide-based CSPs in the analysis and preparation of enantiomers are demonstrated by a comprehensive survey of the literature.^[6, 15] In particular, cellulose triacetate, tribenzoates, and phenyl-carbamate derivatives of cellulose and amylose show high abilities to recognize chirality. The mechanism for discrimination between enantiomers on polysaccharide phases has not yet been satisfactorily elucidated, but some interesting approaches to understanding the mechanism have been performed by chromatographic elucidation and computational and spectroscopic studies. These approaches should provide a guide for the selection of a suitable column and the development of a novel polysaccharide-based CSP. Therefore, the significance of the mechanistic studies on the polysaccharide-based CSPs are comprehensively reviewed here.

2. Historical Background of the Use of Polysaccharides and Their Derivatives in Enantiomer Separation

The earliest chromatographic resolutions of enantiomers were carried out with natural chiral adsorbents such as wool and polysaccharides. Polysaccharides are among the most important and abundant natural biopolymers with optical activity, and usually function as a structural unit or an energy source in living systems. The typical polysaccharides cellulose (**9**), starch (amylose) (**10**), and dextran (**11**) have a regular repeating unit of D-glucose throughout the polymers, and were used as chiral adsorbents for chromatographic enantiomer separation owing to their easy availability.



Resolution by enantioselective adsorption of racemic dyes containing phenylalanine or mandelic acid residues was attained for the first time on wool in the early 1920s.^[18] The first chromatographic resolution was reported by Henderson and Rule in 1938; they partially resolved racemic *p*-phenylenebis(iminocamphor) into its enantiomers on a column packed with the disaccharide lactose; however, the maximum optical purity of the fractions was only about 6%.^[19] Later Prelog and Wieland more efficiently resolved Tröger's base (**12**) with the same lactose column.^[20]



The first utilization of the chirality of polysaccharides appears to be demonstrated by Kotake et al.^[21] They separated several racemic amino acid derivatives, for instance **13**, into two spots of enantiomers by cellulose paper chromatography. Dalglish^[22a] extended this work and proposed the three-point rule.^[22] The rule that three simultaneous interactions are necessary for the discrimination of enantiomers in bimolecular systems has quite often been quoted for explaining the mechanism for discrimination between enantiomers, even nowadays. Furthermore, cellulose thin-layer chromatography^[23] and column liquid chromatography with cellulose and potato starch^[24] were developed and used for the resolution of racemates, usually amino acids.

Most of the early attempts at column chromatography were conducted with a low efficiency. Nevertheless, Musso demonstrated the usefulness of a native polysaccharide as a chiral adsorbent and succeeded in the complete resolution of atropisomeric biphenyl derivatives **14–16** on potato starch.^[25] Later Yuasa found that thoroughly purified native cellulose with a high degree of crystallinity [crystal form I; microcrystalline cellulose (Avicel)] can completely resolve amino acids such as tryptophan by liquid chromatography.^[26] Carboxymethylcellulose and Sephadex ion exchangers composed of a three-dimensional network of dextran cross-linked by epichlorohydrin effectively resolved many chiral metal complexes.^[27] In 1993 Wulff et al. prepared amylose immobilized on silica gel through enzymatic polymerization and found that the CSP resolved racemic menthol by HPLC.^[28] These materials do not seem to be practically useful CSPs because of their relatively low resolving abilities.

However, many water-soluble polysaccharides, including heparin and amylose, have recently been found to be effective chiral additives for high-performance capillary electrophoresis (HPCE).^[29] Although the enantioselectivity of the polysaccharides is not very high, the extremely high column efficiency of HPCE makes them capable of completely resolving many enantiomers including chiral drugs. This has been reviewed elsewhere.^[29, 30]

3. Enantiomer Separation by HPLC

Figure 2 shows a chromatogram for the resolution of Tröger's base (**12**, 0.06 mg) on amylose tris(3,5-dimethylphenylcarbamate) (ADMPC,^[43] **78**). The enantiomers elute at t_1 and t_2 with complete separation. Capacity factors k'_1 and k'_2

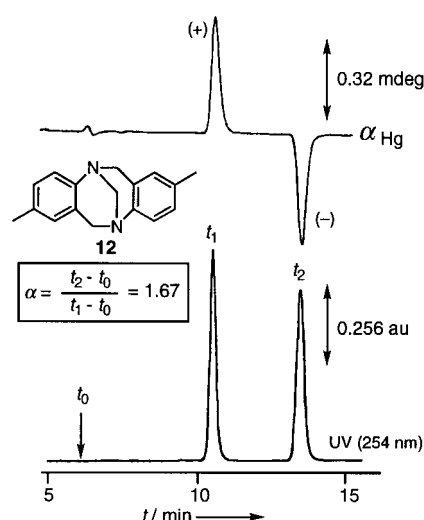


Figure 2. Chromatographic resolution of the enantiomers of **12** on ADMPC (**78**, Chiralpak AD). Column: 25×0.46 cm (inner diameter); eluent: hexane/2-propanol (9/1); flow rate: 0.5 mL min^{-1} . t = elution time, mdeg = $1 \times 10^{-3}^\circ$, au = absorbance units.

and separation factor α are determined as shown in the figure. From the α value the difference in Gibbs energy ($\Delta\Delta G^\ddagger$) at a given temperature can be calculated by using Equation (1). For the base-line separation of enantiomers, a separation factor of about 1.2 is needed, which corresponds to a difference in Gibbs energy of only $0.11 \text{ kcal mol}^{-1}$ between the CSP and the two enantiomers. In chromatographic enantioseparation, in addition to UV or a refractive index (RI) detector, a polarimetric or a circular dichroism (CD) detector,^[31] which are sensitive to only chirality, can also be used. This is a great advantage of HPLC over other analytical methods such as gas chromatography and NMR spectroscopy.

$$\Delta\Delta G^\ddagger = -RT \ln \alpha \quad (1)$$

3.1. Polysaccharide Esters as Chiral Stationary Phases

As mentioned above, native polysaccharides themselves are not practically useful CSPs in HPLC owing to their low enantioselectivities and mechanical properties. However, some modified polysaccharides show high chromatographic properties in the resolution of a variety of racemates.

3.1.1. Cellulose Triacetate as Chiral Stationary Phases

Cellulose triacetate was prepared by Hesse and Hagel in 1973 and is the first practical CSP derived from polysaccharides.^[32] They found that this derivative, which was prepared by heterogeneous acetylation of native microcrystalline cellulose (Avicel) in benzene, possesses interesting properties for resolving chiral compounds by LC, although the resolving power of a partially acetylated cellulose is poor.^[33] The triacetate is believed to preserve a structure closely related to that of native cellulose (form I) and has been called “microcrystalline cellulose triacetate” (CTA-I, **17**). CTA-I has been employed with ethanol/water as the eluent for the resolution

of various racemates, especially stereochemically interesting, nonpolar compounds and aromatic pharmaceuticals.^[1, 13, 15a] The high loading capacity of CTA-I makes it one of the most popular CSPs for a large-scale, medium-pressure separation by LC.^[17] Some stereochemically interesting compounds completely resolved on CTA-I are shown in Figure 3.^[13, 32b, 34]

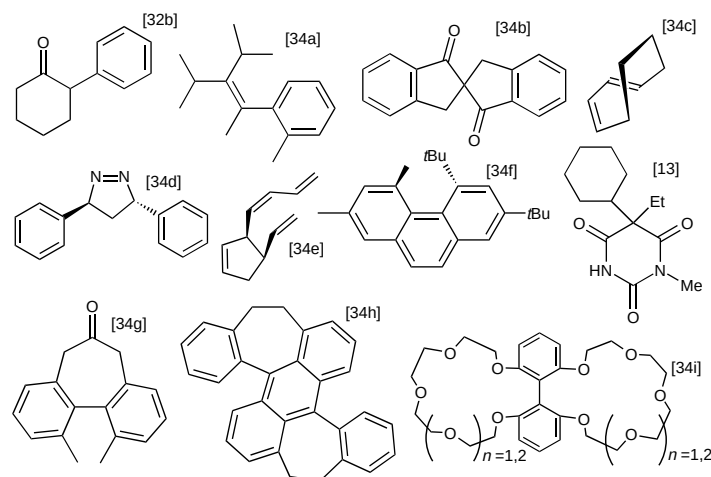
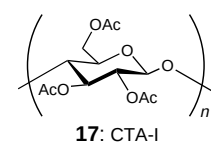
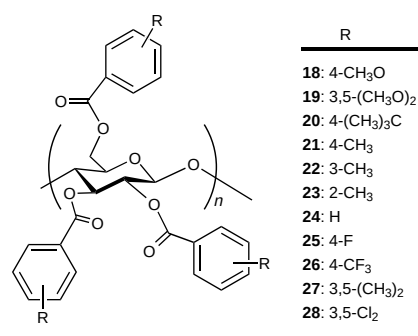


Figure 3. Compounds whose enantiomers were resolved on CTA-I (**17**) with large α values, along with literature references.

Hesse and Hagel pointed out that the microcrystallinity of CTA-I is essential for recognizing chirality. The resolving ability is substantially reduced and, in some cases, there is a reversal of the order in which enantiomers are eluted once CTA-I is dissolved in a solvent.^[32] However, when CTA-I was coated on silica gel for HPLC from a solution, the CTA afforded another useful CSP.^[35] As expected, the ability to recognize chirality was completely different from that of CTA-I. For instance, enantiomers of Tröger's base (**12**) eluted in reversed order on the two triacetate columns.^[35a] The new CSP has greater advantages than CTA-I in column efficiency and durability. These results have aroused wide interest in the use of derivatized polysaccharides such as benzoates and phenylcarbamates as CSPs for HPLC, and most polysaccharide-based CSPs so far developed have been prepared by coating on silica gel.

3.1.2. Cellulose Benzoates as Chiral Stationary Phases

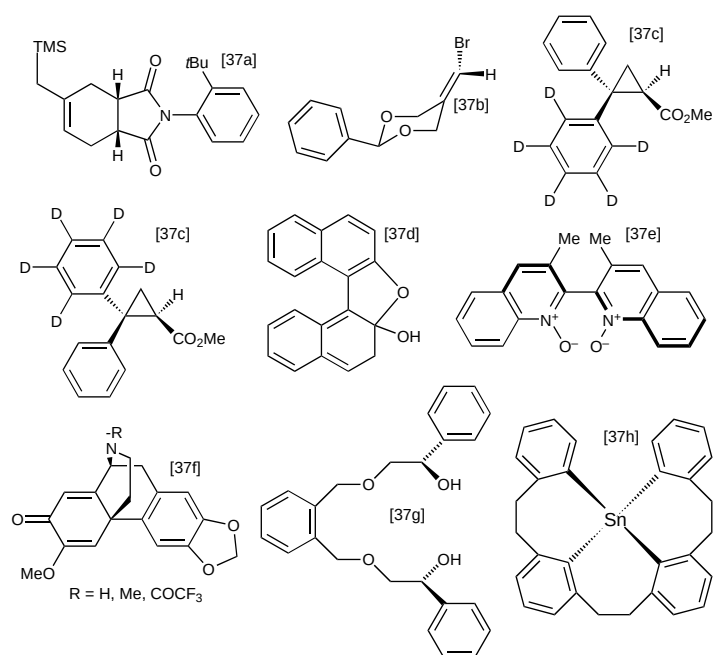
In Scheme 1 are shown the structures of cellulose tribenzoates prepared by our group, some of which are also useful CSPs when coated on silica gel. The effect of alkyl, halogen, trifluoromethyl, and methoxy substituents on the phenyl groups of cellulose tribenzoate (CTB, **24**, Chiralcel OB) was systematically studied.^[36] An inductive effect of the substituents was observed to affect enantioselectivity: The benzoate derivatives having electron-donating substituents, such as a methyl group, showed better recognition of chirality than those having electron-withdrawing substituents, such as a



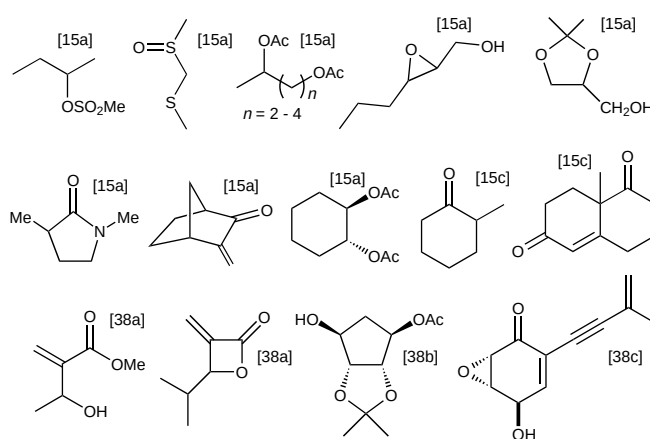
Scheme 1. Structures of cellulose tribenzoate derivatives.

halogen. However, the strongest electron donor, the methoxy group, was not suitable because of the high polarity of the substituent itself.

Among the benzoates, cellulose tris(4-methylbenzoate) (**21**, Chiralcel OJ) exhibits a high resolving power for various racemates, including drugs, and has become a practically useful CSP. Some stereochemically interesting compounds resolved on **21** are shown in Figure 4.^[37] Nonaromatic com-

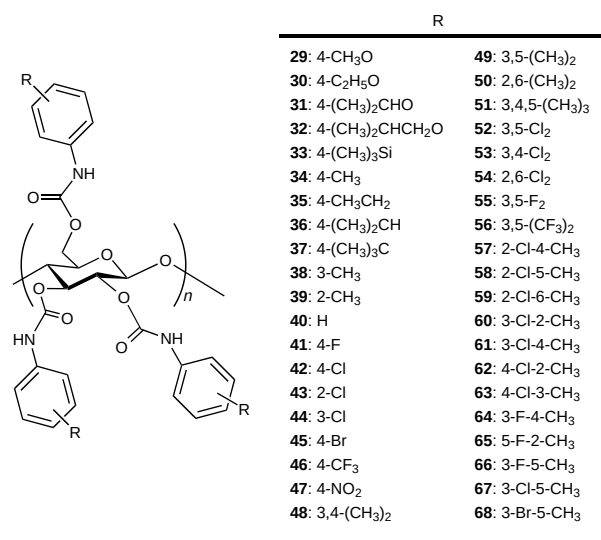
Figure 4. Compounds whose enantiomers were resolved on cellulose tris(4-methylbenzoate) (**21**, Chiralcel OJ), along with literature references.

pounds are also resolved well on CTB (Figure 5).^[15a,c, 38] Mannschreck et al.^[39] and Francotte et al.^[40] independently prepared spherical beads of cellulose tribenzoate derivatives and found them to be useful CSPs, particularly for preparative purposes because of their high loading capacity. Among these cellulose esters, triacetate, tribenzoate, tris(4-methylbenzoate), and tricinnamate have been on the market as CSPs. Tribenzoates of amylose show a low ability to recognize chirality.^[36]

Figure 5. Nonaromatic compounds whose enantiomers were resolved on CTB (**24**, Chiralcel OB), along with literature references.

3.2. Phenylcarbamates of Cellulose and Amylose as Chiral Stationary Phases

We prepared a series of cellulose tris(phenylcarbamate) derivatives (Scheme 2) by the reaction of microcrystalline cellulose (Avicel) with substituted phenyl isocyanates.^[15g, 41]



Scheme 2. Structures of cellulose trisphenylcarbamate derivatives.

They are among the most thoroughly investigated polysaccharide-based CSPs with respect to chromatographic enantioseparation and the mechanism for discrimination between enantiomers. They can resolve a wide range of racemates having various functional groups, although their resolving abilities depend greatly on the substituents on the phenyl groups.

The results for the resolution of ten racemates (**12**, **69**–**77**; acac = acetylacetonate) on *para*- or *meta*-substituted derivatives are presented in Table 1. Most of the CSPs listed in Table 1 can separate all of the racemates, depending on the substituents. Generally, substitution with an electron-donating methyl group or an electron-withdrawing halogen at the *meta* and/or *para* position improves the resolving ability for

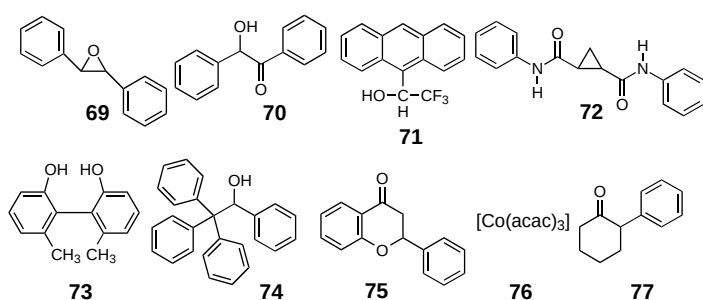
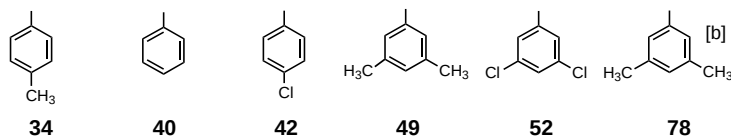


Table 1. Separation factors (α) in the resolution of racemates of **12** and **69–77** on phenylcarbamate derivatives of cellulose and amylose.^[a]

CSP:



Racemate

Racemate	12	69	70	71	72	73	74	75	76	77
12	1.48 (+)	1.37 (+)	1.16 (+)	1.32 (+)	1.65 (+)	1.67 (+)				
69	1.55 (+)	1.46 (+)	1.68 (+)	1.68 (–)	1.84 (+)	3.04 (+)				
70	1.12 (–)	≈ 1 (+)	1.20 (–)	1.58 (+)	1.21 (–)	1.21 (–)				
71	1.52 (–)	1.45 (–)	1.29 (–)	2.59 (–)	1.38 (–)	1.15 (+)				
72	1.35 (–)	1.45 (–)	1.44 (–)	3.17 (–)	1.41 (+)	2.01 (+)				
73	1.30 (–)	1.65 (–)	1.20 (–)	1.83 (–)	1.11 (+)	2.11 (–)				
74	1.37 (+)	1.22 (+)	1.95 (+)	1.34 (+)	1.29 (+)	1.98 (+)				
75	1.16 (+)	1.10 (+)	1.12 (+)	1.41 (–)	1.20 (–)	1.12 (+)				
76	1.75 (+)	1.24 (+)	1.46 (+)	≈ 1 (+)	1.82 (+)	≈ 1 (–)				
77	1.20 (–)	1.17 (–)	1.16 (–)	1.15 (–)	1.26 (–)	≈ 1 (–)				

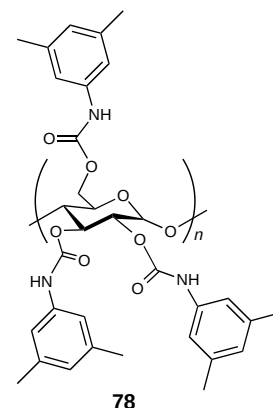
[a] Column: 25 × 0.46 cm (inner diameter); eluent: hexane/2-propanol (90/10); flow rate: 0.5 mL min^{–1}. The sign in parentheses indicates the optical rotation of the first enantiomer to be eluted. [b] Amylose tris(3,5-dimethylphenylcarbamate) (**78**).

many racemates, but *ortho*-substituted derivatives such as **39**, **43**, and **54** do not recognize chirality well. The derivatives with heteroatom substituents, such as the alkoxy group in **29** and **30** or the nitro group **47**, also show poor abilities to recognize chirality.^[41] Phenylcarbamates bearing both electron-donating methyl and electron-withdrawing chloro or fluoro groups on the phenyl moieties exhibit a high resolving ability for many racemates; cellulose phenylcarbamates **61**, **64**, and **67** recognize chirality particularly well.^[42]

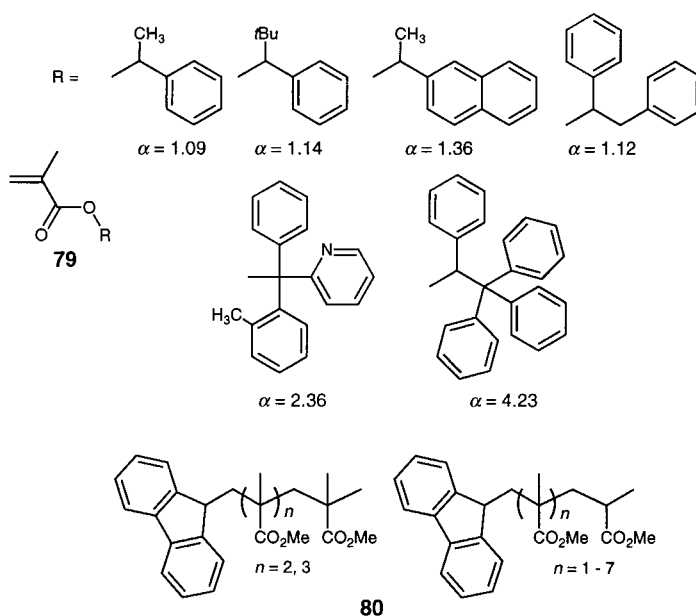
Similarly, the ability of amylose phenylcarbamates to recognize chirality was improved by introducing methyl or chloro groups on the phenyl moieties.^[43] However, in contrast to the cellulose derivatives, tris(4-methoxyphenylcarbamate) and tris(5-chloro-2-methylphenylcarbamate) of amylose show a relatively high recognition of chirality.^[44] This may be ascribed to the differences in their higher order structures. Possible structures are left-handed 3/2 and 4/1 helical chain conformations for tris(phenylcarbamates) of cellulose (CTPC)^[45] and amylose (ATPC),^[46] respectively. These different higher order structures seem to be responsible for the different influence of the substituents on the resolving power of the cellulose and amylose derivatives.

Among the tris(phenylcarbamate) derivatives of cellulose and amylose prepared so far, 3,5-disubstituted derivatives such as 3,5-dimethylphenylcarbamates (CDMPC, **49**, Chiralcel OD) and 3,5-dichlorophenylcarbamates (**52**) of cellulose

and tris(3,5-dimethylphenylcarbamate) of amylose (ADMPC, **78**, Chiralpak AD) show quite excellent enantioselectivity for a variety of racemates (Table 1).^[41, 43] The CSP **52** has a unique ability to recognize

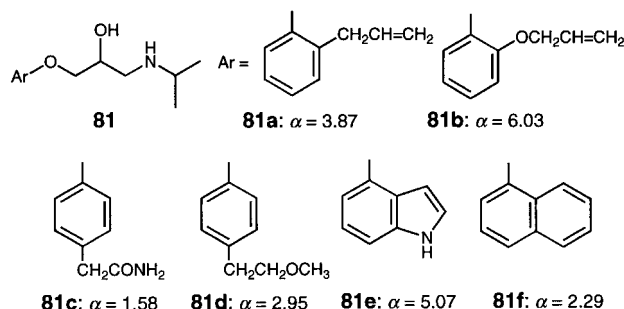


chirality and can resolve bulky methacrylates **79**^[41] and stereoisomers of oligo(methyl methacrylate)s **80**.^[14c,e] This markedly contributes to the elucidation of the mechanism of helix-sense selective polymerization of triarylmethyl methacrylates leading to an optically active, one-handed helical polymethacrylate (CSP **6** in Figure 1). However, owing to the high solubility in an eluent with a high proportion of 2-propanol, application is rather limited. This defect was overcome by chemical bonding of the CSP to 3-aminopropyl-silanized silica gel with a diisocyanate as a spacer.^[47]



CDMPC resolves a variety of chiral compounds, including aromatic hydrocarbons, axial and planar dissymmetric compounds, metal-containing compounds, chiral sulfur or phos-

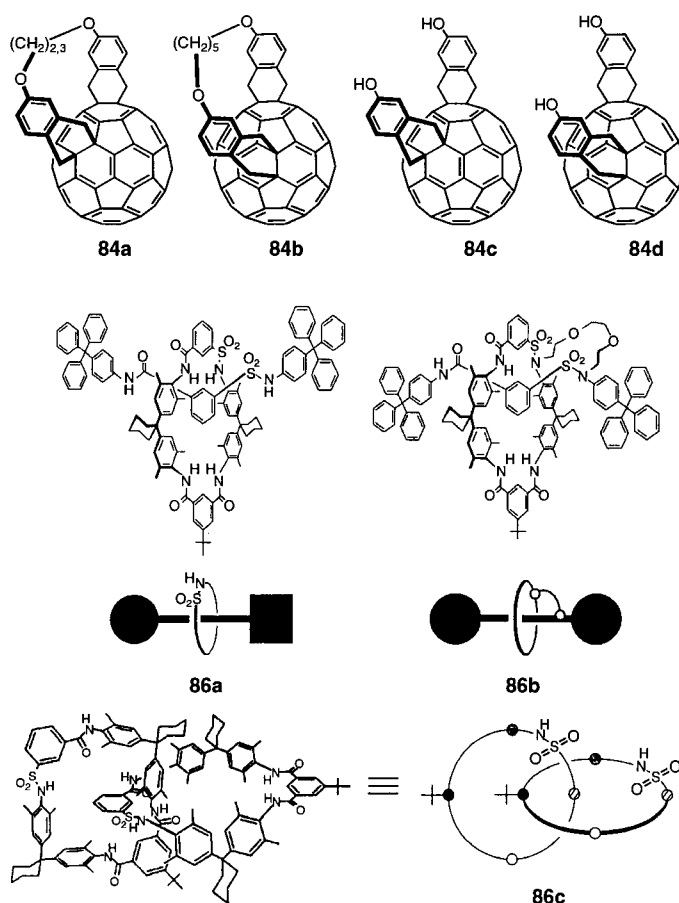
phorus compounds, cyano or carbonyl compounds, amines, carboxylic acids, alcohols, amino acid derivatives, ethers, and many drugs^[6, 15] including β -adrenergic blocking agents (β -blockers) such as **81**. In the resolution of β -blockers on



CDMPC, the (*R*)-(+)-isomers usually eluted first followed by the (*S*)-(–)-isomers, and there was complete separation.^[48]

Some stereochemically interesting compounds and important chiral building blocks recently resolved on CDMPC are shown in Figure 6.^[49, 50] Some of them cannot be separated by other methods and were resolved for the first time by HPLC. Figure 7 displays the chromatograms for the resolution of several racemates on CDMPC. Absciscic acid (**82**),^[51] the metallocene derivative **83**,^[52] the chiral C_{60} derivatives **84**,^[53] the aromatic hydrocarbons **85**,^[54] and the topologically interesting rotaxanes **86a, b** and catenane **86c**^[55] were completely separated into their enantiomers.

The ability of ADMPC to recognize chirality is as effective as that of CDMPC. Some enantiomers are eluted in the reverse order on the two CSPs (Table 1), suggesting that these two are complementary in recognizing chirality. Enantiomers not resolved on CDMPC may be resolved on ADMPC, and



vice versa.^[15g,h] Several chiral compounds recently resolved on ADMPC are shown in Figure 8.^[56]

It is very important to select a suitable eluent to achieve efficient resolution of the enantiomers.^[15] A mixture of

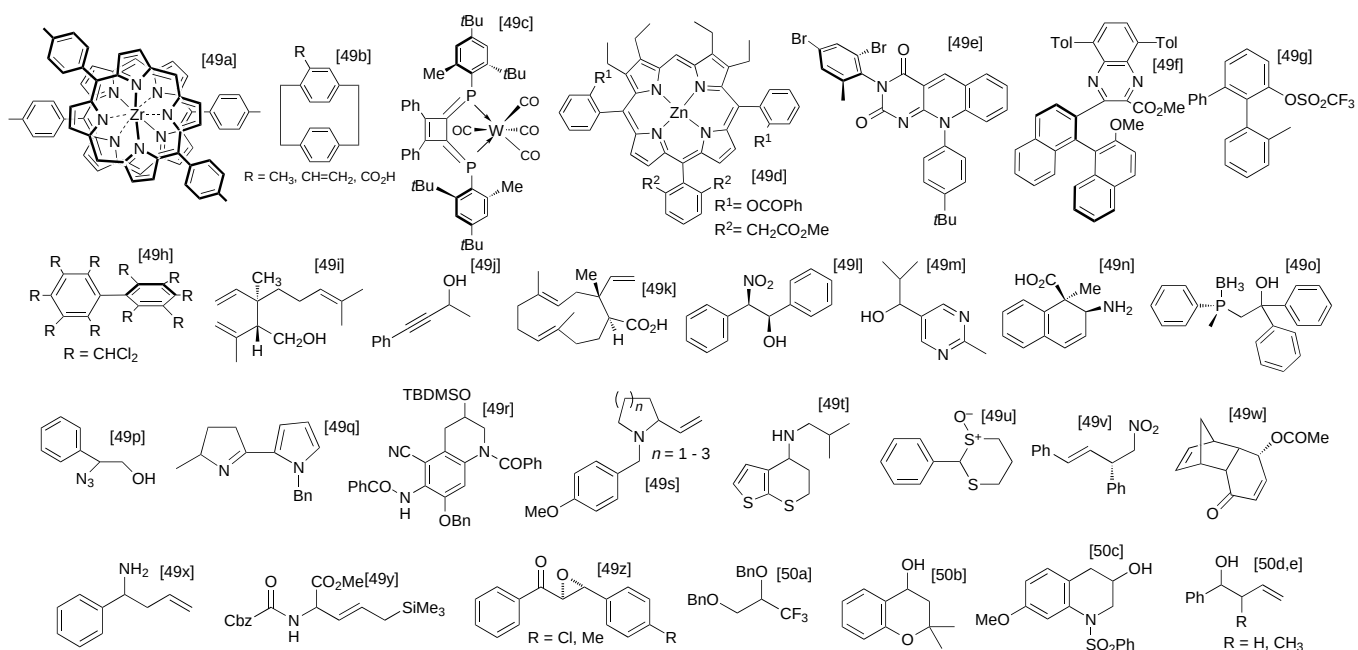


Figure 6. Compounds whose enantiomers were resolved on CDMPC (**49**, Chiralcel OD), along with literature references. Tol = tolyl, Bn = benzyl, TBDMS = *tert*-butyldimethylsilyl.

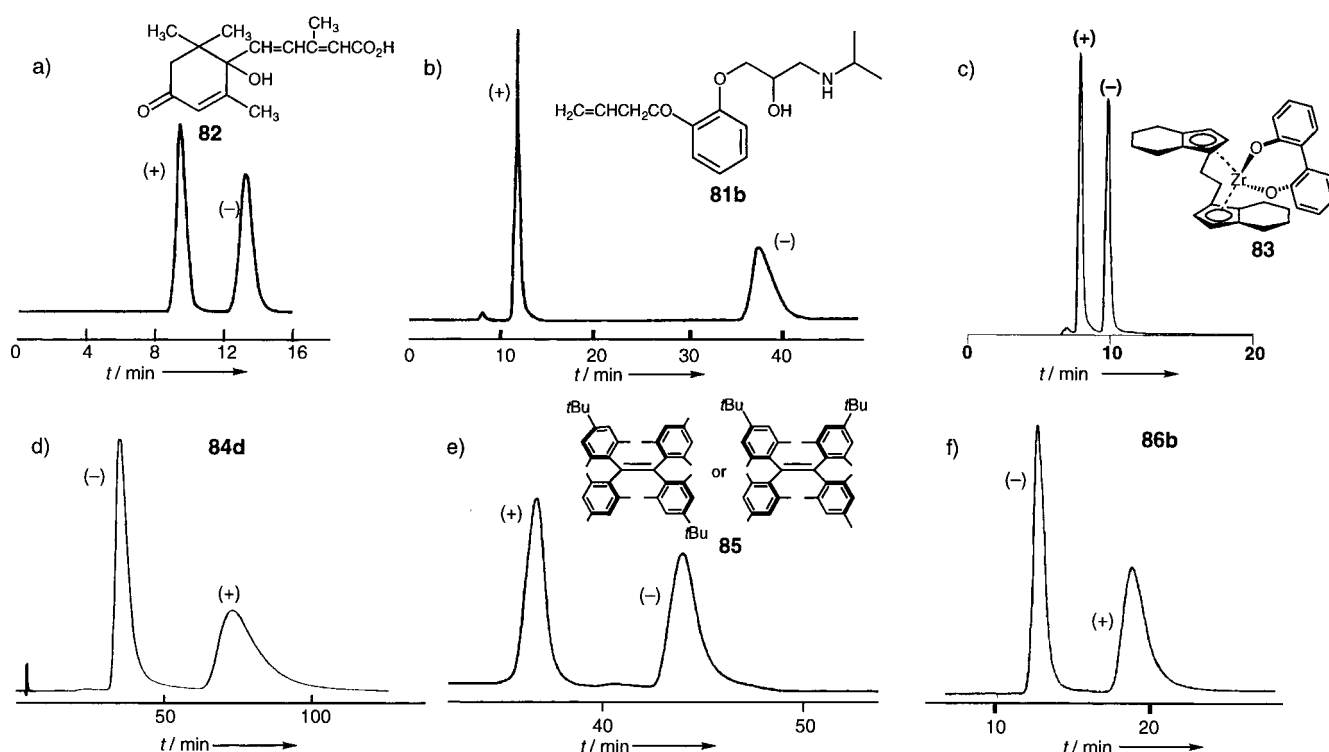


Figure 7. Chromatograms for the resolution of a) abscisic acid (**82**),^[51] b) oxprenolol (**81b**),^[48] c) the *ansa*-zirconocene derivative **83**,^[52] d) the chiral C₆₀ derivative **84d**,^[53] e) the tetraarylethene derivative **85**,^[54] and f) the chiral rotaxane **86b**^[55] on CDMPC (**49**). Column: 25 × 0.46 cm (inner diameter); eluent: a) hexane/2-propanol/trifluoroacetic acid (80/20/0.1), b) hexane/2-propanol/diethylamine (80/20/0.1), c) hexane/ethanol (9/1), d) hexane/2-propanol (7/3), e) isooctane, f) hexane/ethanol (85/15); flow rate: 0.5 mL min⁻¹ (a–c, f), 1.0 mL min⁻¹ (d, e). *t* = elution time.

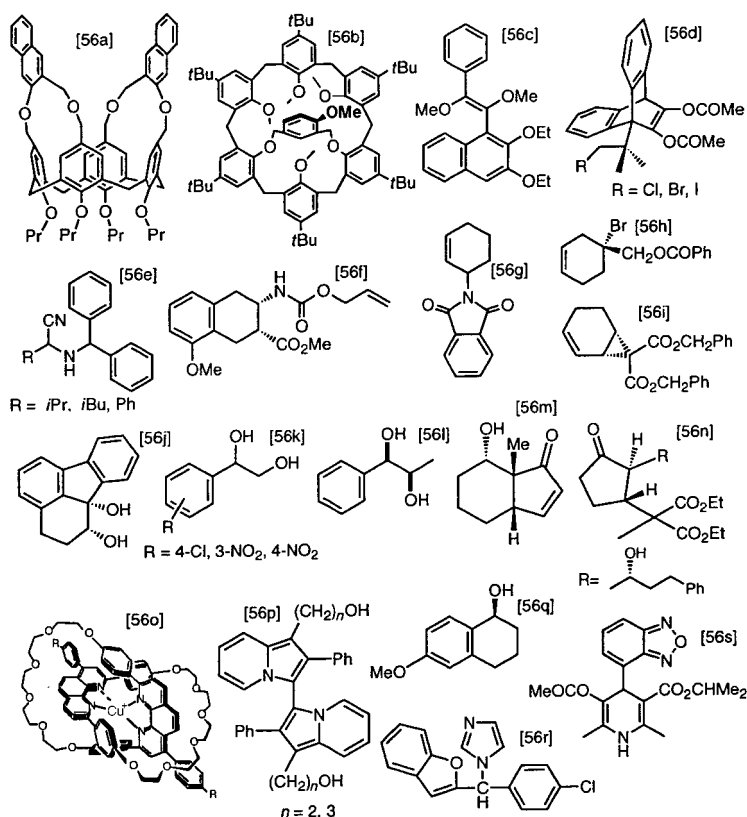


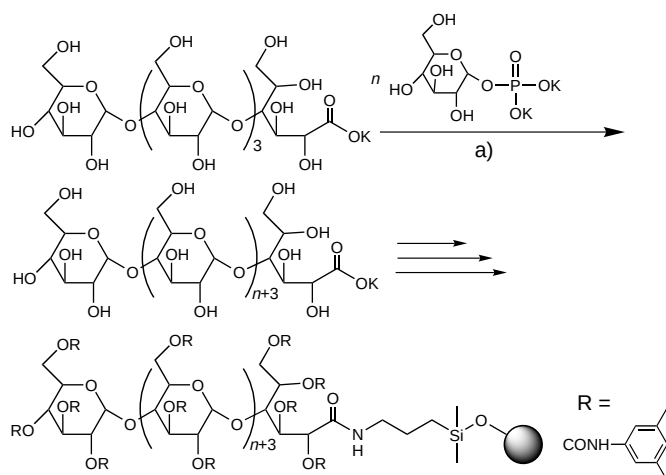
Figure 8. Compounds whose enantiomers were resolved on ADMPC (**78**, Chiralpak AD), along with literature references.

hexane and 2-propanol or ethanol is often used for the separation of enantiomers on polysaccharide-based CSPs. The structures of the alcohol can influence the enantioselectivity.^[57] When an analyte has an acidic group (e.g. **82**), addition of a small amount of strong acid (e.g. CF₃COOH) gives better separation (Figure 7a).^[58] For basic amino compounds, addition of a small amount of diethylamine or isopropylamine is recommended for reducing tailing of the peaks (Figure 7b).^[48] Aqueous eluents are also particularly useful for investigating the pharmacokinetics and pharmacodynamics of chiral drugs in living systems.^[59] Supercritical-fluid liquid chromatography (SFC) with carbon dioxide and alcohols as a mobile phase can also be applied to the polysaccharide phases.^[60] However, other solvents such as chloroform and THF cannot be used as the main mobile phase because the polysaccharide-based CSPs are soluble or swollen in the solvents.

To overcome this defect, CDMPC and ADMPC were regioselectively bonded to silica gel at the 2-, 3-, and 6-positions of the glucose units with a diisocyanate spacer.^[47] These CSPs were able to discriminate between enantiomers better than nonregioselectively bonded CSPs, although their abilities to recognize chirality were slightly lower than those of the coated-type CSPs. The above-mentioned CSPs may be chemically bonded to silica gel through several hydroxyl groups of the polysaccharides, which may

cause an alternation of higher order structures of the polysaccharides and thus decrease the ability to recognize chirality. Similar chemically bonded CDMPC phases were also prepared through radical polymerization of the allyl groups of silica gels and a CDMPC derivative bearing vinyl groups.^[61]

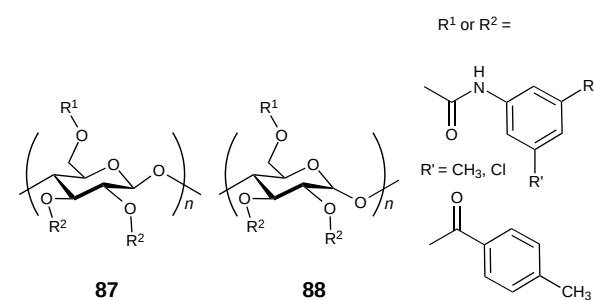
Recently, ADMPC was successfully bonded chemically to silica gel only at the reducing terminal residue of amylose (Scheme 3).^[62a] Amylose with the desired chain length was



Scheme 3. Synthesis of ADMPC bound on silica gel through enzymatic polymerization. a) Potato phosphorylase. The gray sphere represents silica gel.

readily prepared by the polymerization of the dipotassium salt of α -D-glucose 1-phosphate with functionalized maltooligosaccharides in the presence of a phosphorylase isolated from potato.^[28, 62b] The amylose was successfully bonded to silica gel at the reducing terminal residue, and then allowed to react with 3,5-dimethylphenyl isocyanate to afford CSPs with excellent resolving abilities—comparable to that of the coated-type CSP—and high durabilities with respect to solvents such as THF and chloroform. Some racemates were more efficiently resolved on the new bonded-type CSP than the coated-type CSP using chloroform as a component of the mobile phase.^[62a]

Regioselectively carbamoylated and/or benzoylated celluloses **87** and amyloses **88** were prepared, and their abilities to recognize chirality were evaluated.^[63] Some racemates are

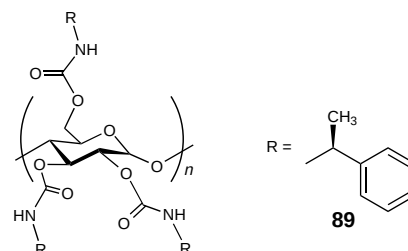


more efficiently resolved on the CSPs. Porous spherical silica gels with a mean particle size of 7–10 μm and a mean pore

diameter of 100–400 nm are often used as a support. However, the surface and type of support also influence the enantioselectivity of the polysaccharide-based CSPs.^[64]

3.3. Aralkylcarbamates of Polysaccharides as Chiral Stationary Phases

Alkylcarbamates, such as methyl- and cyclohexylcarbamates of cellulose, are poor in recognizing chirality. Although tris(*tert*-butylcarbamate) of cellulose can completely resolve some racemates, it cannot resolve as many racemates as the phenylcarbamates of polysaccharides. However, several tris-(aralkylcarbamate)s of cellulose and amylose exhibited characteristic resolving abilities that are different from those of the phenylcarbamates of polysaccharides.^[65] In particular, 1-phenylethylcarbamates of polysaccharides exhibit a high ability to recognize chirality, although benzylcarbamate and other more bulky aralkylcarbamates are not as effective. The resolving abilities of 1-phenylethylcarbamates depend on the chirality of the aralkyl group; the (*S*)-1-phenylethylcarbamate of amylose (**89**, Chiralpak AS) can recognize chirality. Some



of the racemates shown in Figure 9,^[65-67] including the chiral telluroxide **90**,^[66] are better resolved on the CSP than other phenylcarbamates of polysaccharides including CDMPC and ADMPC.

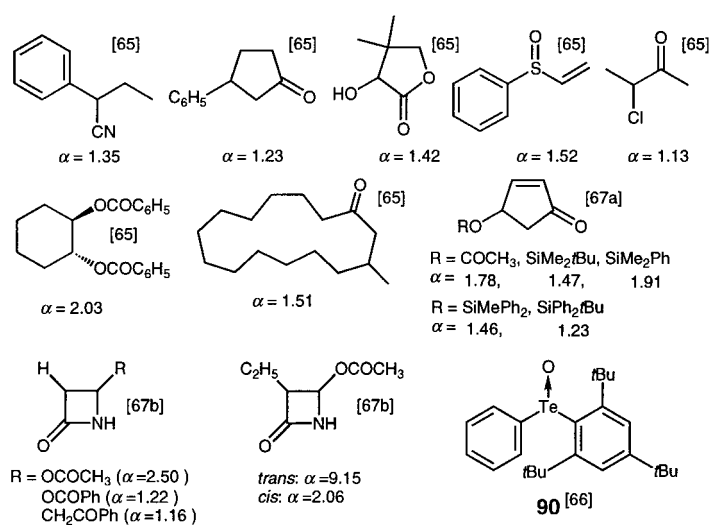


Figure 9. Compounds whose enantiomers were better resolved on amylose tris((*S*)-1-phenylethylcarbamate) (**89**, Chiralpak AS) than other polysaccharide-based CSPs, along with literature references.

4. Mechanism for Discrimination between Enantiomers on Polysaccharide Derivatives

An understanding of the recognition of chirality at a molecular level is of great interest and importance in many fields of chemistry and biology.^[68] Furthermore, recognition of chirality plays an essential role in the fields of enantioseparation. In the past few years, several approaches to clarifying the mechanism for the recognition of chirality on CSPs for liquid chromatographies have been attempted by means of chromatography, NMR spectroscopy,^[69] X-ray analysis, and computational methods.^[70] The CSPs that have been most intensively studied in this respect are cyclodextrin-based CSPs and Pirkle-type CSPs;^[4, 69, 70] rational models for interactions between the CSPs and enantiomers have been proposed.

In contrast, very few mechanistic studies on chiral discrimination at a molecular level have been performed for polymeric CSPs.^[71] Chiral polymers usually have a number of different binding sites with different affinities to enantiomers, and the determination of their exact structures in the solid state or in solution is laborious. This makes it difficult to evaluate a precise mechanism for the recognition of chirality on the polymeric CSPs.

4.1. Cellulose Esters

Although CTA-I has been used as a CSP for a long time, the mechanism for the recognition of chiral has not been satisfactorily elucidated. This is probably because of difficulty in determining the complex structure of CTA-I, which seems to be characterized by the presence of many adsorption sites for interactions, despite structural investigations by means of X-ray crystallography,^[15a, 45a, 72] calculations,^[73] and solid-state ¹³C NMR spectroscopy.^[74] Hesse and Hagel,^[32] and later Francotte et al.,^[72a] proposed an inclusion mechanism by which enantiomers may be adsorbed in the chiral cavities consisting of the laminate CTA-I matrix (Figure 10).^[72c] The inclusion of molecules in the cavity may be governed not by the attractive interaction through functional groups, but mainly by the shape of the molecules.^[75] The inclusion mechanism seems to explain the chiral discrimination of CTA-I, since many fully aromatic or nonaromatic hydrocarbons without any functional groups (Figure 3) can be resolved on this CSP.

Other theoretical studies^[76] and the X-ray analysis of a model compound^[77] also support the inclusion mechanism. Heterogeneous acetylation may provide a supramolecular structure of CTA-I in which multiple interaction sites with specific surface and cavities inside the matrix may be responsible for the high ability to recognize chirality for a wide range of enantiomers.^[75] The existence of such a supramolecular structure of CTA was also proposed based on NMR investigations in solution.^[78] However, such an NMR spectrum may not be useful for elucidating the mechanism for discrimination between enantiomers on CTA-I, because the microcrystallinity in the solid state plays a dominant role

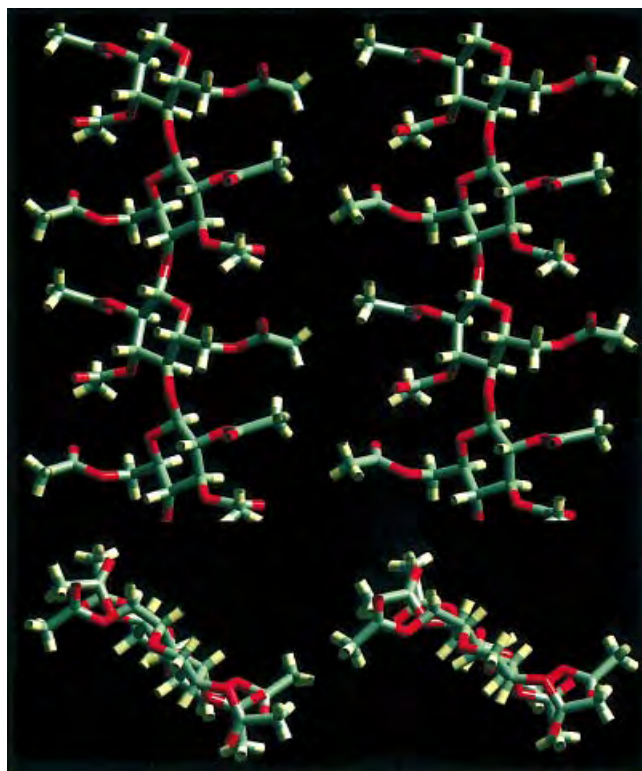


Figure 10. Calculated structure of the laminate CTA-I matrix on the basis of an X-ray structure analysis. The coordinates of each atom are taken from ref. [72c]. View along the chain axis (top) and perpendicular to the chain axis (bottom).

for the enantioselectivity. A detailed solid-state NMR study may be necessary.

Cellulose triacetate coated on silica gel from a solution may consist of CTA-II and amorphous regions; the enantioselectivity is sensitive to the coating solvent.^[15a, 72b] The main chiral adsorption sites of CTB derivatives are considered to be the polar carbonyl groups of esters, which can interact with the racemates through hydrogen bonding and dipole–dipole interactions for discrimination between enantiomers.^[36] Wainer et al. proposed a similar mechanism, an attractive binding with steric fit involving hydrogen bonding and dipole–dipole interactions rather than inclusion, on the basis of the separation properties of a series of structurally related chiral aromatic amides and alcohols on the CTB phases.^[79]

However, the ability to recognize chirality is highly dependent on the conditions for the preparation of the CSPs, and particularly on the solvent used to dissolve CTB derivatives in coating process, as observed for CTA. This means that other factors, such as the morphology of CTB derivatives, may be closely related to the enantioselectivity.^[36] Francotte and Zhang pointed out the importance of the supramolecular structure of CTB derivatives for recognizing chirality.^[40c] Grinberg et al. recently investigated the thermodynamic profiles for the resolution of a chiral diol on cellulose tris(4-methylbenzoate) (**21**).^[80] They found an interesting temperature-dependent enantioseparation behavior: At low temperature the enantioselectivity is driven by entropy due to inclusion, whereas at high temperature it is governed by

enthalpy mainly due to an attractive interaction through hydrogen bonding.

Based on the X-ray structural analysis, Steinmeier and Zugenmaier proposed a left-handed 3/2-helical structure for CTB regardless of the preparation conditions (Figure 11).^[45a] Modeling of CTB was also reported by Francotte et al.^[40a] and

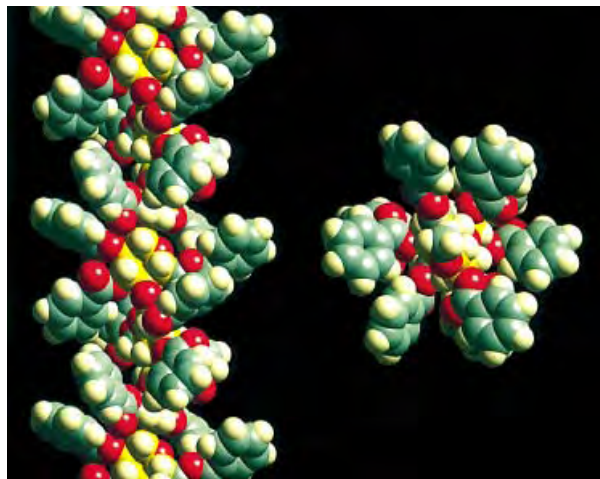


Figure 11. Optimized structure of CTB (**24**) based on the structure determined by X-ray analysis.^[45a] The energy minimization was carried out with the Dreiding force field in Cerius² (MSI). The glucose carbon atoms of CTB are shown in yellow for clarity. View along the helix axis (left) and perpendicular to the helix axis (right).

Grinberg et al.,^[80] and their proposed main-chain structures are rather similar to that of CTA-I. Oguni et al. investigated the mechanism for discrimination between enantiomers on the CTB derivative **21** by means of ¹³C NMR spectroscopy in solution.^[71a,c] Several signals of 1-phenylethanol were split into the signals of enantiomers in the presence of **21**. This is interesting for elucidating the mechanism for discrimination between enantiomers, and further experiments may provide additional information.

4.2. Phenylcarbamates of Cellulose and Amylose

Most of the cellulose tris(phenylcarbamate) derivatives form a lyotropic liquid crystalline phase in a highly concentrated solution (Figure 12)^[41, 81] and show high crystallinity under a polarizing microscope when they are cast from a solution. This indicates that the phenylcarbamates on the silica surface are presumably arranged in a regular fashion. Such an ordered structure seems to be very important for efficient recognition of chirality by CSPs derived from polymers. A few cellulose phenylcarbamate derivatives and alkylcarbamates which do not form such a liquid crystalline phase showed a poor ability to recognize chirality. The mechanism for the recognition of chirality by phenylcarbamates of cellulose and amylose has been proposed on the basis of chromatographic, computational, and spectroscopic studies.

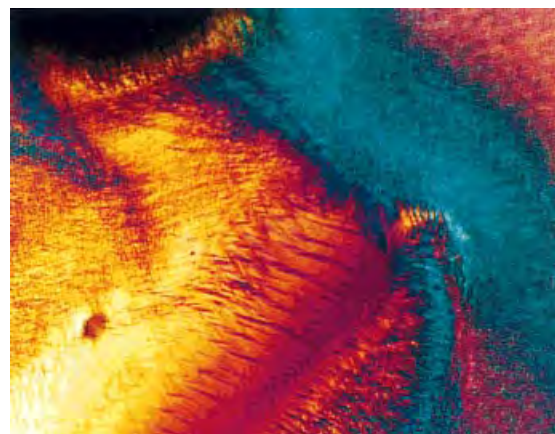


Figure 12. A photomicrograph of a lyotropic liquid crystalline phase of cellulose tris(phenylcarbamate) in a highly concentrated solution under polarized light.

4.2.1. Chromatographic Studies

As mentioned above, the abilities of phenylcarbamates of polysaccharides to recognize chirality are greatly affected by the substituents on the phenyl groups. To understand the effect quantitatively, the retention times of acetone and the first isomer of alcohol **71** eluted on the 4-substituted CSPs are plotted against the Hammett parameter σ of the substituents (Figure 13).^[41] The retention times of acetone tend to increase

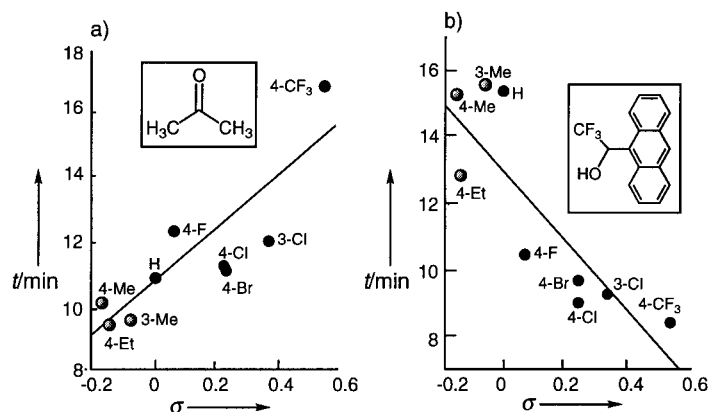


Figure 13. Plots of retention times t of a) acetone and b) the first enantiomer of **71** to elute on cellulose tris(phenylcarbamate) derivatives against the Hammett parameter σ of the substituents.

as the electron-withdrawing power of the substituents increases, whereas those of the first isomer of **71** eluted decrease. These results indicate that the main chiral adsorption sites are probably the polar carbamate groups, which are able to interact with a racemate through hydrogen bonding to the NH and C=O groups; in the case of the latter, dipole–dipole interactions also play a role (Figure 14). The nature of the substituents (X) on the phenyl groups influences the polarity of the carbamate residues, which must change the resolving ability. Therefore, acetone is more strongly adsorbed on the CSPs with the more acidic NH protons through a hydrogen-bonding interaction.

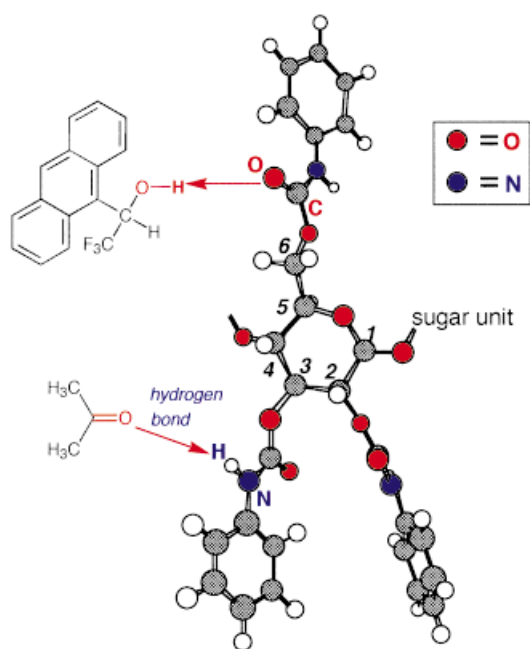


Figure 14. Possible interaction sites of cellulose tris(phenylcarbamate) derivatives.

On the other hand, when X is an electron-donating group (e.g. methyl) the electron density at the carbonyl oxygen atom of the carbamates is expected to increase. Therefore, alcohols are more strongly adsorbed on the CSPs through a hydrogen-bonding interaction. When X is a polar group (e.g. nitro or methoxy) the racemates may interact with X, which will result in a lowering of the resolving ability (see Section 3.2) since X is far away from a chiral glucose residue. Therefore, substitutions with bulky alkoxy groups such as isopropoxy or isobutoxy groups (**31** and **32**, Scheme 2) improve the resolving ability by reducing the interactions at the ether oxygen atom.^[44a]

Although the phenylcarbamate derivatives of polysaccharides have become popular CSPs, the mechanism for discrimination between enantiomers at a molecular level has remained obscure. A determination of the exact structures of the phenylcarbamate derivatives is necessary to reveal the mechanism. Figure 15 shows a stable structure of CTPC that was optimized by molecular-mechanics calculations starting from the proposed X-ray crystal structure of CTPC.^[45] CTPC has a left-handed 3/2-helical conformation, and the glucose residues are regularly arranged along the helical axis. A chiral helical groove with polar carbamate groups exists parallel to the main chain. The polar carbamate groups are preferably located inside, and hydrophobic aromatic groups are placed outside the polymer chain so that polar enantiomers may predominantly interact with the carbamate residues in the groove through hydrogen-bond formation. This interaction seems to be important for efficient chiral discrimination, especially in normal-phase HPLC.

In addition to these polar interactions, π - π interactions between phenyl groups of a CTPC derivative and aromatic groups of a solute may play a role in the recognition of chirality, because several nonpolar aromatic compounds have

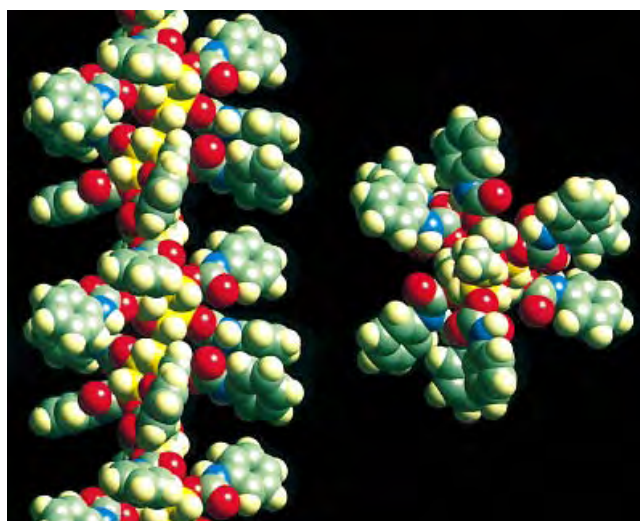


Figure 15. Optimized structure of CTPC based on the structure determined by X-ray analysis.^[45] The glucose carbon atoms of CTPC are shown in yellow for clarity. View along the helix axis (left) and perpendicular to the helix axis (right).

also been resolved.^[49b] Consequently, the interaction of the carbamate groups of CSPs with racemates seems to be most important for effective recognition of chirality. This speculation is supported by NMR studies.

4.2.2. NMR Studies

CTPC seems to maintain its helical structure even in solution.^[82] However, most phenylcarbamates of the polysaccharides with resolving ability as high as CSPs are soluble only in polar solvents such as acetone, pyridine, and THF. In these polar solvents the derivatives show poor recognition of chirality because the solvents preferentially interact with the polar carbamate residues. Therefore, it was difficult to elucidate the mechanism for discrimination between enantiomers with NMR spectroscopy in these solvents. However, we recently found that several phenylcarbamate derivatives—for instance, tris(4-trimethylsilylphenylcarbamate) (**33**)^[83] and tris(5-fluoro-2-methylphenylcarbamate) (**65**)^[42b] of cellulose (Scheme 2)—are soluble in chloroform, and discriminate between enantiomers in ¹H and ¹³C NMR spectroscopies as well as HPLC. This permitted us, for the first time, to investigate the chiral interaction occurring in solution by NMR spectroscopy. The phenylcarbamate derivatives resolved many racemates by HPLC, and the chromatographic results can be directly correlated to those from spectroscopy.

Figure 16 shows the ¹H NMR spectra of (±)-*trans*-stilbene oxide (**69**) in the absence (a) and presence of **33** (b). The signal for the methine proton of **69** is split into two singlets in the presence of **33**,^[83] and only the signal of the (–) isomer is shifted downfield. This clearly indicates that **33** can discriminate between the enantiomers even in solution. In the chromatographic separation of (±)-**69** on the CSP **33**, the (+) isomer was eluted first followed by the (–) isomer, and complete base-line separation was achieved ($\alpha = 1.55$). This order of elution correlates well with the downfield shift of the (–) isomer observed in the ¹H NMR spectrum.

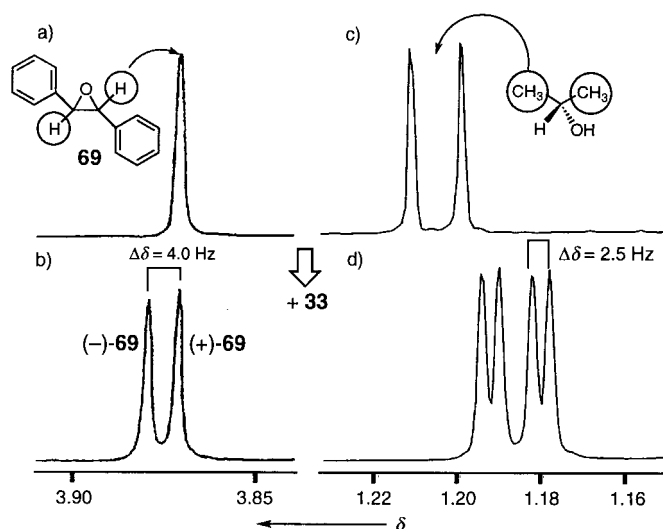


Figure 16. ^1H NMR spectra of *trans*-stilbene oxide (**69**, 5 mg) in a) the absence and b) the presence of **33** (40 mg) in CDCl_3 (1.0 mL) at 22°C . The peaks were assigned with enantiomerically pure (+)- and (–)-**69**. c, d) The changes in the methyl proton resonances of 2-propanol (3 μL) added to **69** (5 mg) and **69** (5 mg) + **33** (20 mg) are also shown.

As previously mentioned, the most important adsorption site for discrimination between enantiomers on phenylcarbamate derivatives may be the polar carbamate residue (Figure 14). For **69**, the oxygen atom of the oxirane ring may interact with the NH proton of the carbamate residue through hydrogen bonding. Therefore, addition of a hydrogen acceptor, such as acetone, does not result in splitting of the methine proton signal.^[83] A similar change in the ^1H NMR spectrum of **69** was also induced upon addition of 2-propanol. Interestingly, the signals for the methyl groups of 2-propanol were shifted upfield and split into a pair of doublets (Figure 16d), indicating that the two methyl groups were magnetically nonequivalent in the presence of **33**. The chirality of **33** seems to force 2-propanol to bind in a diastereotopic environment, and allows the recognition of enantiotopic methyl groups.^[83, 84]

The ^1H NMR signals of other racemic mixtures, including Tröger's base (**12**) and benzoin (**70**), were also separated into two sets of peaks in the presence of **33**. Moreover, in the case of secondary alcohols such as 2-heptanol and 2-octanol, the methyl protons at the end of the longer chain and very remote from the stereogenic center were enantiomerically discriminated in the presence of **33** (Figure 17), whereas the methine and another methyl protons were not recognized. This

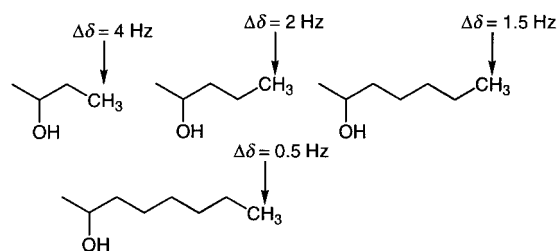


Figure 17. Secondary alcohols whose enantiomers can be distinguished by **33**. The protons marked with an arrow are those that are recognized with ^1H NMR spectroscopy.

suggests that the methyl protons of the alkyl chains may be specifically located near chiral **33**, so that the signals for the methyl protons split into signals for both enantiomers: Compound **33** can function as a chiral shift reagent.

The phenylcarbamate derivative **65** can discriminate between enantiomers of 2,2'-dihydroxy-1,1'-binaphthyl (**91a**) and 2,2'-dihydroxy-6,6'-dimethyl-1,1'-biphenyl (**73**) very well in HPLC.^[85] Figure 18 shows a chromatogram for the resolution of **91a** on **65** with a large separation factor ($\alpha = 4.23$) and complete base-line separation; the *R* isomer is eluted first followed by the *S* isomer. Analogue **73** is also resolved completely with a large α value (3.22). As in the separation of **91a**, the *S* isomer is retained longer.

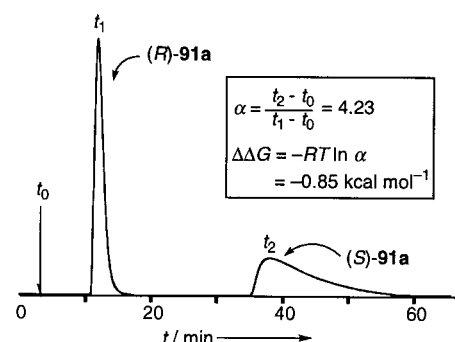
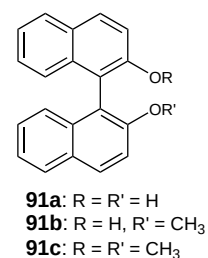
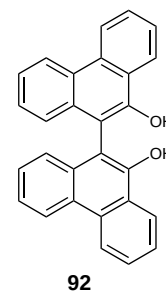


Figure 18. Chromatogram of the enantioseparation of (*RS*)-1,1'-bi-2-naphthol (**91a**) on CSP **65** with hexane/2-propanol (9/1) as the eluent at 20°C . Column: 25×0.46 cm (inner diameter); flow rate: 1.0 mL min^{-1} .

The polymer **65** also discriminates between the enantiomers of **91a** and **73**, as shown by ^1H and ^{13}C NMR spectroscopy.^[85] Figure 19 shows the ^1H NMR (a, b) and ^{13}C NMR spectra (c) of (*RS*)-**91a** in the absence (a) and presence of **65** (b, c) in CDCl_3 . Each signal for the hydroxyl and naphthyl protons H4 and H6 of **91a** is distinctly split into two signals for the enantiomers. The signals for the OH protons of (*S*)-**91a** are more downfield-shifted with line broadening than the corresponding signals for (*R*)-**91a**, whereas the signals for the H4 and H6 protons of (*S*)-**91a** are shifted upfield with broadening. This indicates that (*S*)-**91a** interacts more strongly with **65**. The downfield shift of the OH resonances is ascribed to hydrogen-bond effects, and the upfield shifts for the aromatic protons are probably due to the π -stacking or shielding effect of a neighboring aromatic ring of **65**. There are similar splittings of signals for **73** into those for its enantiomers in the presence of **65**, and the resonances for the OH proton of (*S*)-**73** are more downfield-shifted than the corresponding signals for (*R*)-**73**. Mono- and di-O-methylated derivatives **91b**, **c** and bulky **92** are hardly separated in HPLC and cannot be distinguished in the ^1H NMR spectrum. Hydrogen bonding through the hydroxy group



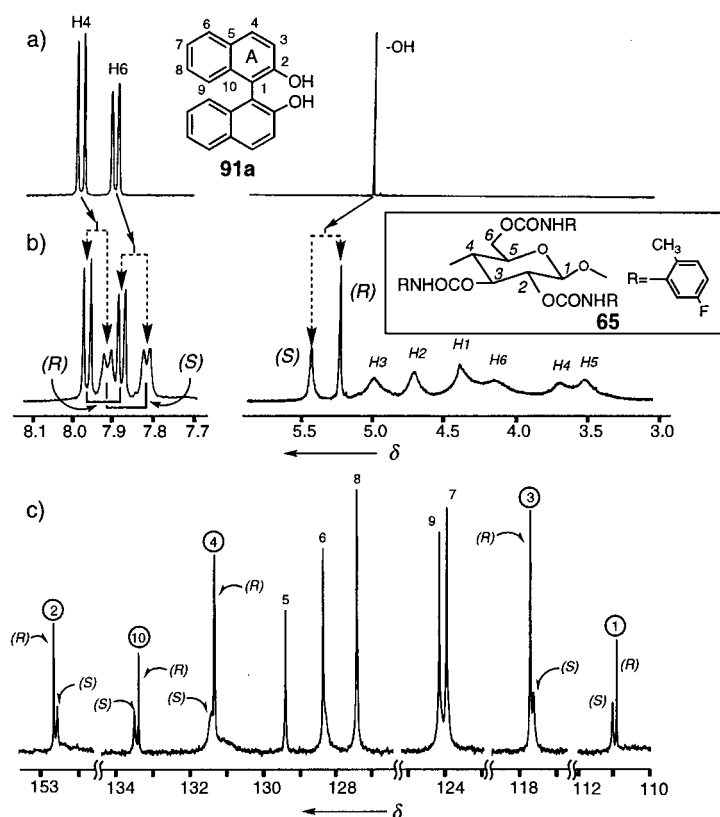


Figure 19. Selected region of the a), b) ^1H and c) ^{13}C NMR spectra of (R,S)-**91a** in the absence (a) and presence (b, c) of **65** in CDCl_3 at 23°C .

of **91a** seems to be the main force for its retention and resolution.

The discrimination of enantiomers in the presence of **65** by ^{13}C NMR spectroscopy is also possible for **91a** and **73**.^[85] The signals for carbon atoms C1–C4 and C10 of **91a** are separated into the signals for the enantiomers, and the resonances for (S)-**91a** are markedly broadened. The signals exhibiting large splittings belong to carbon atoms of ring A (Figure 19), indicating that ring A may be favorably located close to the chiral glucose residue. In other words, with ring A (S)-**91a** may insert into the chiral groove of **65** to form the hydrogen bond. Measurements of the relaxation time of the complexes also support this speculation.^[85] The relaxation times (T_1) of all carbon atoms of (R)- and (S)-**91a** are shorter in the presence of **65** than those of free **91a**, and those T_1 values for (S)-**91a** are always shorter than the corresponding values for (R)-**91a** (Table 2). A remarkable reduction in T_1 is observed for carbon atoms C1–C5 and C10 attached to ring A. These results indicate that the mobility of ring A is restricted by an intermolecular hydrogen bond between the hydroxyl groups

Table 2. Spin-lattice relaxation times T_1 [s] of **91a** in the presence of **65** in CDCl_3 at 19°C .

C atom	T_1 (S)	T_1 (R)	C atom	T_1 (S)	T_1 (R)
1	7.47	8.82	6	0.97	1.02
2	4.20	5.31	7	0.90	0.93
3	0.90	1.07	8	0.86	1.01
4	0.82	0.99	9	0.92	1.00
5	3.07	4.03	10	2.98	4.15

at C2 and the carbonyl group of the carbamate residues of **65**.

^1H NMR titrations of **65** with (S)- and (R)-**91a** were performed and a Job plot of the continuous changes in chemical shifts for the complex **65**·(S)-**91a** was prepared to investigate the binding sites of **65** and the stoichiometry of the complexation. The H2 proton resonance of a glucose unit of **65** is dramatically affected by addition of (S)-**91a** and shifts upfield upon binding, whereas the other glucose proton resonances move only slightly. The significant upfield shift of the H2 proton resonance indicates that a naphthyl ring of (S)-**91a** may be closely located above the H2 proton. In the Job plot the maximal complex formation occurs at about 0.5 mol fraction of the glucose residue of **65**. This indicates that each glucose unit of **65** may have the same binding affinity to (S)-**91a**, which may be attributed to the regular structure of **65** even in a solution.^[85]

The most valuable information for the geometry of the complex between **65** and (S)-**91a** was obtained by 2D NOESY spectroscopy.^[85] Figure 20 shows the NOESY spectrum of **65**·(S)-**91a**. Several cross-peaks for clear intermolecular

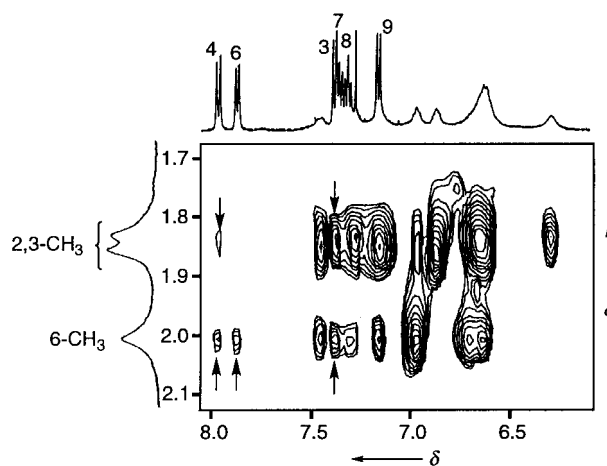


Figure 20. NOESY spectrum (CDCl_3 , 23°C) of a mixture of (S)-**91a** and **65** (molar ratio 1:2) at a mixing time of 300 ms. F_2 axis: region of the arene protons of **65** and **91a**; F_1 axis: region of the methyl protons on the phenyl moiety of **65**. See text for further details.

NOEs between the aromatic H4, H6, and H7 protons of (S)-**91a** and the methyl protons of **65** are represented by arrows. On the other hand, a NOESY spectrum of a mixture of (R)-**91a** and **65** is very similar to the spectrum of free **65**, and no intermolecular NOEs between **65** and (R)-**91a** are observed. These data indicate that (S)-**91a** binds or interacts with **65** more strongly than (R)-**91a**, and that the naphthyl protons of (S)-**91a** are located at a distance of less than 5 Å to the methyl protons of **65**. These observations are in accord with the results of HPLC and 1D NMR experiments.

The enantioselectivities (α) and the thermodynamic parameters $\Delta H^\ddagger$, $\Delta S^\ddagger$, and $\Delta G^\ddagger$ for the more stable complex **65**·(S)-**91a** and the difference in Gibbs energy ($\Delta\Delta G^\ddagger$) in the chiral discrimination process can be separately determined by ^1H NMR titrations in solution and by HPLC. On the basis of the HPLC and NMR data combined with the structural data

of cellulose trisphenylcarbamate (CTPC) determined by X-ray analysis, a model structure for the **65** · (*S*)-**91a** complex can be proposed (Figure 21).^[85] According to this model (*S*)-**91a** is in a chiral groove of **65** and directed toward the H2 proton of the glucose through intermolecular hydrogen bonds between the OH protons and the carbonyl oxygen atoms of **65** (dashed line). This model satisfactorily explains all the NMR data, including the intermolecular NOE data and the results of the titrations. Moreover, the difficulty of 10,10'-dihydroxy-9,9'-biphenanthryl (**92**) to discriminate between enantiomers is

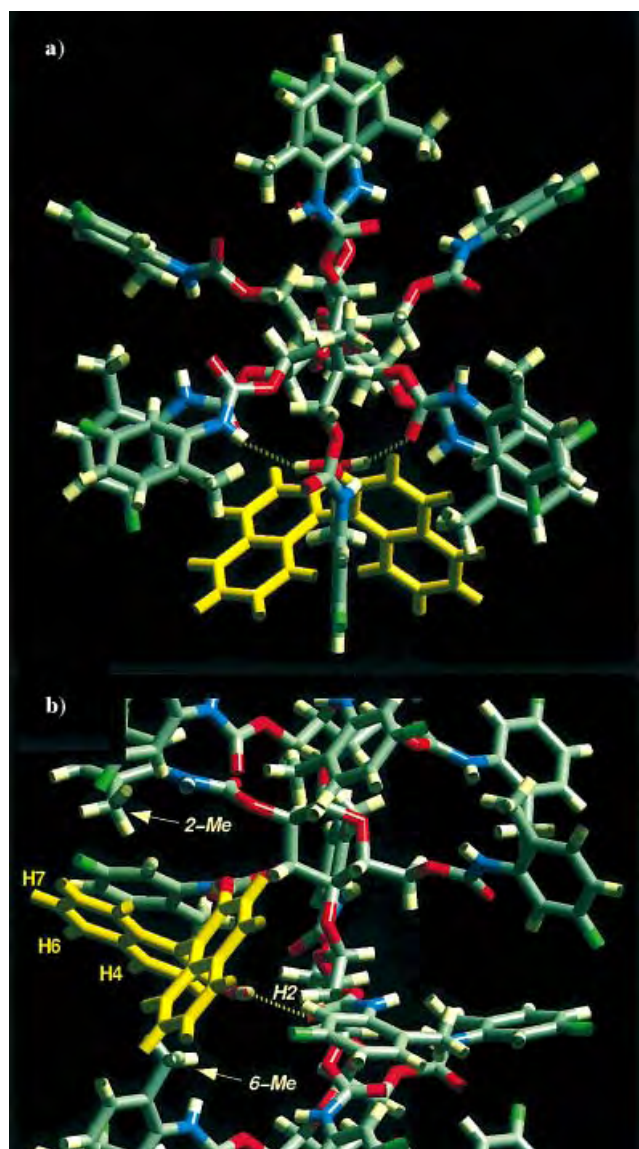


Figure 21. Calculated structure of the complex **65** · (*S*)-**91a**. The (*S*)-**91a** portion is shown in yellow, and dashed lines correspond to hydrogen bonds. a) View perpendicular to the helix axis; b) expanded region of the same structural model as viewed along the helix axis. Reproduced with permission from ref. [85].

reasonably explained: The bulky phenanthryl groups of **92** can prevent the formation of hydrogen bonds. These results should provide useful information both for understanding the mechanism for discrimination between enantiomers on other

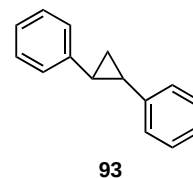
polysaccharide-based CSPs and for designing even better CSPs.

Commercially available amylose-based CSPs **78** and **89** were recently found to be soluble in chloroform, and can discriminate between enantiomers for many compounds in NMR spectroscopy as well as HPLC.^[86] Further NMR studies, especially NOESY experiments coupled with a computer modeling, will certainly serve to propose a rationale for discrimination between enantiomers at a molecular level.

4.2.3. Computational Studies

A computer simulation involving molecular-mechanics (MM) and molecular-dynamics (MD) calculations may be a useful and effective approach for elucidating the mechanism for the recognition of chirality on other CDCl₃-insoluble phenylcarbamate derivatives of polysaccharides, and for predicting the order of elution for the enantiomers. Lipkowitz et al. have been extensively studying the mechanism for the recognition of chirality from theoretical viewpoints with the aid of chromatography on CSPs made from optically active small molecules.^[70] The interaction energies between the CSPs and the enantiomers were calculated by MM, MD, and quantum-mechanical calculations, and the mechanisms for the recognition of chirality have been proposed on the basis of the above calculations.

We recently carried out MM calculations on the interaction energies between CTPC^[87] or CDMPC^[88] and *trans*-stilbene oxide (**69**) or *trans*-1,2-diphenylcyclopropane (**93**) to gain insight into the mechanism for the recognition of chirality on CDCl₃-insoluble phenylcarbamate derivatives. CTPC is a good candidate for such a study, because its structure was postulated on the basis of an X-ray analysis^[45] and it shows a high ability to recognize chirality for HPLC as a CSP as well as a CDMPC. In a chromatographic enantioseparation, **69** was completely resolved on CTPC ($\alpha = 1.46$) and CDMPC ($\alpha = 1.68$). However, the order of elution is reversed: The *R,R* isomer eluted first followed by the *S,S* isomer on CTPC, whereas the *S,S* isomer eluted first on CDMPC. Racemic **93** was not separated on CTPC ($\alpha \approx 1$).



The calculations were performed by two methods:

- 1) A molecule of the enantiomer was placed in space and rotated at specified angles around each NH proton in the 2-, 3-, and 6-positions of the carbamoyl group of CTPC or CDMPC, which may be considered to be the most important adsorption site for **69** on the basis of chromatographic resolution and NMR studies. The interaction energy was then calculated at each point of a grid on the CTPC or CDMPC molecule with all possible combinations of the rotation angles of the enantiomer. The calculation results were evaluated with the lowest interaction energy and the distribution of the interaction energy.

- 2) A molecule of the enantiomer with a particular orientation was randomly generated with the Monte Carlo meth-

od^[89a] on the surface of a CTPC or CDMPC molecule defined by a particular van der Waals radius, which was obtained with the technique of “blowing up” the atomic radii.^[89b] MM calculations between the molecules were then performed step by step. The results of these calculations were evaluated with the averaged interaction energy.

In both calculations an octamer or nanomer of CTPC and CDMPC molecules, whose structure was constructed based on the X-ray data of CTPC followed by optimization with MM and MD calculations, was used. Enantiomers were generated on the middle part of the polymers so as to avoid the influence of the end groups of the polymers.

Although they will not be described in detail here, the results of both calculations were in good agreement with the observed chromatographic resolution on CTPC and CDMPC.^[87, 88] The calculations suggested that the lowest or averaged interaction energy between CTPC and (*S,S*)-**69** is lower than that between CTPC and (*R,R*)-**69**, whereas a reversed enantiomer preference was observed for CDMPC and **69**. This indicates that (*S,S*)-**69** may interact more closely with CTPC than (*R,R*)-**69**, which in turn interacts more strongly with CDMPC.

Figure 22 provides a graphical view of the interaction between CTPC and (*S,S*)-**69**. Compound (*S,S*)-**69** is bound in a chiral groove, and each phenyl group may interact with the phenyl groups of CTPC through π – π interactions; the ether oxygen atom of (*S,S*)-**69** is located near the NH proton of CTPC and forms a hydrogen bond. Although the same calculation was performed for **93** and CTPC, almost no different interaction energy was observed for the enantiomers.

The reason why CDMPC shows the opposite enantioselectivity toward **69** is not clear at present. The optimized structure of CDMPC (Figure 23) shows a similar left-handed 3/2 helix as for CTPC, but the aromatic rings are arranged differently. This may be responsible for the reversed enantioselectivity of CTPC and CDMPC. CTPC and CDMPC also

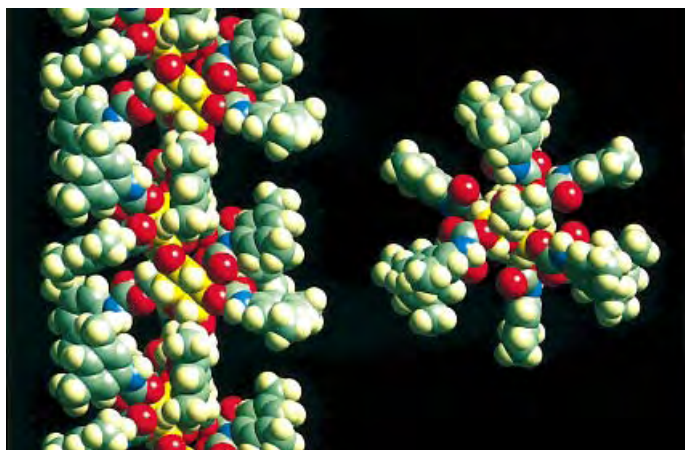


Figure 23. Optimized structure of CDMPC. The glucose carbon atoms of CDMPC are shown in yellow for clarity. View along the helix axis (left) and perpendicular to the helix axis (right).

behave differently in dilute solutions: Norisue et al. reported that CDMPC exhibits pronounced optical anisotropy, in contrast to other cellulose derivatives including CTPC, which may be related to the characteristics of CDMPC.^[90]

In the above calculations, interactions between a single chain of the polysaccharides and an enantiomer are taken into consideration, since polar racemates may interact preferentially with polar carbamate residues inside the polymer chain. However, besides these polar interactions, the π – π interaction between the phenyl group of a CTPC derivative and the aromatic groups of a solute may play a role in the recognition of chirality, because several nonpolar aromatic compounds have also been resolved.^[15, 49b] Especially under reverse-phase conditions with aqueous eluents, certain kinds of hydrophobic chiral cavities between the CTPC chains (Figure 24) must play a dominant role for effective recognition of chirality. Further computational studies of this system will be useful.

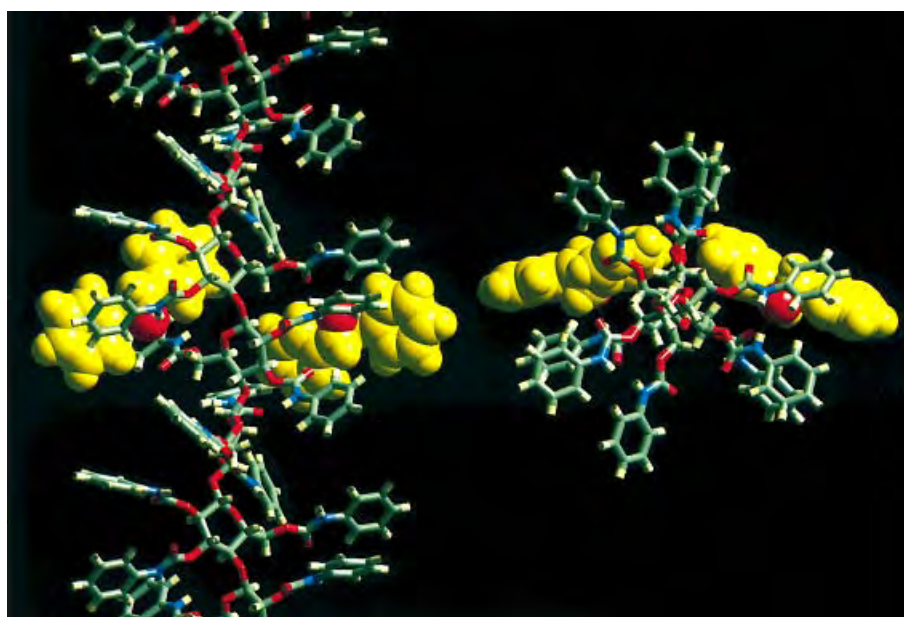


Figure 22. Calculated structure of complex CTPC · (*S,S*)-**69** (yellow) formed through hydrogen bonds. View along the helix axis (left) and perpendicular to the helix axis (right).

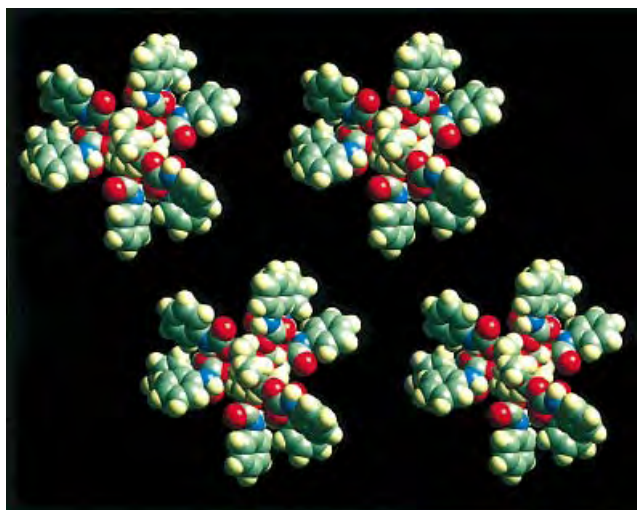
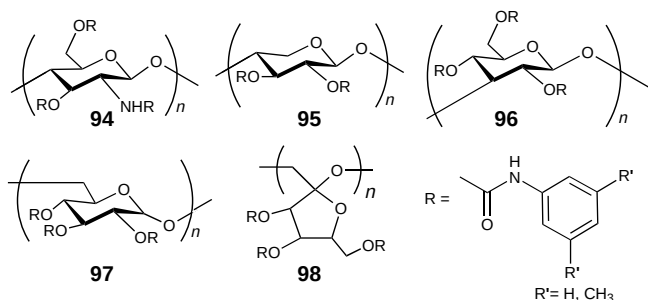


Figure 24. Calculated structures of CTPC aggregates as viewed perpendicular to the helix axis.

5. Other Phenylcarbamates of Polysaccharides, Oligosaccharides, and Cyclodextrins

Phenylcarbamates of other polysaccharides such as chitosan (**94**), xylan (**95**), curdlan (**96**), dextran (**97**), and inulin (**98**) were also prepared and used as CSPs.^[91] The abilities to



recognize chirality depended markedly on the nature of the monosaccharide units and position and type of the linkage. Among the polysaccharide derivatives, the 3,5-dimethylphenylcarbamates of chitosan and xylan show a relatively high ability to recognize chirality, although the 3,5-dimethylphenylcarbamates of cellulose and amylose often exhibit better resolving power. However, some racemates were better resolved on the phenylcarbamates than on the corresponding cellulose and amylose derivatives. For instance, $[\text{Cr}(\text{acac})_3]$ and $[\text{Co}(\text{acac})_3]$ (**76**) were more efficiently resolved on **95b** ($\text{R}' = \text{CH}_3$; Figure 25). The ability of a CSP derived from phenylcarbamoylated chitin to recognize chirality is very low.^[91c] Phenylcarbamates of amylopectin, one of the constituents of starch which is made up of highly branched chains of glucose units, exhibit an enantioselectivity that is rather similar to that of the corresponding amylose derivative ADMPC.^[91d]

3,5-Dimethylphenylcarbamates of celooligosaccharides (**99**) and 3,5-dimethylphenyl-, 4-chloro-, and 4-bromophenylcarbamates of maltooligosaccharides (**100**) were prepared, and their abilities to recognize chirality were compared with

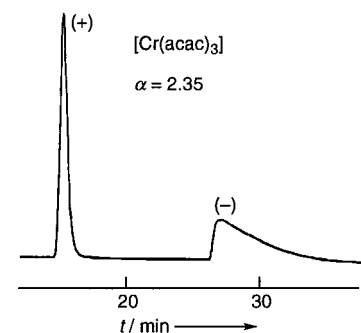
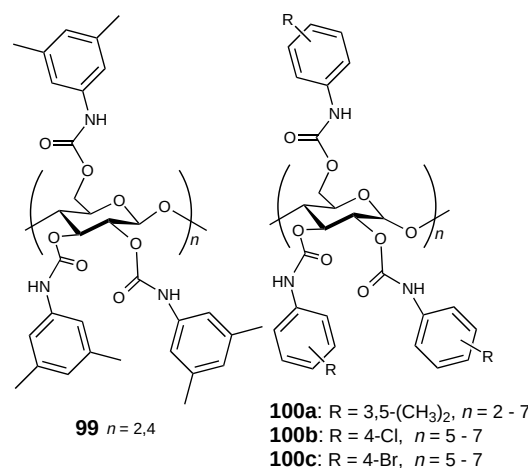


Figure 25. Separation of $(\pm)$ -chromium(III) tris(acetylacetonate) on bis(3,5-dimethylphenylcarbamate) of xylan (**95**, $\text{R} = \text{CH}_3$) with hexane/2-propanol (9/1) as the eluent. Column: 25×0.46 cm (inner diameter); flow rate: 0.5 mL min^{-1} .

those of the corresponding polysaccharide derivatives to obtain information on the influence of the higher order structures of the polysaccharide derivatives.^[92a,b] The ability of



99 to recognize chirality is lower than that of the cellulose derivative CDMPC, whereas the resolving ability of **100a** is not so different from that of the corresponding amylose derivatives when $n = 4 - 7$. This indicates that the celooligosaccharides have a different structure from that of CDMPC, whereas the maltooligosaccharides have an ordered structure similar to those of the amylose derivatives when n is greater than 4. These explanations were supported by conformational studies of the oligomers by CD spectroscopy.^[92a,b] Chemically bonded type CSPs derived from benzoylglucosamine and 1-(1-naphthyl)ethylcarbamoylated maltooligosaccharides were prepared, and their resolving abilities were evaluated; some racemates were completely resolved on the CSPs.^[92c,d]

MM and MD calculations of the 4-chloro- and 4-bromophenylcarbamates of maltohexaose, models of the amylose derivatives, were performed, and their conformations were examined to propose a model structure for the corresponding amylose phenylcarbamates.^[92b] The initial structures were constructed from the crystal structure data of amylose, which has a left-handed 6/1-helical structure.^[93a] The conformations of the 4-chloro- and 4-bromophenylcarbamates of maltohexaose were transformed from a left-handed 6/1 helix to almost left-handed 5/1 and 4/1 helices, respectively, after MD

simulations.^[92b] Figure 26 shows the structures of native amylose (a) and a model of the amylose trisphenylcarbamate (b) derived from the calculated structure of 4-bromophenylcarbamate of maltohexaose. The helical pitch of the amylose phenylcarbamate is similar to that of amylose tris(phenylcarbamate) proposed by Zugenmaier et al.^[46] Although the

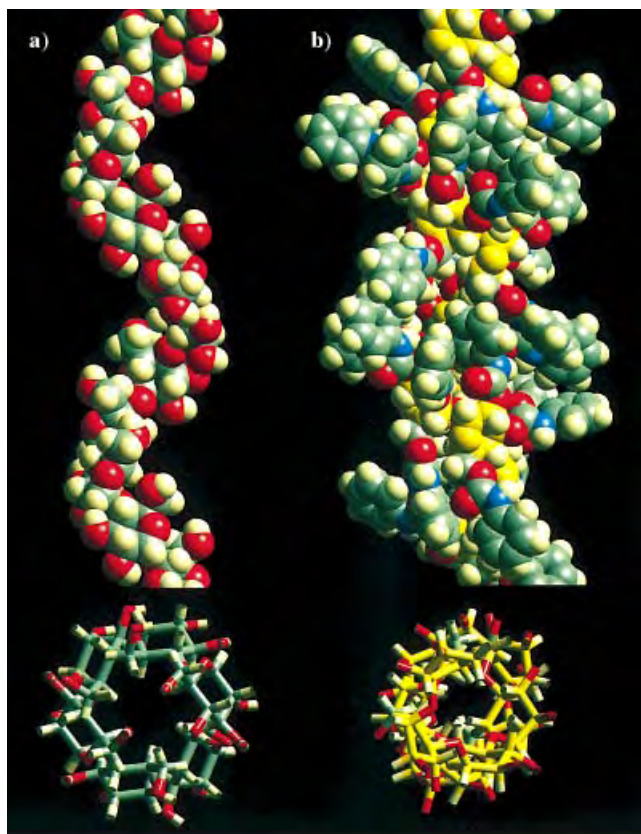
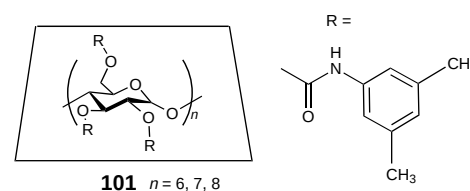


Figure 26. a) Crystal structure of native amylose. b) A possible structure of ATPC. The structure of ATPC was constructed on the basis of the optimized structure of 4-bromophenylcarbamates of maltohexaose.^[92b] The glucose carbon atoms of ATPC are shown in yellow. View along the helix axis (top) and perpendicular to the helix axis (bottom); all side groups and protons are omitted for clarity. The initial atomic coordinates of native amylose were taken from the crystal structure data^[93a] in the Cambridge Structural Database 3D Graphics Search System.^[93b]

reason for the difference in the structures of the oligomers depending on the kind of the halogen atom is not clear, the present results indicate that the amylose phenylcarbamate derivatives may not have a structure similar to that of native amylose (a left-handed 6/1 helix), but rather contain a tight, left-handed 4/1 or 5/1 helix. Wainer et al. also proposed a model of ADMPC on the basis of computer simulations; the helix seems to be larger than a 4/1 or 5/1 helix.^[94]

Cyclic oligosaccharides, cyclodextrins, consist of the same α -D-glucose unit as amylose and can separate many racemates by an inclusion mechanism in GC,^[95] HPCE,^[29, 30] and HPLC.^[11a] The CSPs consisting of cyclodextrins bonded to silica gel are commercially available. On the other hand, the abilities of 3,5-dimethylphenylcarbamates of cyclodextrins **101** to recognize chirality are quite different from those of native cyclodextrins and ADMPC. This indicates that the



amylose derivative must possess a higher order structure that is different from that of the cyclodextrin derivatives.^[92a, 96]

Figure 27 shows the structures of β -cyclodextrin^[97] (a) and its 3,5-dimethylphenylcarbamate (b): Both rims of the derivatized cyclodextrin are covered with 3,5-dimethylphenylcarbamate residues, and, therefore, the enantioselectivity of the derivatized phase may be governed by the interaction with the polar carbamate residues and may be independent of the inclusion known for native β -cyclodextrin. These phenylcarbamates of linear and cyclic oligomers are soluble in CDCl_3 and exhibit chiral discrimination in NMR spectroscopy as well as HPLC;^[83b] the results of NMR spectroscopy, in particular for the cellooligosaccharides, may be useful for understanding the mechanism for the recognition of chirality by CDMPC, which is not soluble in chloroform.

6. Miscellaneous Applications

The polysaccharide derivatives have a great merit for the easy preparation of a film (membrane), which can be used as a new device in the enantiomer-separation system.^[98] The CDMPC membrane prepared by coating a solution of CDMPC in THF on a Teflon membrane filter as a support showed a high ability for enantioselective adsorption; for instance, oxprenolol (**81b**) enriched in the *S* isomer up to 60% *ee* was obtained by a single adsorption–desorption procedure. This system can be applied to the enantioselective permeation of oxprenolol in an organic media.^[99] Oxprenolol obtained through the membrane was enriched in the *S* isomer up to 50% *ee* in the initial stage, and enrichment in the *R* isomer for a source phase (23% *ee*) was achieved.

CDMPC can also be utilized as a “chiral belt” for the continuous, rapid, and preparative resolution of **81b** with a motor.^[100] Figure 28 illustrates an apparatus used for the resolution. A CDMPC belt (111 cm long) was fitted with the apparatus and rotated at a constant speed (66 cm h^{-1}) by a motor. A) The belt entered a solution of racemic **81b** ($100 \text{ mg } 100 \text{ mL}^{-1}$) for enantioselective adsorption, B) hexane/2-propanol (95/5) for enantioselective desorption, C) hexane/2-propanol (7/3) for desorption, and finally D) hexane for rinsing. The source phase A gradually became rich in the *R* isomer, and the enantiomeric excess reached 28% after 8 h when 65 mg of **81b** was transported from the source phase. The receiving phase C became rich in the *S* isomer with up to 68% *ee* at the initial stage (after 2 h). The present method can be scaled up without any difficulty, and may be used for a large-scale separation.

The separation of enantiomers through chiral membranes, such as liquid membranes with a chiral mobile carrier^[101] or solid chiral polymer membranes,^[102] is attractive for the

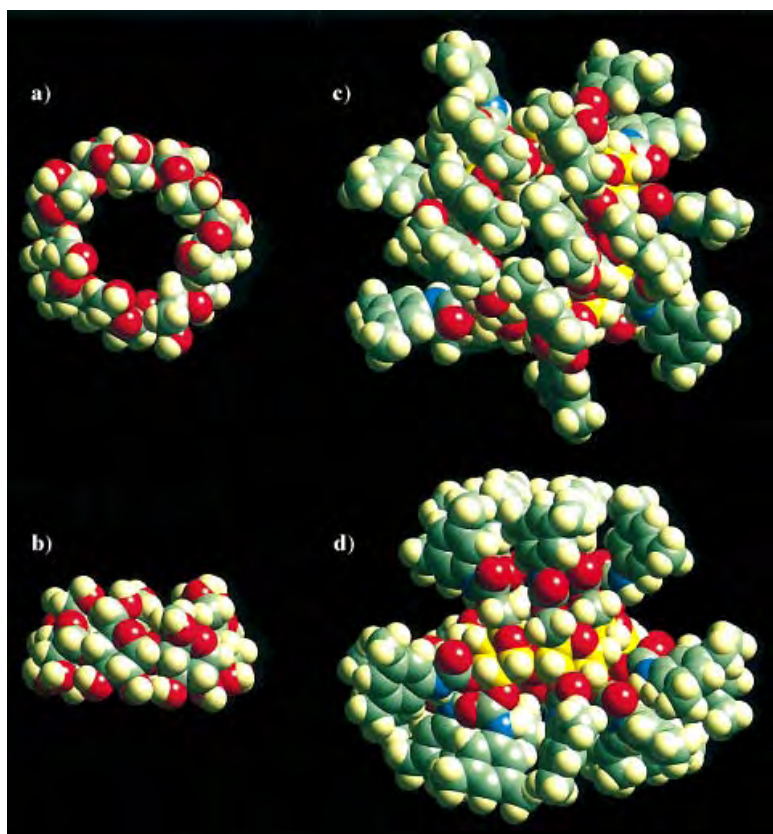


Figure 27. Plan (a, c) and side views (b, d) of the crystal structure of β -cyclodextrin (a, b) and the possible structure of 3,5-dimethylphenylcarbamoylated β -cyclodextrin (c, d) optimized by MM and MD calculations. The glucose carbon atoms of phenylcarbamoylated β -cyclodextrin are shown in yellow for clarity. The initial atomic coordinates of β -cyclodextrin were taken from the crystal structure data^[97] in the Cambridge Structural Database 3D Graphics Search System.^[93b]

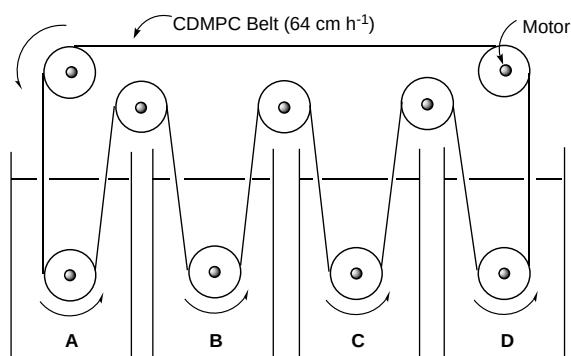
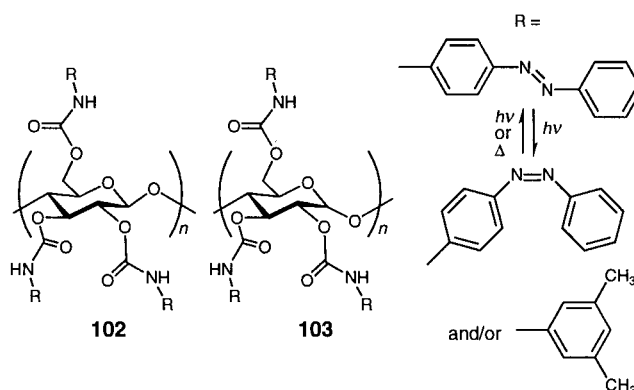


Figure 28. An apparatus used in the resolution of ($\pm$)-oxprenolol (**81b**) with a chiral belt. See text for further details.

further development of separation technology in this field. However, their efficiency and enantioselectivity are, at present, not high enough for practical use.

The polysaccharide derivative membranes bearing a photo-responsive 4-phenylazophenyl residue (**102** and **103**) can sensitively respond to light and/or heat and exhibit interesting chiral properties in enantioselective adsorption.^[103a] The ability to recognize chirality is influenced by *trans*–*cis* isomerization of the pendant azobenzene residues. The *trans* membranes showed higher enantioselectivity than the *cis* membranes, and the selectivity could be reversibly controlled in an on–off fashion by photoisomerization of the pendant azobenzene moieties. When the azo group of the membrane **102** was *trans*-oriented, **81b** with 43% *ee* was adsorbed, and when it was *cis*-oriented, **81b** with 38% *ee* was adsorbed



(Figure 29). Thus, the photocontrol of the recognition of chirality was realized for the first time with the photo-responsive chiral polymer membranes. Interestingly, recognition of chirality by a CSP consisting of **102** depends on the

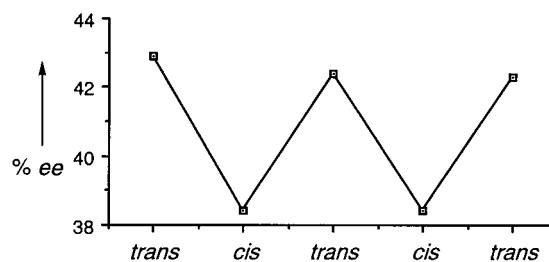


Figure 29. Change in the enantiomeric excesses (*ee*) of **81b** adsorbed on the **102** membrane during the *trans*–*cis* isomerization (irradiation time 4 h for *trans*→*cis*, 2 h for *cis*→*trans*). The portions of *trans* and *cis* were 100 and 80%, respectively.

proportion of *trans* or *cis* orientations of the azobenzene residues.^[103b]

Polysaccharides and their derivatives were also used as chiral catalysts^[104] and chiral templates^[105] in asymmetric synthesis and asymmetric polymerization, respectively. Bredig et al. used diethylaminocellulose as the first polymeric chiral catalyst for an asymmetric cyanohydrin reaction in 1932.^[104a] Relatively high optical yields of up to 77% were obtained in the hydrogenation of 2-phenyl-1-butene with a complex made up of rhodium and 2,3-*O*-bis(diphenylphosphanyl)-6-*O*-triphenylmethylcellulose.^[104b] Similar rhodium catalysts derived from D-glucose show very high enantioselectivities of up to 99% *ee* in asymmetric hydrogenations.^[104c]

7. Summary and Outlook

We have prepared many polysaccharide derivatives and have evaluated them as CSPs for HPLC; some of them are commercially available.^[106] A wide range of racemates including aliphatic and aromatic compounds with or without functional groups and many drugs have been resolved on the CSPs. Among the CSPs prepared so far, 3,5-dimethylphenylcarbamates of cellulose (Chiralcel OD), amylose (Chiralpak AD), and cellulose tris(4-methylbenzoate) (Chiralcel OJ) are excellent for recognizing chirality. This allowed the successful resolution of more than 80% of the racemates tested.^[15g,h] These CSPs can be used not only for analytical purposes, but also for the preparative-scale separation of enantiomers.

The utility of the polysaccharide-based CSPs for the large-scale preparative separation of enantiomers has been realized. Francotte has reviewed the preparative-scale chromatographic resolution of enantiomers, and concludes that even in the preparative resolutions about 70% of the CSPs used for this purpose are derived from polysaccharide derivatives.^[17c] In particular, the recently developed simulated moving-bed (SMB) chromatography has a great potential for the industrial-scale preparation of pure enantiomers, and has been utilized.^[3b, 7b, 17c, 107] SMB chromatography is a continuous solid–liquid countercurrent process. It allows the continuous introduction of the feed and thus permits large amounts of eluent to be saved.

The elucidation of a mechanism for discrimination between enantiomers on the CSPs at a molecular level appears to be essential for further developments in this exciting area. Elucidation of the exact mechanism for the discrimination of chirality on the CSPs must serve to predict the order in which enantiomers are eluted and to develop a superior polysaccharide-based CSP.

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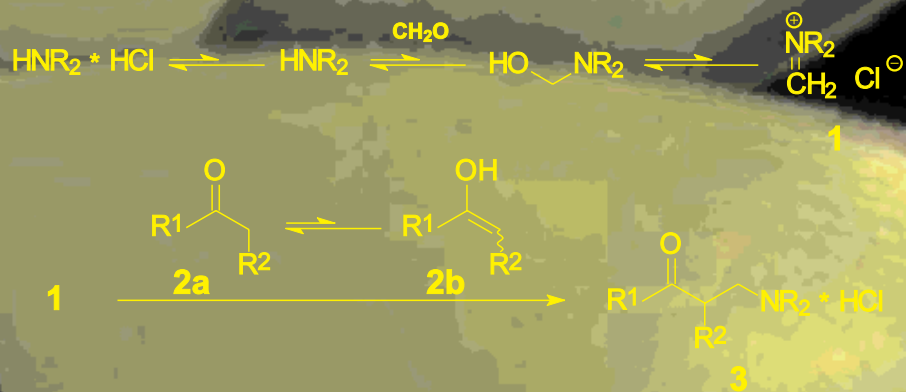
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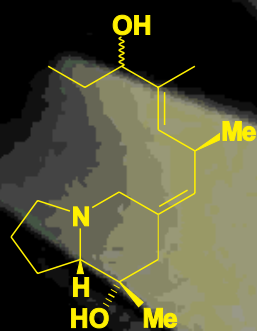
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- [106] Coated-type, cellulose-based CSPs are available from Daicel: triacetate (**17**, Chiralcel OA), tribenzoate (**24**, Chiralcel OB), tris(4-methylbenzoate) (**21**, Chiralcel OJ), tricinamate (Chiralcel OK), trisphenylcarbamate (**40**, Chiralcel OC), tris(4-methylphenylcarbamate) (**34**, Chiralcel OG), tris(4-chlorophenylcarbamate) (**42**, Chiralcel OF), tris(3,5-dimethylphenylcarbamate) (**49**, Chiralcel OD). Microcrystalline CTA-I (**17**) is also available from Daicel (Chiralcel CA-I), Merck (Cellulose triacetate), and Macherey-Nagel (Cellulose Ce-AC-40XF). Coated-type, amylose-based CSPs are commercialized from Daicel: tris(3,5-dimethylphenylcarbamate) (**78**, Chiralpak AD), tris((S)-1-phenylethylcarbamate) (**89**, Chiralpak AS).
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What does Carl Mannich



Dendrobates pumilio
(Costa Rica)



Pumiliotoxin

have to do with frogs ?

Modern Variants of the Mannich Reaction

Michael Arend, Bernhard Westermann, and Nikolaus Risch*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

The Mannich reaction is a classical method for the preparation of β -amino ketones and aldehydes (Mannich bases) and, as such, is one of the most important basic reaction types in organic chemistry. It is the key step in the synthesis of numerous pharmaceuticals and natural products. Mannich bases and derivatives such as 1,3-amino alcohols or Michael acceptors, which are easily formed from Mannich bases, are particularly versatile synthetic intermediates and find great use in, for example, medicinal chemistry. Nevertheless, when seen from a modern viewpoint, the potential of the classical intermolecular Mannich reaction is rather modest. Thus the range of application is limited (e.g. confined to

aminomethylation), and in many cases undesired side products are formed. Additionally, the ability to control regio- and stereoselectivity is generally unsatisfactory. However, the exceptional attractiveness of Mannich bases and their derivatives makes the challenge of overcoming these drawbacks worthwhile. Modern variants, whose range of applications is much wider than that of the classical methodology, and which can be carried out with effective control of regio- and stereoselectivity, form the focus of this review. Intramolecular Mannich reactions are much more versatile than corresponding intermolecular versions. Because of this, they have always excited the imagination of chemists.

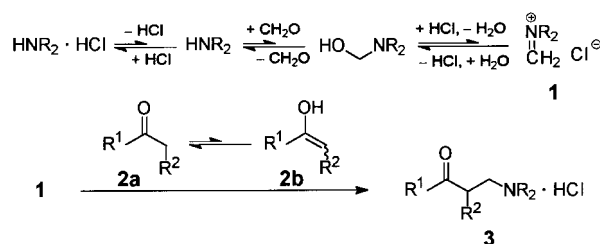
For example, such intramolecular reactions are used for the biomimetic preparation of natural products, and for many other applications. In general, one can use the Mannich reaction as part of a tandem reaction sequence for the elegant and often deceptively simple construction of complex target molecules. Current applications of this chemistry in the preparation of pharmaceutical and natural products will be presented.

Keywords: aminoalkylation • asymmetric synthesis • biomimetic synthesis • domino reactions • Mannich bases

1. Introduction

The aminoalkylation of CH-acidic compounds was described by several authors as early as the 19th. century. However, it was Carl Mannich who was the first to recognize the enormous significance of this reaction type, and it was he who extended the chemistry into a broad based synthetic methodology through systematic research. Since then this reaction that now carries his name has developed into one of the most important C–C bond-forming reactions in organic chemistry.^[1, 2]

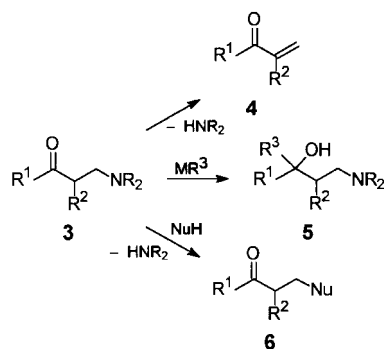
In practice, enolizable aldehydes or ketones serve as the CH-acidic substrate for Mannich reactions. In the most important variation, the carbonyl compound is heated with formaldehyde and an amine hydrochloride in a protic solvent. A simplified mechanism is given in Scheme 1. It is assumed



Scheme 1. Simplified mechanism of the Mannich reaction.

that methylene iminium salts **1** are formed in tiny amounts, by a series of equilibrium reactions. These then react with the enol tautomer **2b** of the carbonyl compound **2a**, also present in very small equilibrium concentrations, to give the hydrochloride of the β -aminocarbonyl compound **3**. These so-called Mannich bases are versatile synthetic building blocks, which can easily be converted into a range of useful and valuable derivatives (Scheme 2). Such derivatives include Michael acceptors **4** (elimination of the amine HNR_2), 1,3-amino alcohols **5** (reduction or addition of organometallic com-

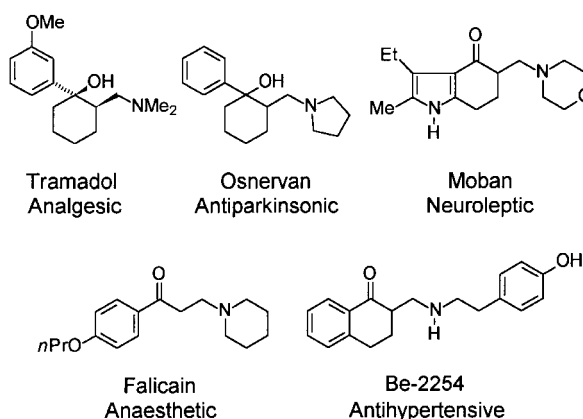
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Scheme 2. Mannich bases as synthetic building blocks.

pounds) and functionalized carbonyl compounds **6** (substitution of NR_2 by nucleophiles).^[1] Mannich bases and their derivatives have many attractive applications, for example in plant protection and in paint and polymer chemistry (hardeners, cross-linkers, and reaction accelerators).^[1] However, the most important application by far is in the area of pharmaceutical products.^[1, 3] A small selection of these is represented in Scheme 3. At the moment, the use of Mannich bases in cancer therapy (as cytostatics) is one of several current areas of research.^[3c, d]

The classical intermolecular Mannich reaction is, however, plagued by a number of serious disadvantages:^[1] Due to the



Scheme 3. Application of Mannich bases and their derivatives in medicine.

drastic reaction conditions and the long reaction times, unwanted side reactions often take place. Major problems here are deamination and the formation of methylene bisketones **7**. Single products **3** are generally only obtained when secondary amines are used. If one uses a primary amine or ammonia as the amine component, reaction can continue until all the H atoms on the nitrogen are replaced. As a consequence, one obtains, in addition to the desired product **3**, the other Mannich bases **8** and **9** as major components. Ketones with two reactive α -positions must be used in large

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N. Risch



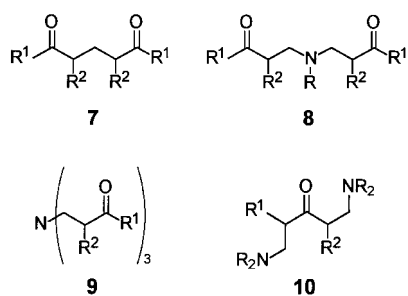
M. Arend



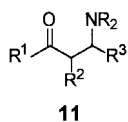
B. Westermann

Michael Arend, born in 1966 in Paderborn, studied chemistry at the Universität Paderborn (1987–1993) and obtained his doctorate in 1996 in the research group of N. Risch with a thesis on regio- and stereoselective synthesis of Mannich bases. In the summer of 1997 he was awarded a Feodor-Lynen fellowship by the Alexander-von-Humboldt Foundation and has since been working as postdoc at the University of Florida, Gainesville (USA) with A. R. Katritzky.

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excess, in order to avoid the production of bis-Mannich bases **10**. In the case of unsymmetrical ketones a further problem is encountered. The regioselectivity cannot be controlled to any significant extent and is often strongly dependent on reaction conditions. Additionally, and with very few exceptions, one can only use formaldehyde.^[4] Therefore, Mannich bases such as **11**, which would very probably also be extremely attractive intermediates, are not accessible by this method. A further limitation is that only aldehydes and ketones can normally be



used, and other carbonyl compounds such as carboxylic acids and their derivatives cannot be aminomethylated. In addition, the classical Mannich reaction is not suited to the enantioselective synthesis of β -amino ketones and amino aldehydes. Thus, the majority of pharmaceutical products, which are derived from the Mannich reaction, are used in the form of racemates. The application of enantiomerically pure Mannich bases is only possible when these are available by separation of the racemate.^[1, 3a,b] This problem becomes more severe when one takes into consideration the increasing importance of stereochemically pure pharmaceuticals (the avoidance of “isomer ballast” and of undesirable side effects).^[5]

Due to the very attractive nature of Mannich bases, there have been many attempts to find alternative synthetic routes to these compounds, which do not suffer the severe drawbacks of the classical procedure. Thus, numerous methods have been developed for the indirect synthesis of β -amino aldehydes and ketones,^[6] as well as β -amino carboxylic acid derivatives,^[7] which do not proceed by aminomethylation or aminoalkylation. Modern versions of the Mannich reaction usually allow a distinctly simpler entry into β -aminocarbonyl compounds through the use of preformed electrophiles (e.g., iminium salts or imines) or nucleophiles (enolates, enol ethers, and enamines). These methods allow, at least in principle, all the limitations of the classical method to be overcome. The level of performance and the versatility of these methods have already been powerfully demonstrated in the synthesis of β -amino acid derivatives and β -lactams. Since this work has already been adequately documented,^[7a, 8, 9] we will restrict ourselves here to modern methods of β -aminomethylation and β -aminoalkylation of aldehydes, ketones, and their derivatives. Emphasis is placed on regioselective and stereoselective variants. Recently, several notable advances have been made in these areas.

Intramolecular Mannich reactions possess a significantly wider range of applications than their intermolecular counter-

parts. Their extremely high value—particularly as the key step in domino reaction sequences—has long been recognized and used, amongst other applications, in biomimetic natural product synthesis. Since the first ground-breaking work, such as Robinson's synthesis of tropinone,^[10a] this work has had a stormy development. Modern methods such as the combination of [3,3] sigmatropic rearrangements with intramolecular aminoalkylation, or powerful new methods for the generation of iminium salts under mild reaction conditions have allowed simple highly regio- and stereoselective access to a large number of complex target molecules. Thanks to this unique synthetic potential—perfectly characterized by the title “Mannich Magic” by Heathcock^[10b]—the intramolecular Mannich reaction has never lost its fascination. It is in the best traditions an eternally young classic, ever ready for the challenges of modern synthetic chemistry. In the context of this review modern variants and current applications of the intramolecular Mannich reaction will be discussed.

Vinylogous versions of the Mannich reaction (γ -aminoalkylation of α,β -unsaturated carbonyl compounds or their derivatives) have rarely been reported. The enormous potential of this method is only now beginning to be employed synthetically. In particular, the possibility of using the vinylogous Mannich reaction to access complex, highly functionalized compounds, which would otherwise be accessible only with great difficulty (if at all), is now exercising the imagination of chemists. Current applications of this chemistry will also be described.

2. Preformed Mannich Reagents: Rejuvenation of the Classic

2.1. General Discussion

The serious limitations of the classical Mannich reaction on the one hand, and the versatility of β -aminocarbonyl compounds on the other,^[1] has led to the search for significantly simpler synthetic methodologies. The key to success is the use of preformed Mannich reagents.^[8c] In comparison to the classical Mannich conditions, these preformed reagents guarantee a higher concentration of the electrophile, leading to lower reaction temperatures and much shorter reaction times. As a consequence, many undesired side reactions, which so often cause problems in the Mannich reaction, are avoided, even with sensitive substrates. Furthermore, one can avoid the use of protic solvents. In this way the carbonyl component can be replaced with much more reactive synthetic equivalents such as enolates. This leads to a greatly extended spectrum of application for the reaction. One can therefore also successfully use reagents which are normally impossible under the classical conditions (e.g. sterically very demanding substrates or carboxylic acid derivatives). In addition, the reaction is not restricted to aminomethylation, but aminoalkylation is also possible. It is also possible to carry out the reaction with high degrees of regio- and stereoselectivity. The most important Mannich reagents will now be briefly discussed.

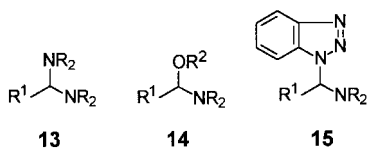
2.2. Imines

Imines **12** ($R^1 = \text{alkyl, aryl}$)^[11] are generally much less electrophilic than the corresponding aldehyde. This drawback can, however, often be overcome by activation with Lewis acids. The use of enolizable imines should allow the reaction to proceed under very mild conditions with the avoidance of aldol-type self-condensation reactions.^[8c] Formaldehyde imines ($R^1 = \text{H}$) are generally only stable at low temperatures. They are therefore best generated in situ or, alternatively, a synthetic equivalent can be used.^[8c, 12]

Imines **12** and related compounds have often been used with a great deal of success in the stereoselective aminoalkylation of carboxylic acid derivatives.^[7a, 8, 9] It is therefore astonishing that so little work exists on the application of imines in the stereoselective synthesis of β -amino ketones.^[13] The possibilities of such chemistry should be thoroughly explored.

2.3. Aminals and N,O-Acetals

Aminals **13** and N,O-acetals **14** resemble imines in terms of their electrophilicity. They must, therefore, normally be activated by Lewis acids, in order to react with nucleophiles.



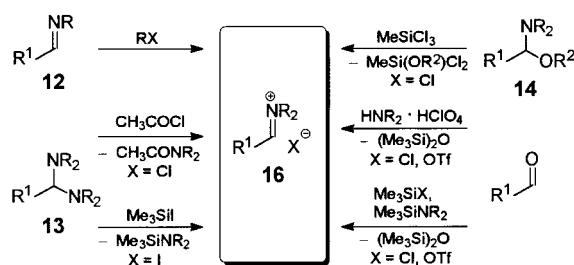
In this context, the formation of iminium intermediates has often been postulated (many times without real investigation) in an S_N1 -type of reaction. There are, however, indications that this behavior—even in the presence of Lewis acids—is not necessarily always the case.^[14] Only aminals **13** and N,O-acetals **14** which are derived from non-enolizable aldehydes (generally $R^1 = \text{H}$ or aryl) have been used as Mannich reagents. The reason for this may be that derivatives of aldehydes with α -H atoms have a tendency to decompose on heating or under acid catalysis (elimination of amines or alcohols, respectively).^[15] The benzotriazole aminals **15** represent a special case. These easily accessible compounds are very well suited for aminoalkylation, when derivatives of enolizable aldehydes or ketones are used, or when derivatives of primary amines are involved.^[12b] Benzotriazole aminals **15** have been used in the synthesis of, amongst others, β -aminocarbonyl compounds.^[16]

The application of aminals **13** and N,O-acetals **14** as Mannich reagents is still in its infancy. Nevertheless, noteworthy results have already been achieved. Particularly interesting examples are the regio- and enantioselective syntheses of β -amino ketones by the aminomethylation of silyl enol ethers,^[17] the use of the N,O-acetal $\text{MeOCH}_2\text{N}(\text{SiMe}_3)_2$ ^[18] as a synthetic equivalent for $[\text{CH}_2\text{NH}_2]^+$, the diastereoselective aminoalkylation of enolates with aminals^[16b, d, 19] and in situ generated N,O-acetals.^[20]

2.4. Iminium Salts

Iminium salts are generally readily accessible from basic chemicals.^[21] One can obtain them from, for example, the alkylation of imines **12**,^[21b] by cleavage of aminals **13** (e.g. with CH_3COCl ^[8a, 22a, b] or Me_3SiI ^[22c]), or N,O-acetals **14** (e.g. with MeSiCl_3).^[22d, e] This is also suitable for the preparation of sterically hindered iminium salts such as $[\text{H}_2\text{C}=\text{N}(\text{iPr})_2]^+\text{Cl}^-$ ^[22f]. Aldehydes can be converted to iminium salts by direct reaction with $\text{HNR}_2 \cdot \text{HClO}_4$ ^[22g, h] and with Me_3SiNR_2 and Me_3SiX ($\text{X} = \text{CF}_3\text{SO}_3, \text{Cl}$)^[22i, j] (Scheme 4). Other powerful synthetic methods are the conversion of enamines with protonic acids such as HCl ^[22k] or the generation of iminium salts from amine oxides with the aid of the Polonovski–Potier reaction.^[22m]

The iminium salts **16** are the most commonly applied Mannich reagents in the synthesis of β -amino ketones and

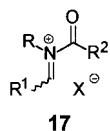


Scheme 4. Synthesis of iminium salts.

aldehydes.^[8c, 23] This is because they are more powerfully electrophilic than imines, aminals, and N,O-acetals. They are also suitable for the preparation of β -amino carboxylic acid derivatives.^[8c, 24] Basically, the preparative uses of these materials have been limited to three compounds: Eschenmoser's salt $[\text{H}_2\text{C}=\text{NMe}_2]^+\text{I}^-$ (**16a**),^[22c, 25a] the corresponding chloride salt (**16b**) made popular by Kinast and Tietze,^[22b] and the trifluoroacetate (**16c**) introduced by Potier et al.^[25b] In contrast to the typical salts **16a** and **16b** (both are commercially available), the trifluoroacetate **16c** is a distillable liquid.^[25c] Ternary iminium salts **16** ($R^1 \neq \text{H}$) have rarely been used for the Mannich reaction.^[24a, 26] There is much to suggest that these derivatives have clear advantages over other Mannich reagents. Their use makes possible several features, including effective control over the regio- and stereoselectivity of aminoalkylation.^[24a, 26a–d]

Iminium salts **16** are normally hygroscopic and sensitive towards hydrolysis. Under exclusion of moisture, they can, however, be stored over long periods. Nonetheless, salts with α -H atoms are often less stable.^[21, 22k] In such cases perchlorates are recommended, as are salts with complex anions (e.g. $[\text{AlCl}_4]^-$, $[\text{SbCl}_6]^-$).^[8a, 22k, 27] Typically, these are significantly more stable and less sensitive towards hydrolysis than salts with simple anions such as Cl^- . On the grounds of convenience, it is quite common to generate these salts **16** in situ.^[26a, 28] The reactivity of **16** towards nucleophiles^[29] decreases, as would be expected, in the sequence $R^1 = \text{H} > \text{aryl} > \text{alkyl}$. However, there is no simple rule relating to the influence of the anion on the reactivity of iminium salts.

Differences in reactivity are likely to be related, at least in part, to differences in solubility.^[25c] In order to achieve the best possible solubility of the iminium salts, and thereby the smoothest and most rapid course of reaction, it is recommended to use polar, aprotic solvents (e.g. MeCN, DMF, CH₂Cl₂). Significant effects of the anion of the iminium salts **16** on the stereochemical course of the addition of nucleophiles are generally not observed^[26a–d, 30a] (an exception is the aminomethylation of the trimethylsilyl enol ether of camphor^[30b] with **16a** or **16b**). However, anions can cause side reactions. Thus, it is known that, for example, iodide can promote the formation of undesired side products.^[8c] When one considers the latest developments and the numerous attractive applications of the related N-acyliminium salts **17**,^[31] it is obvious that the preparative opportunities for iminium salts **16**—despite their lower electrophilicity than **17**—are nowhere near exhausted.



3. Intermolecular Aminomethylations and Alkylations: Control of Regio- and Stereoselectivity and Methods for the Efficient Synthesis of Novel β -Amino Ketones and Aldehydes

3.1. Carbonyl Compounds

Methylene iminium salts **16** ($R^1 = H$) are extremely well suited to the aminomethylation of carbonyl compounds. In particular, ketones^[22b, 32] and aldehydes^[22b, 33] can be converted under mild conditions into the corresponding Mannich bases.

Table 1. Aminomethylation of carbonyl compounds with $[CH_2=NMe_2]^+Cl^-$ (**16b**).

No.	Carbonyl compound	Product	Yield [%]	Ref.
1			53 ^[a]	[22b]
2			82 ^[b]	[22b]
3			87 ^[c]	[32e]
4			83 ^[c,d]	[32g]
5			62 ^[e]	[33b]
6			78 ^[e]	[33b]

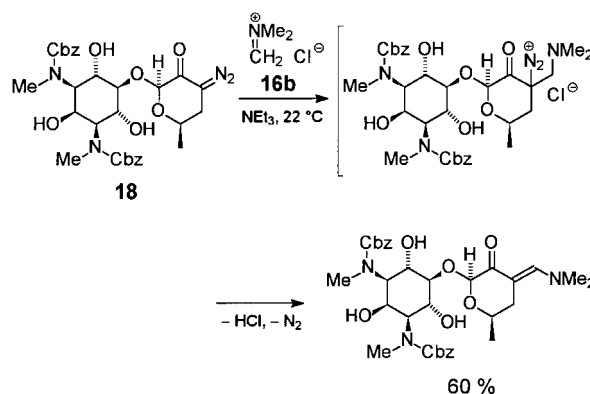
[a] MeCN, reflux, 45 min. [b] MeCN, 20°C, 2 h. [c] If the hydrochloride is dissolved in water, it decomposes immediately. [d] MeCN, 20°C, 3 min. [e] CH₂Cl₂, 20°C, 15 h. The aldehyde is generated in situ from the corresponding alcohol by Swern oxidation (DMSO, (COCl)₂, NEt₃). The yield is based on the alcohol. Under the reaction conditions, the primarily formed β -amino aldehyde is deaminated. Boc = *tert*-butoxycarbonyl.

In general, this methodology yields good results, even when the classical Mannich reaction fails or results in low yields. For example, this route is possible for the aminomethylation of sterically hindered carbonyl compounds (Table 1, No. 1, 2) or in the synthesis of sensitive Mannich bases (Table 1, No. 3, 4). In the course of aminomethylation of aldehydes RCH_2CHO , often only the α -methylene aldehydes are isolated despite the mild reaction conditions. This is due to the relative instability of the initially formed β -amino aldehydes (Table 1, No. 5, 6). Particularly notable is the fact that one can often convert even highly functionalized carbonyl compounds such as **18** into β -aminocarbonyl products with methylene iminium salts.^[34] This can be done without the formation of side products. There have also been some attempts to improve the regioselectivity of aminomethylation of ketones by use of iminium salts. The choice of reaction medium is crucial in these cases. Reaction in trifluoroacetic acid (reflux, 12–48 h) leads to preferential reaction at the more highly substituted α -position of the ketone. In acetonitrile (reflux, 72–96 h) the opposite selectivity is seen.^[35] However, a range of regioselective variants of the Mannich reaction exists, which are clearly milder and more efficient than these (see the following sections).

Apart from methylene iminium salts, many other reagents have been used to convert aldehydes and ketones into the corresponding α -methylenecarbonyl compounds. In general these are imines **12** (usually derivatives of aromatic aldehydes and amines),^[8c] amins **13**,^[36a–e] N,O-acetals **14**^[36f] or ternary iminium salts **16** ($R^1 \neq H$).^[26e, h]

3.2. Enolates

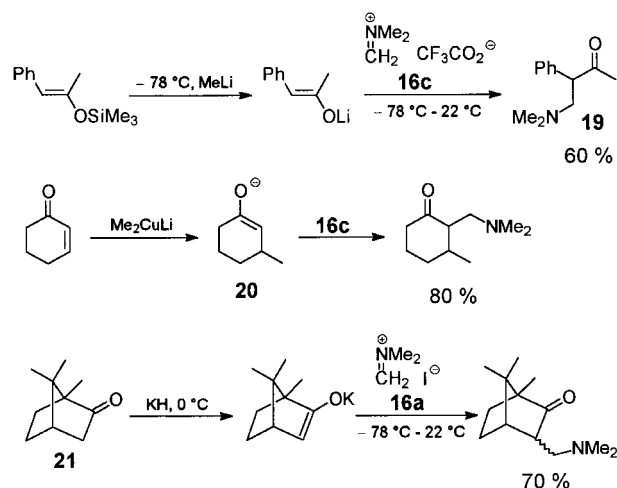
Traditionally the methylene iminium salts **16a**, **16b**, and **16c**^[16b, 25c, 30b, 37] are used to react with aldehyde or ketone enolates. These are normally generated in situ by the reaction of trimethylsilyl enol ethers^[25c, 37c, e] or enol carbonates^[37a, f] with MeLi or by deprotonation of the carbonyl compound with KH^[25c, 30b, 37d] or $Li[N(SiMe_3)_2]$ ^[16b] (in contrast to the deprotonation of carboxylic acid derivatives, the use of LDA is much less suitable^[25c, 37d]). Due to the additional experimental effort required, one is well-advised to use enolates in certain cases. Thus, for example, for the regioselective synthesis of β -amino ketones such as **19**^[25c] (Scheme 5), the extra



Scheme 5. Aminomethylation of the highly functionalized carbonyl compound **18** as example of the aminomethylation of enolates with iminium salts. Cbz = benzyloxycarbonyl.

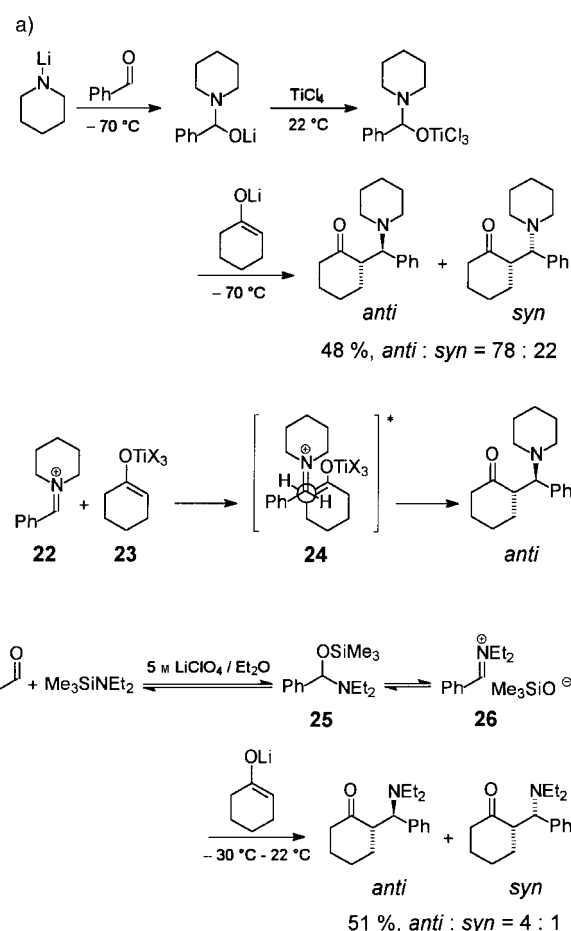
effort would be worthwhile. An elegant variation is the aminomethylation of enolates such as **20**,^[37e] which are generated in situ by the addition of nucleophiles to α,β -unsaturated ketones. By conversion into enolates, even sterically hindered ketones such as camphor (**21**)^[30b, 25c] can be aminomethylated without problems (Scheme 5).

Due to their high nucleophilicity, ketone enolates react with Mannich reagents not derived from formaldehyde in a similar way to ester enolates.^[8c] Their use allows the scope of the classical Mannich reaction to be extended from aminomethylation to aminoalkylation. The reaction of lithium enolates (derivatives of cyclohexanone, acetone, or acetophenone) with in situ generated N,O-acetals (derivatives of secondary amines and aromatic or aliphatic aldehydes) is the first generally applicable method for the aminoalkylation of ketones.^[20c] During the aminoalkylation of cyclohexanone enolates one observes that the corresponding *anti*-Mannich bases are preferentially formed. The *anti*:*syn* diastereoisomer ratio is generally about 4:1. A typical example is given in Scheme 6.^[20c] Seebach et al. have postulated that the cause of



Scheme 6. Diastereoselective aminoalkylation of an enolate with an N,O-acetal generated in situ.

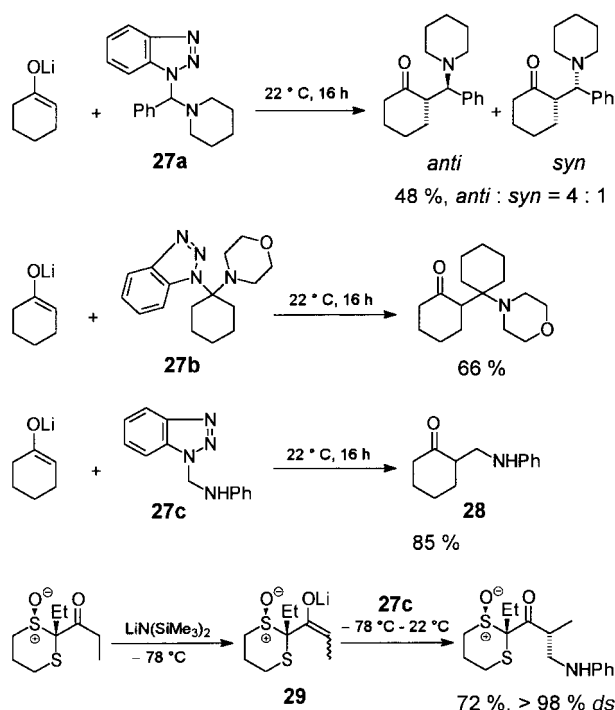
the *anti*-diastereoselectivity may be the formation of an iminium intermediate (**22**). This should react with the in situ generated titanium enolate **23** by an aldol-like reaction sequence involving the electrostatically stabilized transition state **24** (Scheme 6).^[20b] The mechanism cannot yet be considered proven, because a thorough investigation is still lacking.^[38] A related method is the “LiClO₄-induced three-component aminoalkylation”: Here, for example, lithium cyclohexanone enolate is aminoalkylated with N-trimethylsilyldiethylamine and benzaldehyde in a 5 M ether solution of LiClO₄.^[20a] It can be assumed that the first step is the formation of the N,O-acetal **25**, which might exist in equilibrium with the iminium salt **26**. Salt **26** then reacts with the enolate to give the corresponding diastereomeric β -amino ketones (Scheme 7). The preferential formation of the *anti*-diastereoisomers can be explained by an analogous mechanism to that of Seebach et al. (cf. **24**) mentioned previously—that is, by an aldol-type reaction proceeding through an electrostatically stabilized transition state.^[20a]



Scheme 7. a) Diastereoselective aminoalkylation of an enolate with an N,O-acetal. b) Diastereoselective LiClO₄-induced three-component aminoalkylation of a ketone enolate.

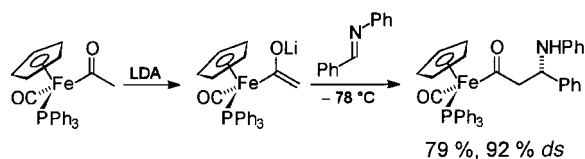
Apart from the in situ generated N,O-acetals, a preformed benzotriazole aminal **27** has been used in aminoalkylation and aminomethylation of ketone enolates (Scheme 8). The advantages of this methodology are the broad applicability and the simple reaction conditions. Thus, one can use benzotriazole aminals such as **27a**^[16d] for the synthesis of Mannich bases. Katritzky and Harris have postulated that the observed *anti*-diastereoselectivity^[39] can be explained by the preferential deamination of the *syn*-diastereoisomer.^[16d] A 25 % yield of benzylidenecyclohexanone is obtained, which is presumably formed by elimination of piperidine. Apart from benzotriazole aminals derived from benzaldehyde, derivatives of enolizable aldehydes (acetaldehyde, isobutyraldehyde) can also be used for the synthesis of β -amino ketones. Additionally, enolates will even undergo aminomethylation with ketone benzotriazole aminals such as **27b**.^[16d] It is also possible to prepare secondary Mannich bases such as **28** by this method. This requires the use of derivatives of primary amines (e.g. **27c**).^[16d] Amine **27c** is also very well suited to the highly diastereoselective aminomethylation of chiral enolates such as **29**.^[16b] Other Mannich reagents such as Eschenmoser's salt (**16a**) deliver poorer yields in this case.^[16b]

Astonishingly, imines have been used almost exclusively in the conversion of ester enolates or related compounds.^[8]



Scheme 8. Aminoalkylation of enolates with benzotriazole amins.

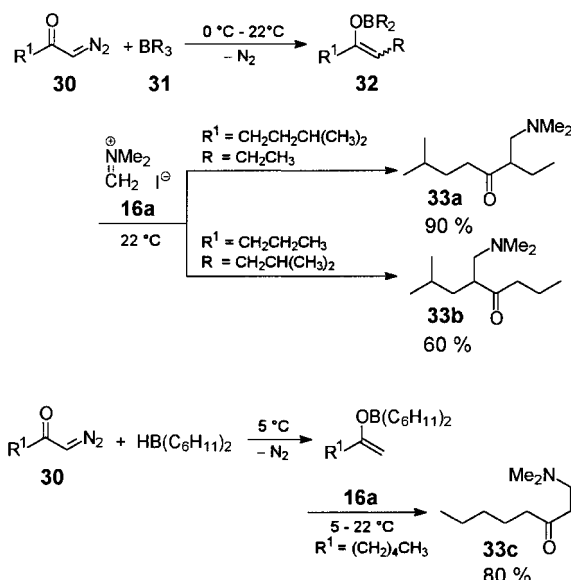
Reactions with other enolates have only sporadically been described.^[13b-d] An example is shown in Scheme 9.^[13c]



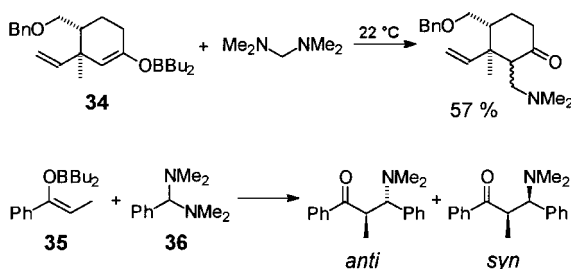
Scheme 9. Diastereoselective aminoalkylation of a chiral acyliron complex.

3.3. Boron Enol Ethers

The reaction of boron enol ethers with Eschenmoser's salt (**16a**) is a powerful method for the regioselective preparation of β -amino ketones (Scheme 10).^[40] This method consists of the conversion of α -diazoketones **30** with trialkylboranes **31** to give the boron enol ethers **32**, which are then aminomethylated by the iminium salt **16a** which is itself generated in situ. A typical example is the synthesis of the two regioisomeric β -amino ketones **33a** and **33b**.^[40b] The use of dicyclohexylborane in the generation of the boron enol ether can also allow the preparation of specific derivatives of methyl ketones such as **33c**.^[40a] Aminomethylation of boron enol ethers makes possible the synthesis of regioisomerically pure Mannich bases in good to very good yields. Their use is, unfortunately, associated with a difficult experimental methodology. The particular advantage of this method lies in the fact that one can prepare, in a highly regioselective manner, β -amino ketones, which are derived from ketones with almost identical α -positions (e.g. **33a** and **33b**).

Scheme 10. Regioselective synthesis of β -amino ketones by aminomethylation of boron enol ethers with Eschenmoser's salt.

On the basis of the Lewis acidic nature of boron enol ethers, these reagents will also react (in contrast to the lithium enolates) with amins, species which are much less electrophilic than the iminium salts (Scheme 11).^[19] In this manner



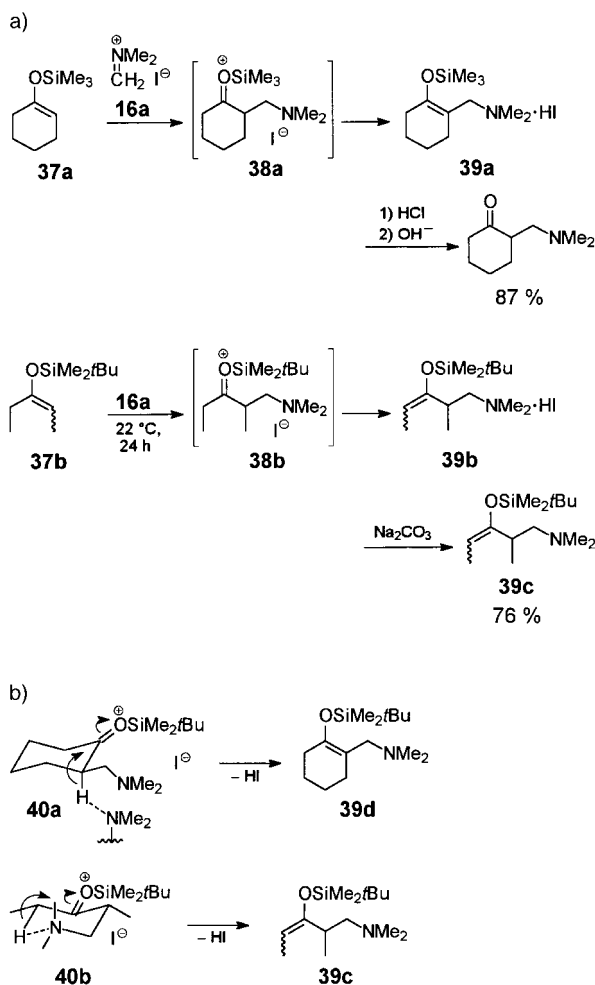
Scheme 11. Aminomethylation and aminoalkylation of boron enol ethers with amins.

one can also successfully aminomethylate even sterically hindered substrates such as **34**.^[19b] In addition, boron enol ethers can be aminoalkylated, with high diastereoselectivity, with amins (only derivatives of non-enolizable aldehydes are suitable; see Section 2.3).^[19a] Conversion of boron enol ether **35** with the amina **36** shows that the diastereoisomeric ratio is influenced decisively by the temperature and time of reaction. At -78 °C (5 to 20 min) (that is, under kinetic control) the *syn*-Mannich base is preferred (33 %, *anti*:*syn* = 1:4). If the reaction is carried out at room temperature, it begins to equilibrate, and after 6 h a diastereoisomeric mixture (90 %, *anti*:*syn* = 1:1) is formed. After 16 to 20 h the almost pure *anti*-Mannich base is obtained (90 %, *anti*:*syn* = 17:1). Nevertheless, similar results are not obtained in every case. If, for example, the corresponding piperidine derivative is used in place of **36**, the diastereoselectivity is marginal at both -78 °C and at room temperature.

3.4. Silyl Enol Ethers

Silyl enol ethers are significantly better nucleophiles than the corresponding carbonyl derivatives. This allows them to be used in the Mannich reaction under much milder conditions. With this method, Mannich bases not accessible with the classical route become available. It is possible, for example, to extend the methodology from aminomethylation to encompass aminoalkylation too.^[13a, 41] This methodology can also be used to achieve effective levels of stereoselectivity in the synthesis of β -aminocarbonyl compounds.^[13a, 17, 30b, 41a] A further advantage is that one can generally convert ketones into silyl enol ethers with a high degree of regioselectivity, and thereby achieve effective control of regioselectivity in the Mannich reaction.^[25c, 28b, e, 37c, 42]

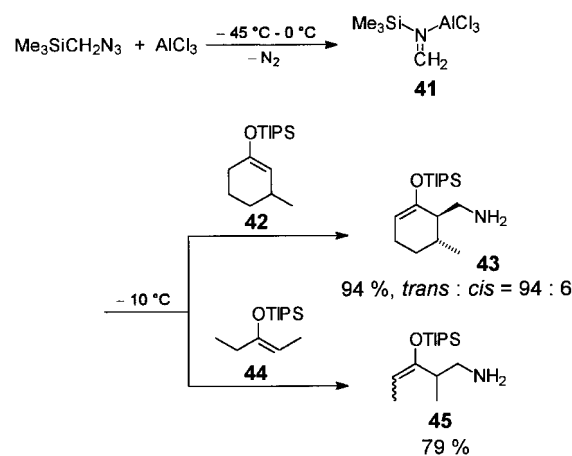
The most commonly used variant of this method is aminomethylation using preformed,^[25c, 30b, 37c, 42a, c, d, f, 43] or in situ generated methylene iminium salts.^[28a–e] Two typical examples are given in Scheme 12. The mechanism has not yet been investigated in detail. Danishefsky et al. have assumed that oxonium salts such as **38a** are initially formed, which are then converted into compounds such as **39a** by deprotonation (formation of **39a** is backed up by evidence from NMR



Scheme 12. a) Aminomethylation of silyl enol ethers with a methylene iminium salt. b) Postulated transition states for the aminomethylation of cyclic and acyclic ketones.

spectroscopy).^[42f] *t*-Butyldimethylsilyl derivatives such as **39b** can even be converted into the free base (**39c**) by aqueous workup and isolated.^[42c] Interestingly, intermediates such as **38a**, which are derived from cyclic ketones, undergo regioselective α -deprotonation;^[42c, f] that is, formation of the double bond takes place exclusively at the original double-bond position. Derivatives of acyclic ketones such as **38b** display the opposite selectivity, that is, deprotonation takes place exclusively at the α' -position, and the double bond is shifted.^[42c] Akiba et al. have tried to explain this phenomenon on the basis of the transition state **40**. In the case of cyclic ketones, a transition state with equatorial aminomethyl groups (e.g. **40a**) should be energetically more favorable. Due to steric hindrance deprotonation can only take place in an intermolecular manner, and this leads to the formation of the more highly substituted double bond—that is, the more thermodynamically favored product is formed (e.g. **39d**).^[42c] The fact that the deprotonation takes place in a highly regioselective manner at the sterically more hindered α -position may be explained by the acidifying $-I$ effect of the dimethylamino group,^[44] which may be substantially reinforced by complexation of the nitrogen with the silicon. For derivatives of acyclic ketones such as **38b**, a cyclic transition state **40b** has been postulated, which allows an intramolecular deprotonation. This results in a shift of the double bond and thus to the formation of products such as **39c**.^[42c]

These results cannot be directly applied to reactions involving other Mannich reagents. Thus, in reactions involving the H_2NCH_2^+ synthetic equivalent **41** (easily prepared from trimethylsilylmethyl azide and AlCl_3 in situ), both cyclic (like **42**) and acyclic silyl enol ethers (like **44**) are deprotonated at the α' -position (Scheme 13). After workup in aqueous NaOH

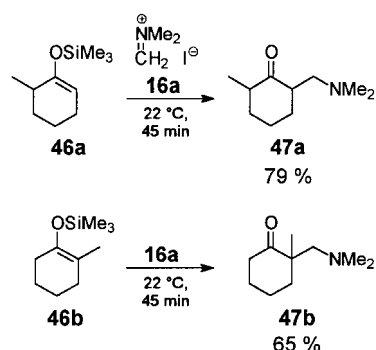


Scheme 13. Aminomethylation of silyl enol ethers with the Mannich reagent **41**, generated in situ. TIPS = triisopropylsilyl.

solution, products such as **43** and **45** are obtained (the corresponding β -amino ketones are generally not stable under basic aqueous conditions).^[42b] Whether reaction with other Mannich reagents such as N,O -acetals or imines leads to α - or α' -deprotonation has not yet, to the best of our knowledge, been ascertained. This question is of particular importance in the interpretation of the stereochemical pathway of aminomethylation and aminoalkylation of silyl enol ethers where α -

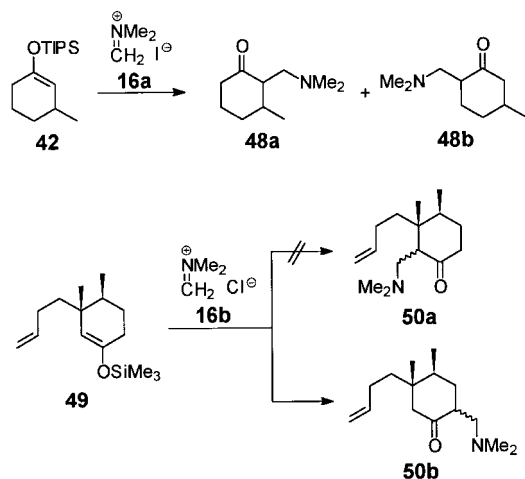
stereogenic centers are formed. The stereochemical information will be lost upon α -deprotonation. The observed stereoisomeric ratios are, therefore, generally not the result of a stereoselective Mannich reaction, but are rather (wholly or, in the case of a mixture of α - and α' -deprotonation, in part) a result of reprotonation during workup. The aminomethylated and aminoalkylated silyl enol ethers which are thus accessible, potentially in a highly regioselective manner, should prove to be synthetic building blocks with many attractive applications.

The aminomethylation of silyl enol ethers with methylene iminium salts is a popular method for the regioselective synthesis of β -amino ketones^[25c, 28b, e, 37c, 42a, c, d, f] such as **47a** and **47b**. (Scheme 14).^[42d] It is worth noting that, upon



Scheme 14. Regioselective synthesis of β -amino ketones by aminomethylation of silyl enol ethers with a methylene iminium salt.

aminomethylation of **46a**, **47b** is formed (about 4%) alongside **47a**, even when the silyl enol ether contains no detectable quantity of the regioisomeric **46b**.^[42d] Really serious deviations from the normal reaction pathway had previously only been seen with the silyl enol ethers **42** and **49** (Scheme 15):

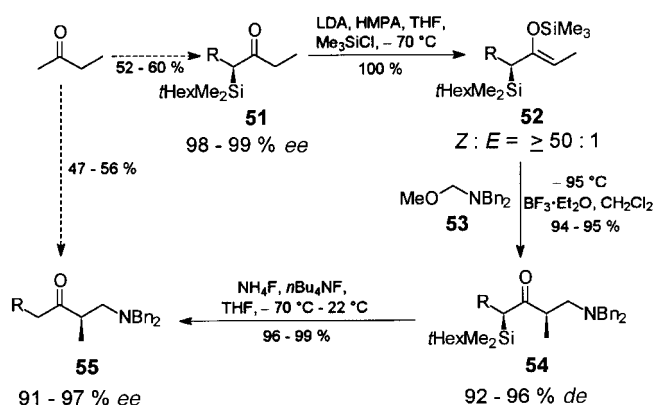


Scheme 15. Unusual behavior in the aminomethylation of silyl enol ethers with methylene iminium salts. TIPS = triisopropylsilyl.

Thus, on aminomethylation of **42** with **16a**, no predominant product, in contrast to the analogous reaction with **41** (compare Scheme 13), but rather a mixture of the regioisomeric β -amino ketones **48a** and **48b** are obtained.^[42b, 45] Upon reaction of **49** with **16b** the expected Mannich base **50a** is not

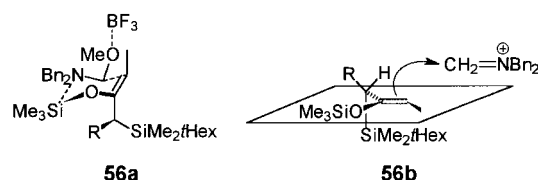
formed, the product being the other regioisomer **50b**. However, if one transforms **49** into the corresponding lithium enolate with MeLi before the addition of **16b**, one obtains only **50a**.^[37c, 45]

In the presence of Lewis acids, silyl enol ethers react readily with aminals^[16a, 46] and with N,O-acetals.^[14d, 17, 28a] In this way one can, for example, synthesize acyclic β -amino ketones **55** in a highly regio- and enantioselective manner (Scheme 16).^[17]

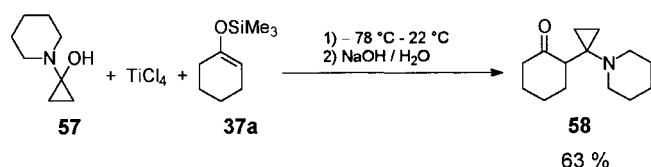


Scheme 16. Regio- and enantioselective synthesis of acyclic β -amino ketones by diastereoselective aminomethylation of silyl enol ethers with an N,O-acetal. *t*Hex = 1,1,2-trimethylpropyl.

Thus, α -silylketones **51** (obtainable by the successive silylation and alkylation of the hydrazone derived from butanone and (*S*)-1-amino-2-methoxymethylpyrrolidone)^[47] can be converted into the silyl enol ether **52** with a high degree of regioselectivity and diastereoselectivity. Aminomethylation of **52** with equimolar quantities of the N,O-acetal **53** and BF₃·Et₂O yields the product **54** in very good yields and high diastereoselectivities. After cleavage of the α -silyl group, which proceeds with almost no racemization, the Mannich bases **55** are obtained in enantiomeric excesses of 91 to 97% ee (Scheme 16). Enders et al. have proposed that the excellent diastereoselectivity of the aminomethylation of **52** can be explained, either by the reaction proceeding through the cyclic transition state **56a** (S_N2 type mechanism) or via the open transition state **56b** (S_N1 type mechanism). In both cases the *Re* side of the silyl enol ether **52** is shielded by the bulky dimethyl-*t*-hexyl group.^[17]

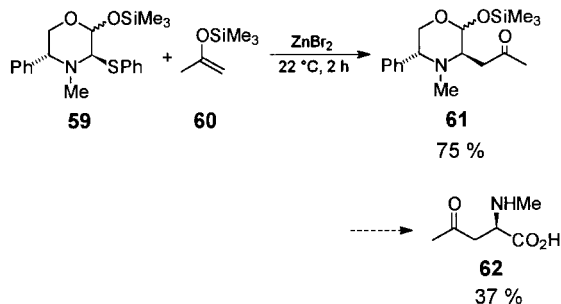


Silyl enol ethers also react with N,O-acetals that are not derived from formaldehyde.^[41c, d, f] Thus, the Mannich base **58** can be synthesized under mild conditions by reacting the silyl enol ether **37a** with the cyclopropane derivative **57** and TiCl₄ (Scheme 17). It has been assumed that the reaction proceeds via an iminium intermediate.^[41d, f] N,S-acetals^[48] are also well suited to the aminoalkylation of silyl enol ethers. An excellent



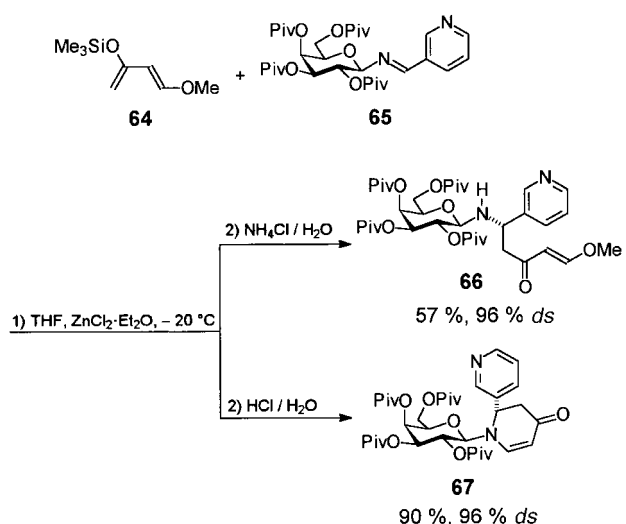
Scheme 17. Aminoalkylation of a silyl enol ether with a N,O-acetal.

example is given by the synthesis of the γ -oxoamino acid **62** (Scheme 18).^[41a] The key step is the highly diastereoselective

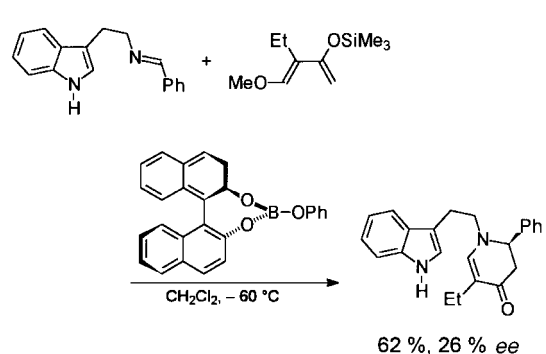
Scheme 18. Enantioselective synthesis of a γ -oxoamino acid by diastereoselective aminoalkylation of a silyl enol ether with a N,S-acetal.

aminoalkylation of the silyl enol ether **60** with the chiral N,S-acetal **59** (glyoxal derivative) in the presence of three equivalents of ZnBr_2 . In this case the β -amino ketone **61** is obtained exclusively. This can be converted into the enantiomerically pure product **62** (three steps, 37%). Agami et al. have rationalized the high diastereoselectivity as being due to the attack of the nucleophile occurring almost exclusively on the front side (the *Re* face) of the initially formed iminium ion **63**, the rear side being effectively shielded by the phenyl group. Silyl enol ethers can also be aminoalkylated with high diastereoselectivity with nucleophiles other than the N,S-acetal **59**.^[41a]

Activation with Lewis acids such as trimethylsilyl triflate,^[41c, e] ytterbium triflate,^[41b] or ZnCl_2 ^[13a] allows the reaction of in situ generated,^[41b] or preformed,^[13a, 41c, e] imines with silyl enol ethers to give β -amino ketones. Both enolizable^[13a, 41b] and non-enolizable^[13a, 41b, c, e] derivatives of aldehydes can be used. The great potential of this method was demonstrated by Kunz and Pfrengle in the aminoalkylation of Danishefsky's diene **64** with enantiomerically pure imines (derivatives of 2,3,4,6-tetra-*O*-pivaloyl- β -galactopyranosylamine).^[13a] After workup with NH_4Cl solution, almost diastereomerically pure β -amino ketones were obtained. Thus, for example, the Mannich base **66** can be synthesized in a highly diastereomerically pure form by the reaction of **64** with the imine **65** in the presence of two equivalents of ZnCl_2 (Scheme 19). If hydrochloric acid is used in the workup rather than NH_4Cl solution, other reactions take place (intramolecular Michael addition and cleavage of methanol). Dehydropiperidones such as **67** are formed with retention of the initially formed stereogenic center. These molecules are of use in the synthesis of, amongst others, piperidine alkaloids.^[13a, 49] The stereochemical progress of the

Scheme 19. Diastereoselective aminoalkylation of a silyl enol ether with an enantiomerically pure imine. Piv = CO₂tBu.

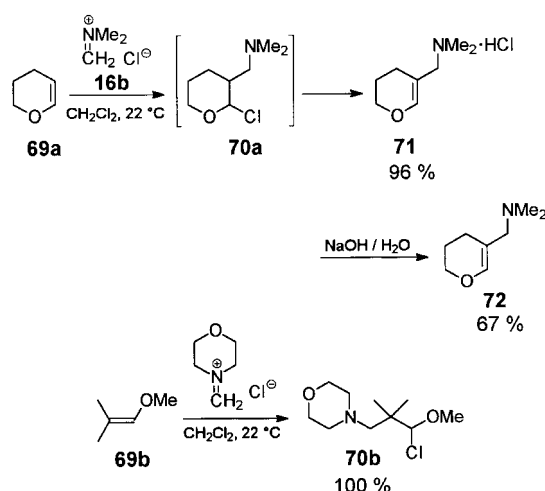
aminoalkylation of **64** with the imine **65** can be explained on the basis of the transition state **68**. One equivalent of ZnCl_2 is bonded to the nitrogen and therefore made inactive. Then the second equivalent activates the C=N double bond by coordination to the imine nitrogen and the carbonyl oxygen of the 2-pivaloyl group (derivatives of nonbasic aldehydes require only one equivalent of ZnCl_2). The attack of the silyl enol ether takes place preferentially on the back face (*Si* face) of the imine, because the front face is shielded by the 2-pivaloyl group.^[13a, 50] As has been demonstrated by Waldmann et al., other imines (from aldehydes and esters of amino acids) can also be used in the highly diastereoselective synthesis of dehydropiperidones.^[52] An enantioselective variant of this reaction has also recently been described (Scheme 20).^[52a, b]



Scheme 20. Enantioselective domino Mannich–Michael reaction.

3.5. Alkyl Enol Ethers

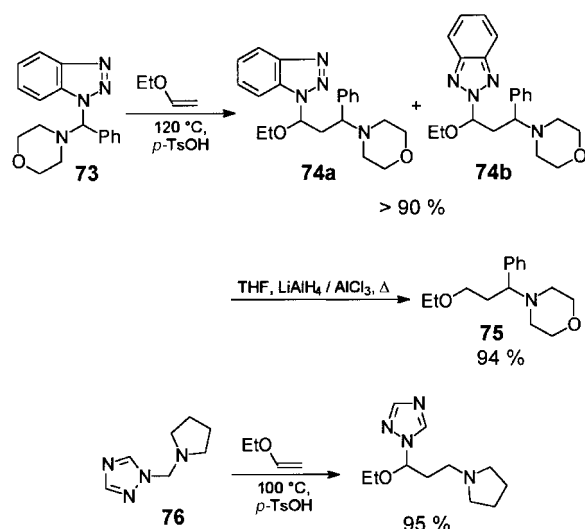
There are relatively few reports of the use of alkyl enol ethers in the Mannich reaction.^[53] Thus, alkyl enol ethers such as **69a** can be aminomethylated with methylene iminium salts such as **16b** under mild conditions (Scheme 21).^[53d] The



Scheme 21. Aminomethylation of alkyl enol ethers with methylene iminium salts.

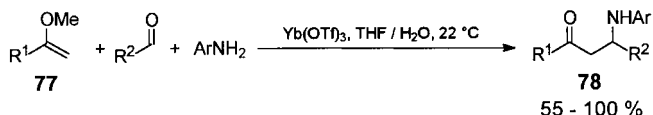
products generally formed are the hydrochlorides of amino-methylated alkyl enol ethers such as **71**, which one can easily convert into the free base (**72** in this example). Böhme and Wagner have proposed that the initially formed product is the α -chloroether (**70a**), which is then instantly transformed into compounds such as **71** by dehydrohalogenation. This assumption is backed up by the observation that the α -chloroether **70b**, which cannot undergo the second reaction step, is formed in quantitative yield by aminomethylation of the alkyl enol ether **69b** (Scheme 21).^[53d]

It is possible to aminoalkylate alkyl enol ethers by use of benzotriazole aminals such as **73**. This method results in the formation of α -benzotriazole ethers **74a** and **74b** (Scheme 22).^[53c] These compounds are valuable synthetic building blocks, since the benzotriazole moiety can easily be displaced by nucleophiles (e.g. Grignard reagents). A further application is the reduction of α -benzotriazole ethers to γ -amino ethers such as **75**.^[53c] 1,2,4-Triazole aminals, for example **76**, can be employed in place of benzotriazole aminals for analogous Mannich reactions.^[53a]



Scheme 22. Aminoalkylation of alkyl enol ethers with benzotriazol- and 1,2,4-triazolaminals.

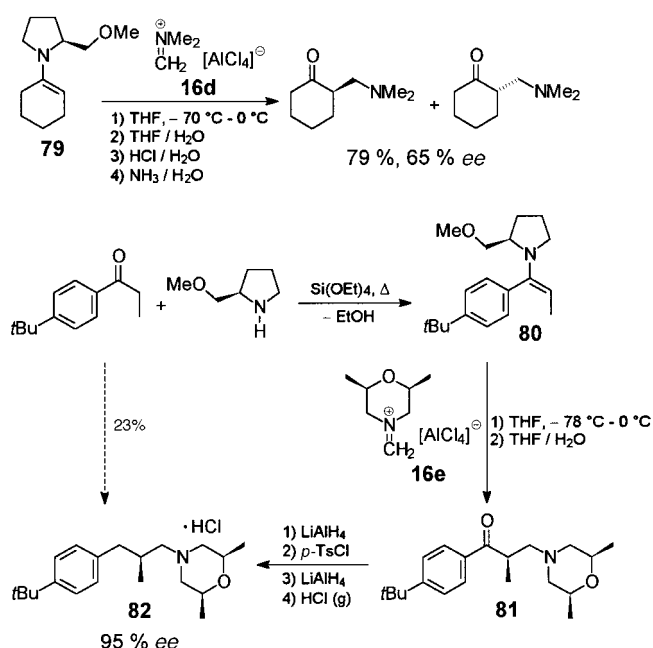
The use of lanthanide triflate catalysts such as ytterbium (III) triflate ($\text{Yb}(\text{OTf})_3$) makes possible the synthesis, in aqueous medium, of secondary β -amino ketones **78** by the aminoalkylation of alkyl enol ethers **77** ($\text{R}^1 = \text{Me}$, Ph) with aldehydes ($\text{R}^2 = \text{H}$, alkyl, Ph , COPh , etc.) and aromatic amines (Scheme 23). Kobayashi and Ishitani have proposed that the reaction proceeds via imines formed in situ.^[53b]



Scheme 23. Lanthanide triflate catalyzed aminoalkylation of alkyl enol ethers in aqueous medium.

3.6. Enamines and Imines

So far, iminium salts have been the preferred reagents for the aminomethylation and aminoalkylation of enamines.^[26a, c, d, g, h, 54] In comparison to iminium salts, other Mannich reagents such as N,O -acetals,^[55] aminals,^[36a, 56] and imines^[57] have played only a minor supporting role. For example, Risch and Esser have shown that methylene iminium salts such as **16d** (tetrachloroaluminates are significantly less sensitive towards hydrolysis and are therefore much more easily handled than the corresponding chlorides)^[26a, c] and enamines such as **79** (derivatives of (*S*)- or (*R*)-2-methoxymethylpyrrolidines) are excellent reaction partners for the enantioselective synthesis of β -amino ketones (Scheme 24).^[54d] The

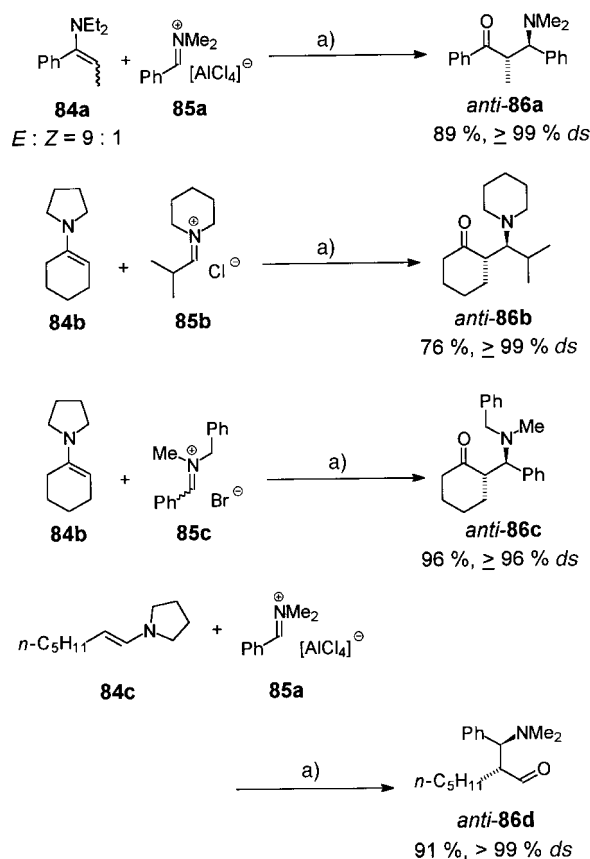


Scheme 24. Enantioselective synthesis of β -amino ketones by amino-methylation of enamines with iminium salts.

execution of the procedure is simple, but gives only moderate *ee* values (30–66% *ee*). More recent results indicate that this is predominantly due to partial racemization of the Mannich bases during the traditional workup procedure.^[54a, b] Omission

of the workup step can yield almost enantiomerically pure β -amino ketones such as **81** for direct use in subsequent reactions, for example the synthesis of the fungicide (*S*)-fenpropimorph **82** (Scheme 24).^[54a] Vinkovic and Sunjic have tried to explain the stereochemical progress of the amino-methylation of 2-methoxymethylpyrrolidine enamines, for example **80**, with methylene iminium salts such as **16e**, on the basis of the aldol-type transition state **83**. This transition state is stabilized by electrostatic interactions. It is noteworthy that the iminium ion attacks the more sterically hindered side of the enamine preferentially. This is likely to be due to Coulombic interactions between the positively charged nitrogen atom and the oxygen.^[54a]

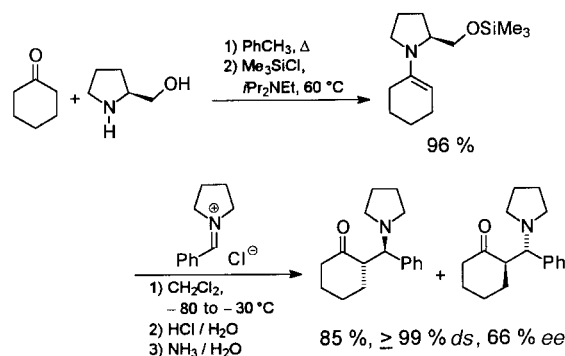
Ternary iminium salts are extremely good in the aminoalkylation of enamines. Thus, β -amino ketones and aldehydes *anti*-**86** can be synthesized in good to very good yields (Scheme 25) and excellent diastereoselectivities (constantly $\geq 96\%$ *ds*).^[26c, d] From those investigations carried out so far,



Scheme 25. Diastereoselective aminoalkylation of enamines with ternary iminium salts. Reaction conditions: a) 1. CH_2Cl_2 , -80 to -30°C ; 2. $\text{HCl}/\text{H}_2\text{O}$; 3. $\text{NH}_3/\text{H}_2\text{O}$.

it has been possible to obtain almost diastereomerically pure products in most cases even at room temperature. It is only under significantly more drastic conditions (e.g. THF, reflux) that significant quantities of the corresponding *syn*-diastereoisomers are observed. The type of iminium salt used has no appreciable effect on the diastereoselectivity of the reaction.

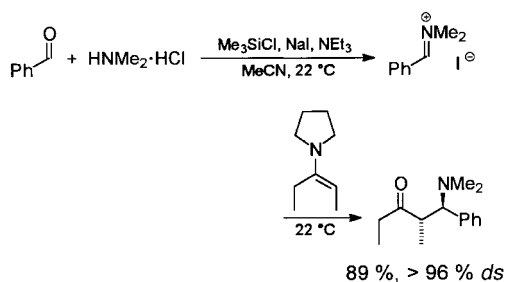
For example, it does not matter whether arylidene iminium salts such as **85a** or alkylidene iminium salts such as **85b** are used. The configuration of the iminium salt employed has no significant influence on the stereochemical progress of the reaction. Thus, even when a diastereoisomeric mixture such as **85c** is used (two diastereoisomers in the ratio 85:15), the almost diastereomerically pure Mannich base *anti*-**86c** is produced. The choice of anion likewise exerts no detectable influence on the diastereoselectivity of the aminoalkylation. Quaternary iminium salts (ketone derivatives) do not react with enamines. Similarly, the type (cyclic or acyclic ketone derivatives such as **84a** or **84b**, or aldehyde derivatives, for example **84c**) or the configuration of the enamine used has no effect on the stereochemical outcome of the reaction. Thus, the aminoalkylation of the diastereoisomeric mixture **84a** yields the β -amino ketone *anti*-**86a** in a highly diastereoselective fashion. Ternary iminium salts can also be utilized in enantioselective syntheses of Mannich bases. An example is shown in Scheme 26 (the β -amino ketone can be readily obtained in enantiomerically pure form by recrystallization).^[26d]



Scheme 26. Asymmetric aminoalkylation of a chiral enamine with a ternary iminium salt.

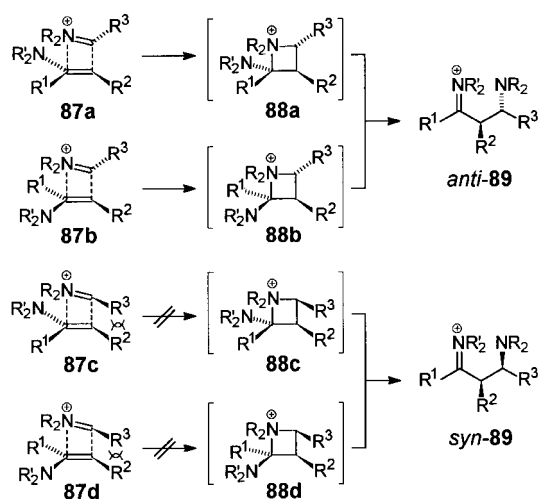
Iminium salts can be generated in situ almost quantitatively from secondary amines (or their hydrochlorides) and non-enolizable aldehydes. These iminium salts can then be used directly, without isolation or purification, in the reaction with enamines or other nucleophiles such as imines or electron rich arenes ("silylogous" Mannich reaction). An example is given in Scheme 27. The experimental effort required can be dramatically reduced with this approach.^[26a, d] The results (yields, diastereoselectivities) are essentially indistinguishable from those obtained with pre-formed iminium salts.^[8a, 26b, c, 58] A further benefit is that iminium salts that are otherwise difficult or impossible to obtain can easily be generated (e.g., derivatives of benzylamine).^[59]

An aldol-type transition state, which has been postulated for the aminomethylation of enamines with methylene iminium salts (e.g. **83**),^[54a] does not fit the consistently high *anti*-diastereoselectivities obtained for the aminoalkylation of enamines with iminium salts. In particular, the fact that the use of a mixture of *E* and *Z* isomers such as **84a** or an aldehyde amine (e.g. **84c**) does not lead to a reduction in diastereoselectivity (Scheme 25) is not consistent with an



Scheme 27. The silylogous Mannich reaction. Aminoalkylation of enamines with iminium salts generated in situ.

aldol-type reaction mechanism (compare **83**). In contrast, the results can be explained satisfactorily by a [2+2] cycloaddition mechanism. Such a mechanism has already been proposed by Viehe et al. for the closely related reaction between ynamines and iminium salts.^[60] The fact that the diastereoselectivities are always high lends weight to the postulate that the aminoalkylation of enamines with iminium salts proceeds in a concerted manner. As has already been put forward for reactions between very electron rich and very electron deficient alkenes, this reaction is supposedly a polar [2s+2s] cycloaddition (Scheme 28).^[8a, 26c, d] In these reactions, the diastereoselectivity is controlled principally by the steric

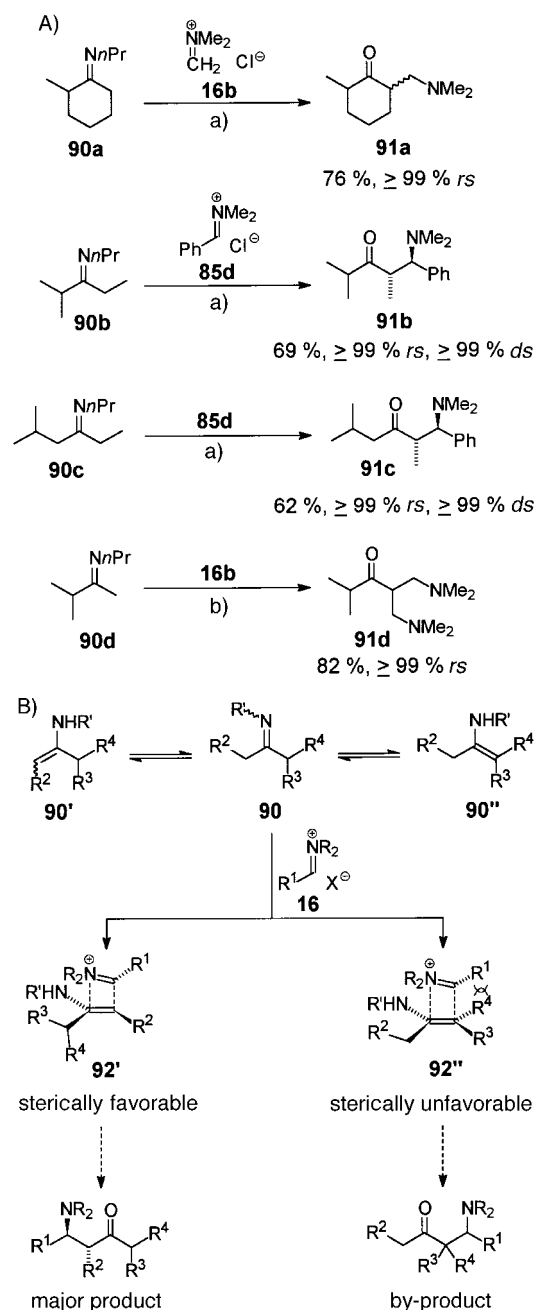


Scheme 28. Possible cycloaddition mechanism of the aminoalkylation of enamines with iminium salts.

interaction of the groups R^2 and R^3 . Cycloadducts such as **88a** or **88b** are only formed from transition states (e.g. **87a** or **87b**) that have relatively little steric hindrance. These rearrange immediately to the iminium salts *anti*-**89**, which can be hydrolyzed to the corresponding β -amino ketones,^[8a, 26c, d] or can be reduced in situ to the 1,3-diamines (> 98 % *ds*).^[26d, 62] Transition states such as **87c** or **87d**, which lead to the formation of iminium salts *syn*-**89**, are energetically very unfavorable due to the eclipsed conformation between R^2 and R^3 . They therefore do not, in general, lead to appreciable quantities of products. This idea also finds support in the fact that enamines do not react, even under drastic reaction conditions, with iminium salts derived from ketones (such salts lead inevitably to eclipsed interactions).^[26d] On the other

hand, the same iminium salts react smoothly with ynamines.^[60] This is also easily explicable on the basis of a cycloaddition mechanism, since the transition state cannot involve sterically unfavorable eclipsed interactions, due to the linear structure of the ynamine.

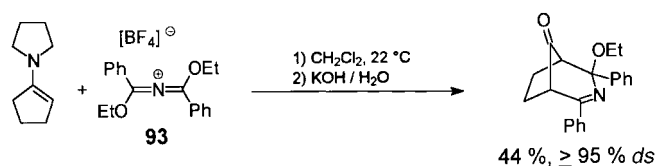
The reaction of imines (or of the tautomeric enamines, with which they are in equilibrium) with iminium salts is a simple method for the highly regioselective preparation of β -amino ketones (Scheme 29A).^[26b, d] In general, Mannich bases (e.g. **91a**, **91b** or **91c**) can be prepared in high yield and excellent regioselectivity, independent of the nature both of the imine



Scheme 29. A) Regioselective aminoalkylation of imines with iminium salts. Reaction conditions: a) 1. CH_2Cl_2 , -80 to -30°C ; 2. $\text{AcOH}/\text{H}_2\text{O}$; 3. $\text{HCl}/\text{H}_2\text{O}$; 4. $\text{NH}_3/\text{H}_2\text{O}$; b) 1. CH_2Cl_2 , -80 to -30°C ; 2. $\text{HCl}/\text{H}_2\text{O}$; 3. $\text{NH}_3/\text{H}_2\text{O}$. B) Transition states for the regioselective aminoalkylation of imines with iminium salts.

used (derivatives of cyclic ketones such as **90a** or acyclic ketones such as **90b** and **90c**) and of the iminium salt. This methodology also allows the preparation of bis-Mannich bases such as **91d** (Scheme 29A). Attack of the iminium salt takes place almost exclusively on the sterically less hindered α -C atom of the imine. Very good selectivity is achieved, even when the α - and α' -positions are only marginally different (for example **90c**). Aminoalkylation with ternary iminium salts such as **85d** is, in addition, highly diastereoselective. As has been seen in the case of the corresponding reaction with enamines (see, for comparison, Scheme 25), the *anti*-diastereoisomer is the only isomer obtained. This result can also be explained on the basis of a polar [2s+2s] cycloaddition mechanism. This model incorporates all the features of the stereochemical reaction profile (analogous to Scheme 28). Additionally, it is also obvious, on the basis of the highly ordered transition states **92'** and **92''**, why even small differences in the regioisomeric secondary enamines **90'** and **90''**, which are in tautomeric equilibrium with the imines **90**, play such a major role and can influence the regioselectivity of the reaction (Scheme 29B).^[26b, d]

An interesting and powerful new variant of the Mannich reaction involves the use of in situ generated^[63] or preformed 2-azaallenium salts.^[64] For example, Würthwein et al. have shown that the reaction of enamines with 2-azaallenium salts^[65] such as **93** can be used to allow the simple and highly diastereoselective synthesis of complex heterocyclic ketones (Scheme 30).^[64b]



Scheme 30. The use of 2-azaallenium salts for Mannich-type reactions.

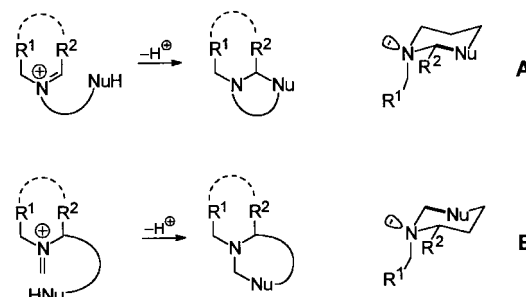
4. Intramolecular Mannich Reactions—A Key Step in the Synthesis of Natural Products

4.1. Preparative and Stereochemical Aspects

Both the inter- and intramolecular versions of the Mannich reaction are undoubtedly amongst the most versatile and powerful methods for the preparation of azacyclic products from acyclic precursors. The practicality of the Mannich reaction is well documented in a multitude of syntheses of alkaloids.^[1a, 2, 66] The reasons for the use of this popular method are just as multifaceted as the reaction itself. In contrast to the intermolecular Mannich reaction, the intramolecular variant is not restricted to aminomethylation, but can be applied in its widest sense to aminoalkylations. Its chemoselectivity also offers a much wider range of potential applications. The carbonyl compound, as is the case with the intermolecular variant, can be used in the form of an acetal or a (silyl) enol ether in the intramolecular reaction (see Section 3). Whereas in the presence of aqueous mineral acid the protecting group is cleaved and the enol is the reactive

species, under anhydrous conditions the enol ether is the nucleophile and the iminium ion is trapped.^[2]

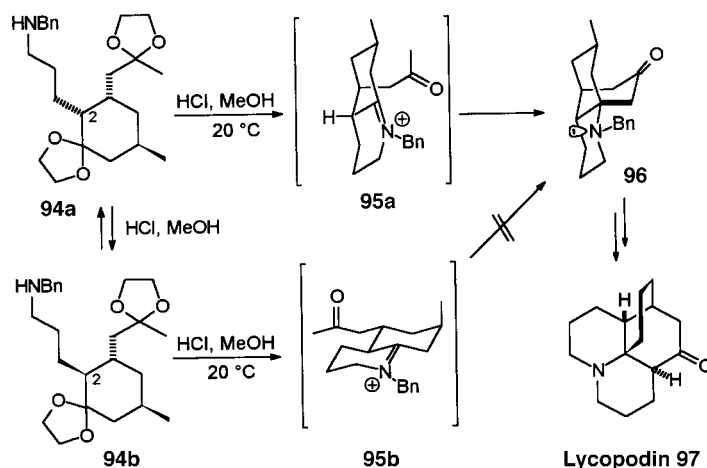
Furthermore, the regioselectivity and stereoselectivity of the intramolecular Mannich reaction are governed by a series of rules that allow the prediction of the reaction path—an important precondition for the synthesis of natural products. Thus, Baldwin's selection rules, developed for the cyclization of olefins, can be applied to iminium ions. Cyclic products can be formed according to either an *exo*-cyclic-trigonal (**A**) or an *endo*-cyclic-trigonal process (**B**; Scheme 31).^[2, 67]



Scheme 31. Stereoelectronic control in the cyclization initiated by iminium ions to form *exo*-trig (**A**) and *endo*-trig (**B**) products.

The stereochemical pathway of a nucleophilic attack on an iminium ion is often controlled by stereoelectronic factors (Scheme 31)^[68] because of the antiperiplanar conformation of the developing electron pair and the incoming electrophile in the product. Reliable predictions can therefore be made about the stereoselectivity of the cyclization.

An excellent example of this stereocontrolled reaction is the synthesis of Lycopodium alkaloid **97** (Scheme 32).^[69] The starting material **94a,b**, which is epimeric at C-2, cyclizes to

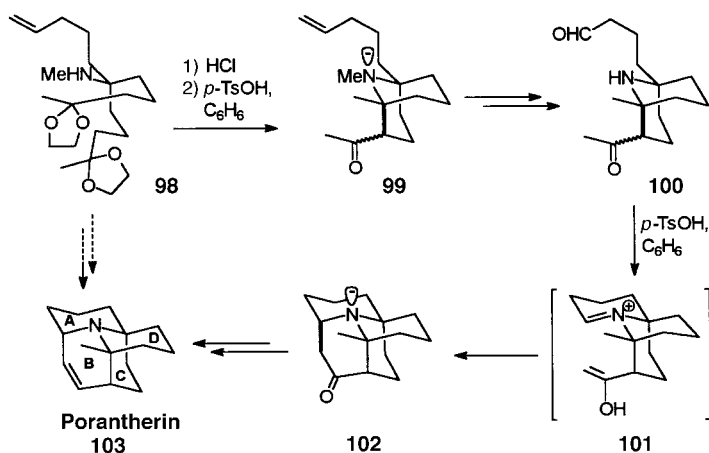


Scheme 32. Redundant synthesis of Lycopodium alkaloid **97**.

give the single isomer **96** in 66% yield. This result can only be explained by assuming an equilibration of the starting material after hydrolysis of the protecting group; a cyclization via the transition state **95b** is impossible on stereoelectronic grounds. In this synthetic sequence another major advantage of *redundant* or *degenerate synthesis* is exemplified. This is a feature of many Mannich cyclizations.^[70] Regio- and stereo-

chemical considerations are reduced to a minimum, and the total number of subsequent steps is thus dramatically reduced.

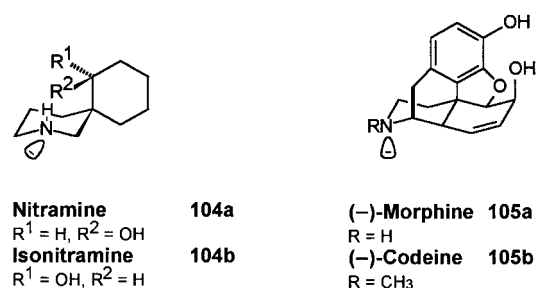
Similarly, the stereoelectronically controlled Mannich cyclization is responsible for the diastereoselective construction of the quadricycle in the synthesis of the Porantherin alkaloid **103**. The principle of *redundant synthesis* is again exemplified in the formation of the C/D rings (Scheme 33).^[71] Starting



Scheme 33. Stereoelectronically controlled synthesis of Porantherin alkaloid **103**.

from the symmetrical starting material **98**, a cyclic enamine is initially formed, with the help of *p*-toluene sulfonic acid. This enamine then yields the bicyclic compound **99** by means of a Mannich cyclization. Due to the symmetry of the starting material, the initial formation of the enamine can take place equally well with either carbonyl group in **98**. The subsequent preparation of the iminium species and cyclization to **99**, starting from the initially formed enamine, is achieved with catalytic quantities of acid. The subsequent transformation of the ω -olefin to the aldehyde **100** follows the same sequence as for the formation of the A/B rings. The complete reaction sequence to **99** and **102** (cleavage of the acetal protecting group, Mannich cyclization) is carried out sequentially, in order to guarantee water-free conditions for the Mannich reaction. The construction of the A/B and C/D rings in the presence of water proceeds with very modest yield.

Further examples of stereoelectronically controlled syntheses of natural products are given by the syntheses of the structurally unusual 2-azaspiro[5.5]undecane alkaloid nitramine (**104a**) and its regioisomer isonitramine (**104b**),^[72] and the analgesics (–)-morphine (**105a**) and (–)-codeine (**105b**) (Scheme 34).^[73]

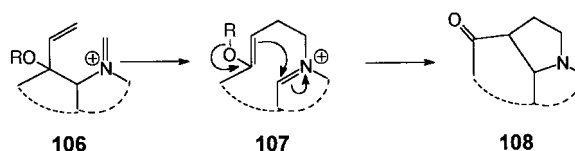


Scheme 34. Alkaloids synthesized by stereoelectronically controlled Mannich reactions.

In the following, syntheses of natural products will be discussed, in which Mannich cyclizations have been used to construct a) pyrrolidines, b) piperidines, c) bicyclo[x.y.1(N)]-alkaloids with nitrogen as the bridge atom, and d) carbocyclic products.

4.2. Mannich Cyclizations Leading to Pyrrolidones

The sequence of cationic aza-Cope rearrangement and Mannich cyclization (Scheme 35) in which pyrrolidines (both mono- and polycyclic) are formed has served many groups in



Scheme 35. Schematic reaction path of the aza-Cope–Mannich cyclization. R = H, alkyl.

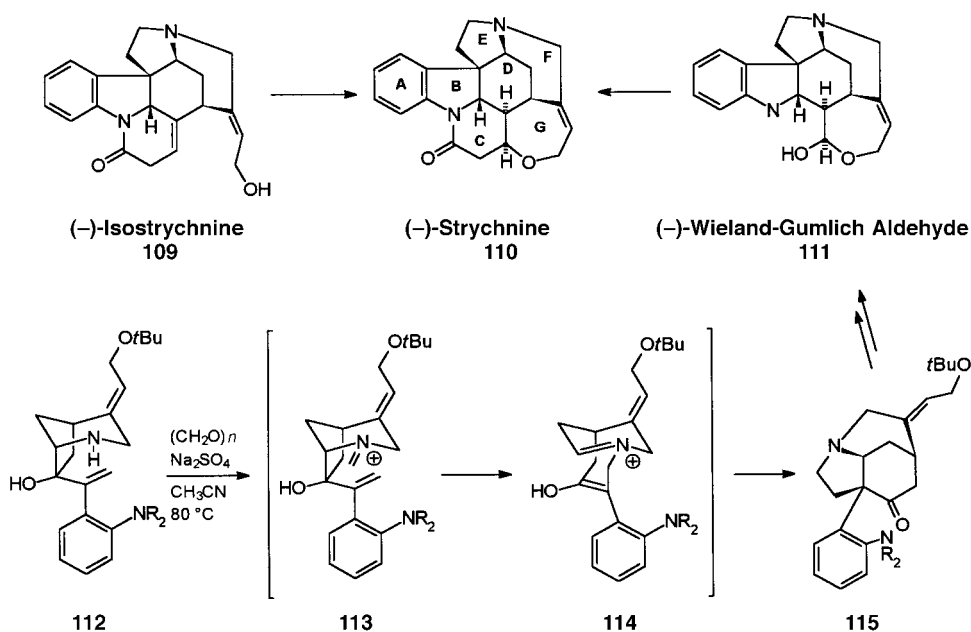
their work relating to the total synthesis of alkaloids. In the simplest case, a *homo*-allylamine functionalized at C-2 with a hydroxyl or alkoxy group is treated with an aldehyde or ketone to give **106**. The cationic iminium component is then converted into **107** by a subsequent aza-Cope rearrangement. Simultaneously, the nucleophile is also activated by the formation of either enol (R = H) or enol ether (R = alkyl). This simple, versatile, and, most of all, regioselective accessibility of the iminium species, coupled with the intermediate activation of the nucleophile, has led to the method's very wide applicability. In all cases, the intermediate is cyclized to the corresponding pyrrolidine **108** by a 5-*exo-trig* process. The 7-*endo-trig* cyclization, which is possible after equilibration of the enolate, though allowed, is not observed. In the case of a carbocyclic starting material, the process leads, overall, to a ring expansion by one carbon.

The possibilities of obtaining enantiomerically pure starting materials are numerous. Not only are amino acid derivatives from the chiral pool utilized, but homochiral starting materials from biocatalytic racemate separations are also used.

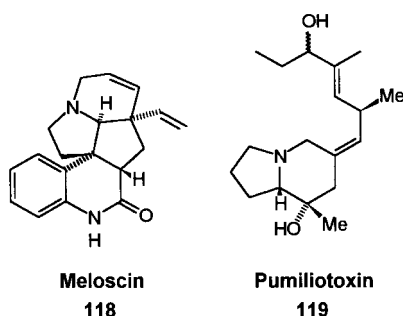
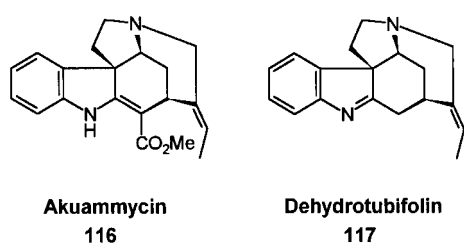
One of the characteristics of the cationic aza-Cope rearrangement is the mild conditions of the reaction.^[74] The reaction proceeds at room temperature or slightly above upon addition of one equivalent of acid (commonly 0.9 eq.). Furthermore, the reaction takes place with a high degree of stereocontrol. Two factors which are responsible for this positive effect are the stereoelectronic control of the Mannich reaction and the characteristic stereoselectivity of [3,3]-sigmatropic rearrangements.^[75]

The synthesis of (–)-strychnine (**110**) by Overman et al. represents one of the highlights of the cationic aza-Cope rearrangement–Mannich reaction strategy.^[76] In contrast to the route of Woodward, who chose to prepare strychnine from isostrychnine (**109**), Overman utilized a route involving the Wieland–Gumlich aldehyde (**111**) (Scheme 36).^[77]

The conversion of the azabicyclooctane **112** with an excess of paraformaldehyde in the presence of Na₂SO₄ as drying agent gives the tricyclic diamine **115** in almost quantitative

Scheme 36. Synthesis of (-)-strychnine (**110**).

yield as a single diastereoisomer. The formation of the iminium ion **113** from the homoallylamine **112** initiates the domino reaction, and the product of the aza-Cope rearrangement **114** is converted diastereoselectively into the amine **115** by the Mannich cyclization. The critical synthesis of the DEF ring system of strychnine thus proceeds with complete stereocontrol. This conversion underlines dramatically the power of this method. The following six steps leading to the enantiomerically pure (-)-Wieland-Gumlich aldehyde (**111**) can be carried out in an overall yield of 24%. The structurally related strychnine alkaloids akuammicin **116** and dihydrotubifolin **117** can also be prepared following this route.^[78a] Besides these examples, the possibil-

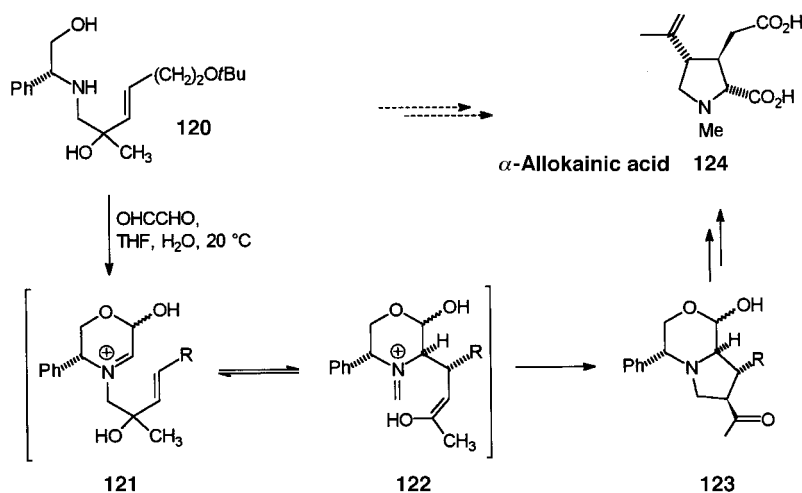


Scheme 37. Alkaloids accessible by aza-Cope/Mannich cyclization.

ities of this tandem sequence appear to set the imagination no limits, since the class of pumiliotoxins **119**^[78b] and the aspidosperma and melodinus alkaloids **118**^[78c, d] can also be synthesized in this way (Scheme 37).

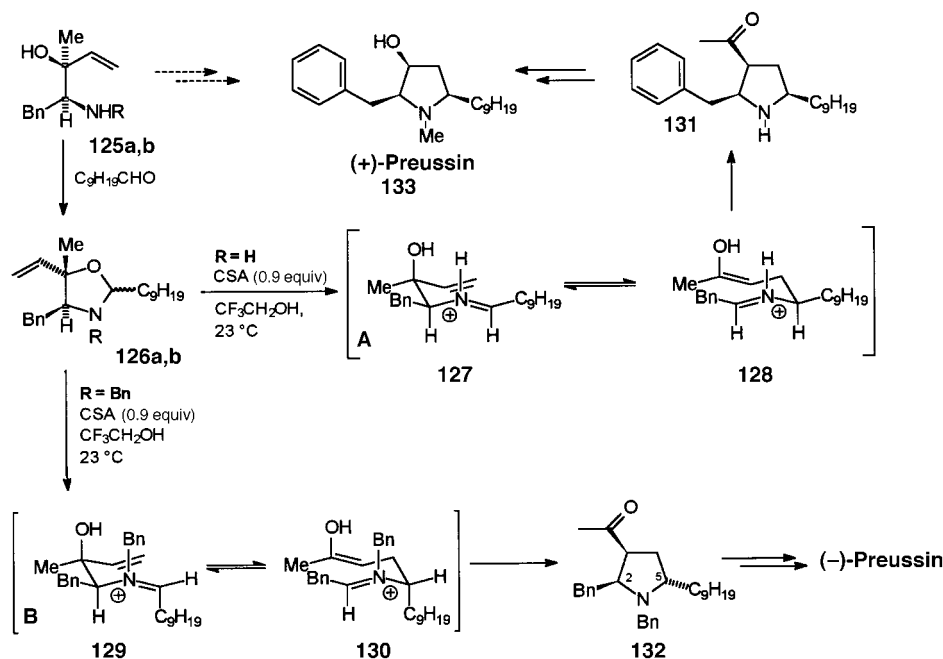
This methodology is not restricted to these very complex structures. Monocyclic, highly functionalized pyrrolidines, such as allokainic acid (**124**)^[79] and the antibiotic preussin (**133**)^[80] can also be prepared along this route. The synthesis of *allo*-kainic acid is an EPC synthesis with a chiral auxiliary (Scheme 38). While the nitrogen of the phenylglycinol is incorporated into the product, the stereogenic center is used as a messenger so that the three

stereogenic centers in the pyrrolidine can be generated stereoselectively. Condensation of the *homo*-allylamine **120** with glyoxal forms the intermediate epimeric hemiacetal **121**, which is cyclized diastereoselectively to the pyrrolidine **123** via **122** in a 5-*exo-trig* Mannich reaction. Finally, phenylethanol is removed, and with it the chiral auxiliary. In this way

Scheme 38. Synthesis of α -alkokainic acid (**124**).

one can also synthesize proline derivatives, which are of great interest as building blocks for peptide mimetics.^[81]

On the other hand, the synthesis of preussin is a classical synthesis *ex chiral pool* (or better: “conversion of natural chiral building blocks”^[82]), which starts from phenylalanine. In this case too, the aza-Cope–Mannich sequence delivers the required control over the stereogenic centers. The synthesis of the natural (+)-preussin (**133**) and of its enantiomer can be carried out enantiodivergently (Scheme 39). The use of the primary amino alcohol starting material ($R = H$) **125a** leads,



Scheme 39. Enantiodivergent synthesis of preussin (**133**). CSA = camphorsulfonic acid.

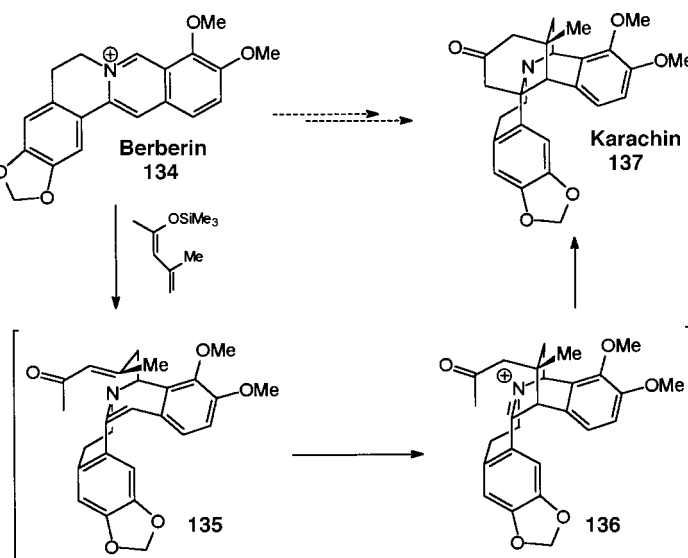
after reaction with decanal and subsequent generation of the iminium species with camphor sulfonic acid, to the all-*cis* product **131**, which can be converted into the natural product. The configuration of the transition state can be concluded from the chair configuration of the intermediate **127** (*E*-iminium stereoisomer) in the rearrangement/cyclization sequence.

Starting from the *N*-benzyl protected derivative **126b**, the major product obtained is the C(2)-C(5)-*trans*-configured pyrrolidine **132**. The transition state is thought to be the *Z*-configured iminium ion **129**. During a sequence of reaction steps (which contain, amongst others, a retro-Mannich–Mannich cyclization) the configuration is inverted at C-2 and C-3, and thus **132** is converted into (-)-preussin.

This application clearly underlines the potential of the aza-Cope/Mannich cyclization sequence, which offers a high level of stereocontrol even in open chain transition states. Despite this situation, this synthetic strategy seems only to have been applied at first to complex polycyclic derivatives, on the basis that their rigidity offers limited scope for epimerization.

4.3. Mannich Cyclizations in the Construction of Alkaloids Containing Piperidine Moieties

Intermolecular Mannich–Michael domino reactions have been successfully applied to the synthesis of a range of piperidine alkaloids (cf. Section 3.4). These domino sequences can also be applied intramolecularly, as the synthesis of the alkaloid karachin (**137**) proves (Scheme 40). In this impressive example, a domino reaction takes place as follows: a vinylogous Mannich reaction (to **135**) is succeeded by a Michael reaction (to **136**) and then another Mannich reaction (to **137**). Three C–C bonds are formed sequentially. This example can also be used as proof of the efficiency with which Mannich cyclizations can be carried out, and thus displays

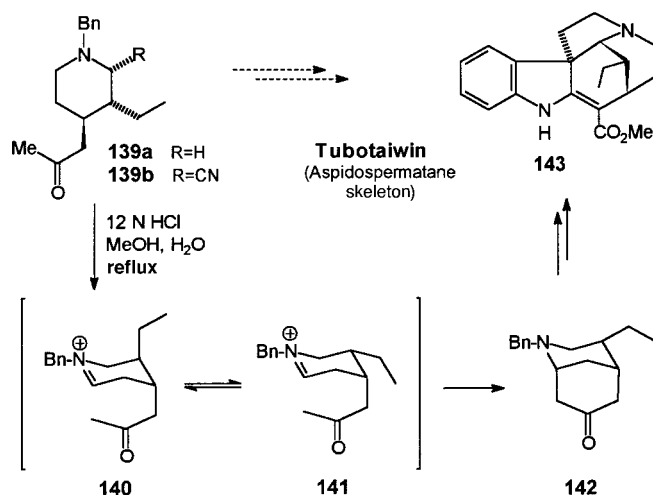


Scheme 40. Domino Mannich–Michael–Mannich cyclization of karachin (**137**).

Trost's atom economy.^[83] When berberin **134** is treated with 20 equivalents of the diene **138** for 18 h at 100°C , the yield of the sequence is 66 %.^[84]

The alkaloids of the Strychnos family (e.g. tubotaiwin (**143**)) have been the subject of much synthetic endeavor. This activity is in part due to their pharmacological properties, but also partly because of their spectacular structures. The synthesis of 2-azabicyclo[3.3.1]nonane, a substructure of this family, can be achieved with the Mannich reaction (Scheme 41).^[85] The starting point of the sequence is the suitably substituted piperidine **139a**, which can be converted into the iminium ion **140** by oxidation with $\text{Hg}(\text{OAc})_2$.^[86] More recently, the iminium ion can be generated by cleavage of the cyano group from the α -cyano-substituted piperidine **139b**, itself accessed by the Polonovski–Potier reaction.^[22m, 87]

Interestingly, the iminium compound **140** epimerizes to the *cis*-isomer **141** in an equilibrium preceding the Mannich cyclization. The cyclization can only take place with an axial carbonyl side chain. Therefore, the more stable *cis*-isomer **141** serves as the compound to be cyclized. The final cyclization to **142** is again an example of the stereoelectronic control of the Mannich reaction and allows efficient control of the relative conformation.



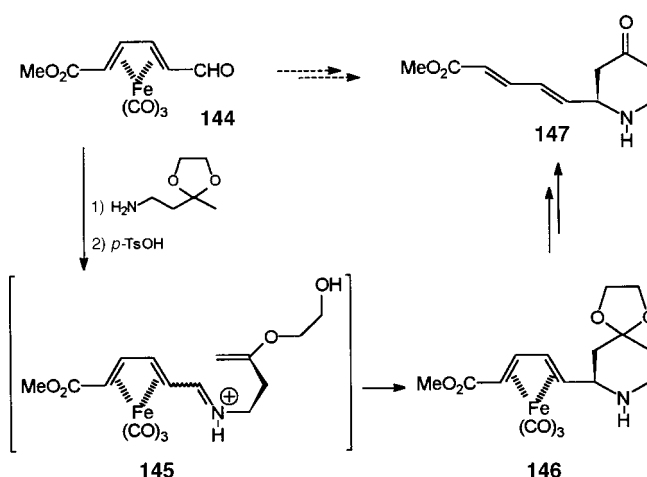
Scheme 41. Synthesis of tubotaiwin (**143**).

Unfortunately, the preceding Polonovski–Potier reaction leading to **139b** proceeds with very unsatisfactory regioselectivity. Thus, the regioisomeric α' -cyanopiperidine is formed in approximately the same quantity as the desired compound **139b**. Furthermore, the conditions required for the conversion into the iminium cation are often very drastic, although in this case help is at hand in the form of a Lewis acid such as TiCl_4 .^[88] A further possibility for the cleavage of the cyano group is the use of *tert*-butyldimethylsilyltrifluoromethyl sulfonate (TBDMSOTf). The elimination takes place even at -78°C in the presence of hydrolysis-sensitive functionalities (e.g. enol ethers) and has been successfully employed in the synthesis of the insect pheromone precocinellin.^[89]

An interesting variation for the synthesis of homochiral piperidine derivatives like **147** is provided by the use of planar chiral tricarbonyl-diene-iron complexes (Scheme 42).^[90] The Mannich cyclization proceeds stereoselectively on the opposite side of the iron tricarbonyl blocking group, with the *E* configuration of the iminium ion in the diastereoisomeric mixture **145** preferentially cyclization. The resulting 4-piperidinone **146** is formed in high diastereoisomeric excess (9:1).

4.4. Mannich Cyclizations for the Construction of Bicyclo[*x.y.1*(N)] alkaloids

The synthesis of bicyclic systems which, in analogy to tropinone **151**, have nitrogen as the bridging atom is considered as a classic example of this methodology. This synthesis, first carried out by Robinson in 1917, is still frequently used today for the synthesis of these pharmacologically interesting materials.^[10, 91]

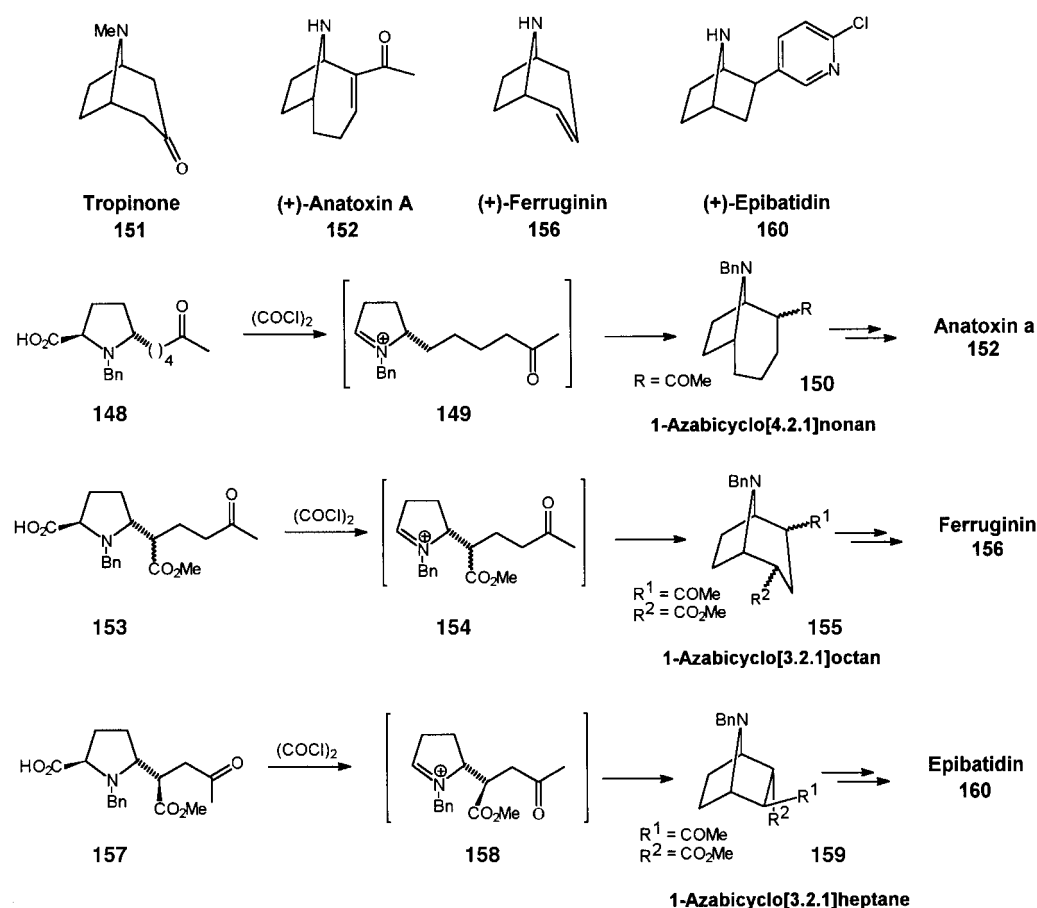


Scheme 42. Synthesis of enantiomerically pure piperidines (**147**).

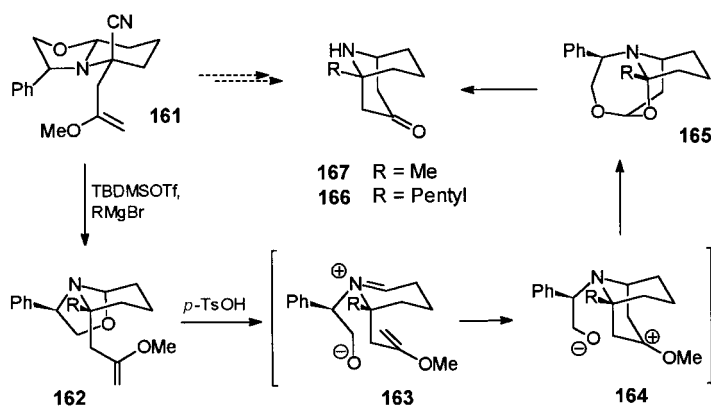
To synthesize alkaloids such as the neurotoxin anatoxin A (**152**, Scheme 43) by intramolecular Mannich reaction, a suitable side chain must be incorporated α to the imine nitrogen. In their fundamentally important work Rapoport et al. demonstrated that iminium ions of the type **149**, **154**, or **158** very readily undergo Mannich reactions to give bicyclic products.^[92] They chose tertiary α -amino acid chlorides as starting materials and could show that these decarboxylate very easily to the corresponding iminium ion. This methodology offers the advantage that the generation of cationic intermediates can be performed regioselectively under mild conditions. Whereas in earlier work POCl_3 was used to form the acid chloride, today it is mostly $(\text{COCl})_2$ that is the reagent of choice. Analogously, this reaction can also take place by the conversion of amino acids with dicyclohexylcarbodiimide (DCC).^[93] L-glutamic acid serves in all cases as the chiral-pool building block. This is converted into the 5-thiopropine derivative. Eschenmoser coupling^[94] is used to incorporate the side chain required for the Mannich cyclization. By variation of the α -side chain, a variety of bicyclic natural products can be prepared, all of which contain the same basic bicyclic structure.^[95] The enantiodivergent synthesis of natural products, leading to both enantiomers, is also possible. Examples of this are given by the syntheses of anatoxin a (**152**), ferruginin (**156**), and epibatidin (**160**).^[96]

One restriction to this method is that the carbonyl component must be a ketone. Aldehydes and β -dicarbonyl compounds lead only to polymerized products.

Nonetheless, bicyclic alkaloids such as the alarm pheromone (–)-euphococinin (**167**) and related compounds (e.g. adalin, **166**) can be prepared in homochiral form using the CN (*R,S*) method (Scheme 44).^[97] α -Cyanoamines **161** are again used in this method—phenylglycinol serves as chiral auxiliary. After the cleavage of the cyano group under mild conditions, the quaternary center in **162** is formed by alkylation of the intermediate iminium ion. The Mannich cyclization then follows from **163**, which is itself formed by cleavage of the *N,O*-acetal. The resulting product, the acetal **165**, is converted into the natural product in a one-pot reaction involving hydrolysis and hydrogenolysis of the benzylamine. This synthesis underlines the efficiency of the method, which is



Scheme 43. Synthesis of bicyclic alkaloids.

Scheme 44. Synthesis of bicyclic insect pheromones (–)-adalin (**166**) and (–)-euphoccocinin (**167**). TBDMSTf = *tert*-butyldimethylsilyltrifluoromethane sulfonate.

due, most of all, to the ease of access to the cationic iminium species **163**.

4.5. Mannich Cyclization to Carbocycles

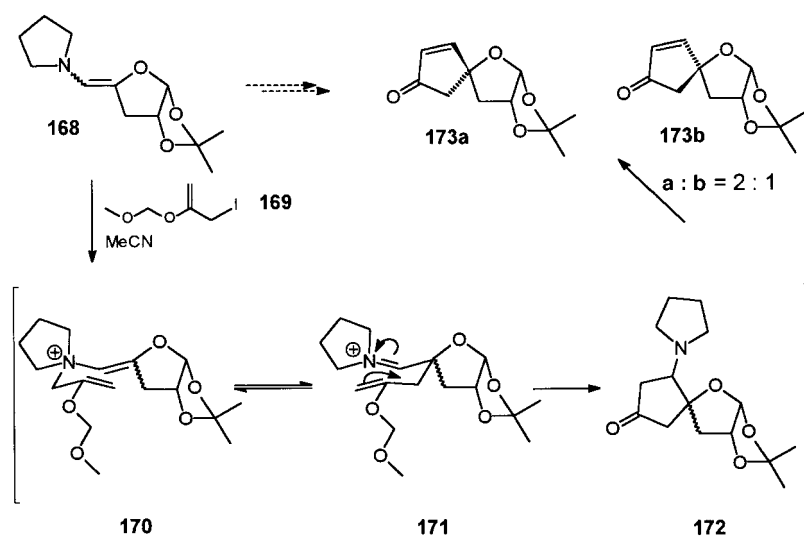
The following synthesis represents a special case in the discussion of the Mannich cyclization to alkaloids. This is because the cyclization leads to cyclopentyl products, with the nitrogen being lost by β -elimination, a side reaction often associated with the Mannich reaction.^[98] However, this is not

the only interesting aspect of this synthesis; the method of generation of the iminium ion is itself worthy of discussion. While the cationic aza-Cope rearrangement is characterized by the fact that the iminium species is already present in the molecule, the use of the aza-Claisen rearrangement offers the possibility of generating the iminium ion in the course of the reaction. This has already been documented in the synthesis of highly functionalized cyclopentenones, which find use as building blocks for the pharmacologically active prostaglandin derivatives (Scheme 45).

The quaternary ammonium compound **170**, formed by N-alkylation of the enamine **168** (*Z/E* isomeric mixture) with the allyl halide **169**, serves as the starting material for the aza-Claisen rearrangement. The iminium ion **171**, formed as an intermediate, is trapped by a Mannich reaction, in which a carbonyl compound in the form of an enol ether functions as the nucleophile. Subsequent β -elimination of the piperidine leads to the spirocyclic product **173 a, b** in a ratio of **a:b** = 2:1.

This example of the synthesis of carbocyclic compounds displays all the advantages of the use of the Mannich reaction as a key step of a rearrangement/cyclization sequence. Thus, the Mannich reaction will play a much more important role in the synthesis of carbocyclic products in the future.

The method of preparation of the carbocyclic part of perhydroindoles consists of a sequence of [2+2] photocyclization, retro-Mannich, and Mannich cyclization to yield dihydroindoles.^[99] A cyclohexyl ring is formed as part of this sequence (Scheme 46). The hydroaromatic part of the struc-

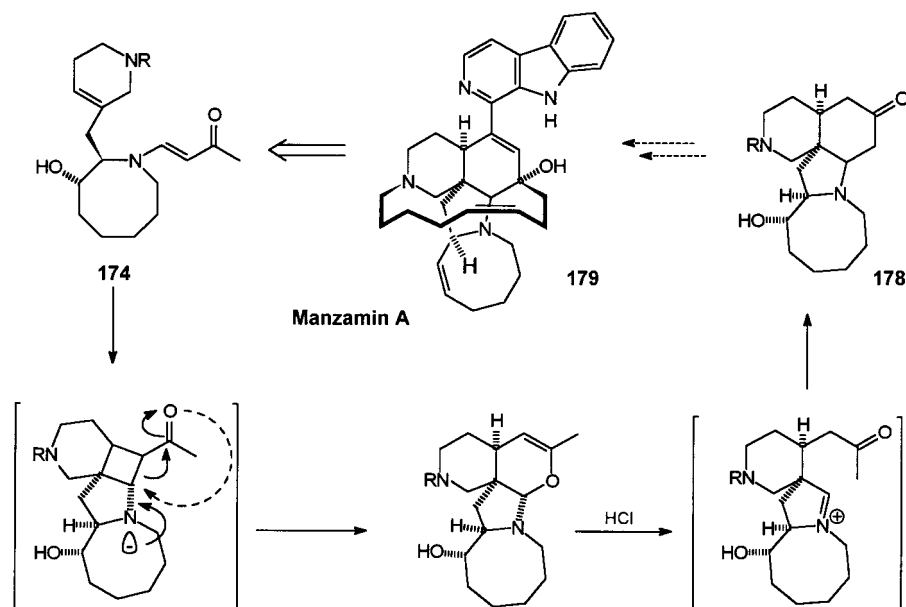
Scheme 45. Domino aza-Claisen/Mannich cyclization to give cyclopentenone **173**.

turally very interesting polycyclic alkaloid manzamin A (**179**) is synthesized with this methodology.^[100]

Manzamin A contains four stereocenters, which are built up from the 2,3-*trans*-configured cyclooctylamine **174** in the correct relative configuration. Irradiation of the vinylogous amide **174** yields the tetracyclic aminal **176** in a [2+2] photocyclization/retro-Mannich domino reaction at -78°C in a diastereoselective manner. Subsequent acid-catalyzed cleavage of the aminal to give the iminium ion **177** leads, by a Mannich cyclization, to the desired tetracycle **178** in only four reaction steps.

5. Vinylogous Mannich Reactions—A Logical Development

The vinylogous variant of the Mannich reaction is the γ -aminoalkylation of α,β -unsaturated carbonyl compounds

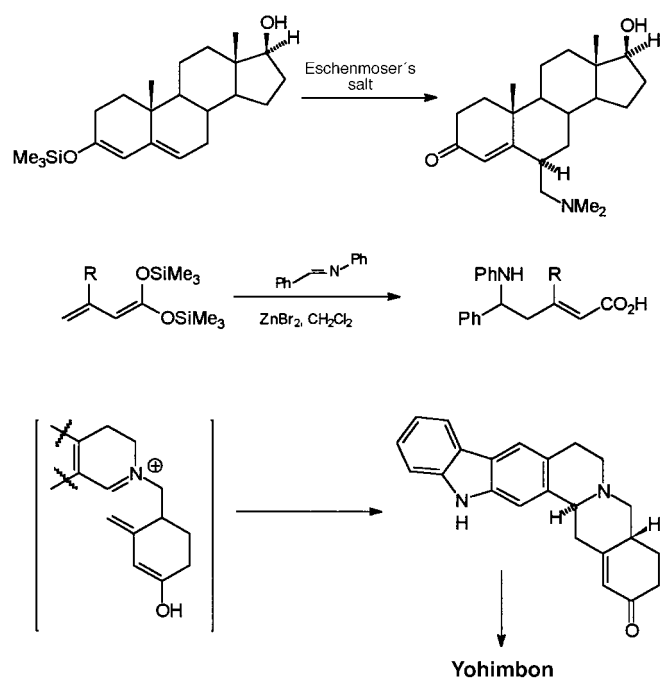
Scheme 46. Synthesis of a structural fragment of the alkaloid manzamin A (**179**).

(Scheme 47).^[42a, b, 101] As has already been demonstrated in the synthesis of the alkaloid karachin (**137**) (cf. Scheme 40), the reaction of an iminium ion with a silyoxydiene can be carried out in the sense of an intermolecular vinylogous Mannich reaction. This type of reaction can also be applied to the synthesis of yohimbon if the tautomer of the β,γ -unsaturated cyclohexenone is prepared.^[102]

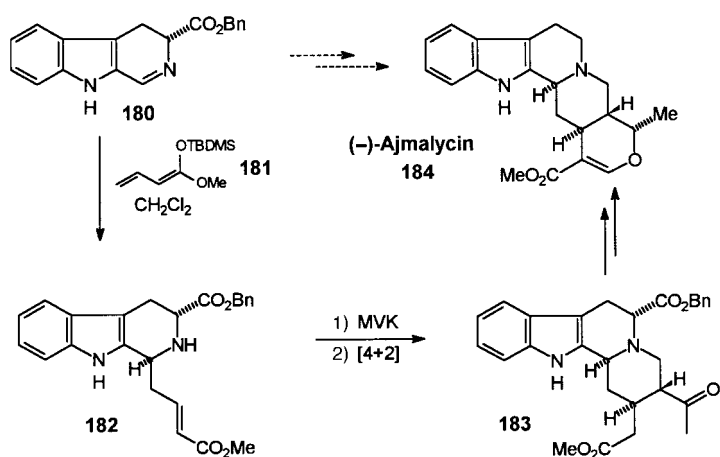
This intermolecular methodology has been successfully applied to the EPC synthesis of the heteroyohimbon alkaloid (–)-ajmalycin (**184**) and its epimer (Scheme 48).^[103] Starting from the imine **180**, which is itself derived from tryptophan, the Mannich reaction is carried out with the silyl ketene acetal of the methyl crotonate **181**. The reaction proceeds in CH_2Cl_2 under mild conditions, and a single diastereoisomer **182** is obtained in 69% yield.

After subsequent Michael addition of the resulting amine with methyl vinyl ketone, Diels–Alder reaction to **183**, and further transformations (including the Barton decarboxylation), the natural product is obtained after a total of nine steps.^[104]

Since trimethylsilyloxybutadiene **191** is not sufficiently nucleophilic to undergo an analogous reaction, the electrophilicity of the iminium reaction partner must be increased. This is done by the in situ generation of an acyliminium ion (Scheme 49).^[105] First, the acyliminium ion is generated from **192** by treatment with crotonyl chloride. This activated iminium species can now undergo a vinylogous Mannich reaction with **190** to give **193**. In this one-pot process, not only the diene but also the dienophile are introduced in 80% yield. Subsequent Diels–Alder reaction leads to a pentacycle in which the product **194** with the *cis* configuration is present in a ratio of 1:2 to the corresponding *trans* isomer. Further transformations lead to products that can be used in the



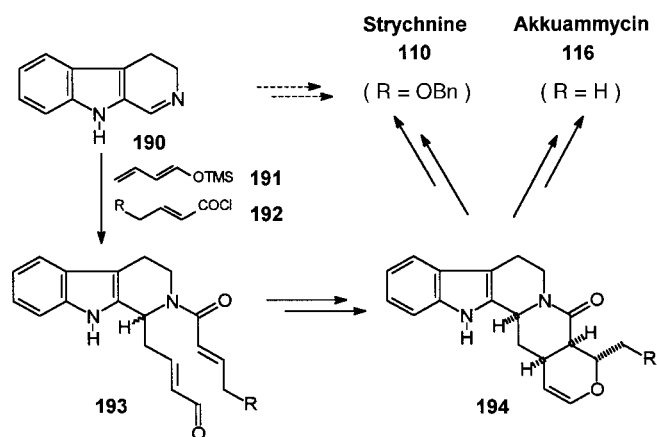
Scheme 47. Vinylogous Mannich reactions.

Scheme 48. Synthesis of (-)-ajmalycin (**184**).

synthesis of, for example, ($\pm$)-strychnine (**110**) (see Scheme 36). Thus, the formal total synthesis of strychnine of Martin et al. serves as a benchmark for the use of the vinylogous Mannich reaction as a key step in the total synthesis of natural products.

Further application of the vinylogous Mannich reaction are illustrated by the use of 2-alkoxyfurans **196** as nucleophilic, α,β -unsaturated components.^[106] Conversion of these building blocks with iminium cations is illustrated in Scheme 50. The structural elements (**197**) thus formed are to be found in alkaloids of the Stemonia family (e.g. croomin, **211**)^[107] and the rugulovasines A and B (**202 a, b**).^[108]

The two last-mentioned natural products from the ergot alkaloid class differ only in the configuration at the tertiary stereogenic center. In the synthesis of this alkaloid, the reaction of the siloxyfuran **200** with the cationic iminium compound **199** leads to two diastereomeric products **201 a, b**

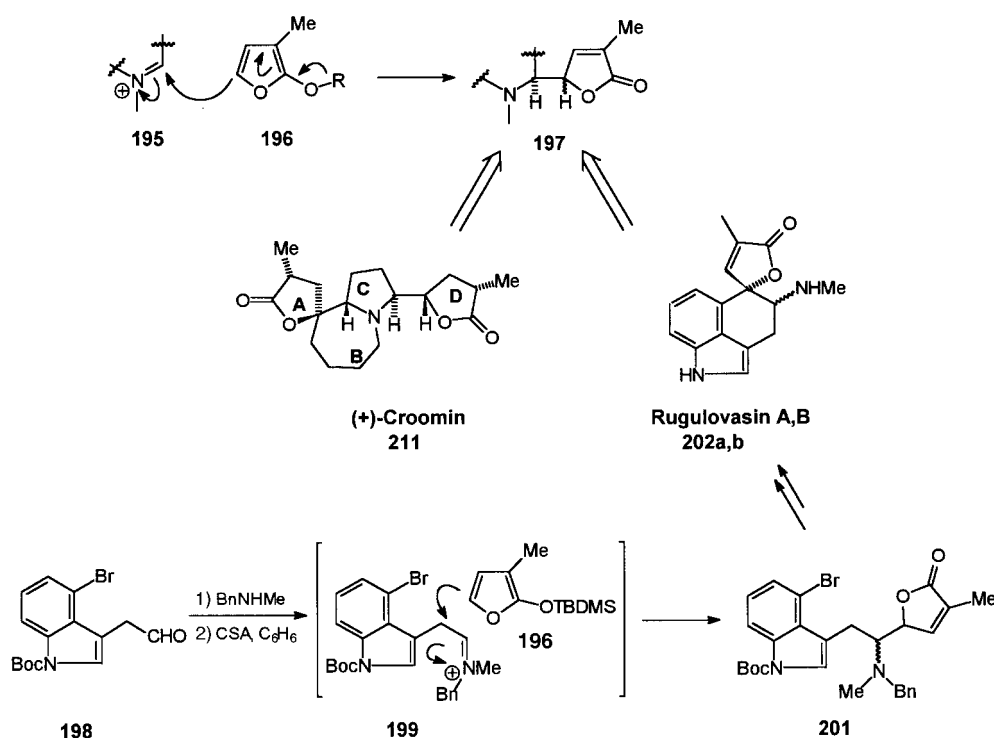
Scheme 49. Formal total synthesis of strychnine (**110**) and akkumammicin (**116**). TMS = trimethylsilyl.

(**a:b** = 2:1) in 80 % yield based on aldehyde **198**. Subsequent photocyclization yields the spirocyclic lactone **202 a, b**.

An intramolecular variant of the vinylogous Mannich reaction has helped to clarify the epimerization of the tertiary stereocenter of rugulovasine (Scheme 51).^[109] The epimerization proceeds spontaneously by a retro Mannich–vinylogous Mannich sequence in which the zwitterionic structure **203** has been assumed to be an intermediate.

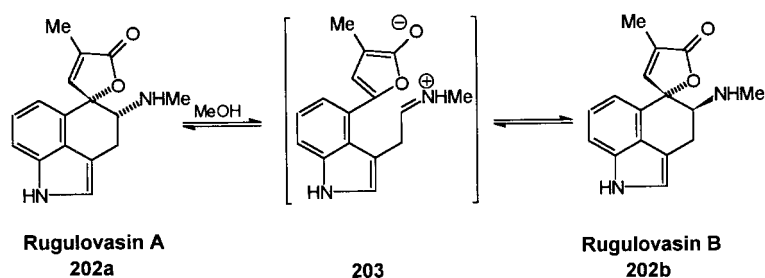
Two vinylogous Mannich reactions are the key steps in the synthesis of (+)-croomin (**211**) (Scheme 52).^[107] The first step is a nucleophilic attack of the alkoxyfuran **204** on the acyliminium ion (**205**). This reactive intermediate is used not for its enhanced electrophilicity, but rather to protect the amino functionality. The major product is the diastereoisomer **206**, which has the *threo* configuration. Subsequent construction of the B ring leads to the bicyclic amine **207**, and then to an intermediate which, under conditions of decarbonylation, is converted into the cationic species **208** (cf. Scheme 43). Repeated vinylogous Mannich reaction with the iminium cation thus formed yields the C–C connected quadricycle **210** with a *threo:erythro* selectivity of 2:1. Finally, stereoselective hydrogenation gives the extremely complex natural product, whose synthesis requires a total of eleven steps.

Similarly, a vinylogous Mannich reaction can be formulated which is applicable to the preparation of dibenzo[*a,g*]quinolidine (**217**), a suitable precursor in the synthesis of (–)-emetin (Scheme 53).^[110] Hydrolysis of the enol ether **212** and subsequent reaction with formaldehyde generates a β,γ -unsaturated carbonyl compound, which exists in equilibrium with its tautomer **213**. This undergoes a spontaneous [3,3]-sigmatropic rearrangement to **214**. This rearrangement is responsible for the synthesis of racemic products from homochiral precursors. It could be proved beyond doubt that this racemization cannot be traced back to a retro-Mannich–Mannich sequence. Its source is the aza-Cope rearrangement. This undesired rearrangement can be completely suppressed by reduction of the carbonyl group, and the synthesis of enantiomerically pure products can be successfully carried out with a Mannich-analogous cyclization. Similar observations have also been in the synthesis of (–)-yohimbon (cf. Scheme 47).^[102b]



Scheme 50. 2-Alkoxyfurans as vinylogous Mannich nucleophiles. Boc = *tert*-butoxycarbonyl; CSA = camphorsulfonic acid; TBDMS = *tert*-butyldimethylsilyl.

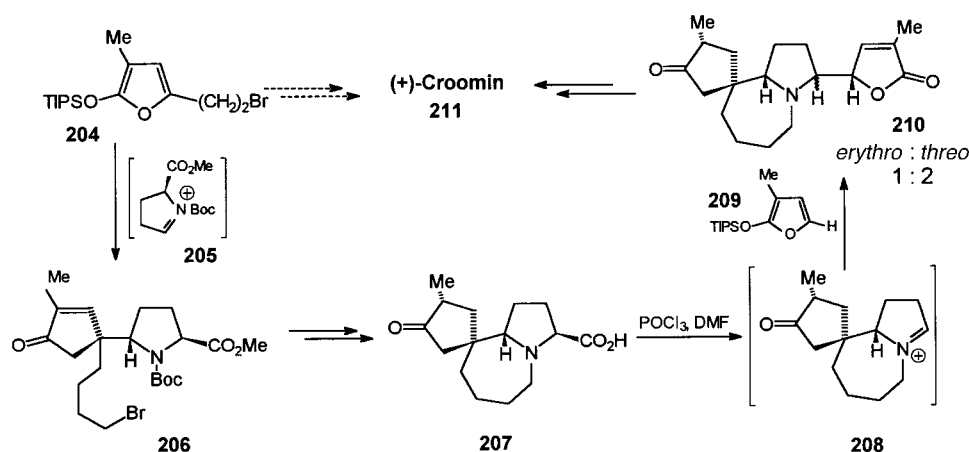
6. Summary and Future Perspectives—The End Is Still Not in Sight



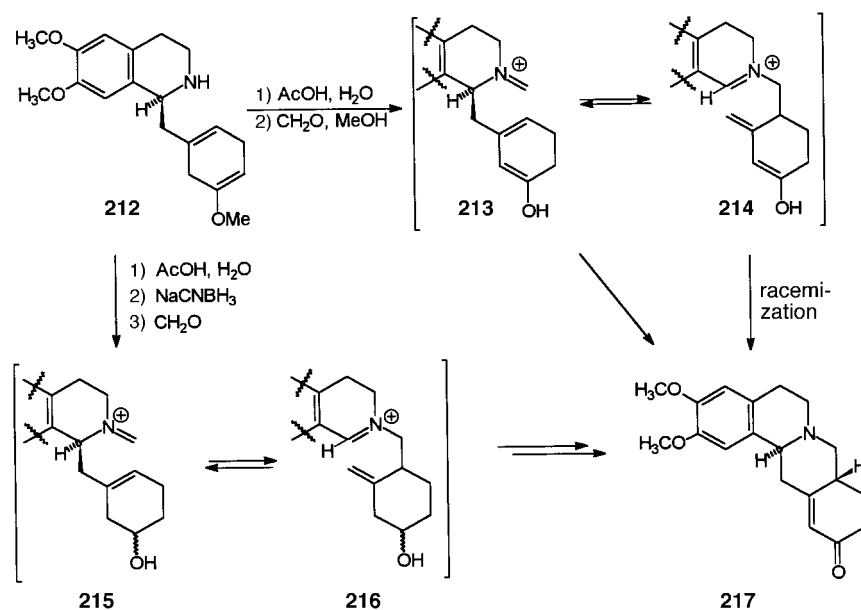
Scheme 51. Epimerization by vinylogous Mannich reaction.

The aspects of the Mannich reaction which we have chosen to discuss represent only a small fraction of the huge body of work that can be associated with the name of Carl Mannich. We wanted to, and indeed had to, limit ourselves to the area defined by us at the start of the article, namely, the aminocarbonyl compounds, and in particular to the more recent work, bearing in mind that earlier studies had already been covered by good quality reviews.

It is clear that this reaction type is unusually valuable and has a remarkably wide range of applications. This means, more specifically, that it starts from cheap starting materials and provides key building blocks for pharmaceuticals and natural products in an inexpensive manner. It is efficient in terms of yields and resources. That the conditions of the Mannich reaction are such that many multi-stage processes (domino reaction sequences) can be carried out as “one-pot” reactions increases its worth even more. This methodology is, however, more than just an economic process. The intensive research



Scheme 52. Synthesis of (+)-croomin (211).



Scheme 53. Vinylogous Mannich cyclization leading to azacyclic fragments of alkaloids.

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carried out on the classical Mannich reaction over the last few years has satisfied the requirements of modern selective chemistry (that is, chemo-, regio-, and diastereoselectivity). The reason for this success is not only the creativity of the chemists involved in the recognition, planning, and realization of its synthetic potential, but also the skilful use of synthetic tools such as preformed aminoalkylation reagents (iminium salts etc.).

The fascination generated by the application of this chemistry has, not without good reason, led to the catch phrase “Mannich Magic”—a term which embodies the fascination and motivation inspired by this chemistry.

In addition to the iminium ions prepared in situ, which have a well-established place in modern Mannich chemistry (particularly in the intramolecular variant), many forms of aminomethylating and aminoalkylating agents now enrich the synthetic palette of selective chemical reagents. Their electrophilic character makes them predestined to react with almost any nucleophile, thereby expanding the potential functionalities. Iminium systems with an increasing variety of selectively deblockable substitution patterns will no doubt follow. Many new routes and preparative chances have been proposed, or at least hinted at.

Despite many studies, and some notable successes, penetration into enantiomerically pure Mannich bases is still only beginning. That the configurational stability of β -amino-carbonyl compounds cannot easily be secured makes this field of endeavor appear less attractive. However, when one thinks of the many in situ and racemization-free routes to derivatization of the kinetic products (to, for example, amino alcohols, diamines, amines etc.), it becomes understandable that the possibility of developing efficient and effective routes to products of controlled absolute configuration may indeed be realizable. Catalytic processes, which are established in many other areas of stereochemistry, are almost completely untouched.

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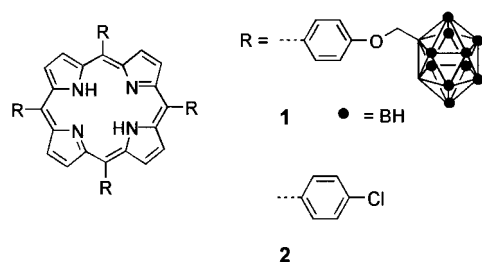
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Porphyrins Like Boron After All**

Mathias O. Senge*

One of the longest running quests in porphyrin chemistry has been the attempt to complex all elements of the periodic table with this intriguing macrocycle. In this century this has been achieved for almost every main group metal or transition metal, giving rise to a cornucopia of metalloporphyrins.^[1] Remaining white specks in the porphyrin landscape are porphyrins in which nonmetals are coordinated to at least two pyrrole nitrogen atoms. While a few examples are known for silicon,^[2] phosphorous,^[3] and carbon,^[4] boron porphyrins have remained a mystery until recently. Except for brief statements in reviews,^[1] the first synthesis of boron porphyrins was published by Carrano and Tsutsui in 1977.^[5] Reaction of tetraphenylporphyrin ($H_2(tpp)$) with $BCl_3 \cdot MeCN$ was reported to yield a porphyrin of the composition $[B_2(OH)_4(tpp)]$. However, the experimental data available did not allow a clear assignment of the coordination geometry.

On the other hand, a considerable body of work has accumulated on the synthesis of porphyrins containing boron functionalities in side chains appended to the porphyrin macrocycle. Typical examples include porphyrins with boronic acid groups, which have been utilized for receptor or coordination studies,^[6] and carboranyl porphyrins.^[7] The latter are porphyrins that carry carboranyl units in side chains at either *meso* (e.g. in **1**)^[7c] or β positions. Such compounds have



great medicinal potential in boron neutron capture therapy. This method combines the preferential localization of porphyrins in tumor tissue with the reaction of the ^{10}B isotope with thermal neutrons for treatment of cancer.^[8] The carbor-

anyl porphyrins functions as carriers to localize the ^{10}B isotope in tumor tissue, and subsequent irradiation with neutrons yields toxic particles through the $^{10}B(n,\alpha)^7Li$ reaction that damage the surrounding tumor tissue.

As useful as these compounds are, they do not contain boron atoms directly in the macrocycle skeleton or in the core. Until recently, the closest boron came to the macrocycle core in compounds clearly characterized by X-ray crystallography was in the form of a carborane anion weakly coordinated through an Fe-H-B bridge to an Fe^{III} porphyrin described by Lee and Scheidt.^[9]

This situation changed with the first structural characterization of a boron porphyrin by Brothers and co-workers in 1994.^[10] Reexamination of the reaction described by Carrano and Tsutsui with 5,10,15,20-tetra-*p*-tolylporphyrin ($H_2(tpp)$) yielded a product with the composition $[B_2O(OH)_2(tpp)]$ (**3**).^[11] Similarly, reaction of 5,10,15,20-tetra-*p*-chloroporphyrin (**2**) with $BF_3 \cdot OEt_2$ in chlorobenzene containing a trace of water followed by chromatographic work-up on basic alumina gave a product with the formula $[B_2OF_2(TpClpp)]$ (**4**, $TpClpp$ = dianion of **2**; Figure 1).

Compound **4**, which could be crystallized and characterized by X-ray crystallography, shows an unusual coordination at the core with two inequivalent boron atoms. Each boron atom is bound to two neighboring nitrogen atoms; one boron atom is located roughly in the plane of the nitrogen atoms, while the other is significantly displaced out of this plane. Thus, the fluorine atoms are located on opposite sites of the macrocycle. One is more or less over the porphyrin center, while the other is oriented outwards. This unusual "threaded through" geometry leads to a nonplanar macrocycle conformation in which the pairs of pyrrole rings bonded to individual boron atoms are displaced from the mean plane towards opposite sides. Interestingly, a symmetric arrangement as shown in **5**, which was originally proposed for compounds of this type,^[1b] is not realized. Calculations performed by Belcher et al. showed that such a structure would be $8.2 \text{ kcal mol}^{-1}$ higher in energy than that adopted by **4** in the crystal.^[10]

Brothers and co-workers have recently shown that porphyrins are even more accommodating towards boron.^[12] Upon careful examination of the reaction conditions leading to the formation of $[B_2O(OH)_2(tpp)]$ (**3**, by the reaction of $H_2(tpp)$ with $BCl_3 \cdot MeCN$), it was noted that a highly reactive blue-green precipitate initially forms, whose NMR spectrum indicates that the compound has higher symmetry than the final product **3**. Compound **3**, whose structure is presumed to

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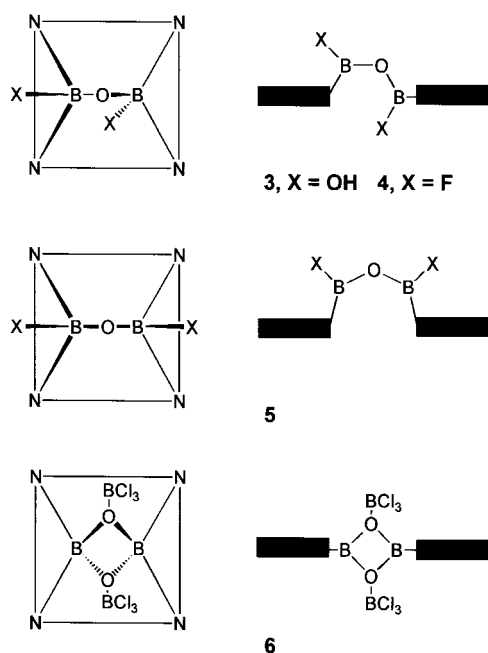
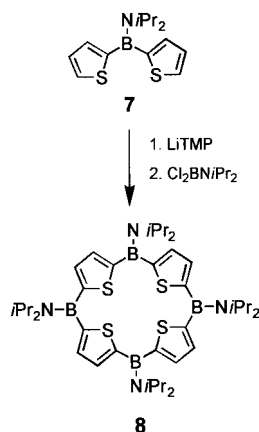


Figure 1. Schematic plan (left) and side views (right) of the core coordination in boron porphyrins 3–6.

be similar to that of **4**, is obtained only after dissolving the precipitate in dichloromethane and subjecting it to chromatography on basic alumina. Isolation of the blue-green precipitate from the reaction of $\text{BCl}_3 \cdot \text{MeCN}$ with **2** yielded a compound of structure type **6**. Crystal structure analysis showed this to be a porphyrin with an unprecedented and highly unusual core geometry. Its salient feature is the presence of a four-membered B_2O_2 ring in the porphyrin core. The two boron atoms are each bonded to two neighboring nitrogen atoms and are located in the mean plane of the molecule, while the oxygen atoms carry BCl_3 units. The plane of the B_2O_2 ring is orthogonal to the porphyrin plane. It is noteworthy that the porphyrin macrocycle is essentially planar. However, to accommodate two small boron atoms in the cavity the macrocycle has undergone a striking in-plane distortion: The macrocycle core is elongated by 1.1 Å along the $\text{B} \cdots \text{B}$ axis! While recent studies on the conformational flexibility of porphyrins have shown how flexible the porphyrin macrocycle is with regard to out-of-plane distortions, compound **6** is an extraordinary example of how accommodating porphyrins can be with regard to in-plane distortions.^[13]



Scheme 1. Synthesis of **8**.

Having shown that boron can be introduced into the central core only one challenge remained—introduction of boron into the tetrapyrrole macrocycle skeleton. This has now been accomplished by Carré et al., who described the synthesis and structure of 5,10,15,20-tetraboro-21,22,23,24-tetrathiaporphyrin

8.^[14] The synthesis involved lithiation of *N,N*-di(isopropyl)-1,1-di-2-thienylboranamine (**7**) with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) followed by reaction with $\text{Cl}_2\text{BNiPr}_2$ (Scheme 1). The reaction product is colorless, and crystallographic and spectroscopic data clearly indicate that the boron-bridged tetrathiaporphyrin **8** has no delocalized π -electron system. Therefore it formally constitutes a porphyrinogen that contains both electron-donor and acceptor groups in the macrocycle skeleton. As surprising as the coordination chemistry of boron porphyrins has turned out to be, compounds such as **8** might open an equally intriguing chemistry with regard to their reactivity and physicochemical properties.

German version: *Angew. Chem.* **1998**, *110*, 1123–1125

Keywords: boron • coordination modes • N ligands • porphyrinogens • porphyrinoids

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Light-Induced Structural Changes in the Primary Processes of Photosynthesis: Watching an Enzyme in Action**

Martina Huber*

Understanding enzyme function at a molecular level is one of the important goals of biochemistry. Moreover, since enzymes often catalyze chemical reactions that are difficult to perform in vitro, one could hope to “learn from nature” and thus find a way to improve the corresponding syntheses.

One of the dilemmas of studying enzyme function is that the reactions usually involve structural and conformational changes of the protein. However, the most accessible state of the enzyme is usually the ground state, whose structure can often be determined by X-ray crystallography or, more recently, by NMR spectroscopy. Conformational changes are harder to determine; therefore, studies of enzymes usually involve a combination of ground-state structural information with spectroscopic evidence for the changes involved in enzyme turnover. This approach is indirect with respect to the conformational changes, and whether a molecular model of function can be derived, and how accurate it is, depends on the quality of the interpretation of the spectroscopic evidence. Structural information on active intermediates in enzyme action would be a more direct and thus more reliable approach towards understanding function, but is often difficult to obtain experimentally.

In a recent publication by the groups of Feher and Rees,^[1] it was demonstrated how such structural changes can be determined directly by crystallographic methods. They investigated the primary processes of photosynthesis, that is, the reactions which allow plants and bacteria to convert sunlight into electrical and ultimately chemical energy with high efficiency.

In photosynthetic bacteria the primary processes take place in the reaction center (RC), which is a membrane protein whose ultimate task is to use light energy to pump electrons and protons across the photosynthetic membrane (Figure 1). This establishes the charge and concentration gradients that are required to drive the synthesis of energy-rich intermediates during the “dark reactions”. Electron transfer (ET) and proton transfer reactions within the RC are performed by the cofactors embedded in the protein. Their arrangement is depicted in Figure 1.

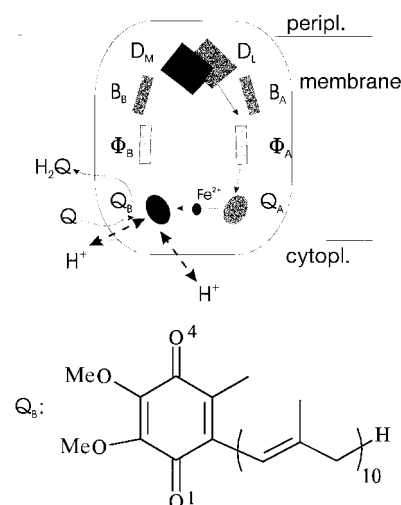


Figure 1. Schematic representation of the reaction center of a photosynthetic bacterium (in analogy to the structure of *Rhodobacter sphaeroides*)^[5] in the photosynthetic membrane, which separates the periplasmic (peripl.) from the cytoplasmic compartments (cytopl.) of the cell. The cofactors are the primary electron donor (a dimer of D_L and D_M , two bacteriochlorophyll a (BChl a) molecules in *Rb. sphaeroides*), the accessory BChl a molecules B_A and B_B , the bacteriopheophytins Φ_A and Φ_B , and the quinones Q_A and Q_B . (The structural formula of Q_B , ubiquinone 10, is given.) Reduction of Q_B by two electrons requires the uptake of two protons from the cytoplasmic side of the membrane. The dashed arrows indicate the pathways for proton transfer through protonable amino acid residues and well-ordered water molecules. For details of the location of pathways see reference [1].

In reference [1] the structural changes accompanying these primary processes (light reactions) are determined by low-temperature X-ray crystallography on a light-induced intermediate occurring during the light reactions. This gives new insight into how the efficient transformation of light into electrical energy is achieved, and helps to solve some of the questions that are currently being heavily debated. Since the primary processes of photosynthesis have been the focus of research interest of a number of groups over a few decades, the results of Feher and Rees et al. can be compared to a large body of spectroscopic data. This makes it a good model for comparing the direct X-ray crystallographic analysis with the more indirect spectroscopic studies.^[2]

To better appreciate the experimental task involved in determining the structure of the light-induced intermediate, it should be recalled that the combination of hydrophobic and hydrophilic surfaces of membrane proteins made them notorious for being difficult to crystallize. Indeed, the first protein of this class for which the X-ray structure was determined was an RC of a photosynthetic bacterium—a feat for which the Nobel prize was awarded to Michel, Deisenhofer, and Huber in 1988^[3]—and even to date there are less than ten membrane proteins for which an X-ray structure is

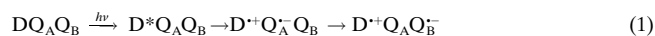
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available. In the study described,^[1] low-temperature X-ray crystallography^[4] made it possible to trap the intermediate, and it significantly improved the resolution of the ground-state structure (to 2.2 Å, which is higher than in any RC structure available to date).^[5] This allowed, for example, determination of the position of a larger number of ordered water molecules than found previously.^[5] These water molecules are considered to be involved in proton-transfer pathways. The term pathway refers to a chain of water molecules and protonable amino acid residues which conduct protons through the unpolar protein interior in a bucket-brigade fashion. Crystallography on the light-induced intermediate additionally requires that a significant fraction of the RCs in the crystal can be converted into and trapped in the excited state, as any superposition of states would make it impossible to solve the structure. Feher and Rees et al. achieved a yield of 90 % charge-separated state by continuous illumination of the crystal and subsequent freezing.

One of the most important results obtained is that substantial motions accompany the primary processes, which is (perhaps) surprising since these reactions are essentially just ET or proton transfer reactions (i.e., processes which are generally not assumed to involve large-scale structural changes). The chemical reactions performed by the RC are a sequence of electron and proton translocations which follow the electronic excitation of the primary electron donor D (a bacteriochlorophyll dimer) into its excited singlet state (D^*). The ubiquinones Q_A and Q_B (ubiquinone 10 (UQ_{10}) for *Rhodobacter sphaeroides*) in Equation (1) act as sequential electron acceptors as shown in Figure 1.



In the RC the reaction is completed by a second charge-separation event, which transfers a second electron onto Q_B . The concomitant uptake of two protons converts Q_B into the hydroquinone H_2Q_B , which leaves the RC and is subsequently replaced by another (oxidized) UQ_{10} . The protons taken up originate from the cytoplasmic side of the membrane (Figure 1). Proton depletion on that side of the membrane constitutes part of the proton gradient required to drive the dark reactions.^[6] As such, the reduction and protonation of Q_B is the process that transmits the electrical energy to chemical energy by coupling ET to the chemical follow-up reactions.

The light-induced intermediate investigated by Stowell et al.^[1] is $D^{*+}Q_AQ_B^-$, and the most pronounced structural changes are observed in the vicinity of Q_B (see Figure 2). Amongst the questions discussed^[1] we will focus on only two: the origin of the difference in binding strengths for the redox and protonation states of Q_B (Q_B , Q_B^- , and H_2Q_B), and ET from Q_A to Q_B . For optimum function the binding strength is required to increase in the order $H_2Q_B < Q_B < Q_B^-$, as this allows the RC to replace H_2Q_B by UQ_{10} and to bind Q_B^- most strongly. This prevents the semiquinone radical, an intermediate of potentially harmful reactivity, from being released prematurely.

Transfer of the first electron from Q_A to Q_B [Eq. (1)], which proceeds on the microsecond timescale at room temperature, is blocked at low temperature (below 90 K). Freezing RCs

under illumination, however, partially restores the ET. A light-induced structural change was suggested to be the origin of this temperature effect;^[7] however, a mode of motion responsible could not be determined.

A comparison of the X-ray structures^[1] of the “dark” state before light excitation and of the light-induced charge-separated state $D^{*+}Q_AQ_B^-$ (“light” structure) indicated that the following changes occur upon reduction of Q_B . Quinone Q_B moves by 4.5 Å inside the binding pocket, and the quinone ring rotates by 180° about the isoprenoid chain (Figure 2; Q_{B1}

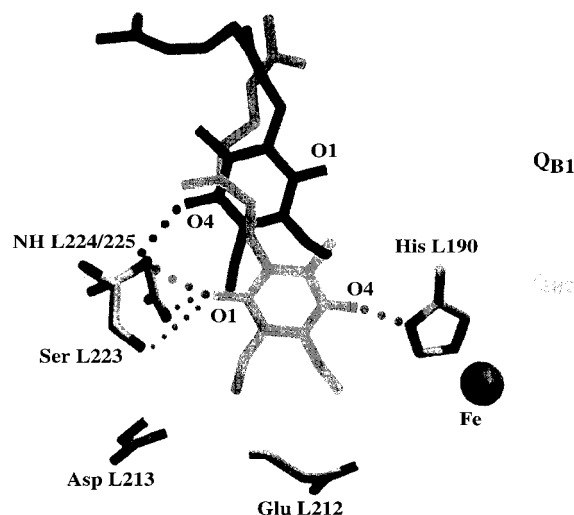


Figure 2. The different positions of the secondary electron acceptor Q_B in the dark (Q_{B1}) and light structures (Q_{B2}) of the reaction center. Selected amino acid residues of the protein with their sequence numbers are shown (L represents the protein subunit L of the RC which is made up of the subunits L, M, and H), and hydrogen bonds are indicated by dotted lines. See text for further details.

is the position of Q_B in the dark, and Q_{B2} that in the light structure). The movement results in visible changes of the hydrogen bonding to the quinone oxygen atoms O1 and O4, allowing Q_B to form a different set of hydrogen bonds after moving to Q_{B2} . It also brings Q_B much closer to the Fe^{2+} ion in the RC and shortens the distance to Q_A , which should make ET from Q_A to Q_B more favorable. Feher and Rees et al. therefore suggest that prior to reduction Q_B has to move to the position corresponding to Q_{B2} to enable ET. The motion required explains why ET from Q_A to Q_B is inhibited at low temperatures: The starting position of Q_B (Q_{B1}) is not suitable for ET, and at low temperatures the motion of Q_B to the new site in the protein pocket is inhibited.

According to these results, the differences in binding affinities of the different functional redox/protonation states of Q_B are due to changes in hydrogen bonds: In the Q_{B1} position the quinone can form only one hydrogen bond to the O4 oxygen, whereas in the Q_{B2} position it can form one short hydrogen bond to O4 and three hydrogen bonds to O1 (Figure 2). These additional hydrogen bonds should supply the extra binding energy to firmly anchor Q_B^- in the RC. The fully protonated H_2Q_B cannot form any hydrogen bonds and can therefore be easily replaced by an oxidized UQ_{10} from the quinone pool in the membrane.

The large-scale motions observed by Feher and Rees et al. suggest that interpretations of the mechanism of quinone reduction must be problematic when based on the dark structure alone. The authors also suggest that some of the differences in the position of Q_B found in earlier crystal structures^[5, 8] may reflect partial reduction of Q_B. The fact that the motions are far beyond the type that could be followed in molecular dynamics simulations underlines the necessity to determine such changes by experiments.

Beyond the immediate interest which these findings will have for the understanding of the primary processes of photosynthesis, they give some new ideas about how large structural changes during the active cycle of an enzyme can be, even if its main task is just to shuffle electrons. It shows how binding affinities of a substrate can be adapted to the function by allowing the substrate to move between different sites, rather than by changing the protein conformation. Ultimately, the beauty of seeing the protein in action and appreciating that it has surprises in store that were not suspected before suggests that the approach taken by Feher and Rees et al. will be a reference point for future investigations.

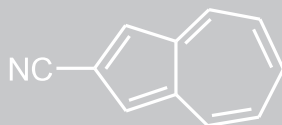
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Keywords: electron transfer • quinones • photosynthesis • protein structures • structure elucidation

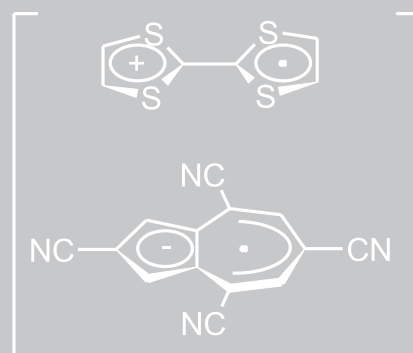
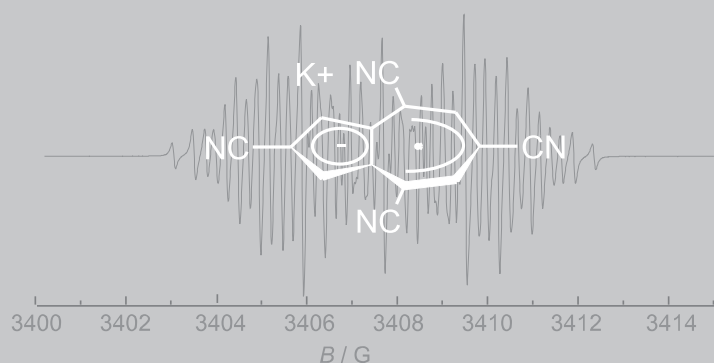
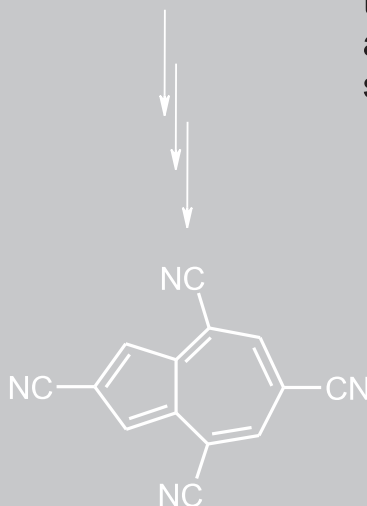
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Azulene Renaissance

The highly symmetric 2,4,6,8-tetracyanoazulene is obtained by stepwise substitution of the seven-membered ring of 2-cyanoazulene by nitrile groups.



It joins the series of strong acceptors (TCNE, TCNQ, and DCNQI) of electrically conductive charge-transfer complexes and radical anion salts.

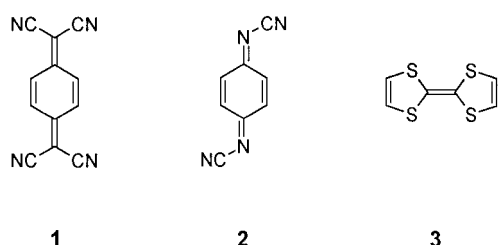


The synthesis and properties of this novel acceptor are reported by K. Hafner et al. on the following pages.

2,4,6,8-Tetracyanoazulene: A New Building Block for "Organic Metals"***

Stefan Schmitt, Martin Baumgarten, Joachim Simon, and Klaus Hafner*

Organic charge-transfer (CT) complexes are being increasingly investigated, both theoretically and experimentally,^[1] as their molecular structure allows an easy preparation of single-crystal, well-characterizable compounds with high electric conductivity. The formation of such CT complexes is based on the interaction of an energetically high-lying HOMO (of the donor) with a low-energy LUMO (of the acceptor). Many one-dimensional compounds derived from the acceptors 7,7,8-tetracyano-*p*-quinodimethane (TCNQ, **1**)^[2] and *N,N'*-dicyano-*p*-quinodimine (DCNQI, **2**)^[3] as well as the donor tetrathiafulvalene (TTF, **3**; Scheme 1)^[4] have already been investigated; superconductivity was proven even for radical ion salts.^[5]



Scheme 1. Electron acceptors and donors.

The transfer of free electrons along separated donor or acceptor stacks can formally be understood as "migration of aromaticity".^[6] Accordingly, resonance structures with a cyclic electron sextet can be formulated for the radical ions of **1–3**.

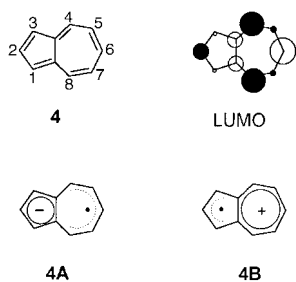
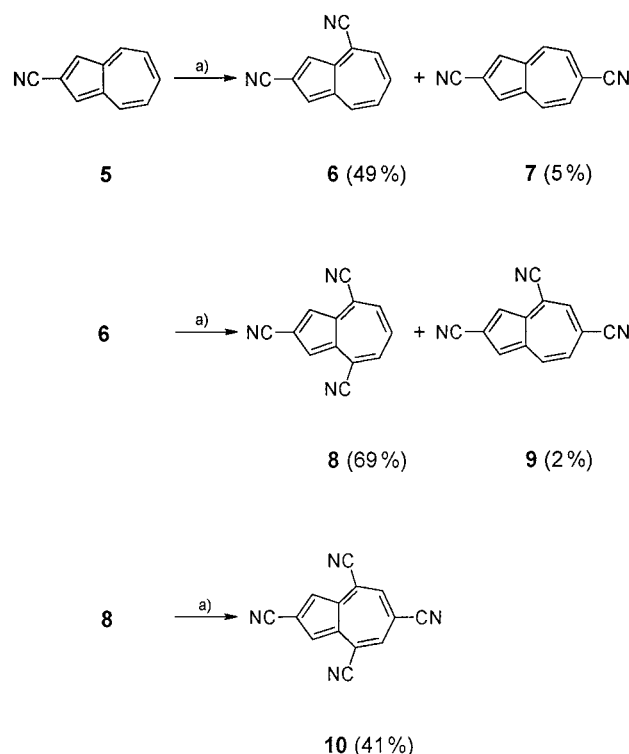


Figure 1. Schematic representation of the radical anion **4A** and the radical cation **4B** as well as the LUMO coefficients of azulene (**4**).

As numerous experimental studies and calculations^[7] of the redox characteristics of azulene (**4**)—a bicyclic, non-alternating hydrocarbon—and its derivatives have shown, its radical anion **4A** (cyclopentadienide ion) and cation **4B** (tropylium cation) can be described with an aromatic partial structure (Figure 1). Whereas the donor properties of azulene have been thoroughly inves-

tigated,^[8] none of its substituted derivatives has been employed so far as an acceptor for the preparation of CT complexes. According to HMO theory, the incorporation of acceptor substituents at the azulene positions with large LUMO coefficients (2-, 4-, 6-, and 8-positions; Figure 1) should lead to a decrease in the energy of the LUMO and consequently to an increased electron affinity.^[9]

We report here on the synthesis of 2,4,6,8-tetracyanoazulene (TCNA, **10**) and the di- and tricyanoazulenes **6–9** (Scheme 2) as well as their chemical and physical properties. Our special interest was focused on the electron affinity of these new π acceptors and their tendency to form CT complexes.



Scheme 2. Synthesis of azulenenitriles **6–10**. a) 1. KCN/DMF; 2. 2N AcOH; 3. *p*-chloranil.

In contrast to azulene (**4**), which can be attacked only by strong nucleophiles such as alkali organometallic compounds at the 4- or 8- and 6-positions,^[10] azulenes with acceptor substituents on the five-membered ring react with cyanide ions in dimethylformamide (DMF) already at room temperature to form σ adducts.^[11] After hydrolysis with 2N AcOH and dehydrogenation with *p*-chloranil, these adducts can be converted into 4-, 8-, and 6-cyanoazulenes as blue or green needles. 2,4,6,8-Tetracyanoazulene (**10**) was thus obtained from 2-cyanoazulene (**5**)^[12] by repeated nucleophilic addition and dehydrogenation.^[13] The ratios of regioisomers are in agreement with findings by McDonald et al.,^[14] according to which the reaction of azulenes with nucleophiles affords mixtures of regioisomers providing an attack at one of these positions is not favored because of steric or electronic reasons. Owing to the differences in symmetry, differentiation between

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compounds **6** and **7** as well as between **8** and **9** is possible by ^1H NMR spectroscopy (Scheme 2).

Characteristic for the substitution at an electron-deficient position of the seven-membered ring by a nitrile group is a bathochromic shift of the long-wave absorption of approximately 50 nm in the electron spectrum of azulenes **6**–**10**. This suggests a decrease in the energy of the frontier orbitals. Additional information on the energy of the frontier orbitals as well as the electron affinity of compounds **6**, **8**, and **10** was obtained by cyclic voltammetry studies. These indicate that the formation of the radical anions and the paratropic dianions is completely reversible (Figure 2). A comparison of the half-wave potentials for the first reduction of **6**, **8**, and **10** shows

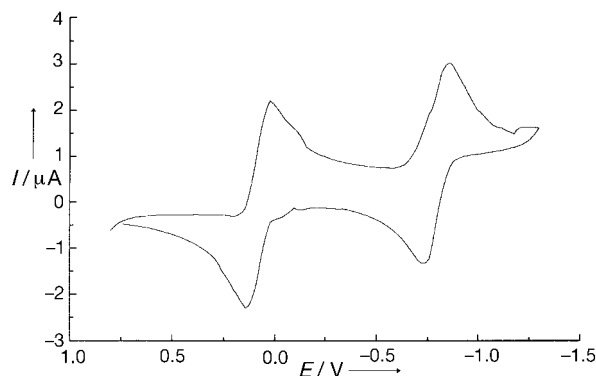


Figure 2. Cyclic voltammogram of **10** ($n\text{Bu}_4\text{NPF}_6$, 10^{-4} M , CH_2Cl_2 , 25°C , 100 mV s^{-1} , working electrode: Pt disk, counter electrode: Pt plate (1 cm^2), reference electrode: saturated calomel electrode (SCE)).

that the half-wave potential increases with rising substitution at the electron-deficient positions of the seven-membered ring (Table 1). These data are in agreement with a resonance stabilization of the negative charge and the unpaired electron by the cyano groups.

Table 1. First and second half-wave potentials of azulenenitriles **6**, **8**, and **10**.

Compd	E_1 [mV]	E_2 [mV]
6	–765	–1631
8	–320	–1240
10	80	–795

First indications for the ability of **10** to form colored CT complexes were provided by UV/Vis studies on solutions of **10** and N,N,N',N' -tetramethyl- p -phenylenediamine (TMPD) in dichloromethane or acetonitrile (Figure 3). Whereas in dichloromethane two unstructured, concentration-dependent CT bands at 513 and 1200 nm appear in addition to the characteristic absorptions of **10** between 600 and 950 nm, in acetonitrile absorption bands are observed that indicate the presence of the Wurster radical $\text{TMPD}^{+\bullet}$ and thus indicate a complete charge transfer.

The concentration of CT complexes in solution and the degree of charge transfer are determined with the complex-formation constant and with the difference in potentials

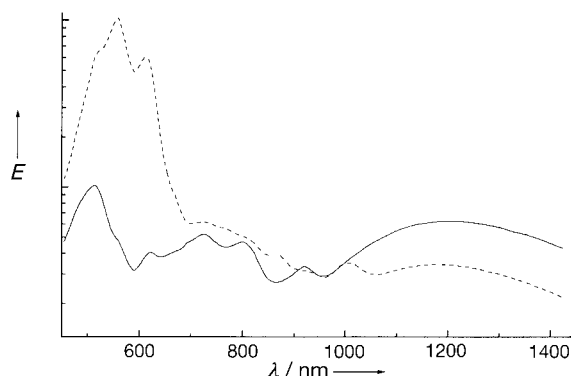
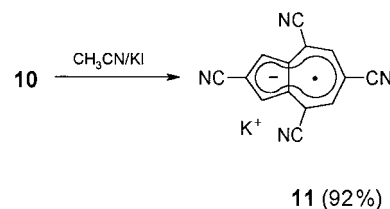


Figure 3. UV/Vis spectra of **10**/TMPD in CH_2Cl_2 (—) and CH_3CN (---). The extinction E is given in arbitrary units.

between the acceptor and donor. Consequently, a more positive reduction or oxidation potential leads to a stronger saltlike character and therefore to lower solubility in organic solvents.^[15] The reaction of **10** with an excess of potassium iodide in acetonitrile yields the potassium salt of the radical anion **11** as a green powder; it is stable in solution and in the solid state at room temperature as well as in the presence of oxygen, and dissolves in polar solvents with an intense violet color (Scheme 3).



Scheme 3. Synthesis of the radical anion salt **11**.

The UV/Vis spectrum of **11** in acetonitrile shows three absorption maxima at $\lambda = 489, 517$ and 554 nm together with a broad band of low extinction with characteristic fine structure between 600 and 1100 nm. Information on the distribution of the spin density at the individual positions was anticipated from the distances of the corresponding multiplets in the ESR spectrum. Numerous lines (about 100) appear in the ESR spectrum (Figure 4 a); however, owing to the small width of

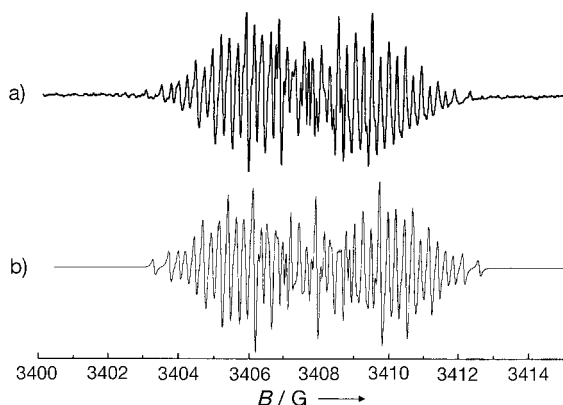


Figure 4. ESR spectra of **11**: a) in CH_3CN ; b) simulated.

the signal, they could not be assigned. The proton hyperfine coupling constants of 0.95 and 0.45 G were clearly determined with the ENDOR technique. The nitrogen coupling constants could be established from these by computer simulation^[16]

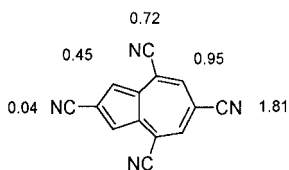
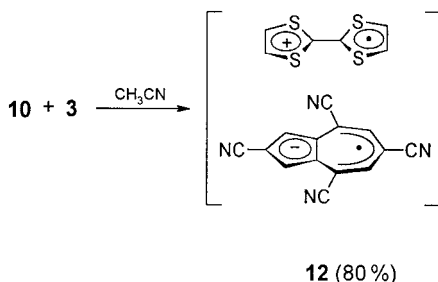


Figure 5. Nitrogen and proton hyperfine coupling constants [G] of **11**.

tions in the g value of the free electron, which are caused by an increase in the spin-orbit coupling value.

Prompted by these findings, it appeared interesting to investigate whether an aprotic, dipolar solvent could also increase the charge transfer of organic donors. In fact, combining solutions of **10** and **3** in acetonitrile provides the CT complex **12** as a microcrystalline powder; the 1:1 ratio of the components was confirmed by elemental analysis.^[13] Complex **12** has a conductivity of $1-3 \text{ Scm}^{-1}$, as determined by a two-point powder measurement (Scheme 4).^[17]



Scheme 4. Synthesis of a CT complex from **10** and **3**.

In accordance with the changed bond character of **11** and **12** as compared to **10**, a characteristic decrease in the CN wavenumber, which is often used as a measure of charge transfer, is observed in the respective IR spectra.

Experimental Section

Standard procedure for the preparation of azulenenitriles: Under an atmosphere of pure nitrogen, the azulene (1.0 mmol) substituted with an acceptor group at the five-membered ring and potassium cyanide (72 mg, 1.1 mmol) are dissolved in anhydrous DMF (10 mL) and stirred at room temperature until the solution turns colorless (ca. 12 h). After subsequent hydrolysis with 2N acetic acid (1 mL), the mixture is poured into a saturated solution of NaCl (100 mL) and extracted with dichloromethane ($3 \times 50 \text{ mL}$). The organic layer is dried with magnesium sulfate, filtered, and treated with *p*-chloranil (245 mg, 1.0 mmol). After 16 h at room temperature the solvent is removed in vacuo, and the residue subjected to chromatography on silica gel. Unchanged *p*-chloranil and starting material can be recovered in early fractions, and then the desired azulene products substituted at the 4-, 6-, and/or 8-position are isolated.

6: M.p. $174-176^\circ\text{C}$; $^1\text{H NMR}$ (300 MHz, CD_2Cl_2 , 25°C , TMS): $\delta = 7.46$ (t, $^3J(\text{H,H}) = 9.8 \text{ Hz}$, 1H, 7-H), 7.51 (d, $^3J(\text{H,H}) = 9.9 \text{ Hz}$, 1H, 5-H), 7.70 (d, $^4J(\text{H,H}) = 1.6 \text{ Hz}$, 1H, 1-H), 7.75 (t, $^3J(\text{H,H}) = 9.1 \text{ Hz}$, 1H, 6-H), 7.85 (d, $^4J(\text{H,H}) = 1.2 \text{ Hz}$, 1H, 3-H), 8.47 (d, $^3J(\text{H,H}) = 9.3 \text{ Hz}$, 1H, 8-H); IR (KBr):

$\tilde{\nu} = 2229 \text{ cm}^{-1}$ (CN); UV/Vis (CH_2Cl_2): λ_{max} ($\lg \epsilon$) = 257 (3.94), 295 (4.24), 307 (sh, 4.02), 348 (3.13), 362 (3.19), 367 (3.16), 379 (3.12), 597 (sh, 2.18), 636 (2.29), 689 (2.27), 758 nm (1.93); MS (70 eV): m/z (%): 178 (100), 151 (19) [$M - \text{HCN}$] $^+$.

7: M.p. 225°C (subl.); $^1\text{H NMR}$ (300 MHz, CD_2Cl_2 , 25°C , TMS): $\delta = 7.47$ (d, $^3J(\text{H,H}) = 10.3 \text{ Hz}$, 1H, 7-H and 5-H), 7.68 (s, 1H, 1-H and 3-H), 8.38 (d, $^3J(\text{H,H}) = 10.4 \text{ Hz}$, 1H, 4-H and 8-H); IR (KBr): $\tilde{\nu} = 2227 \text{ cm}^{-1}$ (CN); UV/Vis (CH_2Cl_2): λ_{max} ($\lg \epsilon$) = 281 (4.76), 327 (sh, 3.49), 338 (3.68), 351 (3.85), 362 (sh, 3.70), 368 (4.06), 603 (sh, 2.55), 646 (2.70), 702 (2.68), 775 nm (2.32); MS (70 eV): m/z (%): 178 (100), 151 (26) [$M - \text{HCN}$] $^+$.

8: M.p. $264-265^\circ\text{C}$; $^1\text{H NMR}$ (300 MHz, CD_2Cl_2 , 25°C , TMS): $\delta = 7.75$ (d, $^3J(\text{H,H}) = 10.2 \text{ Hz}$, 1H, 5-H and 7-H), 7.93 (t, $^3J(\text{H,H}) = 9.4 \text{ Hz}$, 1H, 6-H), 8.10 (s, 1-H and 3-H); IR (KBr): $\tilde{\nu} = 2227 \text{ cm}^{-1}$ (CN); UV/Vis (CH_2Cl_2): λ_{max} ($\lg \epsilon$) = 269 (4.33), 291 (sh, 4.21), 302 (4.30), 311 (4.32), 324 (sh, 4.00), 360 (3.30), 377 (3.39), 395 (3.17), 639 (sh, 2.30), 684 (2.44), 752 (2.42), 840 nm (2.01); MS (70 eV): m/z (%): 203 (100), 176 (15) [$M - \text{HCN}$] $^+$.

9: M.p. 268°C (subl.); $^1\text{H NMR}$ (300 MHz, CD_2Cl_2 , 25°C , TMS): $\delta = 7.67$ (s, 1H, 5-H), 7.71 (d, $^3J(\text{H,H}) = 10.2 \text{ Hz}$, 1H, 7-H), 7.85 (s, 1H, 3-H), 7.97 (s, 1H, 1-H), 8.50 (d, $^3J(\text{H,H}) = 9.7 \text{ Hz}$, 1H, 8-H); IR (KBr): $\tilde{\nu} = 2222 \text{ cm}^{-1}$ (CN); UV/Vis (CH_2Cl_2): λ_{max} ($\lg \epsilon$) = 295 (4.72), 353 (3.54), 371 (3.75), 389 (3.87), 637 (sh, 2.49), 684 (2.63), 752 (2.61), 838 nm (2.21); MS (70 eV): m/z (%): 203 (100), 176 (21) [$M - \text{HCN}$] $^+$.

10: M.p. 348°C (decomp); $^1\text{H NMR}$ (300 MHz, CD_2Cl_2 , 25°C , TMS): $\delta = 7.94$ (s, 2H, 5-H and 7-H), 8.24 (s, 2H, 1-H and 3-H); IR (KBr): $\tilde{\nu} = 2235 \text{ cm}^{-1}$ (CN); UV/Vis (CH_2Cl_2): λ_{max} ($\lg \epsilon$) = 277 (4.45), 306 (4.78), 366 (3.60), 385 (3.83), 404 (3.82), 675 (sh, 2.49), 725 (2.63), 802 (2.58), 912 nm (2.19); MS (70 eV): m/z (%): 228 (100), 201 (20) [$M - \text{HCN}$] $^+$.

11: M.p. 281°C (decomp); IR (KBr): $\tilde{\nu} = 2197 \text{ cm}^{-1}$ (CN); UV/Vis (CH_3CN): λ_{max} = 247 , 306 , 325 (sh), 364 , 380 , 399 , 410 (sh), 462 (sh), 489 , 517 , 554 , 687 , 753 , 864 , 1000 nm .

12: M.p. 256°C (decomp); IR (KBr): $\tilde{\nu} = 2201 \text{ cm}^{-1}$ (CN).

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Effect of Chain Length on the Adsorption Behavior of *n*-Alkanes in Ferrierite

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Zeolites are microporous crystalline materials that are used as catalysts in petrochemical applications because of their acidity and stability.^[1] At present there are more than a hundred types of zeolites, each with characteristic pore sizes and pore topologies. One important aim of zeolite science is to use these differences to tune the selectivity of a given reaction.^[2] To arrive at a rational design, it is essential to have an understanding on the molecular level of the behavior of the sorbates in the pores of these zeolites.^[3] Currently such information is mainly obtained from computer simulations. For example, recent Monte Carlo calculations have allowed many predictions to be made about the behavior of *n*-alkanes in zeolites,^[4–8] in particular regarding the preferential adsorption sites of *n*-alkanes in zeolites. To the best of our knowledge, none of these predictions have been confirmed

experimentally, since direct information on the siting of *n*-alkanes is difficult to obtain.

Here we present work on the siting of *n*-alkanes in the zeolite ferrierite (FER). FER has ten-ring channels which are interconnected by cages with eight-ring windows. The use of this zeolite as an isomerization catalyst for the production of isobutene, an intermediate in the production of methyl *tert*-butyl ether (MTBE, considered to be an environmentally beneficial fuel), has been studied extensively.^[9,10] The comparison of the performance of FER and other zeolites as catalysts for the isomerization of *n*-butene has been mainly focused on the dimensions of the ten-ring channels.^[9] We now find that the characteristic pore topology is an important factor as well. One of the questions still open pertains to the distribution of the molecules over these ten- and eight-ring channels.

To study this distribution, we investigated the siting of *n*-alkanes in FER by means of Monte Carlo simulations and ¹³C NMR spectroscopy. For the simulations we assumed that the zeolite is rigid, and the *n*-alkanes were modeled with a united atom representation; that is, CH₃ and CH₂ groups are considered as “united atoms”. Fixed bond lengths, bond angles, and torsion potentials were used.^[11] Details on the simulation techniques have already been described.^[5,12] The results of Monte Carlo simulations (Figure 1) indicate a

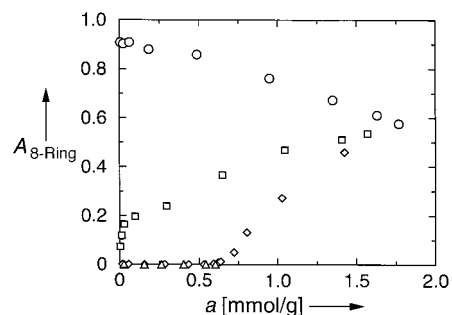


Figure 1. Fraction A_{8-Ring} of the molecules adsorbed in the eight-ring channels as a function of the loading a . The data were obtained from computer simulations with the configurational-bias Monte Carlo method at 333 K. $\circ$ propane, $\square$ butane, $\diamond$ pentane, $\triangle$ hexane.

surprising effect of the chain length. *n*-Alkanes with more than five carbon atoms prefer the ten-ring channels for all loadings; these molecules are too large to fit into the eight-ring channels. At low loadings propane and butane are distributed over the ten-ring and eight-ring channels. While propane prefers adsorption in the eight-ring channel, butane adsorbs preferentially in the ten-ring channel. The adsorption of pentane is at low loading limited to the ten-ring channel, and adsorption in the eight-ring channel occurs only at higher loadings. These simulations show that the adsorption behavior of even simple *n*-alkanes is quite complex and depends strongly on the chain length. One of the purposes of the present work was to present experimental evidence that the above prediction is indeed correct.

An obvious experimental technique to investigate the siting of hydrocarbons in zeolites is ¹³C NMR spectroscopy. The chemical shifts of *n*-alkanes depend on the local environment

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of the carbon atoms, and one would therefore observe different sets of signals depending on whether the *n*-alkane molecules are adsorbed in the eight-ring or ten-ring channels. To unambiguously assign the NMR signals, we used zeolite ZSM-22 as a reference. Since ZSM-22 has only ten-ring channels similar to those in FER, the NMR spectra of molecules adsorbed in the ten-ring channels of FER will be similar to those obtained in ZSM-22. A vacuum system with a calibrated volume was used to prepare the samples for the ^{13}C NMR measurements. A glass tube with a small capsule containing the sample (15 to 30 mg) was connected to this system. After dehydration by evacuation ($p < 10^{-4}$ kPa) at 773 K for FER and 723 K for ZSM-22 for at least one hour, a certain amount of hydrocarbon was brought into contact with the sample. After adsorption, the sample was cooled in liquid nitrogen, and the capsule closed by melting. This capsule was placed into a magic angle spinning (MAS) rotor (diameter 7 mm) and used in the measurements on a Bruker MSL 400 spectrometer at 9.4 T and room temperature. The MAS spinning rate was 2500 Hz, and cross polarization was performed with a contact time of 1 ms and a repetition time of 5 s. The number of scans accumulated was dependent on the loading of the *n*-alkane. H-FER with a Si/Al ratio of 9 was provided by the Shell Research and Technology Center, Amsterdam. The NaZSM-22 sample with a Si/Al ratio of 35 was donated by Exxon Chemical Europe Inc. (Machelen, Belgium).

Figure 2 shows the spectra of hexane in FER and in ZSM-22 at various loadings; the similarity between the spectra is striking. Hexane is too large to fit in the eight-ring channels, and therefore one would expect the spectra to be similar. This indicates that our assumption that ZSM-22 can be used as a reference zeolite is correct.

For pentane we observe (see Figure 3) that at low loadings in FER the spectra are similar to those in ZSM-22, indicating adsorption in the ten-ring channels of FER only. At high loadings, however, additional peaks appear in the spectra in FER that are not present in the spectrum of ZSM-22. This shows that at high loadings the molecules also adsorb in the eight-ring channels. In the case of butane there is adsorption in both the eight- and ten-ring channels at all loadings. For propane we find very different spectra in ZSM-22 and in FER

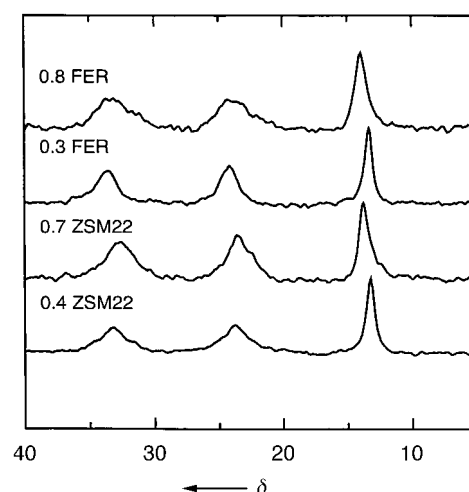


Figure 2. ^{13}C NMR spectra of hexane in ZSM-22 and in FER at different loadings (indicated in mmol g^{-1}).

at low loadings, but at high loadings an additional peak appears in the spectrum in FER at a similar position as the peaks in the spectrum in ZSM-22. This implies that at low loadings the propane molecules adsorb in the eight-ring channels and at high loadings also in the ten-ring channels. This behavior of the *n*-alkanes in FER is exactly what has been predicted based on the computer simulations. In addition, these observations are consistent with the pore volumes occupied by the different *n*-alkanes (Table 1). Table 1 shows that the longer molecules, such as hexane and heptane, occupy significantly less of the FER pore volume than the shorter *n*-alkanes. This observation can be explained by noting that both the NMR spectra and the simulations indicate that hexane and the longer *n*-alkanes do not adsorb in the eight-ring channels.

The implications of our results for the isomerization of *n*-butene in FER are interesting. One of the most striking features of FER as a successful catalyst for the isomerization of *n*-butene to isobutene is the low yield of long-chain molecules,^[9] which is required to obtain a high selectivity for the desired isobutene. A surprising observation is that this suppression of the production of long-chain molecules only

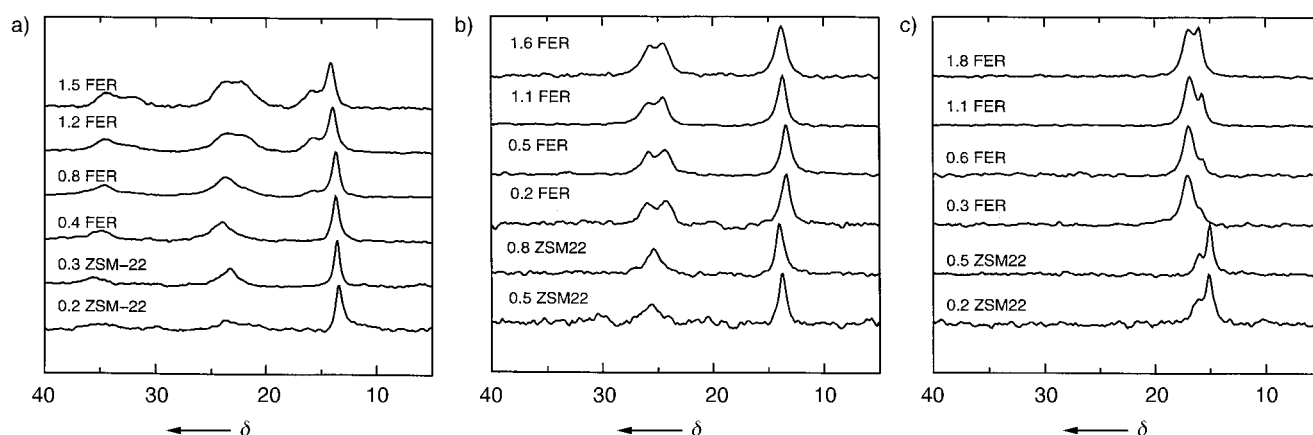


Figure 3. ^{13}C NMR spectra of a) pentane, b) butane, and c) propane in ZSM-22 and in FER at different loadings (indicated in mmol g^{-1}).

Table 1. Pore volume occupied by the different *n*-alkanes at 293 K.^[a]

	propane	butane	pentane	hexane	heptane
V_{ads} [mL g ⁻¹]	0.15	0.16	0.17	0.10	0.10

[a] The values were calculated by using the density of the liquid *n*-alkane at 293 K relative to that of water at 277 K. A Setaram TG-DSC 111 instrument operating under a helium flow of about 3.8 L h⁻¹ was used in these adsorption experiments. The FER samples were dehydrated at 723 K for 10 min. After cooling, adsorption was performed by either saturating 20% of the helium flow with the liquid *n*-alkanes or by replacing 20% of the helium flow by the gaseous *n*-alkanes. This means that the adsorption pressure of the liquid *n*-alkanes was 20% of the saturation pressure, while the propane and butane pressure was 20 kPa.

occurs after the formation of coke residues in the FER pores.^[9,10,13] The results presented here imply that FER behaves as a one-dimensional pore system for long-chain molecules, while its full two-dimensional pore system can be exploited only by the shorter molecules. Pore blocking due to the formation of coke will therefore have a large inhibiting effect on the movements of the long-chain molecules, which are limited by one-dimensional (single-file) diffusion; the movements of shorter molecules are far less restricted. The resulting long residence time of the long-chain molecules causes them to crack. The combination of ten-ring channels with intersecting eight-ring channels, from which the longer molecules are excluded, is a unique feature of the FER pore structure. The results presented provide an excellent demonstration of the importance of understanding adsorption effects in zeolites for predicting differences in catalytic performance of zeolites.

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The First Delocalized Phosphole Containing a Planar Tricoordinate Phosphorus Atom: 1-[Bis(trimethylsilyl)methyl]-3,5-bis-(trimethylsilyl)-1,2,4-triphosphole**

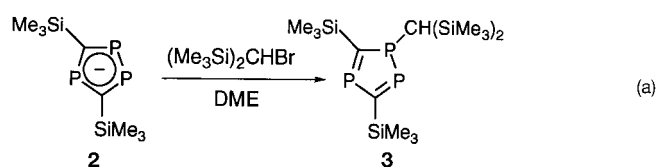
F. Geoffrey N. Cloke, Peter B. Hitchcock, Philip Hunnable, John F. Nixon,* László Nyulászi,* Edgar Niecke,* and Vera Thelen

The generally accepted view that phospholes are not aromatic^[1, 2] must now be revised in light of the first example of a fully delocalized 1,2,4-triphosphole containing a planar tricoordinate phosphorus atom, which is described here. Theoretical calculations predict that a planar phosphole would be strongly aromatic,^[3, 4] and that planarity can be achieved by partial^[5, 6] or full replacement^[6–8] of CH groups by dicoordinate phosphorus atoms in the five-membered phosphole ring. Both the sum of the bond angles (342°)^[9] and the complexing behavior^[10, 11] of the recently described 1-[bis(trimethylsilyl)methyl]-3,5-di-*tert*-butyl-1,2,4-triphosphole (**1**), indeed show the expected increase in the planarity of the tricoordinate phosphorus atom and the enhanced aromaticity of the ring system. Likewise, the incorporation of bulky substituents^[12–15] at the tricoordinate phosphorus atom of a phosphole resulted in characteristic changes both in the photoelectron spectrum^[16] and in the chemical reactivity,^[15] providing the first example of a phosphole that undergoes electrophilic substitution. Schmidpeter et al. recently reported phospholes substituted by electron-withdrawing cationic moieties,^[17, 18] which exhibited NMR spectroscopic characteristics^[17] or structural features (sum of bond angles at the tricoordinate phosphorus atom 338°),^[18] which is in accordance with partial flattening of the phosphorus pyramid. However, a totally planar phosphole which would lead to full aromaticity has not been previously achieved.

Treatment of the recently reported^[19] 3,5-bis(trimethylsilyl)-1,2,4-triphospholide anion (**2**) with (SiMe₃)₂CHBr in 1,2-dimethoxyethane (DME) readily affords yellow 1-[bis(trimethylsilyl)methyl]-3,5-bis(trimethylsilyl)-1,2,4-triphosphole (**3**, Eq. (a)). As anticipated, the compound exhibits a molecular ion at *m/z* 422 in the mass spectrum, four expected resonances in the ¹H NMR spectrum, and three resonances in the ratio 2:1:1 in the ²⁹Si NMR spectrum. The ³¹P{¹H} NMR spectrum of **3**, however, is completely different from that of the corresponding 1,2,4-triphosphole **1**.^[9] Whereas the latter

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shows the expected widely spaced pattern of lines for an AMX spin system (where A represents the tricoordinate phosphorus atom attached to the dicoordinate phosphorus atom M and X is the other dicoordinate phosphorus atom), in the spectrum of **3** the signal of phosphorus atom A is significantly shifted so that it now almost overlaps with the signal of the adjacent dicoordinate phosphorus atom. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of **3** is therefore best described as an ABX spin system and was analyzed accordingly.

Particularly noteworthy is the similarity in chemical shifts of the two adjacent tri- and dicoordinate phosphorus atoms in **3** which to our knowledge is unprecedented. The differences in chemical shifts between **1** and **3** clearly reflect the effect of the significant delocalization of the lone pair electrons of the tricoordinate phosphorus atom into the ring system of **3** (see below).

Good quality crystals of **3** were obtained for a single-crystal X-ray diffraction study (Figure 1).^[28] The structure reveals a

bond length in **3** is similar to those found in bis(methylene)phosphoranes (e.g. 1.661 and 1.674 Å in $\text{Ph}_2\text{CP}(2,4,6\text{-MeC}_6\text{H}_2)\text{C}(\text{SiMe}_3)_2$).^[21]

The observed bond lengths within the triphosphole ring of **3** are also consistent with a contribution of a (canonical) phosphanedimethylenephosphorane unit, as discussed together with a localized $\text{C}=\text{P}$ bond by Schmidpeter et al.^[18] The aromaticity indices, which are larger for **3** than for other five-membered phosphorus heterocycles (see below), are also in agreement with a description of a formalism that takes into account the conventional resonance structure (1,3-diphosphabutadiene and the lone pair of the tricoordinate phosphorus atom) and one involving the bis(methylene)phosphorane unit.

To understand the planarity about the tricoordinate phosphorus atom in **3** better, ab initio quantum-chemical calculations were carried out.^[22] While 1,2,4-triphosphole **1** turned out to be nonplanar at the HF/3-21G* level of theory,^[23] the geometry optimization of **3** resulted in a planar structure even when starting from an initial nonplanar geometry. The optimized bond lengths for **3** are in very good agreement with those obtained by X-ray structure analysis (Table 1). This behavior indicates that the planarity of **3** is unlikely to be attributed to solid-state interactions. The calculated structure is very similar to that obtained at the same level of theory (with one imaginary frequency) for the unsubstituted 1,2,4-

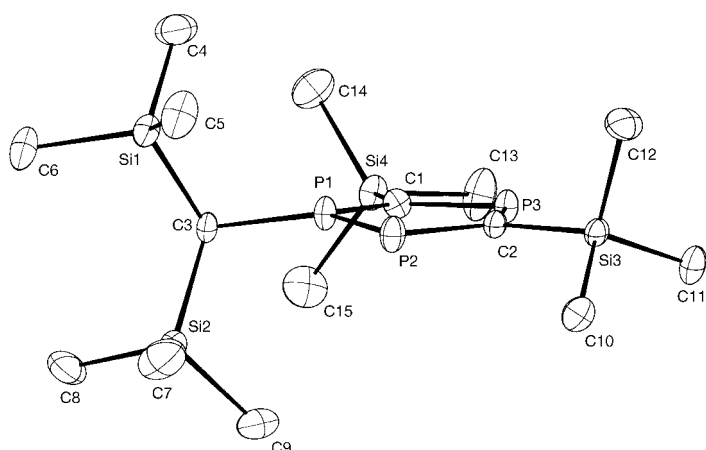


Figure 1. Molecular structure of **3**. Selected bond lengths [Å] and angles [°]: P1–C1 1.684(7), P1–C3 1.811(6), P1–P2 2.056(3), P2–C2 1.745(7), P3–C2 1.715(7), P3–C1 1.743(7); C1–P1–C3 125.1(4), C1–P1–P2 110.5(3), C3–P1–P2 123.1(3), C2–P2–P1 92.3(2), C2–P3–C1 103.8(3).

number of features of considerable interest. The most dramatic aspect of the structure is the planarity of the five-membered 1,2,4-triphosphole ring system with a sum of angles at the tricoordinate phosphorus atom of 358.7°. This value contrasts previously reported values of 342.3° for the analogous 3,5-di-*tert*-butyltriphosphole **1**,^[9] 302.7° for 1-benzyl phosphole,^[20] and 331.7° for the recently described 2,4,6-tri-*tert*-butylphenyl-3-methylphosphole (**4**).^[15] Interestingly, the shortest P–C bond length in **3**, namely P1–C1 (1.684(7) Å), involves the tricoordinate phosphorus atom P1 and is significantly shorter than P2–C2 (1.745(7) Å), P3–C2 (1.715(7) Å), or P3–C1 (1.743(7) Å), which all involve dicoordinate phosphorus atoms. The corresponding values for **1** are 1.734(4), 1.718(4), 1.763(4), and 1.720(3) Å. The P1–C1

Table 1. Selected bond lengths [Å] in **3** (X-ray structure and ab initio calculations) and the unsubstituted 1,2,4-triphosphole (calculated under planarity constraint).

	X-ray	calcd (HF/3-21G*)	H-substituted, planar
P1–P2	2.056	2.054	2.061
P2–C2	1.745	1.739	1.717
C2–P3	1.715	1.725	1.735
P3–C1	1.743	1.750	1.722
C1–P1	1.684	1.692	1.692

triphosphole calculated under planarity constraint. A comparison of the structures of **1** and **3** shows that silyl substituents lengthen while alkyl substituents shorten the neighboring bonds.

The resulting structure is not only fully planar, but also aromatic, in agreement with previous conclusions drawn for planar phospholes from theoretical studies.^[3–8] The Bird aromaticity index^[24] for **3** is 84, which is significantly larger than the values of 46 calculated (HF/3-21G*) for nonplanar phosphole and 35.5 obtained from the X-ray structure of 1-benzyl phosphole^[25] as well as 56 for **1** and 56.5 for **4**. Likewise, the bond-shortening index^[26] of **3** is 60 (compared to 67 for benzene,^[26] 68 for pentaphosphole P_5H_7 ,^[7] 57 for thiophene,^[7] and 50 for nonplanar phosphole and **1**). This reflects the strong π -donor properties of the planar tricoordinate phosphorus atom, as predicted by the previous theoretical work.^[4, 27] The trimethylsilyl substituent is a π -electron acceptor, as is the BH_2 group. The latter reduces the inversion barrier of both phosphole^[4] and 1,3,4-triphosphole^[5] when attached to the 2- and 5-positions of those rings. Presumably the decrease of the π -electron density caused by the

substituent is compensated by an increased contribution of the lone pair of the tricoordinate phosphorus atom, which can be accomplished only by an enhanced flattening of the phosphorus pyramid.

To model the electronic effect of the different substituents on phosphole ring systems, calculations were carried out with a methyl substituent in the 1-position and silyl substituents in the 3- and 5-positions. For 1-methyl-3-silyl-1,2,4-triphosphole and 1-methyl-5-silyl-1,2,4-triphosphole, inversion barriers of 1.92 and 1.89 kcal mol⁻¹ were obtained, which are about 1 kcal mol⁻¹ lower than that for 1-methyl-1,2,4-triphosphole (2.77 kcal mol⁻¹; all calculations at the MP2/6-31G* level). For 1-methyl-3,5-disilyl-1,2,4-triphosphole a further decrease of the inversion barrier results, but full planarity was not attained. These results indicate that the effect of the silyl substituent alone is not enough to stabilize the planar structure. Similarly, 2,5-diboryl-1,3,4-triphosphole was found to be nonplanar at the MP2/6-31G* level.^[5]

The bis(trimethylsilyl)methyl group was shown to flatten the *tert*-butyl-substituted triphosphole ring.^[22] The effect can be attributed to the electron-donor effect of the bis(trimethylsilyl)methyl group and to steric repulsion of the two trimethylsilyl groups which are situated above and below the ring. To examine this effect the structure of 1-[bis(silyl)methyl]-3,5-disilyl-1,2,4-triphosphole was also optimized. This turns out to be nonplanar; the sum of bond angles around the tricoordinate phosphorus atom is 324.3°. Optimization of 1-[bis(trimethylsilyl)methyl]-3,5-disilyl-1,2,4-triphosphole, on the other hand, results in a planar structure, showing that the steric bulk of the substituent in the 1-position of the phosphole ring plays a significant role in making the ring planar.

The 1,2,4-triphosphole **3** is the first example of a neutral five-membered ring containing a tricoordinate phosphorus atom that is fully planar. Furthermore, according to the available measurements, **3** is the most aromatic of all the known neutral five-membered phosphorus heterocycles. The new planar triphosphole is likely to show aromatic chemical behavior, such as formation of η^5 -transition metal complexes. An analysis of the various factors that result in the planarity of the ring indicates that the effects of the dicoordinate phosphorus atoms incorporated into the ring, the π -electron acceptors substituted at the ring atoms (other than the tricoordinate phosphorus), and the sterically demanding groups on the tricoordinate phosphorus atom should all be taken into account.^[23]

Experimental Section

A solution of **2** (0.65 g, 2.5 mmol) in DME (10 mL) was cooled to -78 °C. (SiMe₃)₂CHBr (0.7 mL, 2.6 mmol) was then added. The solution was warmed to room temperature slowly and stirred for 24 h. The volatile components were removed under vacuum, and the product extracted with hexane (30 mL). Purification by column chromatography with hexane as eluent followed by recrystallization in heptane yielded yellow crystals of **3** suitable for X-ray crystallography. Yield: 54% after purification. ³¹P{¹H} NMR (121.5 MHz, C₆D₆): δ = 288.3 (dd, ²J(P_X,P_A) = 14.3, ²J(P_X,P_B) = 11.5 Hz; P_X), 180 (dd, ¹J(P_B,P_A) = 571.2 Hz; P_B), 179 (dd; P_A); ¹H NMR (300 MHz, C₆D₆): δ = 2.24 (dd, ²J(H,P_A) = 8.5, ³J(H,P_B) = 1.1 Hz; (Me₃Si)₂CH), 0.55 (s; Si(CH₃)₃), 0.46 (s; Si(CH₃)₃), 0.07 (s; CH(Si(CH₃)₃)₂); ¹³C{¹H} NMR (75.5 MHz, C₆D₆): δ = 180.2 (ddd, ¹J(C,P_X) = 86.4, ¹J(C,P_B) = 52.6, ²J(C,P_A) = 22.8 Hz; P_BCP_X), 153.4 (ddd, ¹J(C,P_X) = 95.5,

¹J(C,P_A) = 32.4, ²J(C,P_B) = 25.3 Hz; P_ACP_X), 22.1 (ddd, ¹J(C,P_A) = 31.1, ²J(C,P_B) = 17.6, ³J(C,P_X) = 5.7 Hz; CH(SiMe₃)₂), 3.3 (br d; Si(CH₃)₃), 2.9 (m; Si(CH₃)₃), 0.8 (brs; CH(Si(CH₃)₃)₂); ²⁹Si NMR (49.7 MHz, C₆D₆): δ = -5.4 (br m), -1.9 (br m), 2.7 (brs); MS (EI, 70 eV): *m/z* (%): 422 [*M*⁺], 349 [*M*⁺ - SiMe₃], 218 [P₃C₂(SiMe₃)Si⁺], 73 [Me₃Si⁺].

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- [28] Crystal data for **3** ($C_{15}H_{37}P_3Si_4$): $M_r = 422.7$, monoclinic, space group $P2_1/c$ (no. 14), $a = 9.887(3)$, $b = 20.310(3)$, $c = 14.129(2)$ Å, $\beta = 108.21(2)^\circ$, $V = 2695.1$ Å³, $Z = 4$. $Mo(K\alpha)$ radiation, data collection with an Enraf-Nonius CAD4 diffractometer. Of 4727 reflections measured, 2127 were observed ($I > 2\sigma(I)$). $R = 0.083$, $wR2 = 0.182$. 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-101 105. 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).

Facile Synthesis of Cyclic Tetrapeptides from Nonactivated Peptide Esters on Metal Centers**

Katharina Haas, Werner Ponikwar, Heinrich Nöth, and Wolfgang Beck*

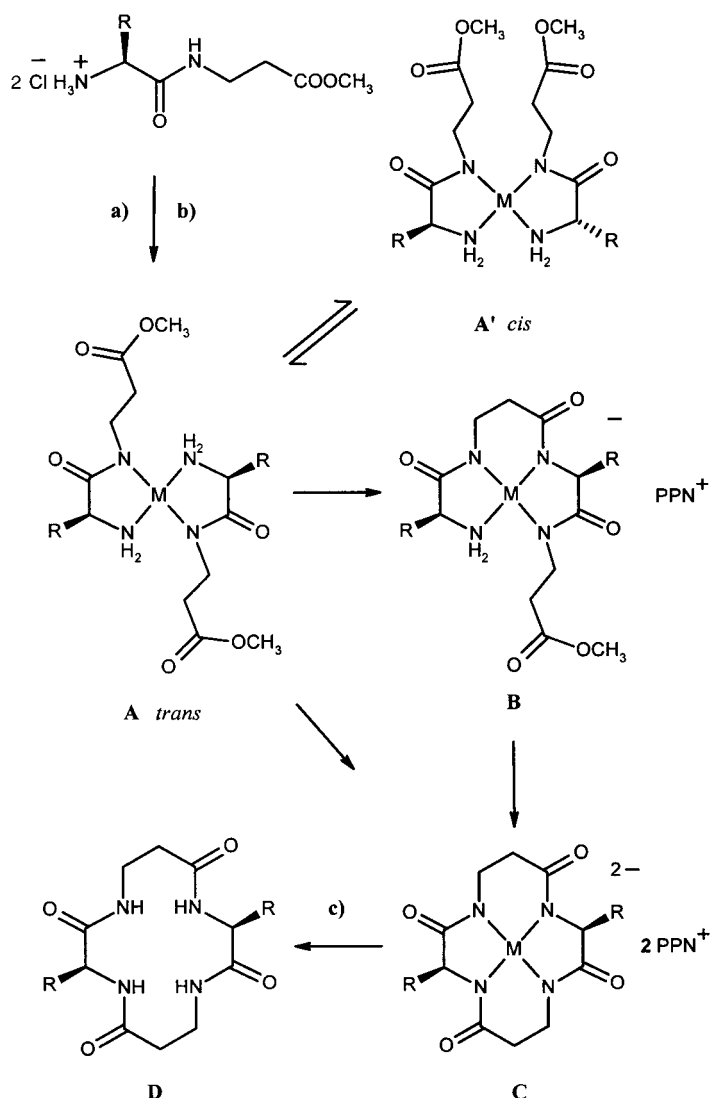
Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

The search for a comprehensive understanding of the structure–activity relationship for conformationally rigid peptides has led to a greater interest in cyclic peptides.^[1, 2] Synthetic cyclopeptides are interesting target molecules owing to their biological activity, their model character for conformational analyses, and their potential as drugs, among other things.^[3] Synthetic analogues of hormones^[4] show the link between reduced peptide flexibility due to cyclization and increased receptor specificity in a particularly impressive fashion. As the metabolic degradation of peptides begins preferably at the C or N terminals,^[1] cyclic peptides are expected to have a longer biological availability than their linear analogues. Cyclic tetrapeptides with biological activity are also found in nature.^[5]

Present methods for the cyclization of peptides generally require a completely protected peptide precursor, which is

cyclized in solution or at a solid phase by using a coupling agent, as well as a strongly activated acyl component. In order to avoid intermolecular oligomerizations, the cyclization of small peptides, in particular (e.g., tetrapeptides), must be performed under high dilution conditions.^[6]

In the course of our continuing studies into the formation of oligopeptides at metal centers,^[7] we have found a facile, metal-mediated synthesis of 12-, 14-, 16-, and 18-membered cyclic tetrapeptides or macrolactams from readily accessible nonactivated dipeptide ester precursors. The reaction of Ni^{II} , Pd^{II} , and Cu^{II} salts with two equivalents of dipeptide ester in methanol in the presence of NaOMe as base results in dianionic complexes, which can be isolated by precipitation with suitable cations (e.g., Ca^{2+} , Cs^+ , $PPN^+ = (Ph_3PNPPh_3)^+$ (**1–11**, see Scheme 2). The cyclization of the dipeptides coordinated to the metal probably occurs as shown in Scheme 1. The crucial step is the same as that assumed for the oligomerization of peptides at metal centers,^[7, 8] namely



Scheme 1. Postulated mechanism of the metal-supported synthesis of C_2 -symmetrical cyclic tetrapeptides, exemplified for a 14-membered ring. a) $Na_2[PdCl_4]$, $NiCl_2 \cdot 6H_2O$ or $CuCl_2 \cdot 2H_2O$, 6 NaOMe, MeOH, 24 h, 65 °C; b) $[PPN]Cl$, H_2O ; c) $HCl/MeOH$ (saturated), room temperature, 15 min.

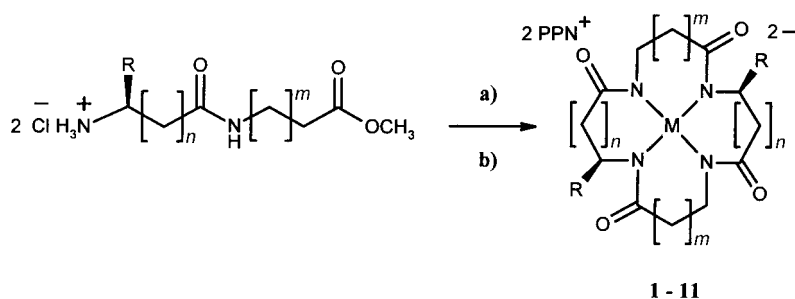
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[+] X-ray crystal structure analysis

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the nucleophilic attack of a coordinated terminal amino group on the carbonyl group of the neighboring *trans*-coordinated dipeptide ester in **A**. It is not clear whether the cyclization in the planar complex is a concerted process, as the hypothetical monoanionic intermediate **B** was not isolated. The prerequisite for such a double head-to-tail condensation is that in the initial step the dipeptide esters coordinate to the metal in a *trans* fashion. It can be assumed that the neutral *trans*-bis(dipeptide ester) complex **A** is in equilibrium with the corresponding *cis* complex **A'** and that during the reaction an isomerization to the *trans* compound takes place.^[9] Several neutral *trans*-bis(dipeptide ester) complexes **A** with M = Pd were isolated and the complex *trans*-[Pd(Gly- β -Ala(-H⁺)-OMe)₂] was characterized by X-ray structure analysis.^[10] The liberation of the tetrapeptide **D** from complex **C** can be achieved nearly quantitatively by using saturated methanolic HCl, and this was exemplified for **8** (see Experimental Section).

In order to determine the limitations of this method, we allowed dipeptide esters of α -, β -, γ -, and δ -amino acids to react with Pd^{II}, Ni^{II}, and Cu^{II} as templates (Scheme 2, Table 1).



Scheme 2. Synthesis of the C₂-symmetrical cyclotetrapeptide complexes **1–11**. a) Na₂[PdCl₄], NiCl₂·6H₂O or CuCl₂·2H₂O, 6NaOMe, MeOH, 24 h, 65 °C; b) [PPN]⁺Cl[−], H₂O.

The X-ray crystal structure analysis^[11] of **1**·8H₂O·3CH₃CN shows that the cyclic tetrapeptide is bound to the metal through the four deprotonated amide nitrogen atoms. The palladium center and the N atoms lie in a plane (sum of the angles around the Pd atom is 360°) (Figure 1). The anions in **1** form layers in the crystal lattice, in which the carbonyl groups are linked by hydrogen bonds to the water molecules that are arranged between the anions (Figure 2). The acetonitrile molecules similarly fill the space between the PPN cations.

Table 1. C₂-symmetrical cyclotetrapeptide complexes prepared according to Scheme 2.

Compound	M	n	m	R	Number of atoms in the ring
1	Pd	0	1	H	14
2	Pd	0	1	CH ₃	14
3	Pd	0	1	CH ₂ OH	14
4	Pd	0	2	H	16
5	Pd	0	3	H	18
6	Pd	1	1	H	16
7	Ni	0	0	CH ₃	12
8	Ni	0	1	H	14
9	Ni	0	1	CH ₃	14
10	Ni	0	1	CH(CH ₃) ₂	14
11	Cu	0	1	H	14

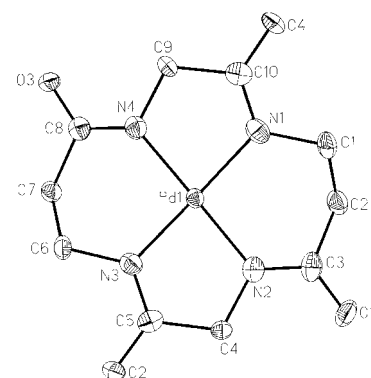


Figure 1. Molecular structure of an anion in the crystal of **1**. Selected bond lengths [Å] and angles [°]: Pd1–N1 1.974(4), Pd1–N2 1.994(4), Pd1–N3 1.971(4), Pd1–N4 1.991(4), N1–C1 1.484(6), N1–C10 1.291(7), C1–C2 1.513(8), C2–C3 1.569(8), C3–O1 1.266(7); N1–Pd1–N2 97.9(2), N2–Pd1–N3 83.2(2), N3–Pd1–N4 96.2(2), N4–Pd1–N1 82.7(2).

The orange-colored Ni^{II} complexes **8–10** are diamagnetic, which indicates a planar arrangement of the nitrogen atoms around the metal center. The results of the cyclizations can be correlated with the ionic radii of the metals: for instance, the condensation of dipeptide esters of α -amino acids to a 12-membered cyclic tetrapeptide occurs only at Ni^{II} (ionic radius 63 pm), while the larger 16- and 18-membered cyclopeptides are only formed at the “larger” template^[12] Pd^{II} (ionic radius 78 pm). All compounds listed in Table 1 have been characterized by elemental analyses, IR, ¹H, and ¹³C NMR spectroscopy, as well as by mass spectrometry (Table 2). The Na salt of the complex anion of **11** had already earlier been directly obtained from cyclo(β -alanylglycyl- β -alanylglycyl).^[13] Cyclic β -tetrapeptides such as that in **6** have been reported by Seebach et al.^[14]

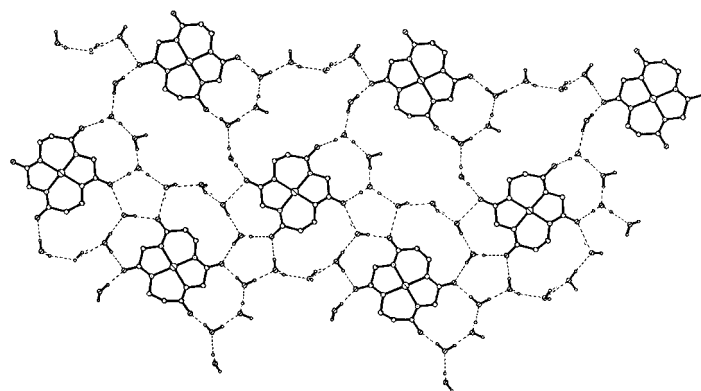


Figure 2. Segment of the layer structure formed by the anions of **1**.

Tetrapeptide esters can be employed instead of two dipeptide esters. This leads to complexes such as **12**, which must form via the open-chain intermediate **E** (Scheme 3).

The synthesis of cyclotetrapeptides described herein represents a facile procedure that requires neither a protecting group nor an activated group or a coupling reagent. It can be performed as a one-pot process. High dilution of the reaction

Table 2. Spectroscopic data for **1–11** and **12**.^[a]

1: ¹H NMR (400 MHz, CD₃OD): δ = 7.64–7.34 [m, 60H, PPN⁺], 3.87 [s, 4H, Gly], 3.12 [ψ -t, ³J = 5.66 Hz, 4H, NCH₂CH₂CO], 2.17 [ψ -t, ³J = 5.66 Hz, 4H, NCH₂CH₂CO]; ¹³C-NMR (100 MHz, CD₃OD): δ = 179.70, 173.56 [C=O], 58.31 [Gly], 43.40, 42.15 [β -Ala]; IR (KBr): $\tilde{\nu}$ = 1568.7 (vs), 1548.1 cm⁻¹ (vs) [amide-I]; MS (–FIB): *m/z* (%): 358 (100) [*M*²–H], 896 (8) [*M*²–PPN⁺]; yield 78 %

2: ¹H NMR (400 MHz, CD₃OD): δ = 7.72–7.50 [m, 60H, PPN⁺], 4.28 [q, ³J = 6.87 Hz, 2H, CH(CH₃)], 3.52 [ABCD system, ddd, ²J_{AB} = 13.36 Hz, ³J_{AC} = ³J_{AD} = 3.95 Hz, 2H, NCH₂AH_BCH_CH_DCO], 2.85 [ddd, ²J_{AB} = 13.36 Hz, ³J_{BC} = 12.35 Hz, ³J_{BD} = 2.60 Hz, 2H, H_B], 2.36 [ddd, ²J_{CD} = 15.79 Hz, ³J_{BC} = 12.35 Hz, ³J_{AC} = 3.95 Hz, 2H, H_C], 2.20 [ddd, ²J_{CD} = 15.79 Hz, ³J_{AD} = 3.95 Hz, ³J_{BD} = 2.60 Hz, 2H, H_D], 1.35 [d, ³J = 6.87 Hz, 6H, CH(CH₃)]; ¹³C NMR (100 MHz, CD₃OD): δ = 182.81, 173.09 [C=O], 63.94 [CH(CH₃)], 43.27 [CH₂], 20.87 [CH(CH₃)]; IR (KBr): $\tilde{\nu}$ = 1562.2 (vs), 1548.4 cm⁻¹ (vs) [amide-I]; MS (–ESI): *m/z* (%): 387 (100) [*M*²–H], 926 (23) [*M*²–PPN⁺]; yield 72 %

3: ¹H NMR (400 MHz, CD₃OD): δ = 7.72–7.50 [m, 60H, PPN⁺], 4.46 [dd, ³J = 7.51 Hz, ²J = 3.25 Hz, 2H, CHCH₂OH], 3.95 [dd, ²J = 10.23 Hz, ³J = 3.25 Hz, 2H, CHHCHOH], 3.72 [dd, ²J = 10.23 Hz, ³J = 7.51 Hz, 2H, CHHCHOH], 3.54 [ddd, ²J_{AB} = 12.36 Hz, ³J_{AC} = ³J_{AD} = 4.13 Hz, 2H, H_A], 2.91 [ddd, ²J_{AB} = 13.57 Hz, ³J_{BC} = 12.36 Hz, ³J_{BD} = 1.01 Hz, 2H, H_B], 2.39 [ddd, ²J_{CD} = 15.12 Hz, ³J_{BC} = 12.36 Hz, ³J_{AC} = 4.13 Hz, 2H, H_C], 2.24 [ABCD system, ddd, ²J_{CD} = 15.12 Hz, ³J_{AD} = 4.13 Hz, ³J_{BD} = 1.01 Hz, 2H, NCH₂AH_BCH_CH_DCO], 1.15 and 1.16 [2s, 1.2H, OH]; ¹³C NMR (68 MHz, CD₃OD): δ = 175.45, 178.98 [C=O], 70.91 [CHCH₂OH], 69.15 [CHCH₂OH], 43.11, 42.83 [CH₂CH₂]; IR (KBr): $\tilde{\nu}$ = 3429.6 (vs, br.) [OH], 1570.6 (vs), 1541.9 cm⁻¹ (vs) [amide-I]; MS (–ESI): *m/z* (%): 419 (100) [*M*²–H], 956 (22) [*M*²–PPN⁺]; yield 62 %

4: ¹H NMR (400 MHz, CD₃OD): δ = 7.74–7.53 [m, 60H, PPN⁺], 4.02 [s, 4H, CH₂], 3.17 [ψ -t, ³J = 6.44 Hz, 4H, NCH₂CH₂CH₂CO], 2.52 [ψ -t, ³J = 6.44 Hz, 4H, NCH₂CH₂CH₂CO], 1.70 [ψ -quint., ³J = 6.44 Hz, 4H, NCH₂CH₂CH₂CO]; ¹³C NMR (100 MHz, CD₃OD): δ = 180.81, 177.90 [C=O], 57.674 [CH₂], 45.34 [NC³H₂C²H₂C³H₂CO], 36.93 [C³], 27.88 [C²]; IR (KBr): $\tilde{\nu}$ = 1565.7 (vs), 1536.3 cm⁻¹ (vs) [amide-I]; MS (–ESI): *m/z* (%): 387 (100) [*M*²–H], 925 (15) [*M*²–PPN⁺]; yield 48 %

5: ¹H NMR (400 MHz, CD₃OD): δ = 7.72–7.49 [m, 60H, PPN⁺], 3.36 [s, 4H, CH₂], 2.85 [ψ -t, ³J = 7.30 Hz, 4H, NCH₂CH₂CH₂CH₂CO], 2.17 [ψ -t, ³J = 7.30 Hz, 4H, NCH₂CH₂CH₂CH₂CO], 1.57 [ψ -quint., ³J = 7.30 Hz, 4H, NCH₂CH₂CH₂CH₂CO], 1.51–1.43 [m, 4H, NCH₂CH₂CH₂CH₂CO]; ¹³C NMR (68 MHz, CD₃OD): δ = 183.07, 181.74 [C=O], 49.97 [CH₂], 46.86 [NC³H₂C²H₂C³H₂C⁴H₂CO], 39.19 [C⁴], 31.57 [C²], 25.51 [C³]; IR (KBr): $\tilde{\nu}$ = 1578.6 (vs), 1564.2 cm⁻¹ (vs) [amide-I]; yield 17 %

6: ¹H NMR (400 MHz, CD₃OD): δ = 7.72–7.50 [m, 60H, PPN⁺], 2.98 [m, 8H, CH₂CH₂], 2.52 [m, 8H, CH₂CH₂]; ¹³C NMR (100 MHz, CD₃OD): δ = 175.44 [C=O], 42.80, 41.27 [CH₂CH₂]; IR (KBr): $\tilde{\nu}$ = 1547.5 cm⁻¹ [amide-I]; MS (–ESI): *m/z* (%): 387 (100) [*M*²–H], 926 (5) [*M*²–PPN⁺]; yield 78 %

7: ¹H NMR (400 MHz, CD₃OD): δ = 7.71–7.50 [m, 60H, PPN⁺], 4.18 [q, br., ³J = 7 Hz, 2H, CH(CH₃)], 3.38 [d, br., ²J = 12 Hz, 2H, HCH], 3.10 [d, br., ²J = 12 Hz, 2H, HCH], 1.38 [d, ³J = 7 Hz, 6H, CH(CH₃)]; IR (KBr): $\tilde{\nu}$ = 1580.3 (vs), 1586.6 cm⁻¹ (vs) [amide-I]; yield 21 %

8: ¹H NMR (400 MHz, CD₃OD): δ = 7.73–7.51 [m, 60H, PPN⁺], 3.59 [s, 4H, CH₂], 2.83 [ψ -t, ³J = 5.89 Hz, 4H, NCH₂CH₂CO], 2.05 [ψ -t, ³J = 5.89 Hz, 4H, NCH₂CH₂CO]; ¹³C NMR (100 MHz, CD₃OD): δ = 179.65, 175.13 [C=O], 56.11 [CH₂], 40.60, 38.90 [CH₂CH₂]; IR (KBr): $\tilde{\nu}$ = 1568.0 (vs), 1540.2 cm⁻¹ (vs) [amide-I]; MS (–ESI): *m/z* (%): 311 (100) [*M*²–H], 848 (19) [*M*²–PPN⁺]; yield 96 %

9: ¹H NMR (400 MHz, CD₃OD): δ = 7.92–7.51 [m, 60H, PPN⁺], 3.69 [q, ³J = 6.90 Hz, CH(CH₃)], 3.22 [ABCD-system, ddd, br., ²J_{AB} = 12.73 Hz, ³J_{AC} = ³J_{AD} = 3.48 Hz, 1H, NCH₂AH_BCH_CH_DCO], 2.33 [ψ -t, br., ²J_{AB} = ³J_{BC} = 12.73 Hz, ³J_{BD} not resolved, 1H, H_B], 2.23 [ddd, ²J_{CD} = 15.27 Hz, ³J_{AC} = 4.15 Hz, ³J_{BC} = 12.73 Hz, 1H, H_C], 1.96 [ddd, br., ²J_{CD} = 15.27 Hz, ³J_{BD} = 2.51 Hz, 1H, H_D], 1.19 [d, ³J = 6.90 Hz, 3H, CH(CH₃)]; ¹³C NMR (100 MHz, CD₃OD): δ = 183.28, 175.10 [C=O], 60.77, [CH(CH₃)], 40.66, 39.93 [CH₂CH₂], 21.06 [CH(CH₃)]; IR (KBr): $\tilde{\nu}$ = 1562.5 (vs), 1541.0 cm⁻¹ (vs) [amide-I]; yield 94 %

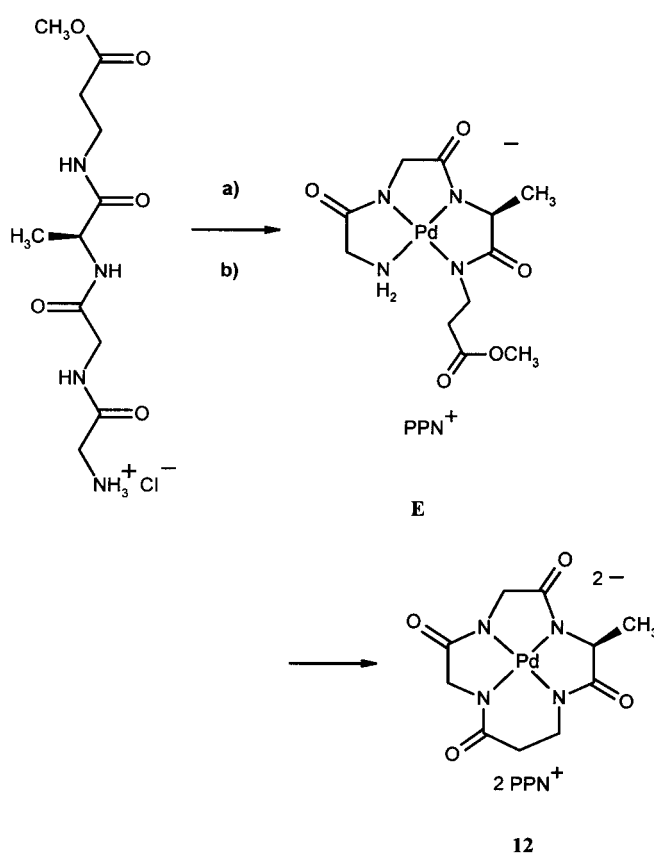
Table 2 (continued)

10: ¹H NMR (400 MHz, CD₃OD): δ = 7.75–7.43 [m, 60H, PPN⁺], 4.07 [d, ³J = 3.06 Hz, 2H, CHCH(CH₃)₂], 3.22–3.19 [m, 2H, NHCHCH₂CO], 2.34–2.26 [m, 4H, NHCHCH₂CO, CHCH(CH₃)₂], 2.09–1.97 [m, 4H, NCH₂CH₂CO], 1.33 and 1.17 [2d, ³J = 6.89 Hz, 6H, CHCH(CH₃)₂]; ¹³C NMR (68 MHz, CD₃OD): δ = 181.45, 175.28 [C=O], 68.86 [CHCH(CH₃)₂], 40.53, 40.41 [CH₂CH₂], 34.34 [CHCH(CH₃)₂], 20.98, 20.16 [CHCH(CH₃)₂]; IR (KBr): $\tilde{\nu}$ = 1564.1 (vs), 1541.1 cm⁻¹ (vs) [amide-I]; MS (–FAB/mNBA): *m/z* (%): 395 (100) [*M*²–H], 932 (1) [*M*²–PPN⁺]; yield 86 %

11: IR (KBr): $\tilde{\nu}$ = 1575.3 (vs), 1542.7 cm⁻¹ (vs) [amide-I]; MS (–FAB, mNBA): *m/z* (%): 316 (100) [*M*²–H], 853 (3) [*M*²–PPN⁺]; yield 37 %

12: ¹H NMR (400 MHz, CD₃OD): δ = 7.63–7.44 [m, 60H, PPN⁺], 3.85 [q, ³J = 6.43 Hz, 1H, CH(CH₃)], 3.76 [d, ²J = 18.4 Hz, 1H, CH₂], 3.69 [d, ²J = 18.4 Hz, 1H, CH₂], 3.34–3.21 [m, 4H, CH₂CH₂ and CH₂], 2.19 [t, ³J = 6.42 Hz, 2H, CH₂CH₂]; ¹³C NMR (100 MHz, CD₃OD): δ = 186.32, 181.66, 180.82, 178.65 [C=O], 55.70, 60.01 [2Gly], 51.32 [CH(CH₃)], 46.58, 41.33 [CH₂CH₂], 20.12 [CH(CH₃)]; IR (KBr): $\tilde{\nu}$ = 1603.0 (sh), 1587.4 (vs), 1566.7 cm⁻¹ (vs) [amide-I]; yield 45 %

[a] CD₃OD as internal standard, ¹³C NMR shifts of the anion.



Scheme 3. Metal-supported cyclization of a tetrapeptide ester to form **12**. a) Na₂[PdCl₄], 5 NaOMe, MeOH, 24 h, 65 °C; b) [PPN]Cl, H₂O.

mixture is also not necessary. We are currently investigating the extension of this method to other metal ions. Furthermore longer peptide chains will be studied to determine whether they can also be cyclized by using a template-supported reaction.

Experimental Section

The peptide ester hydrochlorides were prepared according to standard methods.^[15]

General method for the preparation of **1–12**: Dipeptide ester hydrochloride (2 mmol) or tetrapeptide ester hydrochloride (1 mmol) and metal

salt ($\text{Na}_2[\text{PdCl}_4]$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ or $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$) (1 mmol) were dissolved in methanol (40 mL). A methanolic sodium methanolate solution (6 or 5 mmol, respectively) was added dropwise. The mixture was then heated to 65 °C for 24 h, after which $[\text{PPN}]\text{Cl}$ (2 mmol) was added. Upon the addition of water, the products **1**–**12** were obtained as crystalline solids.

Liberation of the cyclotetrapeptide from **8**: HCl gas was passed through a solution of **8** (2 mmol) in absolute MeOH (2 mL) at room temperature. After 15 min, the cyclic peptide precipitated, was washed three times with as little as possible absolute MeOH and subsequently dried. ^1H NMR (400 MHz, $\text{CF}_3\text{COOD}/\text{CDCl}_3$, 8/2): δ = 4.08 (s, 4H, Gly), 3.69 (t, ^3J = 5.28 Hz, 4H, CH_2CH_2), 2.70 (t, ^3J = 5.28 Hz, 4H, CH_2CH_2); IR (KBr): $\tilde{\nu}$ = 3329.3 (vs), 1646.1 (vs), 1548.0 cm^{-1} (vs); MS (EI): m/z (%): 256 (100) [M^+].

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Keywords: copper • cyclopeptides • nickel • palladium • peptides

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- [11] Single crystals of $1 \cdot 8\text{H}_2\text{O} \cdot 3\text{CH}_3\text{CN}$ in the form of large colorless prisms were obtained by slowly cooling a saturated solution of **1** in acetonitrile. Monoclinic, space group $\text{P}2_1/n$, $Z = 4$. $M_r = 1703.0$, crystal dimensions $0.3 \times 0.23 \times 0.2 \text{ mm}^3$. The crystals were covered with perfluoroether oil, mounted on a glass fiber and centered at -80°C ; all reflections in the range $2\theta = 2-58^\circ$ were measured by using a Siemens P4 diffractometer equipped with a CCD area detector. $a = 17.0397(3)$, $b = 19.2297(3)$, $c = 26.5244(4) \text{ \AA}$, $\beta = 102.14(1)^\circ$, $V = 8497(1) \text{ \AA}^3$, $F(000) = 3560$, $\mu = 0.36 \text{ mm}^{-1}$; $R(\text{int}) = 0.0819$, 15916 symmetry-independent reflections, 10598 observed with $I > 4\sigma(I)$; refinement: 1078 variables, $R = 0.068$, $R_w = 0.119$, $\text{GOF} = 1.112$, largest residual electron density: $0.74 \text{ e \AA}^{-3}$; all calculations using

the program SHELXL-97. 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-100954. 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).

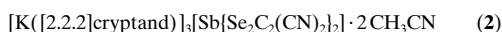
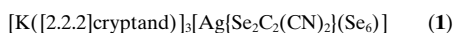
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The $[\text{Ag}\{\text{Se}_2\text{C}_2(\text{CN})_2\}(\text{Se}_6)]^{3-}$, $[\text{Sb}\{\text{Se}_2\text{C}_2(\text{CN})_2\}_2]^{3-}$, and $[\text{As}(\text{Se})_3(\text{CH}_2\text{CN})]^{2-}$ Anions: Facile Formation of the Maleonitrilediselenolate (mns) Ligand, $[\text{Se}_2\text{C}_2(\text{CN})_2]^{2-}$

Donna M. Smith, Thomas E. Albrecht-Schmitt, and James A. Ibers*

Dedicated to Professor Achim Müller
on the occasion of his 60th birthday

Despite numerous reports^[1,2] of complexes containing the maleonitriledithiolate (mnt) ligand, $[\text{Ni}\{\text{Se}_2\text{C}_2(\text{CN})_2\}_2]^{2-}$ is the only reported example of a complex containing the Se analogue maleonitrilediselenolate (mns).^[3] Its synthesis involves several steps as well as the use of CSe_2 and dicyanoacetylene, both difficult reagents to synthesize and use.^[3] We report here facile syntheses of the complexes **1** and **2**, which



contain the mns ligand, and the synthesis of **3**, as its formation is suggestive of possible mechanisms for the formation of **1** and **2**.

Reaction of $[\{\text{IrCl}(\text{cod})\}_2]$ (cod = (Z,Z)-1,5-cyclooctadiene), AgBF_4 , and $[\text{K}([2.2.2]\text{cryptand})]_2[\text{Se}_n]$ ($n = 3, 5, 6$) in liquid ammonia followed by extraction of the residue with CH_3CN results in the formation of **1**. The anion in **1** (Figure 1)

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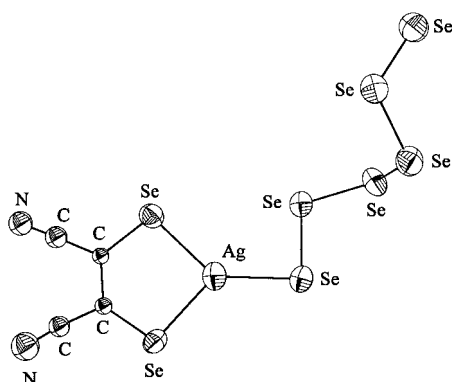


Figure 1. Structure of the anion in **1**. Here and in succeeding figures, 50 % displacement ellipsoids are shown.

consists of a Ag^+ ion chelated by a $[\text{Se}_2\text{C}_2(\text{CN})_2]^{2-}$ ligand and the environment around the Ag^+ center is highly distorted trigonal planar. The $\text{Ag}-\text{Se}$ bond lengths, which range from 2.524(4) to 2.579(4) Å, are normal.^[4] The $\eta^1\text{-Se}_6^{2-}$ ligand is a rarity; chelating and bridging Q_n^{2-} ligands ($\text{Q} = \text{S}, \text{Se}, \text{Te}$) are far more common than η^1 -polychalcogenide ligands. KAuSe_{13} ^[5] and $[\text{K}([2.2.2]\text{cryptand})]_2[\text{Cr}(\text{CO})_5(\text{Te}_3)] \cdot 0.5 \text{en}$ ^[6] ($\text{en} = \text{ethylenediamine}$) are among the few examples of compounds containing an $\eta^1\text{-Q}_n^{2-}$ ligand. The $\text{Se}-\text{Se}$ bond lengths in the Se_6^{2-} ligand range, as expected, from 2.313(5) to 2.340(5) Å; the bond length between the two terminal Se atoms is slightly shorter (2.284(5) Å). A similar shortening of the terminal ends of Se_n^{2-} ligands is observed in the structures of virtually all alkali polyselenide compounds.^[7] Upon dissolution of **1** in CH_3CN , the $[\text{Ag}\{\text{Se}_2\text{C}_2(\text{CN})_2\}(\text{Se}_6)]^{3-}$ anion disproportionates or decomposes; seven ^{77}Se NMR resonances are expected, but fourteen are observed.^[8]

The reaction of K , Sb_2Se_3 , and Se in the presence of $[2.2.2]\text{cryptand}$ in liquid ammonia followed by extraction in CH_3CN results in the isolation of **2**, which features well-separated cations and anions. In the anion of **2** (Figure 2), the

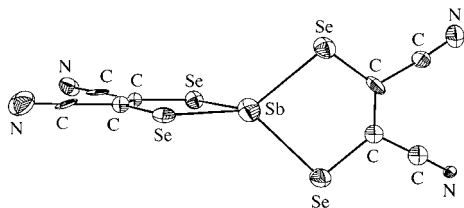


Figure 2. Structure of the anion in **2**.

central Sb atom is coordinated to two planar mns ligands in a distorted tetrahedron with $\text{Se}-\text{Sb}-\text{Se}$ bond angles ranging from 86.47(7) to 129.27(8)°; the dihedral angle between the two planes is 84.0°. The $\text{Sb}-\text{Se}$ bond lengths (av 2.654(2) Å) are slightly longer than those observed for $[\text{K}([2.2.2]\text{cryptand})]_2[\text{Sb}^{\text{III}}\text{Se}_4]$ (av 2.615(1) Å),^[9] as would be expected for a reduced charge on the Sb atom. The “noninnocence” of the mnt ligand is well known;^[1, 2] one expects the same behavior for the mns ligand. Thus, the Sb atom in **2** only formally has the unusual +1 oxidation state. However, $[\text{NEt}_4][\text{Sb}^{\text{III}}(\text{mnt})_2]$ has been synthesized from $\text{Na}_2(\text{mnt})$ and SbX_3 ($\text{X} = \text{Cl}, \text{Br}, \text{I}$),

although it has not been structurally characterized.^[10] In general, the mns ligand resembles the much better known mnt ligand.^[1, 2] The $\text{Se}-\text{C}$ bond lengths are 1.81(2) and 1.89(2) Å in **1**, range from 1.857(17) to 1.874(16) Å in **2**, and are 1.873(4) and 1.878(4) Å in $[\text{PPh}_4]_2[\text{Ni}\{\text{Se}_2\text{C}_2(\text{CN})_2\}_2]$.^[13]

The reaction of K , As , and Se in the presence of $[2.2.2]\text{cryptand}$ followed by extraction in CH_3CN affords **3**. The structure of **3** also features well-separated cations and anions. In the anion of **3** (Figure 3), the central As^{V} atom is coordinated to three terminal Se^{2-} ligands and one terminal CH_2CN^- ligand in a distorted tetrahedron with $\text{C}-\text{As}-\text{Se}$ bond angles ranging from 99.3(2) to 105.2(2)° and $\text{Se}-\text{As}-\text{Se}$ bond angles ranging from 114.91(6) to 115.46(6)°. The $\text{As}-\text{Se}$ (2.275(2), 2.280(2), and 2.284(2) Å), $\text{As}-\text{C}$ (1.973(6) Å), $\text{C}-\text{C}$ (1.392(12) Å), and $\text{C}\equiv\text{N}$ (1.156(10) Å) bond lengths are normal. Structurally characterized main-group compounds containing the CH_2CN^- ligand are rare.^[11, 12]

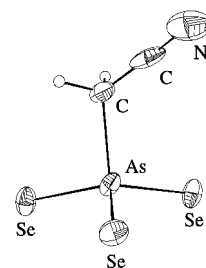
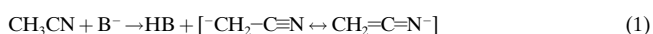


Figure 3. Structure of the anion in **3**.

The syntheses of an Ag^{I} and an Sb^{I} complex of the mns ligand (**1** and **2**, respectively) are unexpected and remarkable. At first glance, there is little in common between the two reactions, save for the use of liquid ammonia, potassium, $[2.2.2]\text{cryptand}$, and CH_3CN . Clearly, the source of the cyano groups in the mns ligand is CH_3CN . This strongly suggests that deprotonation of CH_3CN is an important aspect of these reactions, especially since the mono-deprotonated carbanion CH_2CN^- in **3** is attached to the As^{V} center through an $\text{As}-\text{C}$ bond.

Acetonitrile reacts with strong bases in one of two competing pathways.^[13] The first pathway [Eq. (1)] involves mono-deprotonation of CH_3CN ($\text{pK}_a = 31$) to form the mesomeric-stabilized anion CH_2CN^- ; the second [Eq. (2)] involves the addition of the base to the carbon atom of the cyano group. The reaction pathway can be controlled by the



choice of base and solvent. Pathway (1) is generally favored with bases with high ionic character in polar solvents. In the present instances, what are the bases? The reaction to form the $\text{Ag}(\text{mnt})$ complex **1** does not occur in the absence of $[\text{IrCl}(\text{cod})]_2$, which presumably generates the required base; it is known that the similar Ir complex $[\text{IrCl}(\text{coe})_2]_2$ ($\text{coe} = \text{cyclooctene}$) reacts with liquid ammonia to form stable, amide-bridged, basic dimers.^[14-16] Potassium will react catalytically with ammonia to form the stable basic amide KNH_2 ,^[17] which is presumably the base required in the syntheses of **2** and **3**. The reaction of KNH_2 with CH_3CN can proceed by either pathway. However, it is assumed that pathway (1) dominates since subsequent acylation of the resulting CH_2CN^- anion can be achieved in high yield.^[18]

Given the formation of the CH_2CN^- species in these reactions, a variety of ensuing reactions are possible. Clearly,

in the synthesis of **3** CH_2CN^- attaches itself to the highly nucleophilic As^{V} center. Reactions of ACH_2CN ($\text{A}^+[\text{CH}_2\text{CN}^-]$, where $\text{A} = \text{alkali or alkaline earth metal}$) are similar to those of Grignard reagents; the anion is nucleophilic and acts as a weak base.^[19] ACH_2CN can react “head-to-tail” with the cyano group of another CH_3CN molecule in a manner analogous to the Claisen condensation of esters.^[13] Given the ultimate formation of the mns ligand in the present instances, such a reaction is unlikely. “Head-to-head” coupling of two CH_2CN^- species to form a conjugated nitrile is much more attractive, especially if further deprotonation then occurs to afford dicyanoacetylene. This activated alkyne could readily react with a polyselenometalate to form the metal-bound mns ligand in the manner that dimethylacetylenedicarboxylate does to form the metal-bound $[\text{O}_2\text{C}_2[\text{C}(\text{O})\text{OCH}_3]_2]^{2-}$ species.^[20–22]

It is also possible that the CH_2CN^- species attacks a free selenium source or a polyselenometalate to form a derivatized cyanoaldehyde. Cyanoselenoaldehyde, while too reactive to be isolated, has been trapped with the use of conjugated dienes.^[23, 24] Two adjacent selenoaldehydes could also couple by a condensation reaction. Alternatively, if CH_2CN^- attacked a free selenide source, the mns ligand could conceivably form in situ before reaction with the metal center, as observed in reactions with the mnt ligand.

Experimental Section

1: Approximately 10 mL of NH_3 were condensed into a Schlenk flask containing $[\text{IrCl}(\text{cod})_2]$ (134 mg, 0.2 mmol) and AgBF_4 (80 mg, 0.41 mmol), and 50 mL of NH_3 were condensed into another flask containing K_2Se (126 mg, 0.8 mmol), Se (316 mg, 4 mmol), and [2.2.2]cryptand (509 mg, 1.8 mmol). Both reaction mixtures were stirred for 1 h at -78°C , and then the first solution was transferred with a cannula into the second. The reaction mixture was allowed to warm from -78°C to 24°C over 48 h. The dark residue was extracted into CH_3CN ; the solution was stirred and filtered. The filtrate was layered with Et_2O and stored at 4°C . Brown plates of **1** were isolated after two weeks in 16% yield (based on Ag). IR (KBr): $\tilde{\nu} = 2176\text{ cm}^{-1}$ ($\text{C}\equiv\text{N}$). Crystal structure analysis:^[25] brown plates, $0.023 \times 0.108 \times 0.347\text{ mm}$, triclinic, C_1^1 ($P\bar{1}$), $Z = 2$, $a = 10.407(2)$, $b = 11.285(2)$, $c = 35.190(7)\text{ Å}$, $\alpha = 84.60(3)$, $\beta = 87.72(3)$, $\gamma = 77.96(3)^\circ$, $V = 4023(1)\text{ Å}^3$. Of 6180 reflections measured ($2\theta_{\text{max}} = 80.2^\circ$), 4788 were unique ($R_{\text{int}} = 0.12$) and included in the refinement, $\mu = 81\text{ cm}^{-1}$, min./max. transmission = $0.389/0.802$, 446 parameters, $R_1 = 0.095$ for reflections with $F_o^2 > 2\sigma(F_o^2)$; $wR_2 = 0.195$; residual electron density = 1.05 e Å^{-3} .

2: NH_3 (30 mL) was condensed into a flask charged with [2.2.2]cryptand (189 mg, 0.5 mmol) and K (40 mg, 1 mmol). The blue solution turned colorless within 10 min. More K (40 mg, 1 mmol) was added to regain the blue color. After the solution was stirred for 30 min, Sb_2Se_3 (120 mg, 0.25 mmol) and Se (77 mg, 1 mmol) were added. The reaction mixture was allowed to warm from -78°C to 24°C over 48 h. The resulting residue was extracted into CH_3CN (25 mL) to afford a dark red-orange solution and an uncharacterized powder. Filtration of the solution followed by layering with Et_2O gave long red needles of **2** in 13% yield (based on Sb). IR (KBr): $\tilde{\nu} = 2170\text{ cm}^{-1}$ ($\text{C}\equiv\text{N}$); ^{77}Se NMR (CH_3CN): $\delta = -296$. Crystal structure analysis:^[25] red needles, $0.065 \times 0.086 \times 0.449\text{ mm}$, monoclinic, C_{2h}^2 ($P2_1/c$), $Z = 4$, $a = 13.945(3)$, $b = 21.764(4)$, $c = 28.283(6)\text{ Å}$, $\beta = 98.12(3)^\circ$, $V = 8498(3)\text{ Å}^3$. Of 9054 reflections measured ($2\theta_{\text{max}} = 98.58^\circ$), 6574 were unique ($R_{\text{int}} = 0.072$), $\mu = 64\text{ cm}^{-1}$, min./max. transmission = $0.479/0.687$, 897 parameters, $R_1 = 0.079$, $wR_2 = 0.160$, residual electron density = 0.780 e Å^{-3} .

3: NH_3 (30 mL) was condensed into a flask charged with [2.2.2]cryptand (189 mg, 0.5 mmol) and K (40 mg, 1 mmol). After the solution was stirred for 30 minutes at -78°C , a mixture of As (20 mg, 0.27 mmol) and Se (42 mg, 0.53 mmol) was added. The reaction mixture was allowed to warm

from -78°C to 24°C over 48 h. The residue was extracted into CH_3CN (25 mL) to afford an orange solution and residual starting material. Filtration of the solution followed by layering with Et_2O afforded yellow blocks of **3** in 23% yield (based on Se). ^{77}Se NMR (CH_3CN): $\delta = 602$. Crystal structure analysis:^[25] yellow blocks, $0.057 \times 0.170 \times 0.244\text{ mm}$, triclinic, C_1^1 ($P\bar{1}$), $Z = 2$, $a = 11.701(2)$, $b = 12.216(9)$, $c = 19.703(4)\text{ Å}$, $\alpha = 105.01(4)$, $\beta = 92.93(3)$, $\gamma = 106.09(6)^\circ$, $V = 2591(2)\text{ Å}^3$. Of 9058 reflections measured ($2\theta_{\text{max}} = 96.04^\circ$), 4760 were unique ($R_{\text{int}} = 0.042$), $\mu = 52\text{ cm}^{-1}$, min./max. transmission = $0.794/0.858$, 534 parameters, $R_1 = 0.043$, $wR_2 = 0.097$, residual electron density = 0.552 e Å^{-3} .

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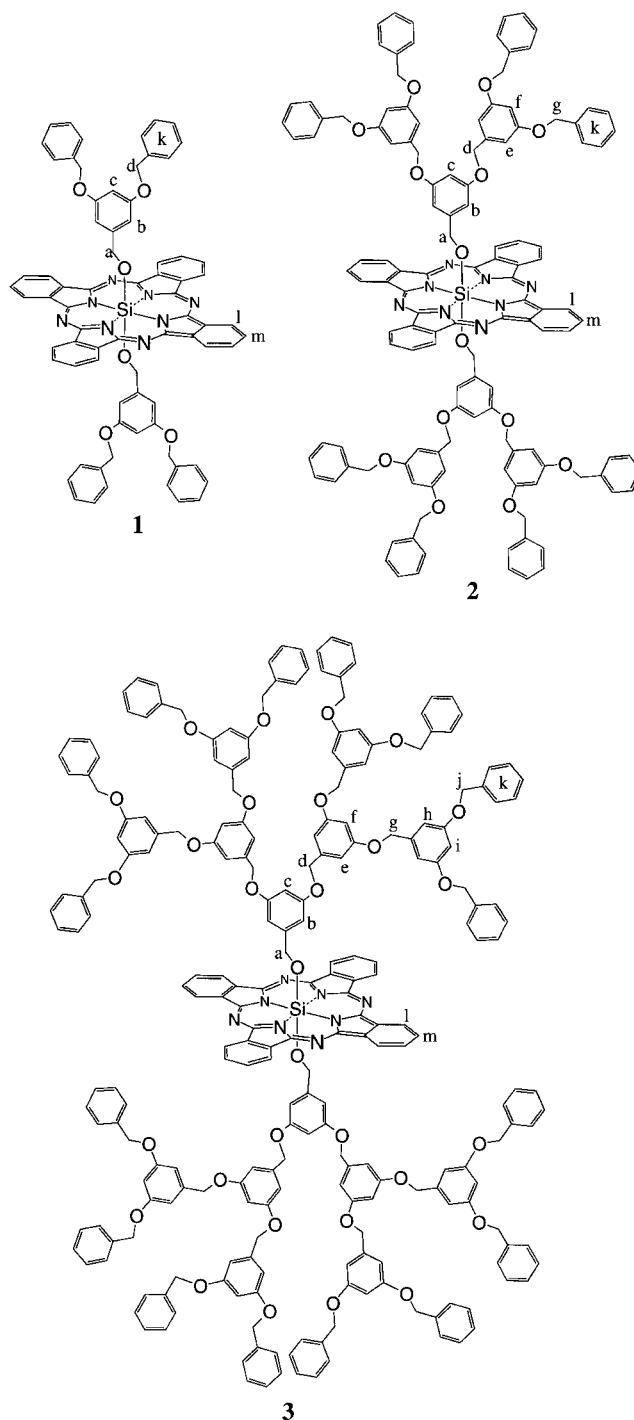
Silicon Phthalocyanines with Axial Dendritic Substituents**

Matthew Brewis, Guy J. Clarkson, Victoria Goddard, Madeleine Helliwell, Andrea M. Holder, and Neil B. McKeown*

In the last few years dendrimers have attracted much attention due to their uniform hierarchical structures, which offer a wide range of potential applications.^[1] Initial studies concentrated on the preparation of materials with high molecular mass, but recent emphasis has been on the functionalization of dendrimers of more modest size. For example, crown ethers,^[2] chiral moieties,^[3] mesogenic groups,^[4] and redox-active substituents based on tetrathiafulvalene,^[5] ferrocene,^[6] or transition metal complexes^[7] have been directly incorporated into dendrimers. In addition, the concept of employing dendritic substituents to effect steric isolation of a functional core (e.g., fullerene, porphyrin, etc.) is being actively studied by a number of groups.^[8]

Our interests lie in the preparation of novel phthalocyanine (Pc) derivatives in which the structure of the bulk material is controlled by attaching suitable substituents to the Pc core.^[9] Such control may help to exploit the fascinating optical and electronic properties of the Pc macrocycle.^[10] For example, the studies on Pcs in solution promise useful applications in nonlinear optics (e.g., as optical limiters), which, however, have not yet been realized in the solid state.^[11] The difference in optical properties between Pcs in solution and in the solid state can be attributed both to excitonic effects, especially cofacial interactions between neighboring Pc molecules, and to scattering at microcrystalline boundaries.^[12] Here we describe the steric isolation of Pc molecules in the solid state by means of substituents composed of Fréchet's poly(aryl ether) dendrons.^[13] Such dendrons produce transparent, glassy solids, and this would be an attractive property for the fabrication of readily processable, nonscattering Pc-containing films for optical applications.^[14, 15]

The Pcs **1–3** were prepared by the substitution of the axial chloro ligands of dichloro(phthalocyaninato)silicon by the benzyl alcohol groups of the first, second, and third generation of Fréchet's dendrons, respectively.^[16] The structures of **1–3** were confirmed by ¹H NMR spectroscopy and FAB-MS. The ¹H NMR spectra are particularly informative, as the strong ring current of the Pc macrocycle helps to differentiate protons of similar type. For example, the aromatic protons at the sites labeled b, e, and h in the structural formula of **3** give rise to well-resolved doublets (³J(H,H) ≈ 1 Hz) at δ = 3.50, 6.30, and 6.65, respectively. The purity of each material was confirmed by elemental analysis and thin layer chromatography.



Compounds **1–3** are all soluble (although **1** only sparingly so) in common aprotic solvents such as THF, toluene, and chloroform but not in diethyl ether and hexane. Slow diffusion of diethyl ether into a concentrated solution of **2** in toluene gave single crystals suitable for X-ray structure analysis. This method failed to yield suitable crystals of **1** or **3** and gave a microcrystalline powder and a clear glass, respectively. Figure 1 shows ORTEP plots of the molecular structure of **2**. The asymmetric unit consists of half a molecule. The Si atom lies on a center of symmetry, and the other half of the molecule is generated by inversion. The O–Si–O bond angle is

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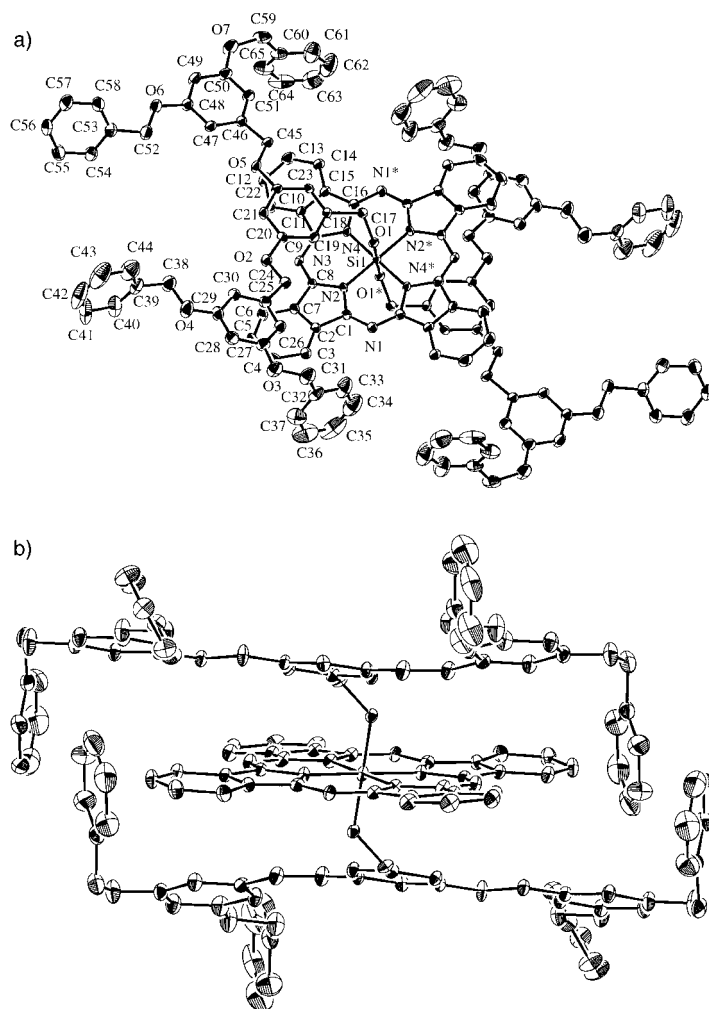


Figure 1. An ORTEP diagram of the molecular structure of **2** with a) crystallographic numbering scheme. b) The symmetrical arrangement of the two dendritic substituents. The Si atom lies on a center of symmetry.

almost linear (179°), and the Pc core is essentially planar. The benzyl group directly attached to the silicon atom forms an angle of 15.64° to the Pc core, with which it appears to interact strongly, as indicated by the short intramolecular distances (e.g., $\text{N4} \cdots \text{C18}$ 3.177(7) Å). The axial substituents result in a distance between the cofacial Pc subunits of 14 Å along the *a* axis of the crystal (Figure 2). This distance is too large for significant exciton coupling. However, there are short edge-to-edge contacts between adjacent Pc cores (e.g., $\text{C5} \cdots \text{C21}$ 3.348(9) Å).

The UV/Vis spectra of spin-coated thin films of **1–3** also illustrate the extent to which the axial dendritic substituents suppress cofacial intermolecular excitonic interactions. Only relatively weak edge-to-edge exciton interactions are present, as is evident from the bathochromic shift of the Q band of the films relative to the spectra in solution.^[17] The magnitude of these interactions can be gauged by the extent of the red shift ($\Delta\lambda_{\text{max}}$) and the broadening (ΔW) of the Q band (Table 1). These values show that edge-to-edge interactions are small for **2** and **3** and that these spin-coated films resemble true solid solutions. Polarized optical microscopy suggests that the films derived from **2** and **3** are uniform and isotropic (nonbirefringent), whereas the spin-coated film of **1** has a micro-

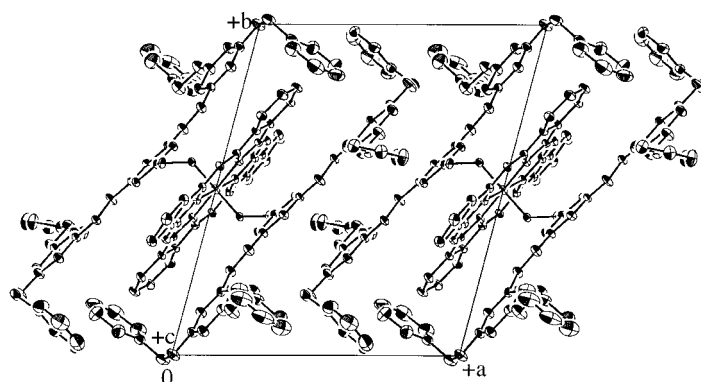


Figure 2. The crystallographic packing of **2** viewed along the *c* axis. The cofacial distance between Pc cores is 14 Å.

Table 1. Comparison of the UV/Vis spectroscopic data of **1–3**.

	1	2	3
$\lambda_{\text{max}}^{[a]}$ [nm]	678	680	680
$\lambda_{\text{max}}^{[b]}$ [nm]	704	692	688
$\Delta\lambda_{\text{max}}^{[c]}$ [nm]	26	12	8
$\Delta W^{[d]}$ [nm]	18	5	2

[a] In toluene. [b] In spin-coated film. [c] $\lambda_{\text{max}}(\text{film}) - \lambda_{\text{max}}(\text{solution})$. [d] Width of peak at half height.

crystalline structure. Each of the Pcs **1–3** displays a distinct glass transition on cooling from the melt ($T_g = 139$, 124, and 110°C , respectively). Therefore, films can also be readily fabricated by melt processing.

This study has yielded robust, nonscattering glasses which appear indefinitely stable with respect to crystallization. These easily processable solid solutions are suitable materials for optical studies, which are now in progress.

Experimental Section

Typical synthesis: **2**: Sodium hydride (0.055 g, 2.3 mmol) was added to a mixture of dichloro(phthalocyaninato)silicon (0.2 g, 0.33 mmol) and 3,5-di-[3',5'-(dibenzoyloxy)benzyloxy]benzyl alcohol (1.15 g, 1.32 mmol) in dry toluene (2 mL). After heating under nitrogen at 80°C for 96 h, the reaction mixture was poured into water, and the aqueous layer was extracted with toluene (3×50 mL), dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The product was purified by column chromatography (silica, toluene) followed by recrystallization from toluene/diethyl ether to give **2** as green prismatic crystals (0.310 mg, 46%).

1: Yield 14%; m.p. 253°C (THF); $T_g = 139^\circ\text{C}$; elemental analysis calcd for $\text{C}_{74}\text{H}_{54}\text{O}_6\text{N}_8\text{Si}$: C 75.36, H 4.61, N 9.50; found: C 75.37, H 4.44, N 9.56; ^1H NMR (500 MHz, CDCl_3 , 60°C): $\delta = -0.69$ (s, 4H, $^a\text{CH}_2$), 3.58 (d, $^3J(\text{H,H}) = 1$ Hz, 4H, ^bCH), 4.11 (s, 8H, $^d\text{CH}_2$), 5.64 (t, $^3J(\text{H,H}) = 1$ Hz, 2H, ^cCH), 7.05–7.30 (m, 20H, $^k\text{C}_6\text{H}_5$), 8.20–8.31 (m, 8H, ^lCH), 9.52–9.62 (m, 8H, ^mCH); UV/Vis (toluene): $\lambda_{\text{max}}(\epsilon) = 678$ nm (250000); FAB-MS: m/z : 1178 [M^+].

2: Yield 46%; m.p. 168°C (toluene/diethyl ether); $T_g = 124^\circ\text{C}$; elemental analysis calcd for $\text{C}_{130}\text{H}_{102}\text{O}_{14}\text{N}_8\text{Si}$: C 76.98, H 5.07, N 5.52; found: C 76.60, H 4.82, N 5.62; ^1H NMR (500 MHz, CDCl_3 , 60°C): $\delta = -0.69$ (s, 4H, $^a\text{CH}_2$), 3.54 (d, $^3J(\text{H,H}) = 1$ Hz, 4H, ^bCH), 4.02 (s, 8H, $^d\text{CH}_2$), 4.96 (s, 16H, $^e\text{CH}_2$), 5.64 (t, $^3J(\text{H,H}) = 1$ Hz, 2H, ^cCH), 6.32 (d, $^3J(\text{H,H}) = 1$ Hz, 8H, ^cCH), 6.46 (t, $^3J(\text{H,H}) = 1$ Hz, 4H, ^lCH), 7.20–7.32 (m, 40H, $^k\text{C}_6\text{H}_5$), 8.12–8.14 (m, 8H, ^lCH), 9.49–9.52 (m, 8H, ^mCH); UV/Vis (toluene): $\lambda_{\text{max}}(\epsilon) = 680$ nm (250000); FAB-MS: m/z : 2028 [M^+].

3: Yield 54%; $T_g = 110^\circ\text{C}$; elemental analysis calcd for $\text{C}_{242}\text{H}_{198}\text{O}_{30}\text{N}_8\text{Si}$: C 78.00, H 5.36, T_g : 110; found: C 78.06, H 5.55, N 2.93; ^1H NMR (500 MHz,

CDCl_3 , 60 °C): $\delta = -0.71$ (s, 4H, $^a\text{CH}_2$), 3.50 (d, $^3J(\text{H,H}) = 1$ Hz, 4H, ^bCH), 3.97 (s, 8H, $^c\text{CH}_2$), 4.87–5.00 (m, 48H, $^d\text{CH}_2 + ^e\text{CH}_2$), 5.65 (t, $^3J(\text{H,H}) = 1$ Hz, 2H, ^fCH), 6.30 (d, 8H, ^gCH), 6.44 (t, $^3J(\text{H,H}) = 1$ Hz, 4H, ^hCH), 6.54 (t, $^3J(\text{H,H}) = 1$ Hz, 8H, ^iCH), 6.65 (d, $^3J(\text{H,H}) = 1$ Hz, 16H, ^jCH), 7.24–7.38 (m, 80H, $^k\text{C}_6\text{H}_5$), 8.12–8.14 (m, 8H, ^lCH), 9.49–9.52 (m, 8H, ^mCH); UV/Vis (toluene): λ_{max} (ϵ) = 680 nm (250 000), FAB-MS: m/z : 3726 [M^+].

Crystal structure analysis of **2**: $\text{C}_{130}\text{H}_{102}\text{N}_8\text{O}_{14}\text{Si}$, $M_r = 2028.37$, green prismatic crystal, crystal dimensions $0.07 \times 0.3 \times 0.4$ mm, triclinic, space group $P\bar{1}$ (no. 2); $a = 14.079(3)$, $b = 16.291(5)$, $c = 12.710(3)$ Å, $\alpha = 103.62(2)$, $\beta = 109.30(2)$, $\gamma = 71.83(2)^\circ$, $V = 2585(1)$ Å³, $Z = 1$, $\rho_{\text{calcd}} = 1.303$ g cm⁻³, $\mu = 0.9$ cm⁻¹; Rigaku AFC5R diffractometer, monochromatized MoK_α radiation ($\lambda = 0.71069$ Å), 20 °C, $\omega - 2\theta$ scan mode; $2\theta_{\text{max}} = 50.1^\circ$; 9709 measured reflections, 9175 unique reflections ($R_{\text{int}} = 0.102$), 691 parameters refined, 4023 reflections included in the refinement. Lorentzian, polarization, and absorption corrections were carried out (transmission factors = 0.9331–1.0000; $\mu = 0.9$ cm⁻¹). A decay correction based on a 4.5 % decrease in the intensity of three standard reflections was also applied. The structure was determined by direct methods (SHELXS86) and expanded by Fourier techniques (DIRDIF94). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in calculated positions but not refined. Refinement was carried out by full-matrix least-squares methods on 4023 observed reflections ($I > 2.50\sigma(I)$) and 691 variable parameters; $R = 0.067$; $R_w = 0.052$; maximum and minimum peaks on the final Fourier map corresponded to 0.29 and -0.24 e Å⁻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-100742. 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).

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Determination of the Disordered Structure of $\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$ with Multiple-Edge EXAFS and Powder Diffractograms**

Mark T. Weller,* Maria J. Pack, and Norman Binsted

The structures of solids are defined by local and long-range order, both of which must be determined to characterize a material. Systems in which perfect crystalline order does not exist and local structural features are important include superconducting oxides, alloys, zeolites containing entrapped molecular species, ferroelectric materials, materials that exhibit high magnetoresistance, and intercalation compounds. The structures of such materials are often determined by separate analyses of data collected by a variety of techniques, sometimes with conflicting results, or an averaged structure is determined by analysis of diffraction data alone.

The structure of the complex oxide $\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$ was determined by using a combination of extended X-ray absorption fine structure (EXAFS) data for all five of the metals with powder X-ray diffraction data and refined with a single set of coordinates consistent with all the experimental data. This combined analysis approach, illustrated here, is a

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powerful tool for the characterization of solids whose local structural features cannot be determined or are averaged by diffraction methods. Analyses of multiple-edge EXAFS data sets from various materials have been reported previously,^[1–3] but these investigations were limited to a few data sets and did not include diffraction data or a single-crystal structural description.

$\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$ was prepared as described previously.^[4] This material provides an excellent example for illustrating the potential of multi-data set analysis, as it adopts a superconductorlike structure with multiple perovskite layers, provides several EXAFS data sets, and has significant local disorder which cannot be fully defined by means of diffraction data alone. The EXAFS spectra were measured at the Daresbury Laboratory Synchrotron Radiation source on stations 8.1 and 7.1. Spectra were recorded in transmission mode, except for the data of the calcium K-edge, which were obtained in fluorescence mode with monochromatic radiation from harmonic-rejecting double-crystal monochromators [Si(111) or Si(220)]. In most cases the samples were poly(vinyl alcohol) disks prepared with a known concentration of sample that depended on the total absorption coefficient of the material, the investigated edge, and the detection technique. A thin disk consisting solely of sample was used for measuring the calcium K-edge. A minimum of four scans were made for each edge, and the collected data were averaged. Powder X-ray diffraction data (XRD) were collected on a Siemens D5000 θ – 2θ diffractometer with $\text{Cu}_{\text{K}\alpha 1}$ radiation ($\lambda = 1.5406 \text{ \AA}$). Data were collected for 15 h with a step size of 0.02° . The background was subtracted from the EXAFS data with the program PAXAS.^[5]

The initial structural model was developed on the basis of powder neutron diffraction data and has been described previously along with those of other members of the 22123 layered perovskite series (Figure 1).^[4] Two important features of the refined model derived are the mixed occupation of the A sites by cations, which statistically occupy 8- and 12-fold sites above and below the titanium–oxygen triple layers, and distortion of the TiO_6 octahedra. Initially, EXAFS data from the absorption edges of all five cations in $\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$, XRD data, and the previously defined structural model were read into the combined refinement program.^[6] Data for the titanium and barium edges were curtailed at modest k values because of overlap with the barium L_{III} - and L_{II} -edges, respectively. The calcium-edge data were also used in a restricted range of k values, since the scattering statistics were poor because of the presence of heavy absorbing elements. These reduced data ranges, while unavoidable in this material, are not of such significance for a combined refinement technique, as shell distances beyond a few Ångström are also defined by the other EXAFS and XRD data. Scattering phase shifts were calculated for each atom in the structure by using ab initio muffin potentials calculated for clusters consisting of two types of atoms. The muffin radii were adjusted so that the charge on the Wigner–Seitz sphere was approximately equal to the atomic number; in each case oxygen atoms were assumed to be the nearest neighbors. In the combined refinement, which required a large number of shells for each of the five edges to simulate the major features of the relative

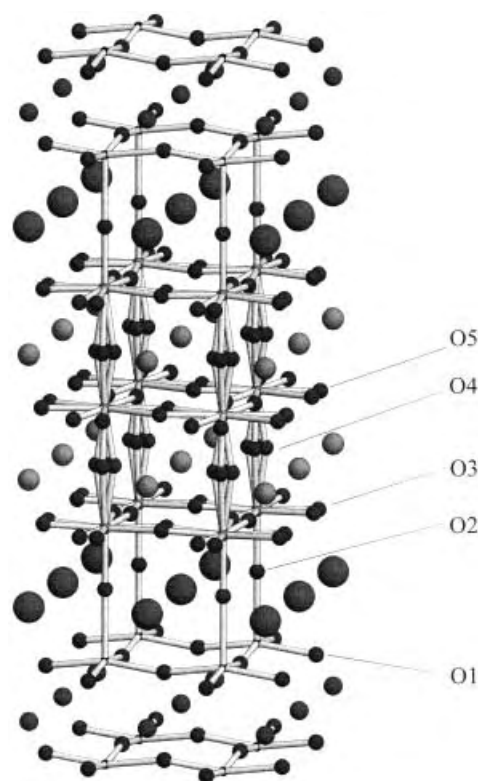


Figure 1. Structure of $\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$. The oxygen atoms are disordered over the sites listed in Table 1. The Cu–O and Ti–O bonds are shown. The Ba atoms are depicted as large, pale gray spheres, the Ca/Gd atoms as medium-sized, dark gray spheres, and Gd atoms that are not bound to O atoms as small, dark spheres.

modulation $\chi(k)$ of the absorption coefficients (k is the contribution of the wave vector of the photoelectron), the EXAFS Debye–Waller factors were calculated by using a very simple model (see below). Owing to the different treatments of thermal motion in the XRD and EXAFS methods, the combined analysis program uses two separate descriptions of thermal parameters.^[6]

Initially, the best fit to the XRD data alone was obtained by refining a number of parameters, which included atomic position and temperature factors, peak shape and background parameters, scale factor, and zero offset. After refinement, this structural model differed from that obtained from neutron-diffraction data in having slightly different cell parameters (but comparable within the estimated standard deviations) and slightly shorter average M–O bond lengths. The M–O bond lengths derived from XRD data are generally shorter because the center of electronic density of the oxygen atom is shifted towards the metal center.

A combined refinement with the scattering data was then performed, and the best fit was obtained with XRD parameters (e.g., atomic positions), Ef and $AFAC$ (Xe and $CFAC$ for each spectrum), and two new parameters which model all the EXAFS Debye–Waller factors for each involved edge as a function of the atomic size (Table 1). Thus the total number of parameters that was required in the refinement was decreased, and convergence of each cycle was achieved in a much shorter time.

Table 1. Final parameters from the combined refinement of five EXAFS spectra and a powder X-ray diffractogram ($W_{\text{XRD}}^{\text{[g]}} = 0.2$, $W_{\text{EXAFS}}^{\text{[g]}} = 0.8$)^[a]

Parameter	Refined value	Parameter	Refined value
a [Å]	3.8769(1)	$Bi1$ (Gd) ^[c]	0.8(3)
c [Å]	19.559(1)	$Bi2$ (Ba)	1.1(1)
		$Bi3$ (Ca/Gd)	0.6(3)
Q_r ^[b]	1.7	$Bi4$ (Cu)	0.1(3)
Q_m	2.0	$Bi5, Bi6$ (Ti)	0.8(1)
		$Bi7 - Bi11$ (O)	1.0(4)
$PZ2$	0.1875(2)		
$PZ3$	0.3972(2)	Ef ^[d]	− 12.00
$PZ4$	0.0853(2)	$Xe1, Xe2$ ^[d, g]	1.8(6)
$PZ5$	0.3015(14)	$Xe3$	1.0(2)
$PZ7$	0.0725(8)	$Xe4$	5.4(11)
$PZ8$	0.2020(19)	$Xe5, Xe6$	9.6(7)
$PX9$	0.061(8)	$Xe7$	7.8(3)
$PZ9$	0.3048(18)		
$PX10$	0.075(12)	$AFAC$ ^[g]	0.85
$PZ10$	0.4050(28)	$CFAC1, CFAC2$ ^[d, g]	0.83(2)
$PX11$	0.122(12)	$CFAC3$	0.99(2)
		$CFAC4$	0.8 ^[e]
		$CFAC5, CFAC6$	0.57(3)
		$CFAC7$	0.94(2)
R_{ex} ^[f]	52.6		
		$R_{\text{wp(XRD)}}$	18.1 %

[a] Atomic positions used to describe the phase $\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$ (space group $P4/mmm$): 1. Gd (1/2,1/2,0); 2. Ba (1/2,1/2, $PZ2$); 3. 0.5 Ca + 0.5 Gd (1/2,1/2, $PZ3$); 4. Cu (0,0, $PZ4$); 5. Ti (0,0, $PZ5$); 6. Ti (0,0,1/2); 7. O1 (0,1/2, $PZ7$); 8. O2 (0,0, $PZ8$); 9. O3 ($PX9, 1/2, PZ9$) $\times$ 1/2; 10. O4 ($PX10, 0, PZ10$) $\times$ 1/4; 11. O5 ($PX11, 1/2, 1/2$) $\times$ 1/2. [b] $A_{in} = Q_m(1/(M_i + M_n)) + Q_r(1/r_{in})$, where A_{in} is the Debye–Waller factor of the i th shell in the n th spectrum, M_i the atomic mass of the atom in shell i , M_n the atomic mass of the central atom in spectrum n , and r_{in} the radius of the atom in shell i of spectrum n . [c] Bi is the temperature factor [Å²] used to fit the diffraction data. [d] For Xe and $CFAC$ values, the clusters are numbered to represent the central absorber: 1, 2: Gd; 3: Ba; 4: Ca; 5, 6: Ti; 7: Cu. [e] No error is given for $CFAC4$ as it was adjusted manually owing to poor-quality data. [f] R_{ex} is the value obtained prior to the inclusion of multiple scattering for copper after variation of all parameters. [g] Ef = contribution of the wave vector of the zero photoelectron relative to the origin of k ; Xe = edge-specific Ef correction; $AFAC$ = amplitude reduction due to many-electron processes; $CFAC$ = edge-specific $AFAC$; W_{EXAFS} and W_{XRD} = weightings applied to EXAFS and XRD data sets ($W_{\text{XRD}} + W_{\text{EXAFS}} = 1$).

Once the basic structural model had been refined, individual EXAFS spectra were calculated (i.e., $W_{\text{EXAFS}} = 1.0$) without any further changes in structural positions. Certain features in the EXAFS spectra were consistent with the structural model based on neutron-diffraction data, but R_{ex} at this stage of the refinement was greater than 80. To fit both the EXAFS and XRD data satisfactorily, modifications of the model were required particularly with respect to the positions of the oxygen atoms; this reflects the sensitivity of EXAFS data to the local structure. In the earlier model, the O3 atom on the (0,1/2, z) site (Table 1) was not disordered, and O4 was disordered on (x, x, z). For refinement with the EXAFS data, these positions were modified: O3 was moved to a disordered ($x, 1/2, z$) site, and O4 to a new disordered site ($x, 0, z$). Moving O3 to the disordered site substantially improved the fit to the data of the barium L_{III} -edge, and the displacement of O4 markedly improved the fits to the calcium- and gadolinium-edge data. Small improvements to the fits to the copper- and

titanium-edge data were also achieved. A combined refinement of the data from all five EXAFS edges and the XRD data ($W_{\text{EXAFS}} = 0.8$, $W_{\text{XRD}} = 0.2$) was then carried out with this modified structural model.

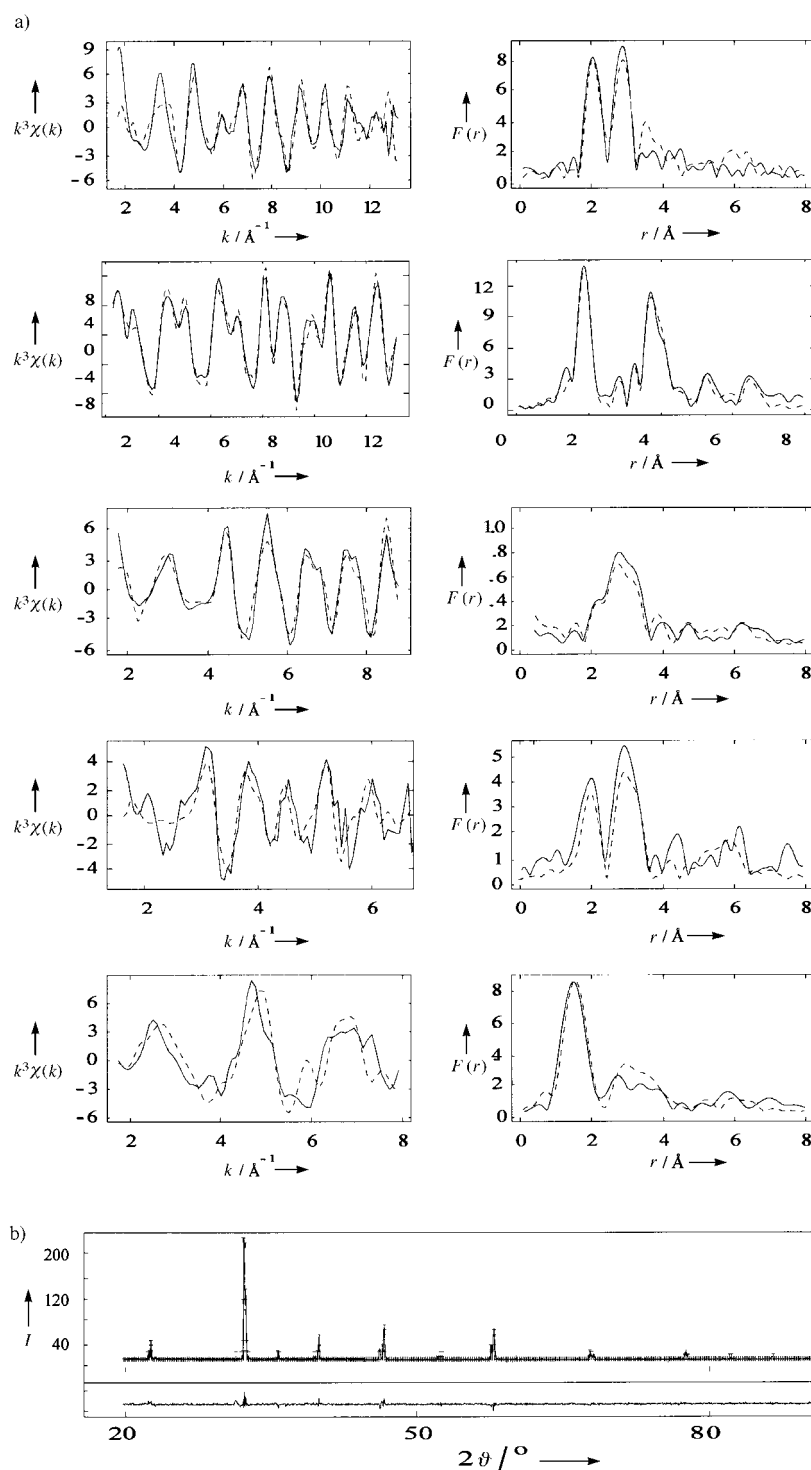
Multiple scattering (MS) can make a significant contribution to all EXAFS spectra, but for $\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$ it is only important for the data of the copper and, to a lesser extent, the titanium K-edges owing to the short bond lengths and large M–O–M bond angles of almost 180°. For this reason and because of the considerable increase in computing time required, a full MS calculation was only carried out for the copper-edge data at a late stage of the refinement. Preliminary refinements incorporating multiple scattering for titanium showed minor improvements to the fit for this edge.

The final refined atomic positions for $\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$ are listed in Table 1. Figure 2 illustrates the EXAFS and Fourier transform plots for all five refined data sets. The value of R_{ex} obtained from the refinement of multiple data sets (Table 1) is still relatively high (>50) but significantly improved relative to the initial model. Addition of multiple scattering for copper considerably improved the fit, but because atomic parameters were not refined again, no meaningful new R_{ex} value could be obtained. Another factor contributing to the high combined R_{ex} value is the quality of the calcium K-edge data which does not match that of the other four spectra; this problem is unavoidable due to the presence of the stronger absorbing elements in the compound.

$\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$ is one of a series of ordered quintuple copper–titanium perovskites that are composed of two CuO_2 layers and three TiO_6 octahedra and in which gadolinium, barium, and calcium cations are incorporated between the layers. However, owing to the presence of several structural features, determination of this structure from diffraction data alone^[4] leads to an approximate structure with an averaged distribution of the cations and local distortions of the TiO_6 octahedra. Even neutron-diffraction data are relatively insensitive to such features and are unable to distinguish between different similarly disordered structural models owing to strong correlations between positional and thermal factors. The combined refinement reported here allows a more accurate determination of this structure.

Our results have led to the best model so far for the structure of $\text{Gd}_2\text{Ba}_2\text{CaCu}_2\text{Ti}_3\text{O}_{14}$, and further small improvements could be made by increasing the complexity of the structural model. These would include further disordering of oxygen atoms adjacent to titanium centers and introduction of Ti–O–Ti multiple scattering to improve the fit to the data of the titanium K-edge. The data of the calcium K-edge indicate that the Ca–O bond lengths are shorter than the average Ca/Gd–O distances, and the inclusion of distinct calcium and gadolinium sites may resolve this minor deficiency. However, preliminary (but very computationally intensive) calculations indicate that this more complex model produces only small improvements to the otherwise good fits for multiple data sets (Figure 2). When the new structural model is used in simple Rietveld refinements of X-ray or neutron diffraction data, almost no change in fitting factors was observed. This is evidence for the insensitivity of the diffraction data to the small displacements of the oxygen atoms.

Figure 2. Fits to the EXAFS (a) and powder X-ray diffraction data (b). EXAFS functions and the radial distribution functions $F(r)$ calculated therefrom by Fourier transformation (from top to bottom): Gd (L_{III}), Cu (K), Ba (L_{III}), Ca (K, fluorescence), Ti (K). Experimental data are shown as a dotted line, and calculated values as a solid line. For the diffraction data the experimental data are shown as crosses, the calculated profile as a solid line, and the difference profile as the lower solid line.



We have shown that five sets of EXAFS data and X-ray powder diffraction data can be refined together with a single set of coordinates that define the structure. In addition to showing that such methods for data analysis are possible, we have demonstrated their importance in developing better structural models, particularly for structures in which perfect crystalline order does not exist. This is important for materials such as oxides, in which local environments consist of weakly scattering atoms whose positions may otherwise be very poorly defined. Also in materials such as superconductors, compounds that exhibit high magnetoresistance, alloys, zeolites, ferroelectrics, and intercalates, structure determination by diffraction methods is not definitive. However, by combining a method for determining long-range order with information about the local environment of as many atoms as possible in a refinement of multiple data sets, a better structure elucidation is possible.

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A Cationic, Macrocyclic, Six-Coordinate Phosphorus(V) Compound Containing a Mixed Valence P^{III}-P^V-P^{III} Linear Chain**

Hongyan Luo, Robert McDonald, and Ronald G. Cavell*

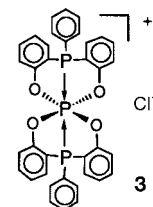
Many types of phosphorus–phosphorus bonds are known,^[1] but it is rare to find such bonds in neutral hexacoordinate (σ^6) pentavalent (λ^5) phosphorus compounds in which the electrovalence and the apparent maximum of sixfold coordination are simultaneously satisfied.^[2, 3] Furthermore, cationic species containing a hexacoordinate, pentavalent phosphorus atom are even more rare. Most such species have been derived from porphyrins,^[4–7] and no examples known to date contain P–P bonds.^[2, 3] Only one non-porphyrin σ^6 complex has been structurally characterized.^[8] An early report of $[\text{P}(\text{Cl}_4)(\text{bpy})]^+$ (bpy = 2,2'-bipyridine) complexes did not contain structural details.^[9]

Typically, hexacoordinate phosphorus(v) centers are formed on strong donor–acceptor interaction between the acidic phosphorus center and a base. The acidity of the phosphorus(v) center is determined by the nature of the substituents; thus a collection of highly electronegative substituents on phosphorus(v) is generally required. Many such compounds are formed as chelates through interaction of the P^V center with a basic site on one of the covalently bound ligands.^[2] Recent studies of phosphorus(v) compounds with dianionic *o,o'*-thiodiphenolato ligands have shown a range of binding interactions between the central sulfur atom and the phosphorus(v) center.^[2, 10–12] At one end of the range an example has no bond (i.e., very long P···S contacts), and the bound dianionic ligand forms large open, (typically eight-membered) macrocyclic rings through a series of nascent P–S bonds, in which the separations are of the order of van der Waals distances. The other limit is a clearly bonded sulfur atom in a compound that displays a pair of bis-chelated pentaatomic rings subtended from the phosphorus.^[2, 10–12] The interaction strengthens with increasingly electronegative substituents on phosphorus, as illustrated by the short P–S bond (2.3307(8) Å) in trichloro(*o,o'*-thio- κ S-diphenolato- κ^2 O)phosphorus(v) $[\text{Cl}_3\text{P}\{\text{S}(\text{o}-\text{C}_6\text{H}_4\text{O})_2\}]$.^[13]

In principle, the strong Lewis base character of phosphanes should yield strong P^{III}–P^V adducts similar to the above S^{II}–P^V system. A series of neutral P^{III}–P^V donor–acceptor adducts were studied by Schultz et al. but none were structurally characterized. Two neutral compounds containing a single P^{III}–P^V bond to a hexacoordinate P^V center have been reported; 1-diethylamino-5-chloro-5-(tetrachlorocatecholato-O,O')-2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1 σ^4 ,5 σ^6 -diphosphabicyclo[3.3.0]octane-3,7-dione (**1**) by Bettermann et al.^[14] and trifluoro(perfluoropinacolato)(trimethylphosphane)phospho-

rus (**2**) by Gibson et al.^[15] Compound **1**^[16] contained a short P^{III}–P^V bond (2.165 Å) between P^{III} and the hexacoordinate P^V center (also bonded to 2 O, 2 N, and one Cl atom), and in **2**^[17] a P^{III} ligand (Me₃P) is bound to the hexacoordinate P^V center (which also subtends 2 O and 3 F atoms) with a short P^{III}–P^V bond distance of 2.234(5) Å, only 0.03 Å longer than the sum of the covalent radii (2.20 Å).

Herein we report a cationic bis-chelate complex of P^V, which provides an encapsulated hexacoordinate pentavalent phosphorus environment from which are subtended two short P^{III}–P^V bonds. The cation **3** also provides an example of an unusual mixed valence, linear triphosphorus chain. Triphosphorus (and polyphosphorus) chains are known for lower coordination environments in the P^V system^[18, 19] and in several complex ions in which λ^4 phosphorus(v) substituents are bound to a formal P^{III} center. These examples are typically based on a low valent phosphorus subtended by σ^4, λ^5 centers, and generally the chains are nonlinear due to the presence of electron pairs on the central phosphorus center. They do not contain hexacoordinate (σ^6) phosphorus.



The complex containing the cation is an off-white, air-stable, crystalline solid. It was prepared by reaction of phenylbis(*o*-(trimethylsiloxy)phenyl)phosphane^[13, 20, 21] with PCl₅ in toluene. The compound was insensitive to moisture and oxygen; even in Me₂SO, “wet” MeOH or CHCl₃ solution, the ³¹P{¹H} NMR of the complex was unchanged after standing for a week. In contrast, the neutral trichloro(*o,o'*-thio- κ S-diphenolato- κ^2 O)phosphorus(v) complex was readily hydrolyzed.^[13]

Full chemical, spectroscopic and structural analysis supports the proposed formulation. The shift of the IR bands relative to the free ligands (the hydrochloride salt of bis(*o*-hydroxyphenol)phenylphosphane)^[22] or phenylbis(*o*-(trimethylsiloxy)phenyl)phenylphosphane confirmed dianionic ligand binding. Mass spectrometric data confirmed the formation of the cationic complex. In methanol, the cation gave a typical AB₂ ³¹P{¹H} NMR spectrum, with a ¹J_{PP} coupling between the P^V center and the two P^{III} donors of 512 Hz, smaller than the ¹J_{PP} coupling constants shown by **2** (710 Hz)^[15] and Me₃PPF₅ (720 Hz).^[23] A *trans* arrangement of the two P^{III} centers was deduced for the cation from the ¹H NMR spectrum, because the seven types of ¹H NMR signals (assigned by means of selective broad-band ³¹P decoupling experiments) that were observed for the aromatic ring hydrogen atoms (δ = 5.0–8.5) indicated that the cation possesses symmetry that makes the four bound phenoxy rings equivalent.

The solid-state X-ray structure^[24] showed the cationic unit (central portion illustrated in Figure 1) containing a P^V center in a highly symmetric, nearly perfect octahedral environment with two facially bonded, dianionic bis(*o*-phenoxy)phenylphosphane ligands. The four phenolate oxygen atoms define the equatorial plane of the octahedron, and the P–O bond lengths are the same (1.726 Å) within experimental error, and somewhat longer than those previously observed for the phenolate oxygen bond to a P^V center in a similar environ-

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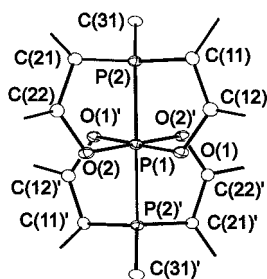


Figure 1. ORTEP drawing (20% probability thermal ellipsoids) showing the central framework and the atom labeling of the cation of **3**. Selected interatomic distances [Å] and angles [°]: P(1)–P(2) 2.2023(10), P(1)–O(1) 1.727(2), P(1)–O(2) 1.726(3), P(2)–C(11) 1.769(4), P(2)–C(21) 1.770(4), P(2)–C(31) 1.781(4), O(1)–C(12) 1.364(4), O(2)–C(22) 1.358(5); P(2)–P(1)–O(1) 89.39(9), P(2)–P(1)–O(1') 90.61(9), P(2)–P(1)–O(2) 89.64(9), P(2)–P(1)–O(2') 90.36(9), O(1)–P(1)–O(2) 89.86(13), O(1)–P(1)–O(2') 90.14(13), P(1)–P(2)–C(11) 95.50(13), P(1)–P(2)–C(21) 95.98(13), P(1)–P(2)–C(31) 120.49(13).

ment.^[13] The C_i symmetry of the cation confirmed the *trans*-(P^{III} , P^{III}) structure (i.e., the ligands are *fac* oriented) deduced from solution NMR data. This structural arrangement is unlike the behavior of this ligand toward transition metals: in these cases six-coordinated complexes of this ligand gave *cis*-related (*mer*) structures.^[22, 25–29] The right angle binding within the chelate contrasts with the more acute bond angles (76–84°) that have been typically observed for similar PO or PS chelate rings bound to the transition metals.^[22, 25, 27–29]

Two axial P^{III} – P^V bonds (2.2023(10) Å) lie perpendicular to the “octahedral” equatorial plane. These P^{III} – P^V bonds are significantly shorter than the single P^{III} – P^V donor–acceptor bond in **2** (2.234(5) Å),^[17] and slightly longer than the single P^{III} – P^V bond length in **1** (2.165 Å).^[16] As the central P^V in our cation is surrounded by a collection of atoms with a total electronegativity smaller than that contributed by the atoms connected to P^V in **1**, it is perhaps not too surprising that the bond lengths are a little longer. If substituent electronegativity were the dominant factor controlling the bond length, the sum of the electronegativity of the ligands at the P^V in the case of **2** would indicate that an even shorter bond was appropriate; however, this P^{III} – P^V bond is the longest of the three examples. Regardless of these small variations, the short bond and the unreactive nature of the pentavalent center in the complex suggests that the P^{III} – P^V donor bonds are strong and that the P^V center is protected. We surmise therefore that the anchored *o*-phenoxy groups provide an unstrained bis-chelate environment about the P^V center which also contributes to the stabilization of the P^{III} – P^V bonds.

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Highly Enantioselective Hydrogenation of Simple Ketones Catalyzed by a Rh–PennPhos Complex**

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The development of new chiral ligands plays a crucial role in expanding the utility of transition metal catalyzed asymmetric reactions.^[1] A major research goal in asymmetric catalysis is to impart high enantioselectivity and activity to important reactions by the invention of new chiral ligands and the optimization of reaction conditions for use of these ligands. Many effective chiral bisphosphanes contain a diarylphosphane as the key steric group that defines the electronic properties.^[1] Recently, we designed conformationally rigid *endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1]heptanes as new chiral scaffolds, and demonstrated that these monophosphane species can be more effective for some asymmetric reactions^[2] than the conformationally flexible 2,5-disubstituted phospholanes characteristic of the DuPhos and BPE ligands^[3] (Figure 1). Herein we report the synthesis of a novel class of conformationally rigid chiral bisphosphanes, *P,P'*-1,2-phenylenebis(*endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1]heptanes) (PennPhos, **5** and **6**).^[4] Although PennPhos shares some features with DuPhos, such as electron-donating properties and a modular structure, it is bulkier, more rigid, and does not form *C*₂-symmetric compounds with many transition metals. In addition, PennPhos can be made in large quantities from inexpensive starting materials and is an air-stable solid.

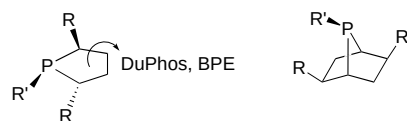
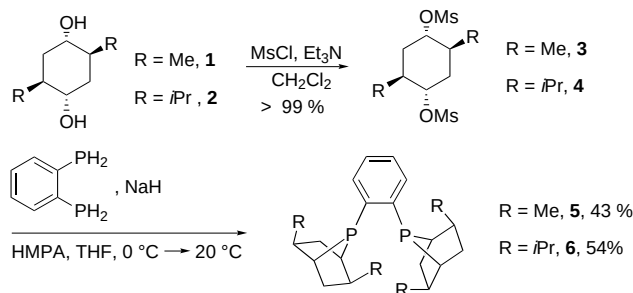


Figure 1. Structural motifs of chiral 1,2-bis(phospholano)benzene (DuPhos) and 1,2-bis(phospholano)ethane (BPE) as well as rigid dialkyl-7-phosphabicyclo[2.2.1]heptane.

We have directed much attention toward enantioselective hydrogenation of simple ketones as a showcase for enantioselective transition metal catalyzed reactions with PennPhos. Asymmetric hydrogenation is one of the most efficient methods of making chiral alcohols, because transition metal hydrogenation catalysts have potentially high catalytic activity compared to stoichiometric^[5] and other catalytic reduction

systems.^[6] While systems for efficient transition metal catalyzed asymmetric hydrogenation of functionalized ketones have been realized,^[7] highly enantioselective hydrogenation of simple ketones that lack anchoring heteroatoms has not been fully developed. Among the direct hydrogenation catalytic systems,^[8] promising results were achieved for asymmetric hydrogenation of alkyl aryl ketones with a mixture of a Ru^{II}–BINAP complex (BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-dinaphthyl), a chiral diamine, and KOH.^[8d] In this catalytic system, the chelating chiral diamine is as important a stereochemistry-controlling element as the chiral BINAP ligand. To date, simple metal complexes with chiral bisphosphane ligands are ineffective for highly enantioselective hydrogenation of simple ketones. Furthermore, asymmetric reduction of simple dialkyl ketones generally proceeds with low enantioselectivity in all reduction systems with few exceptions.^[5b, 5c] With a Rh–PennPhos catalyst, we have achieved unprecedented high enantioselectivity in hydrogenation of both aryl alkyl and dialkyl ketones. This success is based on the important finding that a weak base can facilitate Rh-catalyzed hydrogenation of simple ketones; the discovery itself may have fundamental significance for organometallic chemistry.

The synthesis of PennPhos is illustrated in Scheme 1. Enantiomerically pure cyclic 1,4-diols **1** and **2**, which are easily prepared by Halterman's procedure,^[9] are converted



Scheme 1. Synthesis of the PennPhos ligands. HMPA = hexamethyl phosphoramide, Ms = methanesulfonyl.

into the corresponding mesylates **3** and **4** in high yields. Nucleophilic substitution of the methanesulfonate groups by 1,2-phenylenediphosphane^[10] in the presence of NaH generates the desired products *P,P'*-1,2-phenylenebis[(1*R*,2*S*,4*R*,5*S*)-2,5-dimethyl-7-phosphabicyclo[2.2.1]heptane] (**5**, (*R,S,R,S*)-Me-PennPhos) and *P,P'*-1,2-phenylenebis[(1*R*,2*R*,4*R*,5*R*)-2,5-diisopropyl-7-phosphabicyclo[2.2.1]heptane] (**6**, (*R,R,R,R*)-*i*Pr-PennPhos), respectively.

Effective asymmetric hydrogenation of simple ketones requires high intrinsic activity in the nonchiral form of the reaction. Since simple ketones are typically poorer ligands than are olefins, many Rh–phosphane complexes show no activity for the hydrogenation of simple ketones. An important finding by Osborn and Schrock is that [RhH₂L₂X₂]⁺ (L = electron-donating phosphanes such as PPh₃Me or PMe₃, X = solvent) is a reasonable catalyst for the hydrogenation of simple ketones in the presence of a small amount of water.^[11] Since PennPhos ligands are more electron rich

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than triarylphosphanes, we anticipated that they might show good activity towards asymmetric hydrogenation of simple ketones.

Table 1 outlines the results of asymmetric hydrogenation according to Equation (a) with acetophenone as a typical

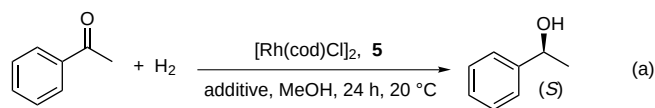


Table 1. Rh-catalyzed asymmetric hydrogenation of acetophenone according to Equation (a).^[a]

Entry	Additive	Conversion [%](<i>ee</i> [%]) for the following ratios of additive:Rh catalyst					
		0.0	0.1	0.15	0.2	0.3	1.0
1	NaOMe	45 (57)	56 (70)	69 (83)	71 (88)	41 (80)	25 (15 <i>R</i>)
2	LiOtBu			80 (91)	58 (89)	19 (78)	20 (23 <i>R</i>)
3	LiCl		49 (66)		46 (70)	47 (72)	44 (67)
4	KBr		74 (80)		82 (88)	85 (89)	89 (92)
5	Et ₃ N			89 (90)	78 (92)	28 (82)	18 (4 <i>R</i>)
6	2-Me-imidazole		86 (87)		94 (94)	79 (92)	12 (1)
7	2,6-lutidine		72 (83)	84 (90)	94 (94)	97 (95)	93 (95)

[a] Reaction conditions: room temperature, 30 atm of H₂, 24 h, 1.0 mmol of substrate, 0.1 M, substrate:[Rh(cod)Cl]₂:5 = 1:0.005:0.01. See Experimental Section for further details.

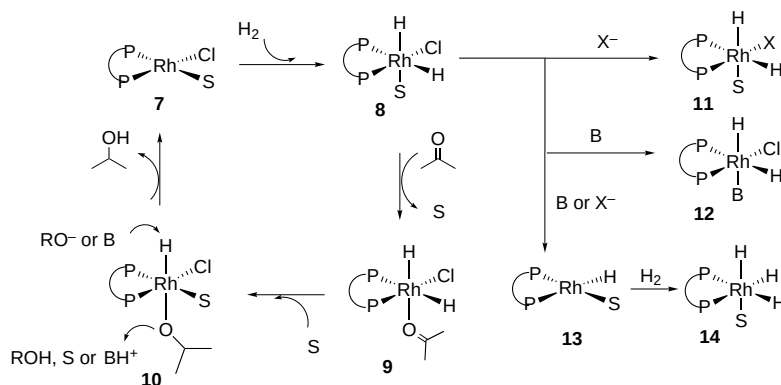
substrate and the Rh complex of **5** as the catalyst. Initially, extensive screening of catalytic conditions showed that the asymmetric hydrogenation gave good enantioselectivity and activity when [Rh(cod)Cl]₂ was used as the precursor under 30 atm of H₂ in MeOH. The Rh complex of **6** is a less effective catalyst than the Rh complex of **5**. Unlike the hydrogenation system of Osborn and Schrock, addition of a small amount of water had no effect on the catalytic activity. However, we found a dramatic effect with other additives. Not only does the enantioselectivity strongly depend on the additive used, but catalytic activity also varies to a great extent.

Three classes of additives were screened in the catalytic system: ionic bases (Table 1, entries 1, 2), halides (entries 3, 4), and neutral bases (entries 5–7). In the absence of additives, asymmetric hydrogenation of acetophenone catalyzed by the Rh complex of **5** was sluggish and gave the secondary alcohol with only 57% *ee* (entry 1). In the presence of catalytic amounts of additives (0.1–0.2 equiv based on Rh), both reactivity and enantioselectivity were increased.

Different effects were observed depending on the type and amount of additives used. For the ionic bases (entries 1, 2), addition of one equivalent of base slowed down the reaction and surprisingly gave the chiral alcohol with the opposite configuration. The halide effect was studied with two different salts. The presence of excess chloride showed little effect on the catalyst activity and selectivity (entry 3). However, the addition of bromide could enhance both the

enantioselectivity and the rate of the reaction over the entire concentration range (0.1–1 equiv, entry 4). With Et₃N as the additive (entry 5), higher conversion and better enantioselectivity were observed when less than 0.2 equivalents of base were present in the catalytic system. Use of more than 0.3 equivalents of Et₃N caused a decrease in reactivity and enantioselectivity. The reaction gave the opposite configuration with low conversion when one equivalent of Et₃N was used. Hydrogenation in the presence of 2-methylimidazole (entry 6) also showed initial enhancement and then erosion of both the reactivity and selectivity. In contrast, both enantioselectivity and conversion were increased when 0.1 to 1 equivalent of 2,6-lutidine was used (entry 7). Up to 95% *ee* was observed for the hydrogenation of acetophenone. This is the highest enantioselectivity achieved with a direct hydrogenation catalyst of a Group 8 transition metal (87% *ee* was obtained with Noyori's Ru system^[8d]). Therefore, bromide and 2,6-lutidine are useful promoters for the Rh-catalyzed enantioselective hydrogenation of acetophenone.

The mechanism of this Rh-catalyzed asymmetric hydrogenation is not well understood at present. Based on the commonly accepted mechanism,^[12] we offer the following rationale to explain our observations (Scheme 2): Addition of **5** to [Rh(cod)Cl]₂ in MeOH generates [Rh(cod)(**5**)]Cl.^[13] This catalytic precursor can be hydrogenated to give the Rh^I intermediate **7**. Oxidative addition of hydrogen to **7** produces the six-coordinate Rh^{III} species **8**, which is converted into **9** by ligand substitution. Insertion of the ketone into the Rh–H bond forms the Rh^{III}–alkoxyl complex **10**, in which the remaining hydride is located *trans* relative to the alkoxide group. Therefore, the reductive elimination of **10** to regenerate **7** is difficult under normal conditions. The major function of the added bases may be to deprotonate **10**, while the conjugate acid can protonate the alkoxide ligand. A similar push–pull mechanism was suggested by Osborn and Schrock for the Rh-catalyzed hydrogenation of simple ketones promoted by small quantities of water.^[11] With a 1:1 ratio of Rh:additives, a variety of Rh derivatives can be generated. For example, halide and alkoxide may displace the chloride in **8** to form **11**, which can lead to a Rh dimer or other unproductive species. With strongly coordinating ligands such as an imidazole, irreversible formation of coordinately



Scheme 2. Proposed mechanism for Rh-catalyzed asymmetric hydrogenation. S = MeOH, B = neutral base, X = halogen, OR.

saturated species **12** is possible. Replacing these ligands by simple ketones is difficult, and low catalytic activity is expected. In the presence of strong bases such as alkoxide or Et₃N, reductive elimination of HCl from **8** will form the Rh^I–hydrido species **13**, which may lead to the opposite enantiomer by a competitive pathway.^[11] Clearly, the enantioselectivity of the reaction is a useful probe for understanding the reaction mechanism of the Rh-catalyzed hydrogenation. Oxidative addition of H₂ to **13** is likely to be slow, as **14** has two hydrido ligands located *trans* to phosphane ligands. On the other hand, substitution of chloride by bromide changes the electronic nature of the Rh complex, and may generate more active catalysts for the hydrogenation of ketones. Use of noncoordinating and weaker bases such as 2,6-lutidine could accelerate the reductive elimination of **10** without unwanted formation of **12** and **13**.

Based on the observation that bromide and 2, 6-lutidine are important promoters for the hydrogenation of simple ketones, we examined the asymmetric hydrogenation of various simple ketones with the Rh complex of **5** as the catalyst [Eq. (b), Table 2]. Two sets of reaction conditions were applied to achieve high enantioselectivity: 1) use of 0.4 equivalents of 2,6-lutidine (based on Rh) or 2) use of 0.8 equivalents of 2,6-lutidine and 1 equivalent of KBr (based on Rh). For most aryl methyl ketones (Table 2, entries 1–8), high enantioselectivities (93–96% *ee*) were observed. The presence of both 2,6-lutidine and KBr accelerated the reaction and enhanced the enantioselectivity (entries 4/3 and 6/5). These conditions were then used for the hydrogenation of other ketones. Increasing the bulk of the alkyl group by going from methyl to ethyl or isopropyl in the alkyl aryl ketone dramatically decreased the reactivity and enantioselectivity (entries 1/5 and 6/7). This clearly indicates that the chiral environment around the Rh complex of **5** can effectively discriminate between methyl and other alkyl groups. To test this speculation, we carried out asymmetric hydrogenations of several alkyl methyl ketones—the toughest problem for asymmetric reduction (entries 9–14). Enantiomeric excesses of up to 94% *ee* for *tert*-butyl methyl ketone (entry 14) and 92% *ee* for cyclohexyl methyl ketone (entry 13) were observed. The enantioselectivity decreased with smaller alkyl groups. With isopropyl methyl ketone and isobutyl methyl ketone, 84% *ee* (entry 12) and 85% *ee* (entry 11) were achieved respectively. However, even with unbranched alkyl groups, good enantioselectivities of 73% *ee* (entry 9) and 75% *ee* (entry 10) were still achieved. To the best of our knowledge, our results of asymmetric hydrogenation of alkyl aryl ketones by the Rh complex of **5** are comparable to or better than those with other hydrogenation catalysts, and our hydrogenation results of alkyl methyl ketones with this system gives the highest enantioselectivity reported to date.

In summary, we have synthesized new conformationally rigid bisphosphanes, the PennPhos ligands. For the asymmetric hydrogenation of ketones catalyzed by Rh complexes of these ligands, remarkable additive effects and high enantioselectivities for both alkyl aryl and alkyl methyl ketones are found. Continuing research will focus on understanding the reaction mechanism and enhancing the reaction rate. Fine-tuning the steric and electronic environment of the PennPhos

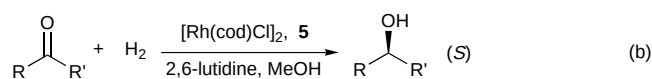


Table 2. Asymmetric hydrogenation of simple ketones catalyzed by a Rh–PennPhos complex according to Equation (b).^[a]

Entry	Ketone	Equiv of lutidine ^[b]	Equiv of KBr	Time[h]	Yield[%]	<i>ee</i> [%]
1		0.4	–	24	97	95
2		0.4	–	53	94	95
3		0.8	–	108	56	91
4		0.8	1.0	48	83	94
5		0.8	–	108	71	89
6		0.8	1.0	88	95	93
7		0.8	1.0	94	20	72
8		0.8	1.0	100	99	96
9		0.8	1.0	56	99	73
10		0.8	1.0	48	96	75
11		0.8	1.0	75	66	85
12		0.8	1.0	94	99	84
13		0.8	1.0	106	90	92
14		0.8	1.0	96	51	94

[a] Reaction conditions: room temperature, 30 atm of H₂, 0.5 mmol of substrate, 0.125 M, substrate:[Rh(cod)Cl]₂:**5** = 1:0.005:0.01. See Experimental Section for further details. Long reaction time was used to achieve the maximum conversion; for many substrates the reaction may be complete within a much shorter time. [b] Based on Rh.

ligand should lead to practical asymmetric hydrogenation catalysts for simple ketones.

Experimental Section

Compounds **1**–**4**^[9] and 1,2-phenylenediphosphane^[10] were made according to literature procedures. MeOH was distilled from Mg/Na over a long column under N₂. All the operations were carried out under a N₂ atmosphere.

5: ¹H NMR (CDCl₃): δ = 7.25–7.10 (m, 2H, aromatic), 7.08–6.95 (m, 2H, aromatic), 3.21 (br d, 2H, ²J(P,H) = 14.5 Hz, PCH), 2.58 (br d, 2H, ²J(P,H) = 13.4 Hz, PCH), 1.90–1.60 (m, 12H), 1.55–1.35 (m, 2H), 1.17 (d, 6H, ³J(H,H) = 6.3 Hz, CH₃), 0.60 (d, 6H, ³J(H,H) = 6.3 Hz, CH₃); ¹³C

NMR (CDCl₃): δ = 143.94, 143.66, 143.48, 143.20, 131.05, 131.00, 130.93, 126.33, 46.24, 46.20, 46.17, 46.13, 45.92, 45.69, 45.61, 45.38, 40.17, 40.05, 39.89, 39.73, 39.61, 39.52, 39.33, 39.29, 39.26, 34.76, 34.61, 34.51, 34.41, 34.26, 22.69, 22.65, 22.61, 20.82; ³¹P NMR (CDCl₃): δ = -7.3; $[\alpha]_D$ = +221.8° (*c* = 1.01, CHCl₃); HR-MS calcd for C₂₂H₃₂P₂: 358.1975; found: 358.1982.

6: ¹H NMR (CDCl₃): δ = 7.20–7.10 (m, 2H, aromatic), 7.05–6.90 (m, 2H, aromatic), 3.38 (br d, 2H, ²J(P,H) = 14.2 Hz, PCH), 2.85 (br d, 2H, ²J(P,H) = 13.5 Hz, PCH), 1.85–1.45 (m, 12H), 1.30–1.08 (m, 4H), 1.03 (d, 6H, ³J(H,H) = 6.4 Hz, CH₃), 0.96 (d, 6H, ³J(H,H) = 5.6 Hz, CH₃), 0.86 (d, 6H, ³J(H,H) = 6.5 Hz, CH₃), 0.47 (s, 6H, CH₃); ¹³C NMR (CDCl₃): δ = 143.97, 143.62, 143.56, 143.50, 143.45, 143.09, 130.96, 130.90, 130.86, 126.11, 54.10, 54.06, 54.03, 48.65, 48.56, 48.46, 42.02, 41.96, 41.24, 41.20, 41.18, 41.14, 37.94, 37.77, 37.60, 37.46, 33.29, 33.27, 33.24, 31.69, 23.45, 23.40, 23.35, 22.22, 20.97, 20.54; ³¹P NMR (CDCl₃): δ = -8.7; $[\alpha]_D$ = +226.7° (*c* = 1.03, CHCl₃); HR-MS calcd for C₃₀H₄₈P₂: 470.3231; found: 470.3229.

General procedure for asymmetric hydrogenation: To a solution of [Rh(cod)Cl]₂ (2.5 mg, 0.005 mmol) in MeOH (10 mL) was added **5** (3.7 mg, 0.01 mmol). After the reaction mixture was stirred at room temperature for 10 min, acetophenone (1.0 mmol) was added. The orange-yellow solution was stirred for 2 min, and the desired amount of the additive (as a solution in MeOH) was then added. This mixture was stirred for about 5 min, and hydrogen was introduced. The hydrogenation was performed in a Parr autoclave at room temperature under 30 atm of hydrogen for 24 h. The residue was passed through a short silica gel column to remove the catalyst, and eluted with diethyl ether. The enantiomeric excesses and reaction conversion were measured by gas chromatography on a Supelco β -DEX 120 column. The absolute configuration of the product was determined by comparing the observed rotation with the reported value.^[5c,8d]

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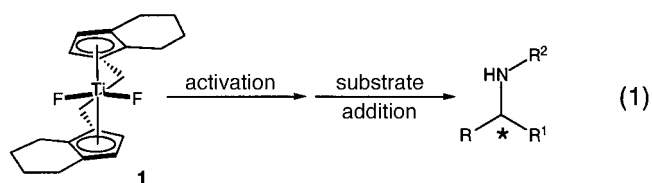
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- [13] ³¹P NMR data for [Rh(cod)**5**]Cl (prepared in situ, CD₃OD): ABX system, δ = 50.7 (dd, ¹J(Rh,P) = 140.6 Hz), ²J(P,P) = 23.6 Hz, 37.1 (dd, ¹J(Rh,P) = 141.6 Hz, ²J(P,P) = 23.6 Hz). It is noteworthy that the ligand **5** in [Rh(cod)(**5**)]Cl does not have C₂ symmetry. A possible explanation is that the phosphabicyclo[2.2.1]heptane is too bulky to allow the PennPhos to exist in a C₂-symmetrical fashion.

Amine Additives Greatly Expand the Scope of Asymmetric Hydrosilylation of Imines**

Xavier Verdaguer, Udo E. W. Lange, and
Stephen L. Buchwald*

Dedicated to Professor Satoru Masamune

The demand for enantiomerically pure secondary amines has prompted considerable effort^[1] in the development of catalytic processes for asymmetric hydrogenation^[2] and hydrosilylation^[3] of imines. We recently reported a highly enantioselective titanium-catalyzed hydrosilylation of imines.^[4] This method involves treatment of (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium difluoride^[5] (**1**) with phenylsilane,^[4,6] which yields a very active catalytic system for the hydrosilylation of *N*-methyl and cyclic imines [Eq. (1)]. For example, *N*-methylimine **2** undergoes complete hydrosilylation within 12 h at room temperature (Table 1, entry 1). Although high turnover numbers (up to 5000) and



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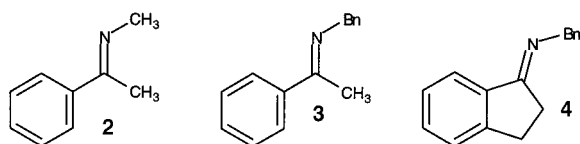


Table 1. Catalytic reduction of imines with and without the addition of primary amine.^[a]

Entry	Silane	Amine additive ^[b]	Imine	<i>t</i> [h]	Conversion [%]	<i>ee</i> [%]
1	PhSiH ₃	–	2	12 ^[c]	100	97
2	PhSiH ₃	–	3	96 ^[d]	55	47
3	PMHS	–	2	48 ^[d]	50	–
4	PMHS	–	4	24	5	–
5	PMHS	<i>n</i> HexNH ₂	4	2	100	85
6	PMHS	<i>t</i> BuNH ₂	4	24	39	–
7	PMHS	pyrrolidine	4	24	4	–
8	PMHS	<i>i</i> BuNH ₂	4	2	100	92
9	PMHS	(±)- <i>s</i> BuNH ₂	4	2	75	78

[a] The reactions were conducted with 5 mol % of **1** at 60 °C unless otherwise noted. [b] The amines were introduced with a syringe pump over a period of 80 min. [c] 1 mol % catalyst, room temperature. [d] 10 mol % catalyst.

excellent enantioselectivity (93–99% *ee*) were achieved, the reaction is extremely sensitive to steric bulk in the nitrogen substituent. When the analogous *N*-benzylimine **3** was subjected to the standard hydrosilylation conditions^[4] the reaction failed to go to completion, and a precipitous drop was observed in enantioselectivity (entry 2). A change in the nature of the silane had a similar effect: When polymethylhydrosiloxane (PMHS) was used instead of PhSiH₃, reduction of **2** reached only 50% conversion after 2 d at 60 °C (entry 3).

The rate-determining step in the titanium-catalyzed hydrogenation of imines has been proposed to be cleavage of the Ti–N bond in the intermediate amido complex through a σ -bond metathesis pathway;^[7] we presume that the same applies to the hydrosilylation reaction.^[8] Our previous work implies that this metathesis, which takes place in the crowded wedge of the bis(tetrahydroindenyl) scaffold, is quite sensitive to steric effects.^[7] Specifically, the rate of Ti–N cleavage for imine substrates with moderate to large nitrogen substituents is very low.

It is common practice in organic chemistry to utilize a nucleophilic catalyst (e.g., 4-dimethylaminopyridine) to transform an intermediate into a more reactive species.^[9a, b] By analogy, we felt that introduction of a nucleophilic additive into the reaction mixture might convert the titanium–amido intermediate into a more reactive complex and thereby lead to a procedure applicable to a wider range of substrates. Several amines, alcohols, and thiols were tested as additives. Among these, primary amines had the most pronounced effect on the reaction. For example, use of our standard reaction protocol (see Table 2) with *N*-benzyl-1-indanimine (**4**) was ineffective, and only 5% conversion into product was observed after 24 h at 60 °C (Table 1, entry 4). However, slow addition of four equivalents of *n*-hexylamine to the hydrosilylation reaction mixture at 60 °C resulted in complete reduction of **4** within 2 h (entry 5). With **4** as the test substrate,

we then studied the influence of the added amine on the outcome of the reaction. Bulky primary amines such as *tert*-butylamine and secondary amines such as pyrrolidine proved to be ineffective (entries 6 and 7). Isobutylamine generally gave the best results: high reaction rate and the greatest enantioselectivity (entry 8).^[9c, d] (±)-2-Butylamine (entry 9) was also found to be useful, although it produced a somewhat smaller enantiomeric excess in the reduction of **4**.

Results for the reduction of a series of acyclic imines and details of the experimental protocol are summarized in Table 2. An important feature of this catalytic system is that, in comparison to analogous hydrogenations with a Brintzinger-type catalyst, acyclic amines are reduced with significantly higher levels of enantioselectivity.^[10] Generally, amine products are obtained with 91–99% *ee*. It is significant that the enantiomeric excess of the product does not correspond to the *E*:*Z* ratio of the starting imine, in contrast to the earlier hydrogenation.^[11] The most dramatic examples of this behavior are represented by entries 8 and 9 in Table 2. Whereas the imines exist as 2.5:1 and 1.8:1 mixtures of *E* and *Z* isomers, titanocene-catalyzed reduction produces amines with 93 and 97% *ee*, respectively. At present we have no explanation for these results, although labeling studies rule out the involvement of enamine intermediates.

An additional practical aspect of the amine-promoted protocol is that it allows use of PMHS, an inexpensive and convenient silylation reagent,^[12] as the stoichiometric reductant.^[13] Typical catalyst loadings range from 0.5–1 mol %. A reduction in the amount of catalyst to 0.05 mol % compromises neither the yield nor the enantioselectivity of the reaction (entry 5). However, slow addition (syringe pump) of the primary amine (1.5–4 equiv) to the reaction mixture is essential to ensure complete reduction of the starting imine. After all the imine has been consumed, acidic workup provides the desired chiral amine in high yield and a purity greater than 95% (GC and ¹H NMR).

Although a detailed mechanistic study has not yet been undertaken, one possible pathway is the catalytic cycle shown in Scheme 1a. Amines are obtained with the same absolute configuration as in the case of titanium-catalyzed hydrogenation, which suggests a chirality-transfer step in which the imine is inserted into the Ti–H bond of the titanocene hydride **5** in analogy to the hydrogenation case.^[7] The additive would then react with the sterically encumbered titanium–amido complex **6** to release a chiral amine and to generate the new amido complex **7**. Finally, reaction of the less hindered complex **7** with silane regenerates **5**. When PMHS is used as a hydride source the ¹H NMR spectrum of the crude product shows the presence of free amine, whereas the isobutylamine additive is attached to the siloxane polymer.

The proposed catalytic cycle also explains why slow addition of the additive is required. Thus, the promoter can also react with titanocene hydride **5**, in a process that competes with imine reduction, to generate complex **7** with concomitant loss of hydrogen (Scheme 1b). Further reaction of **7** with silane affords a silylated primary amine. When the primary amine is present in high concentration, this reaction pathway becomes an important side reaction.^[14]

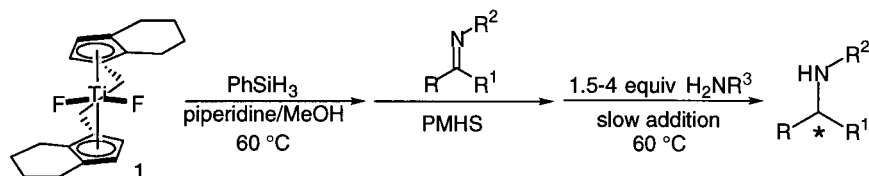


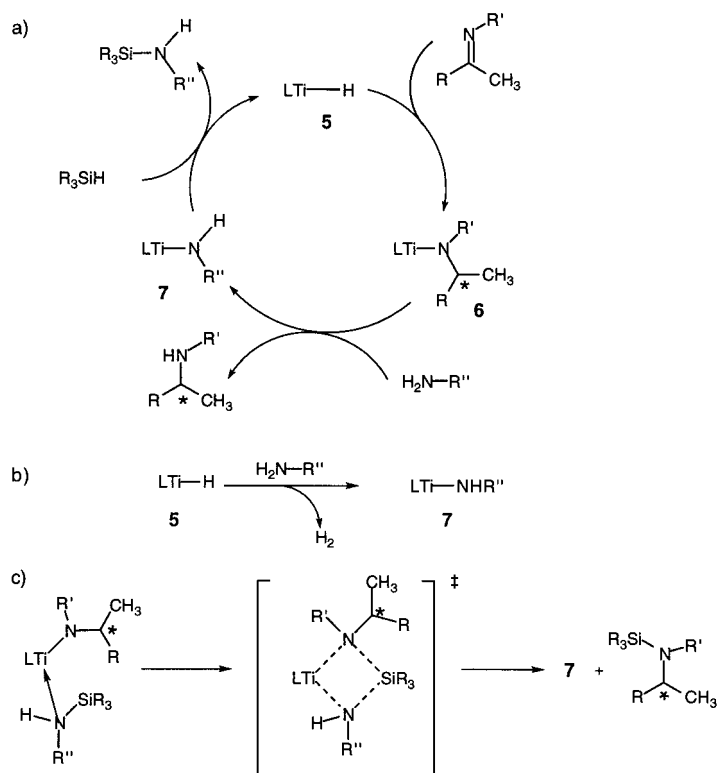
Table 2. Amine-promoted catalytic asymmetric reduction of acyclic imines.

Entry	Imine	<i>E</i> : <i>Z</i> ^[a]	Cat. [mol %]	Silane	Amine	Yield [%] ^[b]	<i>ee</i> [%]
1		> 50:1	1	PMHS	<i>i</i> BuNH ₂	96	92 ^[c]
2		15:1	0.5	PMHS	<i>i</i> BuNH ₂	95	98 ^[c, d]
3		15:1	0.5	PMHS	<i>i</i> BuNH ₂	92	99 ^[c]
4		18:1 18:1	2 1	PhSiH ₃ PMHS	<i>s</i> BuNH ₂ <i>i</i> BuNH ₂	88 97	96 ^[c] 98
5		20:1 20:1	2 0.05	PhSiH ₃ PMHS	<i>s</i> BuNH ₂ <i>i</i> BuNH ₂	73 95	93 ^[c] 98
6		23:1	0.5	PMHS	<i>i</i> BuNH ₂	96	91 ^[c, d]
7		3.5:1	1	PMHS	<i>i</i> BuNH ₂	96	69 ^[c]
8		2.5:1	5	PMHS	<i>i</i> BuNH ₂	86	93 ^[d, f]
9		1.8:1	1	PhSiH ₃	<i>i</i> BuNH ₂	90	97 ^[f]

[a] Established by ¹H NMR spectroscopy. [b] Yields are based on isolated compounds with greater than 95% purity (determined by GC and ¹H NMR spectroscopy). [c] The enantiomeric excess (*ee*) was established by HPLC (Chiralcel-OD column). [d] The absolute configuration of the *S* product was determined by polarimetry. [e] The enantiomeric excess (*ee*) was determined by GC (Chiraldex-B-PH and Chiraldex-G-TA columns). [f] The enantiomeric excess (*ee*) was determined by ¹H NMR analysis of the diastereomeric salts formed upon addition of (*R*)- or (*S*)-*O*-acetylmandelic acid.

An alternative explanation for the effect of added amine is shown in Scheme 1 c. As mentioned above, the primary amine can be silylated to an *N*-silylamine. This species might facilitate cleavage through silylation of the Ti–N bond by

coordination to the titanium center followed by σ -bond metathesis. Such an amine exchange process would be intramolecular, which may make it particularly facile. The product of amine exchange is **7**, which can then be rapidly



Scheme 1. a) Postulated catalytic cycle. b, c) See text. L = (S,S)-ethylene-1,2-bis(η⁵-4,5,6,7-tetrahydro-1-indenyl).

converted into **5** and the silylated amine.^[15] Experiments are currently underway to probe the viability of these possible mechanisms.

Thus, use of primary amines as additives in titanium-catalyzed asymmetric hydrosilylation of imines greatly expands the scope of the reaction. This new protocol utilizes PMHS, a convenient and inexpensive hydride source, and encourages the preparation of a wide array of almost enantiomerically pure secondary amines. It is significant that the enantioselectivity achieved is not limited by the *E*:*Z* ratio of the starting imine.^[8] Further work is in progress to clarify the mechanism of the transformation and its application to other asymmetric processes.^[16]

Experimental Section

Typical experimental procedure: A dry resealable Schlenk flask was charged with **1** (9 mg, 0.025 mmol) and dry THF (1 mL) under argon. The resulting yellow solution was heated to 60 °C, and PhSiH₃ (12 μL, 0.1 mmol), piperidine (9 μL, 0.1 mmol), and methanol (4 μL, 0.1 mmol) were added by syringe. The mixture was stirred at 60 °C for 15–20 min, which produced a color change from yellow to green. THF (1 mL) and PMHS (1.65 mL, 27 mmol) were then added by syringe. The sealed Schlenk flask was removed from the oil bath, cooled to room temperature, and introduced into an argon-filled glovebox. *N*-Benzyl-1-indanimine (0.64 g, 2.9 mmol) was added, and the reaction mixture was heated to 65 °C; the color of the reaction mixture changed to brown. Isobutylamine (0.6 mL, 6 mmol) was added to this solution over a period of 2.5 h (0.25 mL h⁻¹ flow rate) with a syringe pump. After addition of the amine the color of the reaction mixture had changed from brown to green, and GC analysis showed complete consumption of the starting material. The reaction mixture was cooled to room temperature, removed from the glovebox, diluted with Et₂O (30 mL), and stirred with 1M HCl (15 mL) for 30 min (**caution**: vigorous bubbling). The aqueous layer was separated, made basic

with 3M NaOH, and extracted with Et₂O. The combined Et₂O layers were dried (MgSO₄) and concentrated in vacuo to afford 611 mg of (+)-*N*-benzylindan-1-amine (95% yield, 92% *ee*). In the case of more reactive substrates or with use of a higher catalyst loading it proved feasible to add the amine promoter portionwise by syringe. For reactions with 1 mol % or more of catalyst, amine addition was conducted in a hood under argon in a septum-capped Schlenk flask.

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Facile *meso* Functionalization of Porphyrins by Nucleophilic Substitution with Organolithium Reagents**

Werner W. Kalisch and Mathias O. Senge*

*Dedicated to Professor Emanuel Vogel
on the occasion of his 70th birthday*

It is generally accepted that the *meso* positions of porphyrins are the most reactive both for electrophilic and nucleophilic substitutions.^[1] While several examples have been described for S_E reactions on porphyrins^[1, 2] only scattered attempts have been made to use S_N reactions for the modification of porphyrins. Published examples of the latter all utilized some form of activated porphyrin, for example π -radical cations or dications,^[3] high-valent metal derivatives,^[4] or activated porphyrins with electron-withdrawing substituents.^[5] Some of these reactions are suitable only for the preparation of 5,5'-disubstituted dihydroporphyrins (phlorins).^[4b, 6] At best two substituents could be introduced with electrophilic or nucleophilic reagents, and the methods were limited with regard to the starting porphyrin or the introduction of different substituents.^[7] To date, no general method exists for the direct *meso* substitution of unactivated porphyrins with alkyl or aryl residues or for the introduction of more than two substituents.

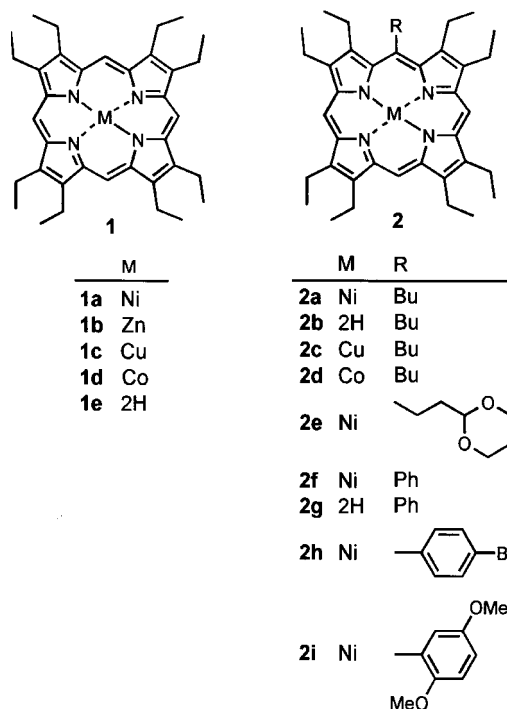
During a systematic study on the use of organometallic reagents for C–C coupling reactions, we found that octaethylporphyrin (H₂(oep); oep = dianion of octaethylporphyrin) undergoes facile substitution reactions with organolithium reagents; this allows the synthesis of a variety of porphyrins with alkyl or aryl substituents at the *meso* positions. Treatment of [Ni(oep)] (**1a**) with butyllithium (3–4 equiv) between –80 and –100 °C in THF followed by hydrolysis of the intermediate (a Meisenheimer-type complex) provided the corresponding 5-butyl-15-hydroporphodimethene. Subse-

quent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the *meso*-butylporphyrin **2a** in quantitative yield. The reaction sequence formally proceeds as shown in Equation (a).



The reaction is easily extended to a variety of different alkyl and aryl reagents, including those that allow further chemical modifications and coupling reactions. For example, reaction of **1a** with 2-(1,3-dioxane-2-yl)ethylolithium gave **2e** in 70 % yield. The reaction is not limited to alkylolithium reagents, but can also be used for the convenient introduction of aryl groups. Reaction of phenyllithium with **1a** gave **2f** in 65 % yield. Again, aryl substituents could be introduced which will allow further chemical transformations. Compound **2h**, whose 4-bromophenyl group is useful for other organometallic coupling reactions, could be prepared from **1a** with *p*-bromophenyllithium in 40 % yield. Introduction of the 2,5-dimethoxyphenyl group in **2i**, which proceeded in 65 % yield, is an example of the synthesis of donor–acceptor systems (by formation of the benzoquinone). The free base porphyrins substituted in the 5-position are available by demetalation of the nickel(II) complexes. For example, treatment of **2a** with concentrated sulfuric acid gave **2b** in 75 % yield.

Next, we turned our attention to the reactivity of different metals in the same porphyrin. Treatment of **1b** with butyllithium under standard conditions gave the respective free base **2b** in 40 % yield, while **1c** and **1d** could be converted into the monobutylmetalloporphyrins **2c** and **2d** in 75 and 40 % yield, respectively. Even more surprising was the result that free base porphyrins such as **1e** could be treated directly with butyllithium to give **2b** in 50 % yield or with phenyllithium to give **2g** in 90 % yield. Presumably, this reaction proceeds by initial formation of a dilithioporphyrin [Li₂(oep)] of the type

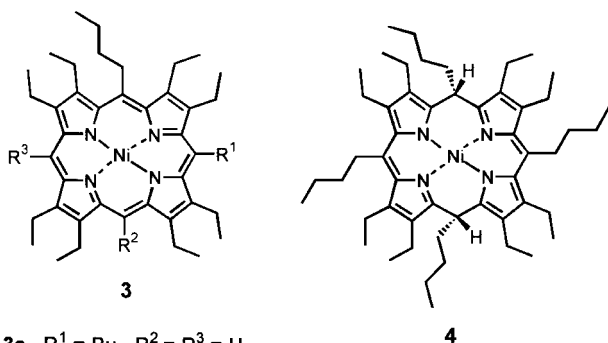


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described by Arnold.^[8] With the exception of the reaction of free base porphyrins with phenyllithium, nickel complexes gave higher yields and were used for most reactions.

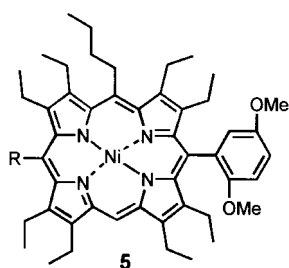
The reaction is not limited to the introduction of one *meso* substituent. With butyllithium as reagent, **2a** (λ_{max} (CH₂Cl₂) = 410, 572 nm) could be converted into a dialkylated product, which was present as a regioisomeric mixture (**3a**, 70 %, λ_{max} = 427, 595 nm; **3b**, 15 %, λ_{max} = 423, 595 nm). The regioisomers could be separated by chromatography and again be used for another substitution/oxidation cycle with butyllithium to yield 5,10,15-tributylporphyrin (**3c**) quantitatively



- 3a**, R¹ = Bu, R² = R³ = H
3b, R¹ = R³ = H, R² = Bu
3c, R¹ = R² = Bu, R³ = H
3d, R¹ = R² = R³ = Bu

(λ_{max} = 441, 613 nm). A further reaction sequence starting with butyllithium resulted in the conversion of **3c** into **3d** (50 %, λ_{max} = 459, 634 nm); porphyrin **4** was formed as a side product (40 %, λ_{max} = 451, 551 nm).

Highly substituted porphyrins such as **3a–d** are of principal interest with regard to studies on the conformational flexibility of porphyrins.^[9] Sterically encumbered dodecaalkylporphyrins such as **3d** cannot be obtained by conventional porphyrin syntheses (acid-catalyzed condensation of pyrroles and aldehydes followed by oxidation); instead, an unoxidizable porphodimethene of unknown configuration is formed.^[9a] The structure of **3c**, one of the highly substituted alkylporphyrins we prepared, is shown in Figure 1.^[10] The macrocycle adopts a ruffled conformation, and the *meso* positions are significantly displaced out of the plane (average displacement of the *meso*-carbon atoms 0.93 Å). Despite the presence of only three *meso*-butyl groups in **3c** the conformation is already more nonplanar than that in (pyridine)[5,10,15,20-tetra(*tert*-butyl)porphyrinato]zinc(II) (average displacement of the *meso*-carbon atoms 0.9 Å), the most nonplanar porphyrin with a ruffled conformation described so far.^[9b] Therefore, **3d** will be even more nonplanar. The synthetic methodology presented here should allow the facile preparation of a wide



- 5a**, R = H
5b, R = Bu

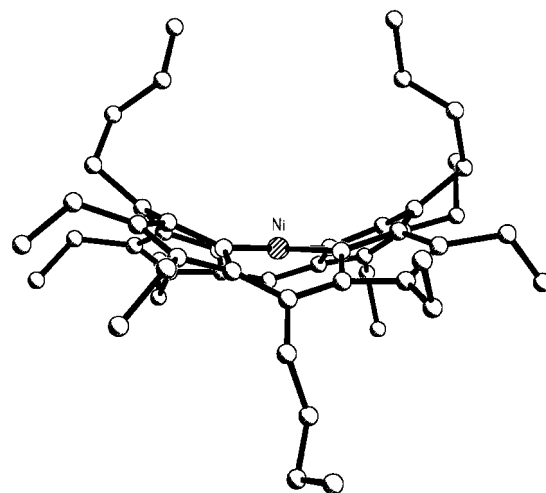


Figure 1. Side view of the molecular structure of **3c** in the crystal. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å]: Ni–N21 1.882(3), Ni–N22 1.873(3), Ni–N23 1.883(3), Ni–N24 1.880(3); the average deviation of the 24 macrocycle atoms from their least-squares plane is 0.45 Å; the average deviation of the *meso*-carbon atoms from the N–N–N–N plane is 0.93 Å; individual displacements of *meso*-carbon atoms [Å]: C5 0.94, C10 1.04, C15 0.94, C20 0.80.

variety of novel nonplanar porphyrins with tailor-made distortion modes. As examples of porphyrins with mixed substitution patterns, **5a** was prepared from **2a** in 50 % yield and **5b** from **3a** in 50 % yield with use of 2,5-dimethoxyphenyllithium.

While working with the more sterically encumbered porphyrins **3a–d**, we obtained brown side products in high yield when the reaction temperature was allowed to rise above –80 °C. These products were identified as 5,15-dialkylporphodimethenes with *syn*-axial orientation of the *meso*-alkyl substituents. The molecular structure of the side product **4** formed during the synthesis of **3d** is shown in Figure 2.^[10, 11] These porphodimethenes could not be oxidized to porphyrins with either DDQ or Br₂. The exact structure of the porphodimethene intermediates in our porphyrin synthesis is still unknown. We assume that it might be different

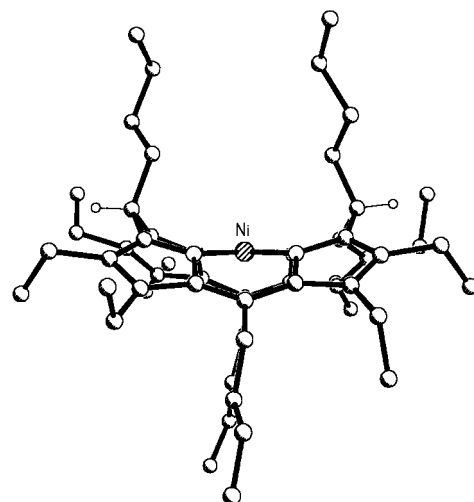
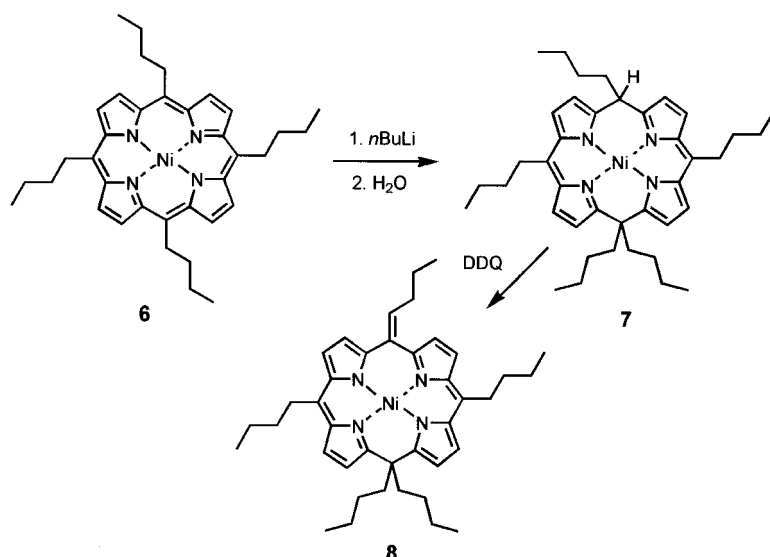


Figure 2. Side view of the molecular structure of **4** in the crystal. Only the *meso*-hydrogen atoms are shown for clarity.



Scheme 1. Synthesis of **8**.

from the *syn*-axial structure of **4** and that the configuration of the porphodimethene intermediates formed during the synthesis of sterically encumbered porphyrins is of crucial importance for the potential oxidation to the desired porphyrin.

To study the reaction in more detail we utilized tetra-*meso*-alkylporphyrins such as **6** as starting materials (Scheme 1). Krattinger and Callot^[6] showed that tetraphenylporphyrin reacts with butyllithium under formation of a phlorin and chlorin. Treatment of **6** with butyllithium at -100°C followed by addition of water gave **7** in 90 % yield ($\lambda_{\text{max}} = 432, 525 \text{ nm}$). Owing to the dialkylated *meso* position the porphodimethene **7** cannot be converted into a porphyrin. Nevertheless, treatment of **7** with DDQ gave **8** in 80 % yield ($\lambda_{\text{max}} = 434, 541 \text{ nm}$); here a *meso*- and an *ipso*-carbon atom were oxidized, leading to a novel porphodimethene with an exocyclic double bond. We are currently expanding the scope of this reaction towards the synthesis of asymmetric porphyrins with mixed substituent types and towards biomimetic systems, and are studying the reaction mechanism in more detail.

Experimental Section

[Ni(oep)] (**1a**) (100 mg, 0.17 mmol) was dissolved in dried THF (60 mL) and cooled to -70°C . Within 10 min butyllithium (0.6 mmol, 0.3 mL of a 2 M solution in cyclohexane) was added dropwise. The cold bath was removed, and water (1 mL) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 10 min, DDQ (10 mL of a 0.06 M solution in dichloromethane) added, and the mixture stirred for another 20 min. Finally, the reaction mixture was filtered through neutral alumina (Brockmann grade I) and subjected to column chromatography on neutral alumina (grade III) with hexane/ CH_2Cl_2 (4/1) as eluant. Preparation of higher alkylated porphyrins **3a–d** required lower temperatures (-80 to -100°C) and less solvent.

UV/Vis and ^1H NMR data for **2a** and **3a–d**: UV/Vis (CH_2Cl_2): λ_{max} (**2a**) ($\lg \epsilon$) = 410 nm (5.23), 535 (4.02), 572 (4.10); λ_{max} (**3a**) ($\lg \epsilon$) = 427 nm (5.19), 555 (4.09), 595 (3.99); λ_{max} (**3b**) ($\lg \epsilon$) = 423 nm (5.20), 552 (4.00), 595 (3.82); λ_{max} (**3c**) ($\lg \epsilon$) = 441 nm (5.08), 570 (3.91), 613 sh (3.20); λ_{max} (**3d**) ($\lg \epsilon$) = 459 nm (4.93), 5.91 (3.92), 634 (3.56). ^1H NMR (500 MHz, CDCl_3): δ (**2a**) = 0.51 (t, $J = 7.5 \text{ Hz}$, 3H, butyl- CH_3), 0.85 (m, 4H, butyl- CH_2), 1.68, 1.74, 1.75, 1.85 (each t, $J = 7.5 \text{ Hz}$, 24H, ethyl- CH_3), 3.79 (brs, 16H, ethyl- CH_2), 4.42 (t, $J = 7.5 \text{ Hz}$, 2H, 5- $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 9.32 (s, 1H, 15- H), 9.33 (s, 2H,

10,20- H); δ (**3a**) = 0.60 (t, $J = 7.5 \text{ Hz}$, 6H, butyl- CH_3), 0.77 (br s, 4H, butyl- CH_2), 1.05 (m, 4H, butyl- CH_2), 1.69, 1.75, 1.85 (each t, $J = 7.5 \text{ Hz}$, 24H, ethyl- CH_3), 3.73 (br s, 16H, ethyl- CH_2), 4.27 (t, $J = 7.5 \text{ Hz}$, 4H, 5,10- $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 9.05 (s, 2H, 15,20- H); δ (**3b**) = 0.53 (t, $J = 7.5 \text{ Hz}$, 6H, butyl- CH_3), 0.85 (m, 6H, butyl- CH_2), 0.93 (m, 4H, butyl- CH_2), 1.65, 1.79 (each t, $J = 7.5 \text{ Hz}$, 24H, ethyl- CH_3), 3.69 (br s, 16H, ethyl- CH_2), 4.29 (t, $J = 7.5 \text{ Hz}$, 4H, 10,20- $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 9.05 (s, 2H, 10,20- H); δ (**3c**) = 0.58 (t, $J = 7.5 \text{ Hz}$, 6H, butyl- CH_3), 0.65 (br s, 2H, butyl- CH_2), 0.97 (br s, 4H, butyl- CH_2), 1.04 (br s, 6H, butyl- CH_2), 1.65, 1.75, 1.78, 1.79 (each t, $J = 7.5 \text{ Hz}$, 24H, ethyl- CH_3), 3.44–3.52 (m, 16H, ethyl- CH_2), 4.03–4.18 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 8.77 (s, 1H, 20- H); δ (**3d**) = 0.59 (t, $J = 7.5 \text{ Hz}$, 12H, butyl- CH_3), 0.73, 1.06 (each m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.74 (t, $J = 7.5 \text{ Hz}$, 24H, ethyl- CH_3), 3.48, 3.58 (each br s, 16H, ethyl- CH_2), 4.03 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

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- [11] The formation of different configuration isomers for 5,5',15,15'-substituted decaalkylporphyrins has been described by Buchler in his elegant studies on the reductive alkylation of [Zn(oep)].^[7] Crystal structures of his stable porphodimethenes showed the same *syn*-axial orientation of the *meso*-alkyl groups as described here for **4**. See ref. [7b–d] and references therein.

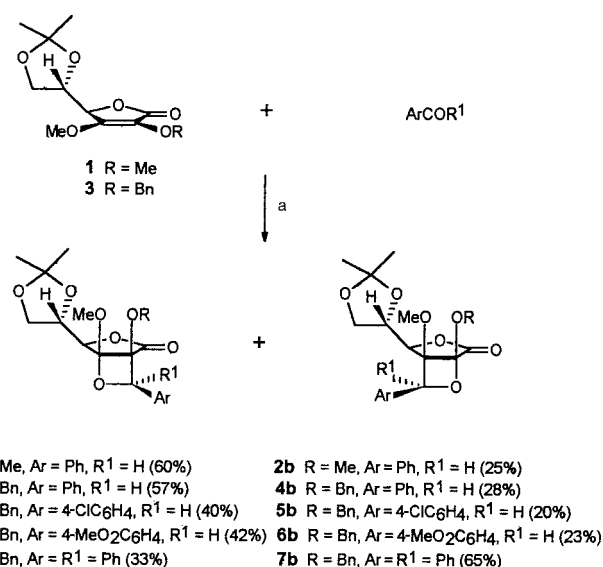
The Paternò–Büchi Reaction of L-Ascorbic Acid**

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The biological and pharmacological activity as well as the therapeutic potential of L-ascorbic acid and its derivatives have been studied extensively.^[1] However, despite the fact that L-ascorbic acid possesses several interesting functionalities, the organic chemistry and synthetic potential of this molecule and its derivatives have never been explored to any significant extent. The complex chemical properties^[1] of L-ascorbic acid may have hindered developments in this regard. Alkylation of L-ascorbic acid has been extensively studied, and conditions for both O- and C-alkylations have been worked out.^[2] With these alkylation reactions, natural products such as as delesserine, dilaspirolactone aglycon, leucodrin, leudrin, methyl rhodomelol, reflexin, and rhodomelol have been synthesized.^[3] Apart from alkylation, however, virtually no other reactions of L-ascorbic acid have been documented, except for reports on the Claisen rearrangement of its O-allyl derivatives.^[1]

The conjugated electron-rich enediol unit in L-ascorbic acid is a rather unique and interesting functionality. Such an olefin should be amenable to various noteworthy transformations and might display intriguing reactivity. Enediol or 2-amino-enol moieties in the form of 1,3-dioxol-2-one,^[4] 2,3-dihydrooxazol-2-one,^[5] and 1,3-dioxole^[6] have already yielded corresponding oxetanes through Paternò–Büchi reactions. Enantiomerically pure oxetanes have been synthesized from chiral substrates^[7] and with the aid of chiral auxiliaries.^[8] Bach and co-workers investigated the stereochemical aspects of oxetane formation, including facial diastereoselection.^[9] L-Ascorbic acid constitutes a convenient reactive chiral olefin that should also furnish chiral oxetanes through Paternò–Büchi reactions. Further transformations of the resulting oxetanes by way of ring-opening reactions would afford novel C-2-branched 3-ketosugars and C-3-branched 2-ketosugars. We describe here the preliminary results of our investigations in this area.

Irradiation of a solution of **1** and benzaldehyde in benzene with UV light through a pyrex filter produced compounds **2a** and **2b** in 60 and 25% yield, respectively (Scheme 1). Spectroscopic data and elemental analyses indicate that these



Scheme 1. Paternò–Büchi reactions of **1** and **3**. a) *hν*, C₆H₆, N₂, 30–60 h. Bn = benzyl.

compounds are oxetanes.^[10] As compared to **1**, ¹H NMR signals for protons in the methoxy groups at C-2 and C-3 in **2a** and **2b** were shifted to the upfield region. These shifts^[11] are characteristic, but proved inadequate to permit regio- and stereochemical assignments for these particular oxetanes. However, the observed pattern of chemical shifts might be useful for structural assignments in other oxetanes derived from L-ascorbic acid. Photochemical cycloaddition of benzaldehyde to L-ascorbic acid derivative **3** afforded oxetanes **4a** and **4b** in 57 and 28% yield, respectively (Scheme 1).

The preferred mode of attack for the photoexcited carbonyl group of benzaldehyde on enediols **1** and **3** would presumably be from the less hindered α face, with the aldehyde proton oriented in *endo* fashion. Therefore, one would expect a *cis* orientation of the phenyl residue and alkoxy groups on the oxetane ring for products **2a**, **2b**, **4a**, and **4b**; this orientation was verified unambiguously by X-ray crystallographic analysis of **2a**^[12] (Figure 1). This structure determination also made

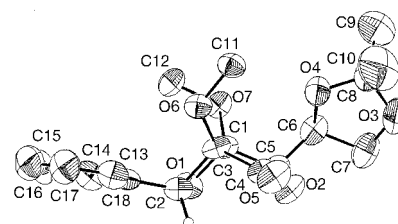


Figure 1. An ORTEP representation of **2a** with the crystallographic numbering of the atoms (thermal ellipsoids are drawn at the 50% probability level).

clear that the major regioisomers formed in the reaction of **1** and **3** with benzaldehyde are **2a** and **4a**, respectively. To investigate the regiochemistry further, substituted benzaldehydes were allowed to react with **3** (Scheme 1). In the case of 4-chlorobenzaldehyde, oxetanes **5a** and **5b** were obtained in 40 and 20% yield, respectively. Similarly, reaction of methyl

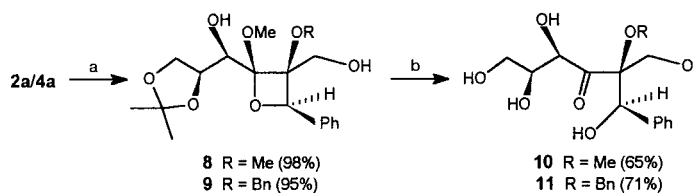
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4-formylbenzoate with **3** led to oxetanes **6a** (42%) and **6b** (23%). The regiochemical preferences observed in these reactions are similar to those in the reaction of **3** with benzaldehyde. Photochemical cycloaddition of **3** to benzophenone furnished the two regioisomeric oxetanes **7a** and **7b** in 33 and 65% yield, respectively (Scheme 1). The observed difference in regiochemical preferences in the reactions of **3** with benzaldehydes versus benzophenone indicates that two different mechanisms may be operative. The measured oxidation potential of **3** and the reduction potentials of the benzaldehydes used suggest a photoinduced electron transfer mechanism^[13] for reaction of **3** with the benzaldehydes, while reaction with benzophenone most probably occurs by a 1,4-diradical pathway.^[14] These mechanisms would indeed account for the regiochemistry observed in the reactions of **1** and **3** with benzaldehydes and benzophenone, but further investigations in this context will be necessary.

The resulting oxetanes are in themselves interesting compounds, and they are also useful synthetic intermediates. Oxetanes are known to yield ring-opened products under various reaction conditions.^[15] Analogous transformations of the oxetanes described above could lead to a variety of optically pure materials. Thus, treatment of oxetanes **2a** and **4a** with lithium aluminum hydride gave compounds **8** and **9** in 98 and 95% yield, respectively (Scheme 2). Spectroscopic



Scheme 2. Ring-opening reactions of oxetanes **2a** and **4a**. a) Lithium aluminum hydride, THF, 0°C, 1 h; b) H₂SO₄ (10%), THF, 20°C, 2–6 h. Bn = benzyl.

data for **8** and **9** showed that the lactone group had been reduced. Under aqueous, acidic conditions, oxetanes **8** and **9** were opened to 2-hydroxymethyl-3-ketohexose derivatives **10** (65%) and **11** (71%, Scheme 2). However, attempted selective removal of the benzyl group in oxetane **4a** under hydrogenolytic conditions (H₂, Pd/C, room temperature, atmospheric pressure) did not succeed, and starting material was recovered quantitatively from the reaction mixture.

The results presented here demonstrate that 2-hydroxymethyl-1-phenyl-3-ketohexose derivatives are readily accessible through the Paternò–Büchi adducts derived from L-ascorbic acid. Similarly, a 2-ketohexose derivative might possibly be obtained from **4b**. Further investigations are in progress into the chemistry of the oxetanes and the mechanisms by which they are formed.

Experimental Section

A mixture of **1** or **3** (10 mmol) and freshly distilled benzaldehyde (12 mmol) in dry benzene (125 mL) was purged with dry nitrogen for 5 min. The solution was then irradiated for 30–60 h with UV light (125 W, medium-pressure mercury lamp) in an immersion-well photoreactor at ambient temperature under nitrogen. After completion of the reaction, the

solution was washed with aqueous NaHCO₃ (10%), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate).

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- [10] All new compounds gave satisfactory spectroscopic data and elemental analyses.
- [11] In the case of **2a** and **4a** the resonances for the 2-alkoxy and 3-methoxy protons were shifted to higher field by 0.50 to 0.37 ppm relative to those of **1** and **3**. With oxetanes **2b** and **4b** the upfield shift was 1.15 to 1.32 ppm for the 3-methoxy protons and 0.05 to 0.182 ppm for the 2-alkoxy protons.
- [12] X-ray structure analysis of (1*S*,4*R*,4'*S*,5*R*,7*R*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,5-dimethoxy-7-phenyl-3,6-dioxabicyclo[3.2.0]heptan-2-one (**2a**): C₁₈H₂₂O₇, *M_r* = 350.36, crystal dimensions 0.13 × 0.3 × 0.6 mm, PC-controlled Enraf–Nonius CAD4 diffractometer, MoK_α radiation (λ = 0.7093 Å), ω/2θ scan mode, scan speed 1° min⁻¹, *a* = 6.581(2), *b* = 26.171(8), *c* = 10.269(2) Å, *V* = 1768.6(8) Å³, ρ_{calcd} = 1.316 g cm⁻³, μ_{MoK_α} = 0.101 mm⁻¹, *Z* = 4, orthorhombic, space group *P*2₁2₁2₁ (no. 19); of 2931 measured reflections (*h* = 0 to 7, *k* = 0 to 29, *l* = 0 to 11), 2621 were unique and 1974 observed [*F* ≥ 2σ(*F*)]; 226 refined parameters, *R* = 0.0618, *WR* = 0.171, refinement on *F*². The structure was solved by direct methods and refined with SHELXL-93. Hydrogen atoms were fixed geometrically on the basis of difference Fourier maps and held fixed during refinement. 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-100425.” 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).
- [13] Photoinduced electron transfer is a well-known phenomenon that has been extensively studied^[16] and reviewed.^[17] It has been demonstrated that the probability of photoinduced electron transfer is a function of the reduction potential of the acceptor and the oxidation potential of the donor through the Rehm–Weller equation.^[18] The measured reduction potential of L-ascorbic acid derivatives **1** and **3** was found to be 0.15 V. Cyclic voltammograms of these compounds revealed only the reduction peak, but such data are still applicable for calculation of Δ*G* values^[19a] according to Arnold and Humphreys.^[19b] The measured reduction potentials of the aldehydes studied were: benzaldehyde 1.93 V (reported^[20] 1.93 V), 4-chlorobenzaldehyde 1.41 V (reported^[21] 1.26 V), methyl 4-formylbenzoate 1.23 V. Based on the Rehm–Weller equation, photoinduced electron transfer for L-ascorbic acid derivatives **1** and **3** and the above benzaldehydes has a sufficiently negative

- ΔG value (ca. $-25 \text{ kcal mol}^{-1}$ to ca. $-35 \text{ kcal mol}^{-1}$), so a photo-induced electron-transfer mechanism is apparently favored for these photochemical cycloaddition reactions.
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A Porphyrin as a Binucleating Ligand: Preparation and Crystal Structure of a Porphyrin Complex Containing a Coordinated B_2O_2 Ring

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The enormously wide utility of the porphyrin ligand in coordination chemistry derives in part from the fact that there is a distance of 2 Å from the center of the square-planar N_4 coordination site to one nitrogen atom; a broad range of elements in various oxidation states can be accommodated. Even larger elements can be coordinated as out-of-plane complexes, and to some extent smaller elements can be

accommodated by ruffling of the ligand and compression of the porphyrin core. We recently demonstrated that boron can form a porphyrin complex^[1] which contains two boron atoms as an F-B-O-B-F moiety threaded through the cavity in the porphyrin, such that each boron atom is coordinated to two different porphyrin nitrogen donor atoms. One boron atom lies approximately in the plane of the ligand, while the other is displaced significantly out of this plane (overall C_s symmetry). This compound, $[\text{B}_2\text{OF}_2(\text{ttp})]$ (**1**, ttp = dianion of 5,10,15,20-tetra-*p*-tolylporphyrin), was prepared by the reaction of $\text{BF}_3 \cdot \text{OEt}_2$ with the free base porphyrin $\text{H}_2(\text{ttp})$ in the presence of a trace of water. The structure of **1** was confirmed by an X-ray crystal structure determination of $[\text{B}_2\text{OF}_2(\text{TpClpp})]$ (**2**, TpClpp = dianion of 5,10,15,20-tetra-*p*-chlorophenylporphyrin).^[1]

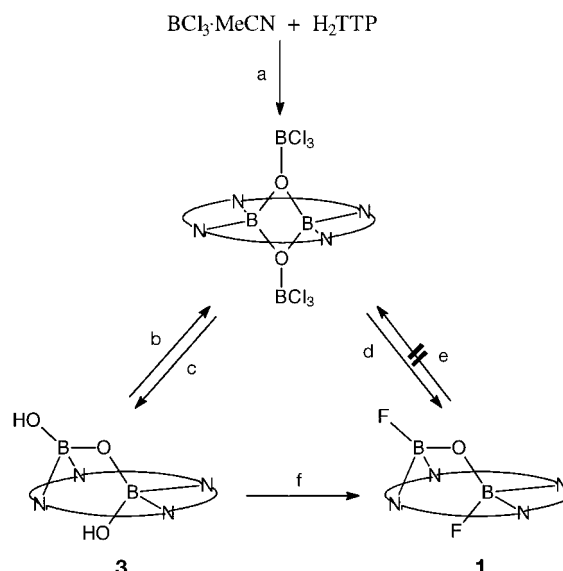
The corresponding reaction of $\text{BCl}_3 \cdot \text{MeCN}$ with $\text{H}_2(\text{ttp})$ in chlorobenzene containing a trace of water^[2] is more complex than that of $\text{BF}_3 \cdot \text{OEt}_2$. Initially a blue-green precipitate forms which is highly reactive and releases the bound boron atoms to provide the free base porphyrin if dissolved in a neutral or acidic solvent. When the precipitate is dissolved in dichloromethane and subjected to chromatography on basic alumina, $[\text{B}_2\text{O}(\text{OH})_2(\text{ttp})]$ (**3**) is formed. This compound is analogous to the fluoroboron complex $[\text{B}_2\text{OF}_2(\text{ttp})]$ but contains hydroxo groups in place of the fluorine substituents.^[1]

The blue-green precipitate formed in the reaction of $\text{BCl}_3 \cdot \text{MeCN}$ with $\text{H}_2(\text{ttp})$ persists in solution for a few minutes, which is long enough to obtain its ^1H NMR spectrum in CDCl_3 . The spectrum shows the compound to have higher symmetry than $[\text{B}_2\text{OX}_2(\text{ttp})]$ ($\text{X} = \text{F}, \text{OH}$), and the tolyl methyl groups appear as two singlets in a 1:1 ratio. By careful control of the reaction conditions and use of $\text{H}_2(\text{TpClpp})$ as the porphyrin and benzene as the solvent, it proved possible to isolate crystals of the blue-green compound following recrystallization from CHCl_3 saturated with $\text{BCl}_3 \cdot \text{MeCN}$. X-ray crystallography revealed a second structural type for a boron porphyrin and a new coordination mode for the porphyrin ligand.^[3]

The compound $[\text{B}_2\text{O}_2(\text{BCl}_3)_2(\text{TpClpp})]$ (**4**) contains a four-membered B_2O_2 ring coordinated in the cavity of the porphyrin; the plane of the B_2O_2 ring is perpendicular to the ligand plane (Figure 1). Two porphyrin nitrogen atoms coordinate to each boron atom, and the two boron atoms are essentially coplanar with the porphyrin. Each bridging oxygen atom is coordinated to a BCl_3 molecule. The crystals contain two independent half-molecules that are related through a center of symmetry. Each B_2O_2 ring has two unique B–O distances which are almost the same (av 1.49(2) Å), and the $\text{B1} \cdots \text{B1}'$ distance across the ring is close to 2.1 Å. The $\text{B2} \cdots \text{O1}$ distances involving the coordinated BCl_3 molecules average 1.49(2) Å.

To accommodate two boron atoms in the same plane as the porphyrin, the macrocycle has undergone an elongation along one axis to result in a rectangular rather than a square core. The $\text{N1} \cdots \text{N2}$ distance parallel to the $\text{B} \cdots \text{B}$ axis averages 3.63 Å, over 1.1 Å longer than the $\text{N1} \cdots \text{N2}'$ distance within the N–B–N chelate rings (2.49 Å). This elongation is reflected in the bond angles at C4, C5, and C6, which have opened

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Topochemical Conversion of a Hydrogen-Bonded Three-Dimensional Network into a Covalently Bonded Framework**

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The design and construction of supramolecular, three-dimensional networks has been an area of increasing interest over recent years with respect to engineering crystal packing at will.^[1] Strategies for crystal engineering include the use of

various intermolecular forces, from weak van der Waals forces, hydrogen and covalent bonding,^[2,3] to ionic interactions.^[4] Most of the reported three-dimensional architectures are formed as a result of self-assembly from solution.^[5] An exciting, yet little explored area of supramolecular chemistry, is the reversible interconversion between monomers and oligomers initiated by the input of external information (e.g. protons, electrons, photons). Such materials may have functional use due to their switching ability and the possibility to sequester and release guest molecules. Recently a proton-dependent monomer–oligomer interconversion in solution was reported.^[6] Here we report the topochemical thermal conversion of a novel, three-dimensional network held together by strong hydrogen bonding into a covalent, supramolecular framework by dehydration of coordinated water. This unexpected transformation of hydrogen-bonded to covalent network appears to be assisted by strong $\text{NH} \cdots \text{O}$ hydrogen bonds and irreversible.

$[\{\text{Zn}(\text{sala})(\text{H}_2\text{O})_2\}_2] \cdot 2\text{H}_2\text{O}$ (**1**) was prepared by the reaction of $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ with $\text{Li}_2(\text{sala})$ in aqueous solution and characterized by single-crystal X-ray diffraction techniques^[7] ($\text{H}_2(\text{sala}) = N$ -(2-hydroxybenzyl)-L-alanine). Figure 1 shows the structure of the basic dimeric building block,

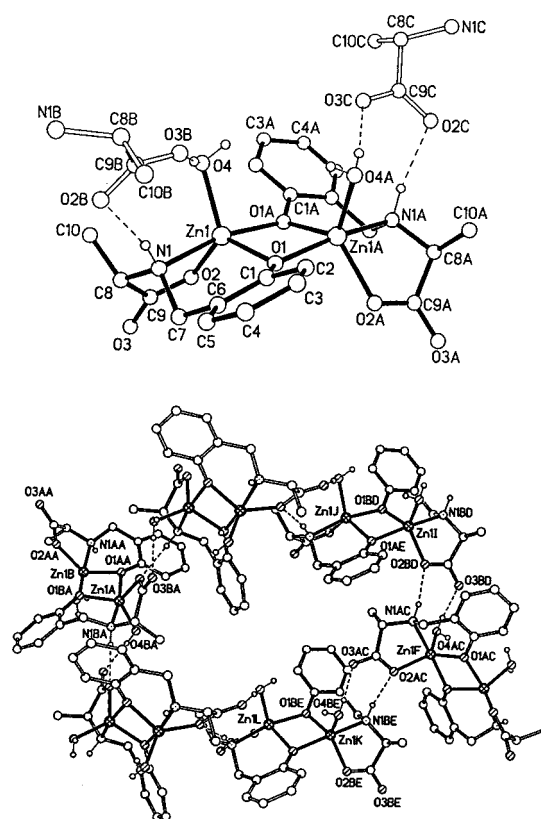


Figure 1. Top: Structure of the binuclear complex **1**. Hydrogen bonds are drawn with dotted lines. The hydrogen atoms attached to carbon atoms are omitted for clarity. Selected fragments of neighboring molecules involved in hydrogen bonding are shown with open bonds. Selected bond distances [Å] and angles [°]: $\text{Zn1} \cdots \text{Zn1A}$ 3.092(1), $\text{Zn1}-\text{O1}$ 2.009(2), $\text{Zn1}-\text{O1A}$ 2.040(2), $\text{Zn1}-\text{O2}$ 2.027(2), $\text{Zn1}-\text{O4}$ 2.030(2), $\text{Zn1}-\text{N1}$ 2.140(2), $\text{C9}-\text{O2}$ 1.270(4), $\text{C9}-\text{O3}$ 1.246(4); $\text{Zn1}-\text{O1}-\text{Zn1A}$ 99.58(7), $\text{O1}-\text{Zn1}-\text{N1}$ 93.00(8), $\text{O1}-\text{Zn1}-\text{O1A}$ 79.56(8), $\text{O2}-\text{C9}-\text{O3}$ 124.1(3). Bottom: The hydrogen bonds link the dimers together to form hexagonal rings.

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$[\{\text{Zn}(\text{sala})(\text{H}_2\text{O})_2\}_2]$, along with the coordination around the Zn^{II} centers and the hydrogen-bonding network. The zinc center has distorted square pyramidal geometry with the base comprised of the tridentate, dianionic sala ligand and the bridging phenolate moiety. Water completes the coordination sphere in the apical site. The crystallographically imposed twofold symmetry results in the two water molecules being on the same side of the dimeric unit. The dimer has two sets of NH and OH_2 hydrogen donors and two carboxylate anions as acceptors. The presence of complementary molecular functionalities leads to efficient hydrogen bonding^[8] between the neutral dimeric complexes (Figure 1, bottom). Six dimers link to give a hexagonal ring containing ten zinc centers. The carboxylate oxygen atoms (O3) that are not involved in bonding in the ring act as acceptors for hydrogen bonds to bound water molecules in other rings, thus linking together the ten-membered hexagonal rings. The result is a honey-combed, open-framework coordination polymer (Figure 2).

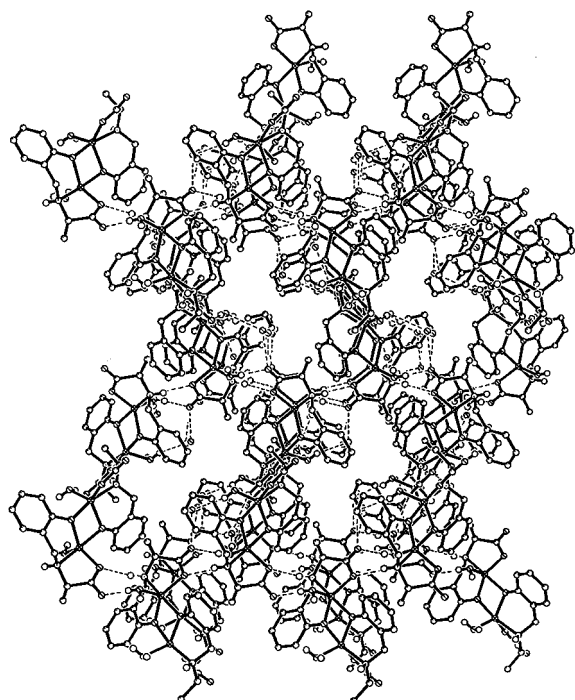


Figure 2. View of **1** along the crystallographic axis *b* illustrating the channels of the open-framework coordination polymer.

The hydrogen-bonded network in **1** provides favorable conditions for the topochemical reaction to take place. The geometric proximity between the Zn centers and the carboxylate oxygen atoms from adjacent molecules in **1** (e.g. $\text{Zn1} \cdots \text{O3C}$ 3.736(2) Å) is maintained by $\text{OH} \cdots \text{O}$ hydrogen bonding. Thermal dehydration can remove ligated and non-bonded water, which can then escape through the channels without disrupting the solid-state structure.^[9] Minimal atom movements and conformational changes are anticipated during dehydration.

On heating, all water molecules are lost from **1**.^[10, 11] The X-ray structure determination^[12] of the anhydrous compound, $[\{\text{Zn}(\text{sala})\}_n]$ (**2**), reveals a number of unique features

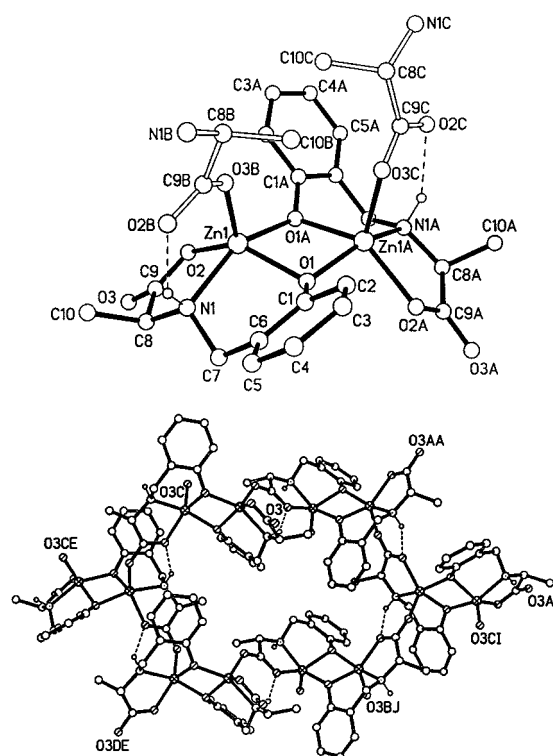
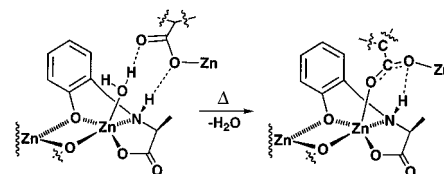


Figure 3. Top: Structure of the dimeric unit of **2**. Hydrogen bonds are drawn with dotted lines. Selected bond distances [Å] and angles [°]: $\text{Zn1} \cdots \text{Zn1A}$ 3.152(1), $\text{Zn1}-\text{O1}$ 2.072(1), $\text{Zn1}-\text{O1A}$ 1.999(1), $\text{Zn1}-\text{O2}$ 2.073(1), $\text{Zn1}-\text{O3A}$ 2.017(1), $\text{Zn1}-\text{N1}$ 2.108(1), $\text{C9}-\text{O2}$ 1.258(2), $\text{C9}-\text{O3}$ 1.260(2); $\text{Zn1}-\text{O1}-\text{Zn1A}$ 101.48(4), $\text{O1}-\text{Zn1}-\text{N1}$ 90.39(4), $\text{O1}-\text{Zn1}-\text{O1A}$ 77.19(4), $\text{O2}-\text{C9}-\text{O3}$ 125.1(1). Bottom: A segment of the three-dimensional network of **2**. The close resemblance to **1** which results from the topochemical dehydration and formation of the covalent $\text{Zn1}-\text{O2}$ bond can be seen.

(Figure 3). The structure of this solid-state dehydration product^[13] **2** bears a close relationship to that of the reactant **1**; they have the same crystal and point-group symmetry. Owing to the chiral ligand, the space group is also chiral. In **1** and **2** the channels are helical in nature and therefore orient in the same direction. The intermolecular interactions stabilizing the structure have changed from hydrogen bonding only in **1** to both covalent and hydrogen bonding in **2**, as shown in Figure 3 and Scheme 1. It is interesting to note that the $\text{NH} \cdots \text{O}$ hydrogen bonding^[14] is preserved in **2**. From the proximity of the atoms Zn1 and O3 in **1** and the presence of $\text{NH} \cdots \text{O}$ hydrogen bonding in both **1** and **2**, it appears that the $\text{Zn}-\text{O}(\text{carboxylate})$ bond formation is aided by the presence of both hydrogen-donor N–H groups and hydrogen acceptors in the binuclear complex. This appears to be the first example of topochemical conversion of a hydrogen-bonded into a



Scheme 1. Coordination environments and hydrogen bonding in the hydrated **1** and dehydrated **2**, illustrating the transformation from hydrogen bonding to covalent bonding.

covalent-bonded supramolecular network. Attempts to rehydrate **2** to give **1** have been unsuccessful; therefore, dehydration appears to be irreversible.

Experimental Section

The synthesis of $H_2(sala)$ was adapted from reference [15]: Salicylaldehyde (134 mg, 1.10 mmol) in ethanol (10 mL) was added to a solution of L-alanine (89 mg, 1.00 mmol) and KOH (56 mg, 1.00 mmol) in water (10 mL). The yellow solution was stirred for 30 min at room temperature prior to cooling in an ice bath. The pH was adjusted to 6–7 with acetic acid, and then $NaBH_4$ (46 mg, 1.20 mmol) was added. After 15 min the yellow color had discharged and the solution was acidified with acetic acid to pH 5.0 and left for one hour. The product was filtered off, washed with ethanol and diethyl ether, dried in vacuo, and recrystallized from water/ethanol (1/1). Yield: 109 mg (56%), m.p. 241–242 °C, $[\alpha]_D^{20} = -22.2$ ($c = 0.5$ in water).

1: $H_2(sala)$ (195 mg, 1.00 mmol) was added to a solution containing LiOH (48 mg, 2.00 mmol) and $CH_3CO_2Na \cdot 3H_2O$ (136 mg, 1.00 mmol) in water (20 mL). A solution of $Zn(ClO_4)_2 \cdot 6H_2O$ (372 mg, 1.00 mmol) in water (10 mL) was gradually added to the above stirred solution. The mixture was stirred for 30 min, filtered, and kept at room temperature for several days to yield distorted, octahedral-shaped crystals. The crystals were separated by decantation and dried in air. Yield: 191 mg (65%). C, H, N analysis: calcd for $C_{10}H_{13}NO_5Zn$: C 40.7, H 5.1, N 4.7; found: C 40.4, H 5.1, N 4.5; IR (KBr): $\tilde{\nu} = 1588$ (s, $\nu_{as}(CO_2)$), 1413 (s, $\nu_s(CO_2)$), 1282 cm^{-1} (s, $\nu(C-O)_{carb}$).

2: A solution of $H_2(sala)$ (195 mg, 1.00 mmol) and LiOH (24 mg, 1.00 mmol) in water (10 mL) was added to a solution of $Zn(ClO_4)_2 \cdot 6H_2O$ (372 mg, 1.00 mmol) in water (10 mL). The solution was stirred for 30 min and left at room temperature to evaporate. Large, distorted diamond-shaped, colorless crystals were separated by decantation and dried in air. Yield: 176 mg (68%). C, H, N analysis: calcd for $C_{10}H_{11}NO_5Zn$: C 45.6, H 4.4, N 5.3; found: C 45.4, H 4.7, N 5.1; IR (KBr): $\tilde{\nu} = 1598$ (s, $\nu_{as}(CO_2)$), 1404 (s, $\nu_s(CO_2)$), 1284 cm^{-1} (s, $\nu(C-O)_{carb}$).

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and isotropic thermal parameters were refined for the H atoms in the coordinated water molecules, and riding models were used for the rest. In the final least-squares refinement cycles on $|F|^2$, the model converged at $R_1 = 0.0333$, $wR_2 = 0.0609$, and GOF = 1.090 for 2808 reflections with $F_o > 4\sigma(F_o)$ and 182 parameters, and $R_1 = 0.0504$ and $wR_2 = 0.0662$ for all 3385 data. The Flack parameter x was refined to 0.003(15).

- [8] Close intermolecular hydrogen-bonding distances [Å] and angles [°]: O2...H1 2.050, O3...H4B 1.857, O2...N1 2.950, O3...O4 2.645; O2-H1-N1 169.6, O3-H4B-O4 174.0.
- [9] The channels are oval with approximate dimensions 7×10 Å (non-hydrogen contacts). However, the alternating, stacked arrangement means that the effective pore size is bigger than this. The channels are occupied by (disordered) water molecules and held together by hydrogen bonds. Selected hydrogen-bonded distances [Å]: O3...O5 2.771, O3...O5A 2.781, O3...O5B 2.556.
- [10] Thermogravimetric analysis of **1** indicated a weight loss of 11.2% in the temperature range 50–120 °C, corresponding to the loss of two molecules of water (expected weight loss 12.2%) and the formation of the anhydrous compound **2**. The X-ray powder pattern of this anhydrous material was the same as that of **2**. Both **1** and **2** show the same decomposition pattern, which starts at about 340 °C.
- [11] The structures of the bulk materials for **1** and **2** were confirmed by matching their X-ray powder patterns with those generated from the corresponding single crystals. Compound **2** was also prepared independently. The crystal structure was carried out on the single crystal grown from aqueous solution.
- [12] Crystal structure determination of **2**:^[16] Tetragonal, space group $P4_32_12$, $a = 8.997(1)$, $c = 24.571(4)$ Å, $V = 1988.8(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.727$ g cm⁻³. All H atoms were located successfully and refined with riding models. In the final least-squares refinement cycles on $|F|^2$, the model converged at $R_1 = 0.0152$, $wR_2 = 0.0422$, and GOF = 1.031 for 2525 reflections with $F_o > 4\sigma(F_o)$ and 138 parameters, and $R_1 = 0.0158$ and $wR_2 = 0.0425$ for all 2571 data. The Flack parameter x was refined to $-0.004(8)$.
- [13] The single crystal of **1** became opaque and brittle on heating at 90 °C for two hours.
- [14] Distances [Å] and angles [°] of the hydrogen bonds: O2...H1 2.161, O2...N1 2.944; N1-H1-O2 144.
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- [16] General crystallographic details: Data were collected on a Siemens SMART CCD system with graphite-monochromated MoK_{α} radiation and a sealed tube (2.4 kW) at 23 °C. Absorption corrections were made with the program SADABS (G. M. Sheldrick, Göttingen, 1996), and the crystallographic software package SHELXTL (SHELXTL Reference Manual, Version 5.03, Wisconsin, 1996) was used for all calculations. 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-100837. 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).

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- [7] Crystal structure determination of **1**:^[16] Tetragonal, space group $P4_32_12$, $a = 10.7799(1)$, $c = 23.0372(1)$ Å, $V = 2677.07(4)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.462$ g cm⁻³. All H atoms were located successfully. Positional

A New "Old" Sodium Boride: Linked Pentagonal Bipyramids and Octahedra in Na_3B_{20} **

Barbara Albert*

Few alkali metal borides can be considered to be well defined with regard to their composition and crystal structure. The reasons for this stem from difficulties in the synthesis and analysis of these compounds. First, it is difficult to carry out a reaction of the low-melting alkali metals with boron; second, the products often form microcrystalline powders instead of single crystals. The existence, composition, and structure of just one lithium–boron compound can be considered confirmed: Li_3B_{14} .^[1] Two sodium borides have also been described, which will be discussed here, as well as potassium hexaboride, KB_6 .^[2]

Since boron-rich metal borides have interesting chemical, mechanical, and electronic properties, the lack of well-defined binary compounds in the system alkali metal/boron is unfortunate. Furthermore, the chemical bonding in these compounds is not fully understood. Additional motivation for these studies was the interesting structural chemistry of metal–boron compounds, which in its variety reflects the richness of the chemistry of boron-containing molecules.

Earlier, products of the reaction of sodium with boron were described as " NaB_6 "^[3] and NaB_{15} .^[4] While the structure of NaB_{15} was determined from single-crystal data, the characterization of " NaB_6 " remained unsatisfactory. Hagenmüller and Naslain prepared powders, the analysis of which indicated an approximate Na:B ratio of 1 to 6–7. The experimentally determined density was 2.11 g cm^{-3} . The powder diffraction pattern could not be indexed and differed from those of all other hexaborides, which crystallize without exception in the cubic CaB_6 structural type.^[5]

We have now reproduced the synthesis of " NaB_6 " from elemental sodium and boron. After removing the excess of sodium by distillation, we obtained bluish black powders^[6] whose diffraction patterns were very similar to the one reported in the literature.^[7] The product is air-sensitive and pyrophoric, which is not due to the presence of finely divided elemental sodium. This was proved by dispersing the sample in liquid ammonia, which did not turn blue.

The reflections of a high-resolution powder diffraction pattern^[8] of the micro-crystalline product could be indexed in the monoclinic crystal system under the assumption that the unit cell is roughly three times larger than that of cubic CaB_6 .^[9] Relying on a relationship between the structures of " NaB_6 " and CaB_6 , we fixed the position of one Na atom

analogous to that of the Ca atom in CaB_6 (Wyckhoff symbol $1a$). The positions of all other atoms (first Na, then B) were localized by analyzing difference Fourier maps. It became clear that the structure, which was solved in the monoclinic space group $P2_1/m$, contains two additional mirror planes (perpendicular to $[201]$ and $[001]$ through the origin of the monoclinic unit cell). Therefore, a description in the orthorhombic system with an unit cell of twice the volume of a monoclinic cell is required.^[10] The positions and thermal displacement parameters of the atoms were thus refined in the space group $Cmmm$ (Figure 1).^[11, 12]

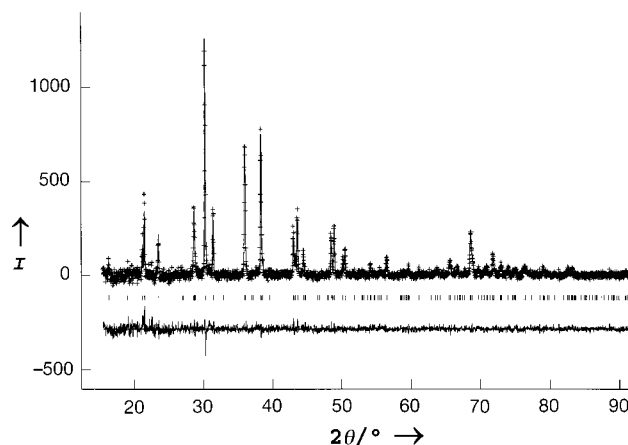


Figure 1. Observed (+) and calculated (solid line) powder diffraction pattern (corrected for the background) with the difference curve (bottom). The vertical dashes indicate the positions of reflections. I = intensity.

In the determination of the structure, two surprising discoveries were made. First, instead of the expected 18 boron atoms per monoclinic unit cell, 20 were localized. Therefore, the investigated compound is not NaB_6 (Na_3B_{18}) but Na_3B_{20} . Second, the occurrence of a pentagonal bipyramid consisting of seven boron atoms as a structural unit was proven for the first time by X-ray structure analysis. The boron framework in Na_3B_{20} thus is not composed entirely of linked octahedra, as in the hexaborides.^[5] Figure 2^[13] shows the arrangement of the polyhedra in a projection of the structure on the ab plane. A section of the structure of Na_3B_{20} (Figure 3) illustrates the position and the coordination of the sodium atoms in the cages of boron atoms.^[14]

The mean boron–boron distances of 176 and 180 pm within the polyhedra and 171 pm between polyhedra are comparable to those in other boron compounds (e.g., Li_3B_{14} ^[1]). It is typical of boron-rich compounds that distances between atoms in the polyhedra are larger than those between them.

The compound first synthesized by Hagenmüller and Naslain in 1972 and known since as NaB_6 has been identified as a new sodium boride of composition Na_3B_{20} with an unusual crystal structure. The pentagonal bipyramid, which was previously detected in a few boron compounds by spectroscopic techniques, can now be regarded as a new structural unit in the domain of boron-rich compounds. The further characterization and analysis of the properties of this boride are currently under investigation.^[15]

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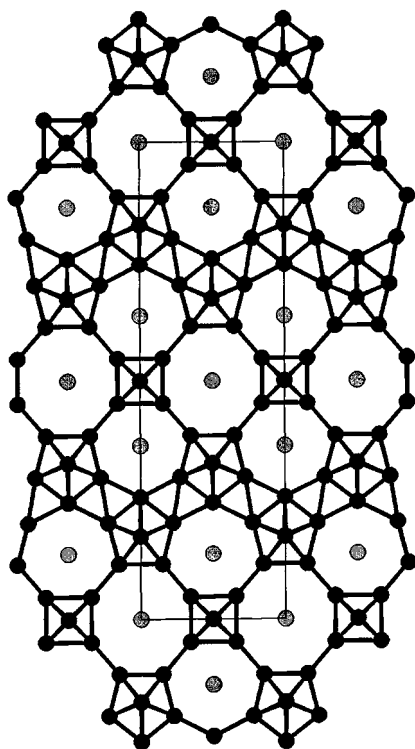


Figure 2. Projection of the structure of Na_3B_{20} on the ab plane (Na: light gray, B: dark gray, rectangle: unit cell).

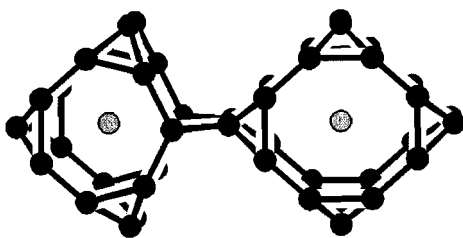


Figure 3. Section of the structure of Na_3B_{20} in the direction $[001]$ (Na: light gray, B: dark gray). All boron atoms whose distance to a sodium atom is less than 340 pm are shown.

Experimental Section

Sodium (Merck, Darmstadt, p.a.) was refined by segregation and treated with boron (Chempur, Karlsruhe, 99.9 + %) in a molar ratio of 1:1 at 1050 °C for 3 h in crucibles made of pyrolytic boron nitride, which were sealed in iron crucibles under helium by arc welding. The excess of sodium was removed by distillation at 10^{-2} mbar and 350 °C. The starting materials and products were handled under argon.

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 [7] Powder diffraction patterns of our samples, which were prepared in iron ampoules with inner crucibles of pyrolytic boron nitride do not exhibit the reflection at about $2\theta = 44.1^\circ$ which is present in the diffractograms of Hagenmüller and Naslain. It is probably the highest intensity reflection of Fe_{23}B_6 (PDF 34-0991).
 [8] Huber powder diffractometer G645, quartz monochromator, $\text{Cu}_{K\alpha 1}$ radiation ($\lambda = 1.54056 \text{ \AA}$), flat-plate sample holder, measurement in transmission mode at 23.0(5) °C and 5×10^{-5} mbar, step width 0.004° , measurement range $\theta = 3 - 50^\circ$.
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 [15] B. Albert, K. Hofmann, unpublished results.

Binuclear Homoleptic Manganese(III,III) and Manganese(IV,III) Complexes with Deprotonated D-Mannose from Aqueous Solution**

Andreas Geisselmann, Peter Klüfers,* and Bernd Pilawa

A significant principle of bioinorganic chemistry is that the potentials of (mostly oligonuclear) redox systems increase only gradually with increasing oxidation state when the respective higher oxidation number of the central metal is stabilized by deprotonation of the Brønsted acid ligands.^[1] Carbohydrates, which are polybasic acids and ubiquitous in organisms, should be of some significance for such reactions. However, the polyanionic ligands derived from carbohydrates appear to be strongly prone to oxidation. Here we report that even anions of a “reducing” sugar are able to form surprisingly stable coordination compounds with higher oxidation states of the important “biometal” manganese, thus giving rise to unexpected chemistry in aqueous solution at circumneutral pH.

“Manganese(III) acetate”^[2] is a common oxidizing agent in organic chemistry.^[3] At pH 13 and under cooling with ice a stable, red solution that absorbs oxygen is formed on reaction with the reducing^[4] aldohexose D-mannose (D-Man) and sodium hydroxide solution (molar ratio NaOH:Mn:D-Man = 20:1:3, $c_{\text{Mn}} = 0.04 \text{ mol L}^{-1}$). On exclusion of air, diffusion of barium chloride into the reaction solution yields red, rhombic crystals of $\text{Ba}_2[\text{Mn}_2^{\text{III}}(\beta\text{-D-Manf/H}_{-5})_2] \cdot 13 \text{H}_2\text{O}$ (**1**, Manf = mannofuranose).^[5] This is simply a homoleptic coordination compound of mannose pentaanions and manganese(III) formed without any redox reactions taking place. Complex **1** is isotypic with analogous metalates of the nonoxidizing trivalent states of vanadium, chromium, iron, aluminium, and gallium with entirely deprotonated D-mannose ligands.^[6] In the binuclear anions (Figure 1a), the manganese(III) atoms are the central atoms of two edge-sharing, distorted octahedra. The assignment of the oxidation state is particularly supported by the Jahn–Teller (JT) distortion of the high-spin d^4 central atoms, which may be separated from distortion due to steric strain by comparison with the isotypic compounds (Figure 2). The coordination of the second metal-atom site may be analyzed analogously. The resulting tetragonal elongation is the same when iron(III) and manganese(III) are compared as two ions with the same crystal radius.^[7]

When calcium hydroxide is used instead of caustic soda, stable solutions may be prepared even for biochemically more

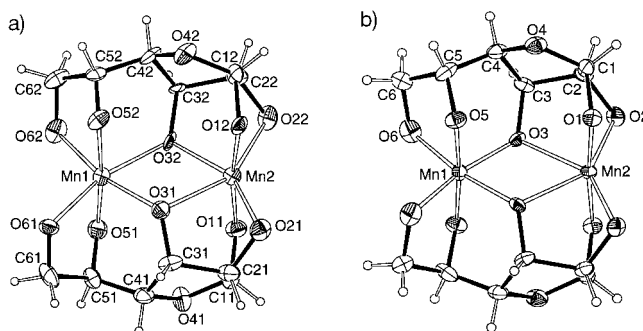


Figure 1. a) The tetraanion in **1** (ORTEP plot, ellipsoids for the 60% probability level). Bond distances [pm] and angles [°]: from Mn1 to: O51 186.9(9), O52 191.1(8), O62 196.1(8), O31 197.0(8), O61 214.7(9), O32 218.9(9); from Mn2 to: O11 188.9(9), O12 189.6(9), O21 194.8(9), O32 205.5(7), O22 206.5(9), O31 224.4(9); Mn1...Mn2 332.3(3); Mn1–O31–Mn2 103.9(4), Mn1–O32–Mn2 103.0(4). b) The C_2 symmetrical tetraanion in **2** (ORTEP plot, ellipsoids for the 70% probability level; the C_2 axis runs through the two manganese atoms). Bond distances [pm] and angles [°]: from Mn1 (Mn^{IV}) to: O5 185.1(5), O6 189.0(5), O3 191.9(5); from Mn2 (Mn^{III}) to: O1 188.3(5), O2 196.6(4), O3 218.2(5); Mn1...Mn2 324.5(2); Mn1–O3–Mn2 104.4(2).

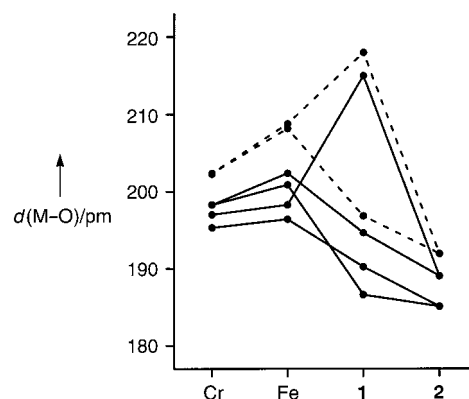


Figure 2. Bond lengths between the central metal and O atoms of the open-chain part of the deprotonated mannose ligands (O3,5,6) in $\text{Ba}_2[\text{M}_2^{\text{III}}(\beta\text{-D-Manf/H}_{-5})_2] \cdot 13 \text{H}_2\text{O}$ ($\text{M} = \text{Cr}, \text{Fe}$)^[6] as well as in **1** and **2**. The data points for bonds to bridging O atoms (O3) are connected by dashed lines. The variance of the distance for crystal field stabilized chromium(III) is smaller than for the high-spin d^5 Fe^{III} ion, which shows no crystal-field effects; furthermore, the distances are larger when bridging O atoms are involved. The tetragonal distortion of the MnO_6 octahedra in **1** takes place along the O61–Mn1–O32 and O31–Mn2–O22 axes.

relevant circumneutral pH values. When a molar ratio of $\text{Ca}:\text{Mn}^{\text{III}}:\text{D-Man} = 3:2:6$ ($c_{\text{Mn}} = 0.04 \text{ mol L}^{-1}$) is used, a red-brown solution of pH 7 is obtained; use of 3.5 equivalents of $\text{Ca}(\text{OH})_2$ yields solutions of pH 9.^[8] Addition of barium chloride results in formation of a precipitate, which may be isolated as red-brown rhombic crystals when barium chloride is allowed to slowly diffuse into the reaction solution. X-ray analysis^[5] reveals a mixed-valence compound of analogous structure with the formula $\text{Ba}_2[\text{Mn}^{\text{IV}}\text{Mn}^{\text{III}}(\beta\text{-D-Manf/H}_{-5})_2]\text{Cl} \cdot 14 \text{H}_2\text{O}$ (**2**). The crystals of **2** were of good quality, and the unexpected oxidation state +IV for one of the central atoms of the likewise binuclear complex anions could be unambiguously assigned (Figure 1b): 1) All hydrogen atoms could be located with satisfactory certainty; hence, the charge of the ligands can be determined directly. 2) The Mn–O bond lengths in **2** (as in **1**) lie within the range observed for other manganese compounds with MnO_6 coordination (Table 1). 3) For **2** the

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Table 1. Mean Mn–O bond lengths [pm] in manganese compounds with octahedral O₆ coordination.^[a]

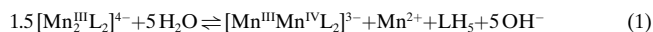
	Mn ^{III}	Mn ^{IV}
1 : Mn1	200.2 ± 12.0	–
1 : Mn2	201.7 ± 12.2	–
2	201.0 ± 12.6	188.7 ± 2.8
[Mn ^{IV} (cat) ₃] ^{2–} ^[b] ^[14]	–	189.5 ± 1.7
groutite (α-MnO(OH)) ^[15]	204.1 ± 16.4	–
pyrolusite (β-MnO ₂) ^[16]	–	188.7

[a] Crystal radius of six-coordinate high-spin Mn³⁺: 78.5, of Mn⁴⁺: 67.0 pm.^[7] [b] (cat = catecholate).

diagnostic JT distortion of the trivalent stage is cancelled, and, hence, the variance of the bond lengths is as small as for the isosteric chromium(III) ion.

In **1** the spins of the high-spin manganese centers ($S = 2$) are coupled antiferromagnetically ($J = -3 \text{ cm}^{-1}$). In **2** ($S = 3/2$ and $S = 2$) ferromagnetic coupling is observed; the coupling constant is $+19 \text{ cm}^{-1}$.^[9] For **2** χT increases from $4.8 \text{ emu K mol}^{-1}$ at 300 K with decreasing temperature until a maximum of $7.6 \text{ emu K mol}^{-1}$ is reached at 20 K.

Neutral solutions from which **2** may be isolated are surprisingly stable. They remain visually unchanged for some days, and even heating for 1 h to 80 °C does not alter the appearance of the solutions. The UV/Vis spectrum of a solution that has been stored at room temperature for one week indicates a slight decrease in the Mn^{IV} content. The solutions do not absorb oxygen from air. Hence, **2** may be prepared even under a nitrogen atmosphere by partial disproportionation of manganese(III).^[10] The dependence of equilibrium (1) ($L = \beta\text{-D-Man}/\text{H}_2\text{O}$) on pH can be quantified



by UV/Vis spectroscopy on exclusion of oxygen (Figure 3). The formation of the Mn^{IV}Mn^{III} species, which can be monitored by means of the red shift of the charge-transfer absorption, is complete below pH 10 when sodium counterions are present, whereas the Mn^{III} species is stable against disproportionation above pH 11. The isosbestic point at the right of Figure 3 is defined precisely by five of the seven

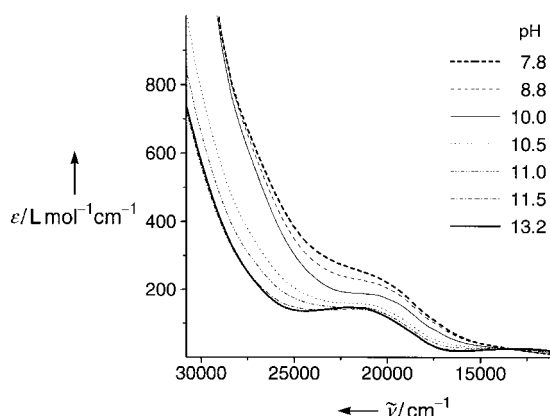


Figure 3. UV/Vis spectra of alkaline solutions (NaOH) of manganese(III) acetate and D-mannose ($\text{Mn}^{\text{III}}:\text{D-Man} = 2:5$, $c_{\text{Mn}} = 0.064 \text{ mol L}^{-1}$) at various pH values (recorded under nitrogen and cooling with ice).

spectra; there are further species only in the narrow range between pH 10 and 10.5 (deviation of the extinction values at the isobestic point at 13400 cm^{-1} : $2 \text{ L mol}^{-1} \text{ cm}^{-1}$, too low for pH 10; $1 \text{ L mol}^{-1} \text{ cm}^{-1}$, too high at pH 10.5). Disproportionation takes place at a somewhat lower pH when calcium is the counterion. In this case the spectrum of a solution at pH 9.5 indicates a mixture of approximately equal parts of the Mn^{III} and the Mn^{IV}Mn^{III} species. The equilibrium is reversible in solutions containing either sodium or calcium as counterions.

The unexpected inertness of the higher oxidation states of manganese towards a reducing sugar is best highlighted by experiments on oxygen absorption. When the pH value of neutral solutions containing calcium ions is shifted to the weakly alkaline region, oxygen is absorbed (with a decrease in pH).^[11] The result of the reaction with excess oxygen in a noncoordinating buffer at pH 9.5 is depicted in Figure 4: At

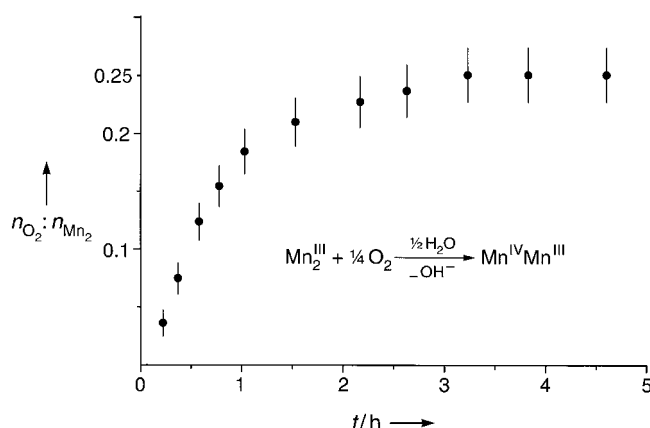


Figure 4. Oxidation of a solution of $\text{Ca(OH)}_2/\text{NaOH}/\text{manganese(III) acetate}/\text{D-mannose}$ (0.12, 0.144, 0.064, 0.15 M) buffered with 2-cyclohexylaminoethanesulfonic acid (CHES, 0.24 M) with oxygen (ca. pH 9.5, room temperature, vigorous stirring); the volumetrically determined molar ratio of absorbed oxygen and binuclear complex is drawn as a sum curve. The reaction equation given is valid for the Mn_2^{III} part (see text); the electron balance of the disproportionated part is naturally the same, however, Mn^{II} oxidation and complexation needs more OH^- ions than are released in the parallel reaction. The OH^- consumption determined by titration shows about equal concentration of the species of equilibrium (1).

room temperature, the deprotonated mannose ligands are not oxidized, even by pure oxygen in the presence of the proven redox catalyst manganese. Instead, the Mn^{IV}Mn^{III} compound is formed quantitatively, and O₂ absorption is then brought to a standstill! Further absorption of oxygen, which then results in decomposition of the solution, needs strongly alkaline conditions. A binuclear Mn^{IV} species, which was recently found for binuclear complexes with bridging boronate ligands,^[12] has not been observed yet with mannose ligands.

Complexes **1** and **2** are related to the manganese (hydr)oxides not only in terms of atomic distances (Table 1), but also electrochemical potentials. The known mixed-valence stage as in **2** is the (rather poorly defined) “groutellite” ($\text{Mn}_2\text{O}_3(\text{OH})$), which is formed in the course of electrochemical reduction of ramsdellite (MnO_2) to groutite (MnO(OH)) domains on half-reduction. In 1 M KOH groutellite is reduced to groutite between $+0.05$ and -0.05 V (versus the standard hydrogen electrode, SHE).^[13] Correspondingly, the cyclic voltammo-

gram of the mannose system shows a quasi-reversible $\text{Mn}^{\text{III}} \leftrightarrow \text{Mn}^{\text{IV}}\text{Mn}^{\text{III}}$ transition in strongly alkaline solution at a potential of -0.31 V versus $\text{AgCl}/\text{Ag}, \text{Cl}^-$ (-0.09 V versus SHE; Figure 5). In the pH range of the disproportionation of the Mn_2^{III} species, increasingly higher scan speeds are required to achieve reoxidation. When the potential range is extended

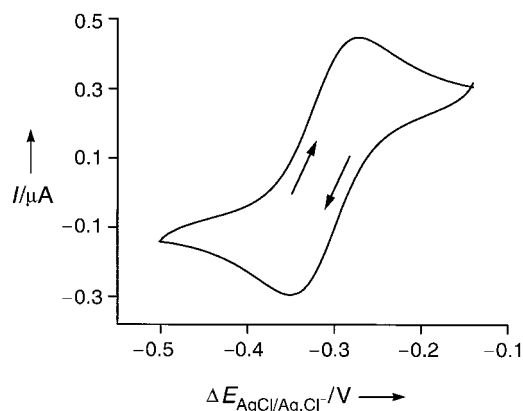


Figure 5. Cyclic voltammogram for the $\text{Mn}_2^{\text{III}}/\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}$ redox pair (0.005 M manganese(III) acetate, 0.0138 M mannose, pH 13.5, 40 mV sec^{-1} scan speed, Hg working electrode, the second cycle is depicted). The transition is quasi-reversible ($\Delta E = 79$ mV; cf. 56.5 mV for a reversible single-electron transition^[17]). Reversibility decreases with decreasing pH value. The potential is almost independent of pH in the range pH 12 to 14; in the range of pH 9 to 12 the pH dependence corresponds to an addition of about one proton to the reduced form (dilution is much larger in the voltammetric investigation than for other experiments; thus, protolysis reactions are more important).

to more negative values, reduction to manganese(II) is observed about 0.3 V below the quasi-reversible stage, as with the oxides. The manganese(II) species now formed in higher concentration decompose quickly with respect to various scan speeds applied; therefore, no reoxidation is observed in these experiments, and the individual cycles are no longer identical. We will report on a deeper insight into the interplay between stereo and redox chemistry, which may be obtained from experiments with *rac*-mannose as ligand.

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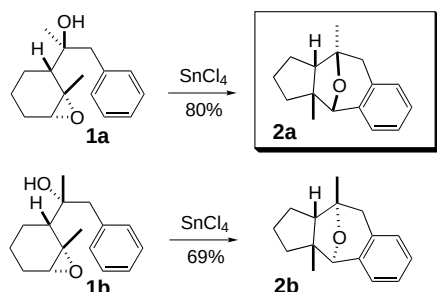
and graphics by PLATON, ORTEP, and SCHAKAL. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666 (Frau S. Höhler-Schlimm); e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-407817 (**1**) and -407818 (**2**). **1**: $\text{C}_{12}\text{H}_{14}\text{Ba}_2\text{Mn}_2\text{O}_{12} \cdot 13.5 \text{H}_2\text{O}$, $M_r = 977.97$, $\rho_{\text{calcd}} = 2.3042(1) \text{ g cm}^{-3}$, crystal size $0.18 \times 0.08 \times 0.05$ mm, rhombic, $P2_12_12_1$, $a = 10.7547(8)$, $b = 14.8992(12)$, $c = 17.5938(15) \text{ Å}$, $V = 2819.2(4) \text{ Å}^3$, $Z = 4$, $T = 200 \text{ K}$, $\mu = 3.732 \text{ mm}^{-1}$, 19209 *hkl* measured, $2\theta_{\text{max}} = 56^\circ$, 6483 *hkl* unique, L_p correction, $R_{\text{int}} = 0.1126$, numerical absorption correction (6 faces), mean $\sigma(I)/I = 0.1255$, 4199 *hkl* with $I > 2\sigma(I)$, $w^{-1} = \sigma^2(F_o) + (0.0636 P)^2$, $3P = \max(F_o^2; 0 + 2F_o^2)$, abs. structure parameter (according to H. D. Flack, *Acta Crystallogr. Sect. A* **1983**, *39*, 876–881): 0.03(4), 3.5 water molecules disordered, H atoms of some water molecules localized and refined as for **2**, 426 parameters, 25 restraints, $R_{20} = 0.0529$, $R_w(F^2) = 0.1142$, $S = 1.009$, min./max. difference density: $-2.974/1.583 \text{ e Å}^{-3}$ near Ba1. **2**: $\text{C}_{12}\text{H}_{14}\text{Ba}_2\text{ClMn}_2\text{O}_{12} \cdot 14 \text{H}_2\text{O}$, $M_r = 1022.433$, $\rho_{\text{calcd}} = 2.1192(1) \text{ g cm}^{-3}$, crystal size $0.20 \times 0.04 \times 0.03$ mm, rhombic, $C222_1$, $a = 1643.4(2)$, $b = 1294.0(1)$, $c = 1507.0(2) \text{ pm}$, $V = 3204.7(6) \cdot 10^6 \text{ pm}^3$, $Z = 4$, $T = 200 \text{ K}$, $\mu = 3.373 \text{ mm}^{-1}$, 12681 *hkl* measured, $2\theta_{\text{max}} = 56^\circ$, 3809 *hkl* unique, L_p correction, $R_{\text{int}} = 0.0961$, numerical absorption correction (6 faces), mean $\sigma(I)/I = 0.0954$, 2881 *hkl* with $I > 2\sigma(I)$, $w^{-1} = \sigma^2(F_o) + (0.0314 P)^2$, $3P = \max(F_o^2; 0 + 2F_o^2)$, abs. structure parameter: $-0.02(3)$, one common O–H bond length for all water molecules and $d(\text{H} \cdots \text{H}) = 1.57 \times d(\text{O} \cdots \text{H})$, one common U_{iso} for all H atoms, 242 parameters, 22 restraints, $R_{20} = 0.0386$, $R_w(F^2) = 0.0797$, $S = 0.910$, max. difference density: 1.041 e Å^{-3} near Ba.

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- [10] Disproportionation is quick; the UV/Vis spectrum of a solution at pH 7, recorded immediately after preparation, is the same as that of the mother liquors of the crystals and of the crystal powder of **2** (the latter was measured as the diffuse reflexion versus barium sulfate; analysis with the Kubelka–Munk function).
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Stereocontrolled Routes to Bridged Ethers by Tandem Cyclizations

Charles M. Marson,* Jon Campbell, Michael B. Hursthouse, and K. M. Abdul Malik

The construction of carbocyclic seven-membered rings continues to present an appreciable challenge, particularly when stereocontrolled placement of multiple chiral centers is required.^[1,2] The 8-oxabicyclo[3.2.1]octane system and its fused analogues form a fundamental class of compounds which include hydroazulenoid diterpene natural products.^[3] Currently, the most general methods of access to the oxabicyclo[3.2.1]octane system are by [3+4] cycloadditions^[4] and annulations.^[5] Herein we report the first examples of cyclizations involving 3,4-epoxy alcohols, and disclose a new tandem contraction–lactolization–cyclization sequence (Scheme 1). This reaction sequence has led to the development of lactol cyclizations and hence a general route to bridged bicyclo ethers.



Scheme 1. Cyclizations giving bis-fused 8-oxabicyclo[3.2.1]octane systems.

Epoxides are powerful initiators in cyclizations involving π nucleophiles, particularly when activated by a Lewis acid.^[6] The stereochemical control of an epoxide can be further enhanced by the presence of an hydroxyl group adjacent to the epoxide;^[2] such 2,3-epoxy alcohols can participate in bidentate chelation, which usually leads to high regio- and stereocontrol during cyclization.^[2] In contrast, cyclizations involving epoxides derived from homoallylic alcohols (3,4-epoxy alcohols) appear to be without precedent. Since the epoxidation of acyclic homoallylic alcohols is not usually diastereoselective,^[7] advantage was taken of a cycloalkenyl unit in which epoxidation could be face-selective on account

of conformational restriction to a ring. This proved to be the case, and 3,4-epoxy alcohols **1a** and **1b** were the only isomers resulting from the epoxidation of 2-(2-methylcyclohex-2-enyl)-1-phenylpropan-2-ol with *tert*-butyl hydroperoxide in the presence of $[\text{VO}(\text{acac})_2]$ (acac = acetylacetonate). Epoxides **1a** and **1b** were separated by chromatography and independently treated with SnCl_4 (2.0 equiv) in CH_2Cl_2 at -78°C . Each underwent a remarkable skeletal rearrangement to give **2a** and **2b**, respectively, as the result of rearrangement followed by consecutive cyclizations. An X-ray crystal structure determination^[8] of **1a** disclosed the relative configuration shown in Figure 1, in which the ether bridge is *trans* to the cyclopentane ring. Epoxy alcohol **1b**, being epimeric with **1a**, gave **2b** in which the epimeric configuration at the carbinol center results in the ether bridge that is *syn* to the cyclopentane ring. In each case, **2a** and **2b** were the only cyclized products isolated.

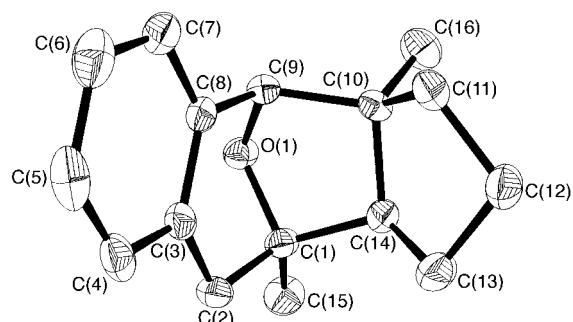
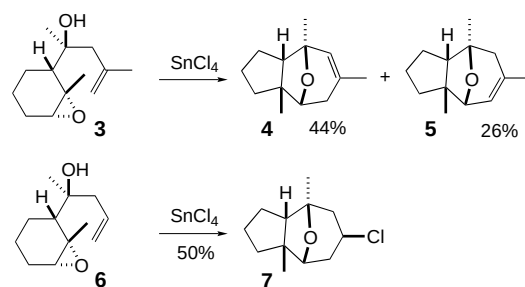


Figure 1. Crystal structure of **2a**.

The novel tandem cyclization was explored with other π nucleophiles as terminating groups. Reaction of 1-acetyl-2-methylcyclohex-2-ene with 2-methyl-2-propenylmagnesium chloride in place of a benzyl Grignard reagent in the above sequence afforded a 1:1 mixture of homoallylic alcohols, which was epoxidized with *m*-chloroperbenzoic acid and then separated by chromatography. Treatment of epoxy alcohol **3** with SnCl_4 (2.0 equiv) in CH_2Cl_2 (-78°C , 20 min) gave the bicyclic ethers **4** and **5** (Scheme 2). Constitutional isomerism



Scheme 2. Cyclizations with alkenes.

had arisen as a consequence of lack of control during deprotonation of the presumed tertiary carbocation. The carbinol epimer of **3** did not afford any identifiable cyclized products.

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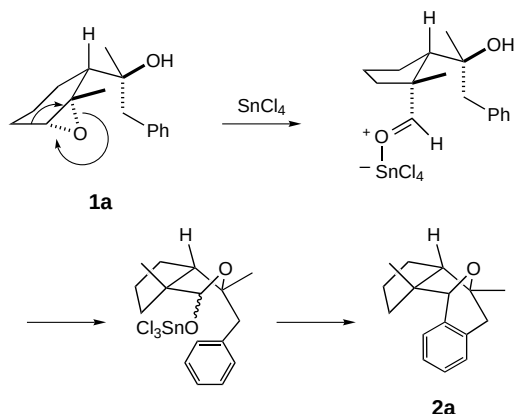
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The less substituted alkenyl substrate **6** was prepared by addition of allylmagnesium chloride to 1-acetyl-2-methylcyclohex-2-ene to give a 1:1 mixture of 2-(2-methylcyclohex-2-en-1-yl)-pent-4-en-2-ols (67%), which was epoxidized; the epoxy alcohols were then separated by chromatography. Treatment of **6** with SnCl_4 (2.0 equiv) in CH_2Cl_2 (-78°C , 15 min) gave **7** (50%). Instead of a cycloalkene ring being formed, chloride trapping occurred, a phenomenon consistent with the reactivity of the developing secondary carbocation leading to rapid nucleophilic quenching. The trajectory of approach is consistent with a chairlike transition state in which the C–C bond of the newly forming ring is parallel with the equatorially forming C–Cl bond (the α -chloro epimer of **7** would require a boatlike transition state); chloro ether **7** was the only cyclized product isolated. The CHCl unit of **7** ($\delta = 4.38$) exhibits a triplet of triplets ($J = 11.5$ and 5.5 Hz) in the ^1H NMR spectrum, consistent only with *trans*-diaxial coupling and an equatorially disposed chloro substituent. As in the case of **3**, the carbinol epimer of **6** did not afford any identifiable cyclized products.

The above cyclizations can be understood in terms of the following sequence of events: First, epoxide ring opening and ring contraction^[9] take place, mediated by the Lewis acid (Scheme 3). The configurations of the final products imply that



Scheme 3. Possible mechanism for the formation of **2a**.

the contraction is stereoselective and proceeds with inversion at the new quaternary center. The carbinol oxygen atom then participates in an intramolecular attack upon the activated carbonylic electrophile, resulting in a fused lactol intermediate. Lastly, the effect of SnCl_4 upon the lactol intermediate leads to an electrophile presumed to be the oxonium cation, which undergoes attack by the aryl or alkenyl π nucleophile.

The above rationale suggested that independently prepared lactol intermediates could be expected to undergo cyclization to give related bridged ethers. This was demonstrated for the two lactols **8** and **10** (Scheme 4), which were prepared as follows: Addition of benzylmagnesium chloride and 2-methyl-2-propenylmagnesium chloride, respectively, to ethyl levulinate followed by hydrolysis of the hydroxy esters with aqueous NaOH and acidification gave the γ -hydroxy acids, which were cyclodehydrated to the γ -lactones by heating in benzene at reflux. The lactones were reduced with diiso-

butylaluminum hydride (1.5 equiv) in toluene at -78°C to give the lactols **8** and **10**. Treatment at -78°C in CH_2Cl_2 with SnCl_4 (2.8 equiv, 1 h for **8**; 2.0 equiv, 2 h for **10**) gave bridged ethers **9** and **11**, respectively, as single diastereomers. The stereoelectronic preference resulting in the *syn* relation of chloro substituent to ether bridge can be explained on the basis of a chairlike transition state prior to chloride trapping, as for the formation of **7**.

In conclusion, bridged ethers incorporating stereocontrolled placement of functionality can be prepared by Lewis acid induced cyclizations. A reaction sequence with a ring contraction and a tandem cyclization allows the 8-oxabicyclo[3.2.1]octane system to be constructed with one or two additional fused rings from unfunctionalized alkenes or arenes. Cleavage of the 8-oxabicyclo[3.2.1]octane system affords a stereoselective synthesis of *cis*-2,5-disubstituted tetrahydrofurans,^[5b] which are useful precursors of ionophore antibiotics. The potential of the new ring-construction processes in total synthesis is currently being explored.

Experimental Section

2-(2-Methylcyclohex-2-en-1-yl)-1-phenylpropan-2-ol: A solution of 1-acetyl-(2-methylcyclohex-2-en-1-yl)^[10] (6.0 g, 43.0 mmol) in dry THF (100 mL) was treated with benzylmagnesium chloride (32.6 mL, 2.5 M in THF) under nitrogen at 0°C . The mixture was stirred at 20°C for 16 h, and the reaction quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was then extracted with Et_2O (2×150 mL), and the combined organic extracts were dried (MgSO_4) and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 95/5) to give a 1:1 mixture of the two epimers of 2-(2-methylcyclohex-2-en-1-yl)-1-phenylpropan-2-ol as a colorless oil (6.0 g, 60%); IR (KBr): $\tilde{\nu} = 3400, 2900, 1600, 1500\text{ cm}^{-1}$; ^1H NMR (250 MHz, CDCl_3): $\delta = 7.40\text{--}7.15$ (5 H, m), 5.60 (1 H, m), 2.80 (1 H, m), 1.10–2.40 (15 H, m); ^{13}C NMR (68.8 MHz, CDCl_3): $\delta = 137.9$ (s), 137.5 (s), 135.1 (s), 135.0 (s), 131.0 (d), 131.0 (d), 128.2 (d), 128.2 (d), 127.1 (d), 127.0 (d), 126.5 (d), 126.4 (d), 75.4 (s), 49.3 (d), 48.4 (d), 47.5 (t), 43.1 (t), 27.8 (q), 26.8 (t), 26.6 (t), 26.4 (q), 26.3 (q), 25.6 (t), 25.5 (t), 23.2 (q), 21.5 (t), 21.0 (t); MS (EI 70 eV): m/z (%): 213 (9), 181 (10), 135 (65), 123 (35), 95 (100), 81 (20), 43 (30); HR-MS calcd for $\text{C}_{16}\text{H}_{22}\text{O}$: 230.1671; found: 230.1669.

2-(2-Methyl-2,3-epoxycyclohexyl)-1-phenylpropan-2-ol (1a** and **1b**):** A solution of 2-(2-methylcyclohex-2-en-1-yl)-1-phenylpropan-2-ol (5.5 g, 0.024 mol) in benzene (150 mL) was treated with $[\text{VO}(\text{acac})_2]$ (10 mg) and aqueous *tert*-butyl hydroperoxide (4.0 g, 70%), and then heated at reflux for 3 h. The mixture was allowed to cool, and was then poured onto saturated aqueous Na_2SO_3 . The organic extract was dried (MgSO_4) and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 94/6) to give **1a** (1.65 g, 29%) as microprisms and **1b** (1.65 g, 29%) as an oil; **1a**: M.p. 76.5°C ; IR (KBr): $\tilde{\nu} = 3480, 2950, 1600, 1500\text{ cm}^{-1}$; ^1H NMR (250 MHz, CDCl_3): $\delta = 7.40\text{--}7.15$ (5 H, m), 3.05–2.80 (2 H, AB q, $J = 18$ Hz), 2.85 (1 H, m), 2.10–1.00 (14 H, m); ^{13}C NMR (68.8 MHz, CDCl_3): $\delta = 138.0$ (s), 130.7 (d), 128.1 (d), 126.3 (d), 77.1 (s), 60.2 (t), 59.9 (q), 45.5 (t), 43.7 (d), 28.4 (q), 26.5 (q), 24.4 (t), 23.0 (t), 18.2 (t); elemental analysis calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2$: C 78.01, H 9.00; found C 77.96, H 9.02; **1b**: IR (KBr): $\tilde{\nu} = 3500, 2950, 1500\text{ cm}^{-1}$; ^1H NMR (250 MHz, CDCl_3): $\delta = 7.40\text{--}7.20$ (5 H, m), 3.10–2.70 (2 H, AB q, $J = 18$ Hz), 2.80 (1 H, m), 2.30 (1 H, s), 2.00–1.10 (13 H, m); ^{13}C NMR (68.8 MHz, CDCl_3): $\delta = 137.5$ (s), 131.0 (d), 128.0 (d), 126.4 (d), 76.7 (s), 60.3 (d), 59.6 (s), 48.2 (t),

46.4 (d), 26.5 (q), 25.6 (t), 24.4 (q), 22.9 (t), 18.9 (t); MS (EI 70 eV): m/z (%): 246 (3), 228 (20), 185 (10), 155 (36), 135 (28), 112 (29), 95 (100), 91 (52); HR-MS calcd for $C_{16}H_{20}O_2$: 246.1620; found: 246.1621.

1,2,3,3a,4,9,10,10a-Octahydro-3a,10-dimethyl-4,10-epoxybenz[*f*]azulene (**2a**): A solution of **1a** (0.30 g, 1.22 mmol) in CH_2Cl_2 (50 mL) at $-78^\circ C$ was treated with $SnCl_4$ (0.29 mL, 2.44 mmol) and then stirred at that temperature for 105 min. The mixture was poured onto ice (10 g), and the solution extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Evaporation gave an oil, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 94/6) to give **2a** (0.22 g, 80%) as a white solid. M.p. $37^\circ C$. IR (KBr): $\tilde{\nu}$ = 3950, 1450, 1000 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.18–7.07 (2 H, m), 7.02 (1 H, t, J = 8 Hz), 6.92 (1 H, d, J = 8 Hz), 4.46 (1 H, s), 2.93 (1 H, d, J = 17 Hz), 2.78 (1 H, d, J = 17 Hz), 2.10 (1 H, m), 1.65–0.90 (6 H, m), 1.48 (3 H, s), 1.38 (3 H, s); ^{13}C NMR (68.8 MHz, $CDCl_3$): δ = 138.5 (s), 134.2 (s), 127.9 (d), 127.0 (d), 126.1 (d), 125.0 (d), 86.6 (d), 83.0 (s), 63.8 (d), 59.7 (s), 36.9 (t), 35.5 (t), 30.8 (q), 29.0 (t), 29.0 (q), 27.9 (t); MS (EI 70 eV): m/z (%): 228 (M, 10), 145 (100), 131 (27), 109 (55); HR-MS calcd for $C_{16}H_{20}O$: 228.3370; found: 228.3365.

1,2,3,3a,4,9,10,10a-Octahydro-3a,10-dimethyl-4,10-epoxybenz[*f*]azulene (**2b**): A solution of **1b** (0.30 g, 1.22 mmol) in CH_2Cl_2 (50 mL) at $-78^\circ C$ was treated with $SnCl_4$ (0.29 mL, 2.44 mmol) and then stirred at that temperature for 75 min. The mixture was poured onto ice (10 g), and the solution extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Evaporation gave an oil, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 94/6) to give **2b** (0.19 g, 69%) as an oil; IR (KBr): $\tilde{\nu}$ = 3950, 1450, 1370, 1000 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.15–7.05 (2 H, m), 7.00 (1 H, t, J = 8 Hz), 6.88 (1 H, d, J = 8 Hz), 4.47 (1 H, s), 2.96 (1 H, d, J = 17 Hz), 2.54 (1 H, d, J = 17 Hz), 1.90–1.45 (7 H, m), 1.32 (3 H, s), 0.63 (3 H, s); ^{13}C NMR (68.8 MHz, $CDCl_3$): δ = 138.9 (s), 132.6 (s), 128.8 (d), 126.8 (d), 125.6 (d), 125.0 (d), 86.2 (d), 81.6 (s), 59.3 (s), 58.5 (d), 43.7 (t), 41.7 (t), 29.7 (t), 27.3 (t), 24.6 (q), 23.0 (q); HR-MS calcd for $C_{16}H_{20}O$: 228.3370; found: 228.3377.

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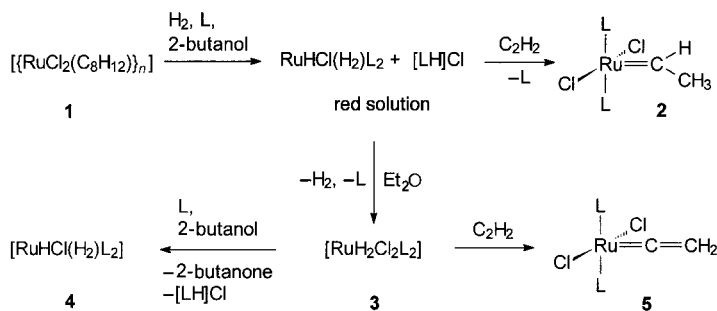
Keywords: cyclizations • domino reactions • ethers • rearrangements • tin

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Ruthenium Trichloride, Tricyclohexylphosphane, 1-Alkynes, Magnesium, Hydrogen, and Water—Ingredients of an Efficient One-Pot Synthesis of Ruthenium Catalysts for Olefin Metathesis

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Ruthenium carbene complexes of the type $[RuCl_2(=CHR)(PR_3)_2]$, are highly efficient catalysts for olefin metathesis. On account of their unique properties, for example, their stability to oxygen and their tolerance of diverse functional groups, they have been increasingly used in organic synthesis, since their discovery by Grubbs and co-workers.^[1] The extreme demand and the manifold applications of these catalysts have inevitably initiated the search for alternative synthetic routes that avoid the use of carbene precursors such as diphenylcyclopropenes or diazoalkanes utilized in the established routes. These carbene precursors are either difficult to access or problematic in their handling.^[2] The goal set by these demands is fulfilled by a synthetic route recently established in our laboratory that starts from hydrido complexes of ruthenium and 1-alkynes.^[3] We found that on reaction of $[RuCl_2(C_8H_{12})_n]$ (**1**) with hydrogen and $PiPr_3$ in 2-butanol at $80^\circ C$ a red solution is formed, which reacts with ethyne (at $25^\circ C$) to afford the carbene complex $[RuCl_2(=CHCH_3)(PiPr_3)_2]$ (**2**). After workup of the red solution with ether, the dihydridoruthenium(IV) compound **3** is obtained in nearly quantitative yield (based on **1**). Complex **3**, however, does not give the carbene complex **2** on reaction with ethyne but rather the vinylidene complex **5** (see Scheme 1).^[3, 4]



Scheme 1. L = $PiPr_3$.

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[Ru(η_4 -C₈H₁₂)(η_6 -C₈H₁₀)],^[9] or [RuH₂(H₂)₂(PCy₃)₂],^[5, 10] and uses 1-alkynes instead of cyclopropenes, diazoalkanes, vinyl chlorides, or propargylic chlorides as carbene source. The complexes **7** and **8**, which display about the same catalytic activity as the hitherto most commonly used compound [RuCl₂(=CHPh)(PCy₃)₂], can now be prepared on a larger scale. Our method of using 1-alkynes also allows the synthesis of other carbene compounds such as [RuCl(X)(=CHCH₂R)(PCy₃)₂] (X = CF₃CO₂, CN), the catalytic properties of which are currently being investigated.^[11]

Experimental Section

7: Mg (2 g, 82.3 mmol) in THF (100 mL) was activated with 1,2-dichloroethane (2 mL). Tricyclohexylphosphane (9 g, 32.1 mmol) and RuCl₃ · 3 H₂O (2 g, 7.65 mmol) were then added. The mixture was warmed under an atmosphere of hydrogen and vigorously stirred first for 2 h at 65 °C and then for 2 h at 85 °C. A red solution formed and an orange solid precipitated. The reaction mixture was then cooled to –40 °C, and ethyne (380 mL, ca. 15.8 mmol) was introduced by gas burette. The solution was then stirred for 5 min at –40 °C, followed by the addition of H₂O (0.5 mL, 27.8 mmol). After the reaction mixture was warmed to room temperature the solvent was removed, the crude product was transferred to a soxhlet apparatus and extracted with pentane (250 mL) for 12 h. A pink solid was isolated, which was washed with pentane (20 mL) and dried in vacuo. Yield: 4.37 g (75 %). For spectroscopic data see ref. [2d].

8: As described for **7**, with RuCl₃ · 3 H₂O (0.5 g, 1.91 mmol), THF (25 mL), Mg (0.5 g, 20.6 mmol), ClCH₂CH₂Cl (0.5 mL), and PCy₃ (2.31 g, 8.2 mmol) as starting materials. After the reduction the reaction mixture was cooled to –40 °C and phenylacetylene (0.22 mL, 1.91 mmol) was added dropwise, which caused a vigorous evolution of gas. The solution was stirred for 20 min at –40 °C, and then warmed to 0 °C, and H₂O (0.13 mL, 7.2 mmol) was added. After further warming to room temperature and continuous stirring for another 10 min, the solvent was removed, and the residue extracted with toluene (60 mL). The extract was dried in vacuo, and the purple residue was washed four times with pentane (4 × 10 mL) and twice with methanol (2 × 40 mL). Yield: 1.21 g (76 %). ¹H NMR (400 MHz, CDCl₃): δ = 19.40 [t, ³J(H,H) = 5 Hz, 1H, CHCH₂Ph], 7.30–7.12 (m, 5H, Ph-H), 3.98 [d, ³J(H,H) = 5 Hz, 2H, CHCH₂Ph]; ¹³C NMR (100.6 MHz, CDCl₃): δ = 316.5 [t, ²J(C,P) = 7 Hz, CHCH₂Ph], 138.9, 128.3, 128.2, 126.3 (je s, C-Ph), 64.5 (s, CHCH₂Ph); ³¹P NMR (162 MHz, CDCl₃): δ = 34.6 (s).

9: Ethyne was passed through a stirred solution of **6** (102 mg, 0.146 mmol) in CH₂Cl₂ (10 mL) at –78 °C for 30 s. The solvent was removed under reduced pressure, and the brown residue was washed with pentane (5 mL) and dried in vacuo. Yield: 99 mg (94 %). ¹H NMR (400 MHz, C₆D₆): δ = 2.70 [d, ³J(P,H) = 3 Hz, 2H, RuCCH₂], –16.17 [t, ²J(P,H) = 18 Hz, 1H, RuH]; ¹³C NMR (100.6 MHz, C₆D₆): δ = 326.2 [t, ²J(P,C) = 15 Hz, RuCCH₂], 86.6 [t, ³J(P,C) = 4 Hz, RuCCH₂]; ³¹P NMR (162 MHz, CDCl₃): δ = 41.5 (s).

10: To a solution of **6** (96 mg, 0.137 mmol) in CH₂Cl₂ (10 mL) phenylacetylene (28.0 μ L, 0.274 mmol) was added at –78 °C. After warming to room temperature, the solution was concentrated under reduced pressure to ca. 2 mL. Upon addition of pentane a green solid precipitated, which was removed by filtration and dried in vacuo. Yield: 80 mg (73 %). ¹H NMR (200 MHz, C₆D₆): δ = 4.41 (br s, RuCCHPh), –12.88 [t, ²J(P,H) = 17 Hz, 1H, RuH]; ³¹P NMR (162 MHz, C₆D₆): δ = 41.3 (s).

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Exceptionally Simple Enantioselective Syntheses of Chiral Hexa- and Tetracyclic Polyprenoids of Sedimentary Origin**

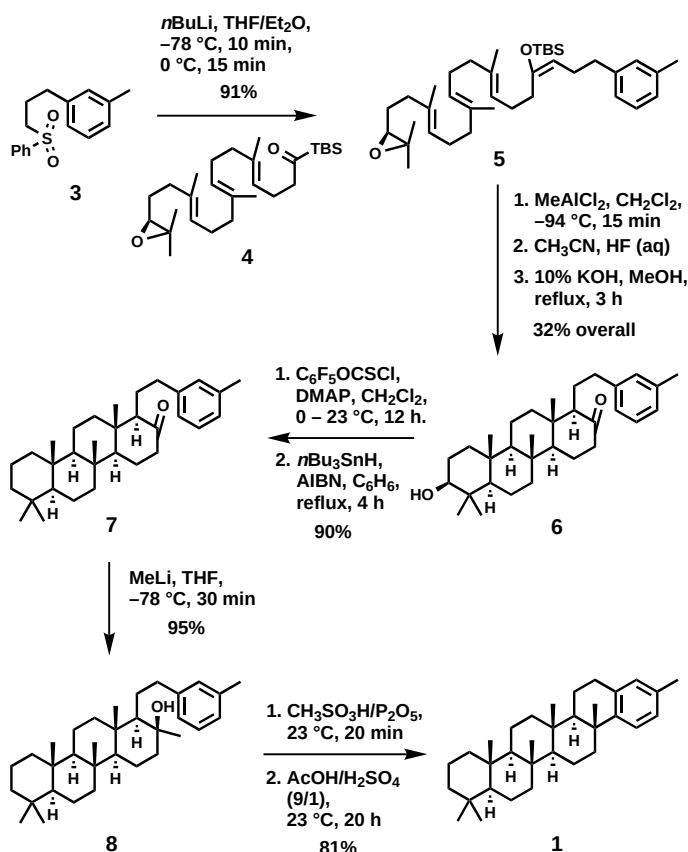
Elias J. Corey,* Guanglin Luo, and
Linus Shouzhong Lin

A recent publication described the isolation of a series of four novel chiral polycyclic hydrocarbons from Eocene Messel shale (Germany), which appear to be remnants of an ancient family of cyclopolyprenoids.^[1] This series includes the hexacyclic and tetracyclic hydrocarbons **1** and **2** as well as their pentacyclic analogue. In addition, GC-MS evidence was obtained for the occurrence in other sediments of the hepta- and octacyclic homologues of **1** and **2** in small amounts.^[1] We report here the first syntheses of **1** and **2** by relatively short routes that take advantage of several recently introduced synthetic methods, especially regio- and enantioselective catalytic dihydroxylation of polyprenol esters,^[2–4] stereospecific two-component synthesis of tri- and tetrasubstituted olefins,^[3–5] and stereoselective Lewis acid catalyzed polycyclization of chiral polyunsaturated oxiranes.^[3, 4, 6, 7]

The synthesis of the benzoperhydropicene derivative **1** is outlined in Scheme 1. α -Deprotonation of sulfone **3** with *n*BuLi generated the corresponding α -lithio derivative, which upon treatment with chiral acylsilane **4**^[4] provided stereospecifically the coupling product **5** in a reaction that proceeds

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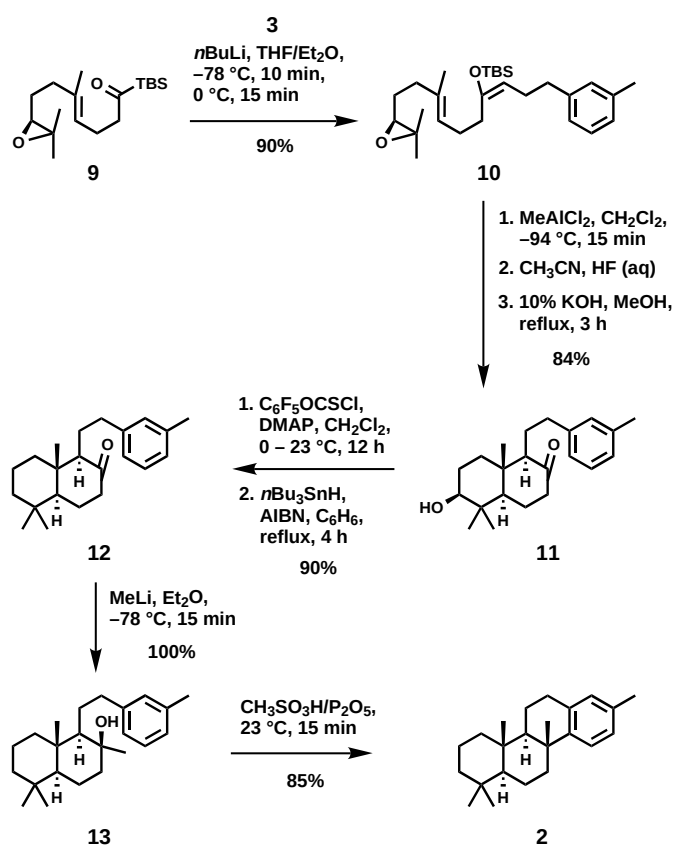
[**] This work was supported by grants from the National Institutes of Health and the National Science Foundation.



Scheme 1. Synthesis of **1**. TBS = *t*BuMe₂Si, DMAP = 4-dimethylaminopyridine, AIBN = 2,2'-azobisisobutyronitrile.

by 1) carbonyl addition, 2) Brook rearrangement, and 3) β -elimination of benzenesulfinate.^[4] The efficiency and power of this fragment coupling are particularly noteworthy. Stereoselective tetracyclization of the epoxy tetraene **5** was induced by methylaluminum dichloride in CH₂Cl₂ at -94°C to give, after sequential treatment of the crude product with HF in H₂O/CH₃CN (to effect desilylation of the 3-hydroxyl group) and 10% KOH in MeOH (to effect $\alpha \rightarrow \beta$ equilibration of the 3-methylphenylethyl sidechain), hydroxy ketone **6** as the only detectable pentacyclic product. Barton–McCombie deoxygenation at C(3) of **6**^[8] to give **7** followed by reaction with methylolithium produced the tertiary alcohol **8**. Exposure of **8** to Eaton's acid (CH₃SO₃H/P₂O₅, 10/1)^[9] afforded a mixture of **1** and olefinic dehydration products of **8**. Therefore, the resulting mixture was further treated with H₂SO₄/HOAc, which effected cyclization of the olefinic components to give **1** in good yield. The identity of synthetic and naturally derived **1** was rigorously established by comparison of ¹H and ¹³C NMR spectra, infrared and mass spectra, optical rotation, and thin layer chromatographic mobility in two different solvent systems.^[1, 10]

The enantioselective total synthesis of the hydrochrysene derivative **2** was carried out in a way completely analogous to that described above for the hexacyclic homologue **1** starting with sulfone **3** and acylsilane **9** (Scheme 2).¹¹ Uniformly fine yields were obtained, which resulted in a remarkably direct synthesis of **2** in 58% overall yield. The physical properties of **2** matched exactly those previously reported.^[1]



Scheme 2. Synthesis of **2**.

The short, efficient syntheses of **1** and **2**, together with previously described syntheses of dammarenediol II^[3] and scalarenedial,^[4] clearly demonstrate the effectiveness of the underlying strategy and methodology for enantioselective synthesis of many polycyclic polyprenols, including the natural precursors of shale components **1** and **2**.

Experimental Section

5: To a solution of sulfone **3** (168.6 mg, 0.614 mmol) in THF (2.8 mL) at -78°C was added dropwise *n*BuLi (1.6M in hexane, 0.385 mL, 0.614 mmol). The resulting yellow solution was stirred for 5 min at -78°C and then added dropwise through a cannula to a solution of acylsilane **4** (183 mg, 0.41 mmol) in ether (2.8 mL). The mixture was stirred at -78°C for 10 min, allowed to warm to 0°C , and stirred for 15 min. The reaction was quenched by addition of a saturated aqueous solution of NH₄Cl, and the mixture was extracted with hexane (3 $\times$ 10 mL). The combined organic phases were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Column chromatography of the residue (silica gel, hexane/ether/Et₃N, 100/10/1) provided enolsilane **5** (216 mg, 91%) as a colorless oil: $[\alpha]_D^{25} = -4.39$ ($c = 1.48$ in C₆H₆); IR (neat): $\tilde{\nu} = 2955, 2929, 2921, 1666, 1462, 1454, 1252, 1140, 839\text{ cm}^{-1}$; ¹H NMR (500 MHz, C₆D₆): $\delta = 7.16\text{--}6.90$ (4H, m), 5.31–5.20 (3H, m), 4.72 (1H, t, $J = 5.7\text{ Hz}$), 2.59–1.99 (21H, m), 2.17 (3H, s), 1.63 (3H, s), 1.57 (3H, s), 1.53 (3H, s), 1.14 (3H, s), 1.09 (3H, s), 0.98 (9H, s), 0.13 (6H, s); ¹³C NMR (125 MHz, C₆D₆): $\delta = 152.1, 142.2, 137.7, 135.4, 134.9, 134.3, 129.8, 128.5, 126.8, 126.0, 125.1, 124.9, 124.4, 106.5, 63.4, 57.3, 40.2, 40.1, 37.5, 36.9, 32.0, 29.6, 28.0, 27.13, 27.08, 26.1, 26.0, 25.0, 21.5, 18.9, 18.3, 16.2, 16.12, 16.07, -4.3$.

6: To a solution of **5** (214 mg, 0.37 mmol) in anhydrous CH₂Cl₂ (90 mL) at -95°C was added a precooled solution of MeAlCl₂ (1M in hexane, 0.45 mL, 0.45 mmol) in 20 mL of anhydrous CH₂Cl₂ (-95°C); the addition was carried out along the side of the flask through a cannula. The reaction mixture was stirred at -95°C for 15 min, and then the reaction was

quenched by successive addition of Et₃N (1.6 mL) and a MeOH/H₂O solution (4/1, 1.6 mL); introduction was again along the side of the flask at -95 °C. The resulting mixture was then poured into a half-saturated aqueous solution of NH₄Cl (40 mL), the organic phase was separated, and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic phases were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The diastereomeric α and β sidechain isomers were separated by chromatography and treated individually with aqueous HF (48%) in CH₃CN at 23 °C for 1.5 h to effect desilylation. The α isomer was dissolved in 10% KOH in MeOH and heated under reflux for 3 h under argon to generate the thermodynamically more stable β diastereomer **6**. After chromatography (silica gel), pure **6** (55 mg, 32%) was obtained as a colorless oil: [α]_D²³ = +15.38 (c = 1.45 in CHCl₃); IR (neat): ν̄ = 3456, 2938, 2855, 1708, 1451, 1389, 1028, 909 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.20–6.92 (4H, m), 3.20 (1H, dd, J = 4.8, 11.6 Hz), 2.70–2.60 (1H, m), 2.48–1.00 (23H, m), 2.32 (3H, s), 0.97 (3H, s), 0.84 (3H, s), 0.82 (3H, s), 0.77 (3H, s), 0.70 (3H, s); ¹³C NMR (125 MHz, CDCl₃): δ = 212.2, 142.6, 137.9, 129.3, 128.2, 126.5, 125.4, 78.9, 63.6, 60.8, 59.2, 55.4, 43.0, 42.5, 42.1, 40.6, 38.9, 38.3, 38.1, 35.1, 28.0, 27.4, 23.9, 23.0, 21.4, 18.0, 17.8, 17.3, 16.3, 15.5, 15.2, 14.2; HR-MS (CI) calcd for [C₃₂H₄₈O₂+NH₄]⁺: 482.3998, found: 482.4004.

1: To freshly distilled CH₃SO₃H (0.18 mL) under argon was added P₂O₅ (29 mg) in one portion, and the mixture was stirred at 23 °C for 2 h until a homogeneous solution was obtained. Alcohol **8** (4.9 mg, 10.5 μmol) was dissolved in ether (0.1 mL plus 0.1 mL for rinsing) and added dropwise to the acid mixture through a cannula. The resulting cloudy mixture was stirred at 23 °C for 15 min, at which point thin-layer chromatography indicated complete conversion into a single spot suggestive of a very nonpolar substance. Crushed ice was then added, and the mixture was extracted with ether (3 × 10 mL). The ethereal extracts were washed with water, aqueous NaHCO₃, and brine, dried (Na₂SO₄), and concentrated in vacuo. Since ¹H NMR analysis indicated that two olefinic products (70%) were present in addition to the desired product **1** (30%), the mixture was treated with CH₃COOH (0.9 mL) and concentrated H₂SO₄ (0.1 mL) in the form of a suspension at 23 °C for 20 h. The acidic mixture was then diluted with water and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic solution was washed with saturated solution of NaHCO₃ and then brine, dried (Na₂SO₄), and concentrated in vacuo. The ¹H NMR spectrum of the residue now indicated a homogeneous final product, which was crystallized from CH₂Cl₂/MeOH to afford pure **1** (3.8 mg, 81%) as very fine thin plates: [α]_D²³ = -35.38 (c = 0.26 in CHCl₃) [ref.^[1] [α]_D²³ = -38 (c = 0.37 in CHCl₃)]; m.p. 268–270 °C (ref.^[1] m.p. 268–269 °C); IR (neat): ν̄ = 2942, 2924 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂): δ = 7.10 (1H, d, J = 8.0 Hz), 6.89 (1H, d, J = 8.0 Hz), 6.81 (1H, s), 2.85 (1H, dd, J = 6.5, 16.5 Hz), 2.76 (1H, dd, J = 7.1, 11.4 Hz), 2.35 (1H, dt, J = 3.2, 12.4 Hz), 2.23 (3H, s), 1.90–1.00 (23H, m), 1.14 (3H, s), 0.91 (3H, s), 0.86 (3H, s), 0.83 (6H, s), 0.80 (3H, s); ¹³C NMR (125 MHz, CD₂Cl₂): δ = 147.90, 135.34, 134.65, 129.51, 126.74, 124.80, 61.58, 61.50, 56.88, 56.24, 42.50, 42.11, 42.08, 41.14, 40.13, 38.10, 38.07, 38.06, 37.81, 33.53, 33.38, 31.22, 26.23, 21.45, 20.81, 19.06, 18.70, 18.27, 18.20, 17.57 (two peaks in CDCl₃: 17.52, 17.49), 17.43, 16.29; HR-MS (EI) calcd for [C₃₃H₅₀]⁺: 446.3913, found: 446.3921. All data matched those of the authentic natural product. The synthetic material coeluted with the authentic natural product on thin-layer chromatography: R_f = 0.41 (hexane), 0.67 (benzene/pentane, 1/10).

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[11] Prepared from (6S)-6,7-oxidogeranyl bromide as described previously for the farnesyl^[3] and geranylgeranyl^[4] homologues.

A Short Synthesis of (±)-Matrine**

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Matrine (**1**) is the main alkaloid found in *Sophora flavescens* Ait. and belongs to a family of about two dozen members with the same basic tetracyclic skeleton (Figure 1).^[1] Some of these compounds (such as allomatrine, sophoridine,

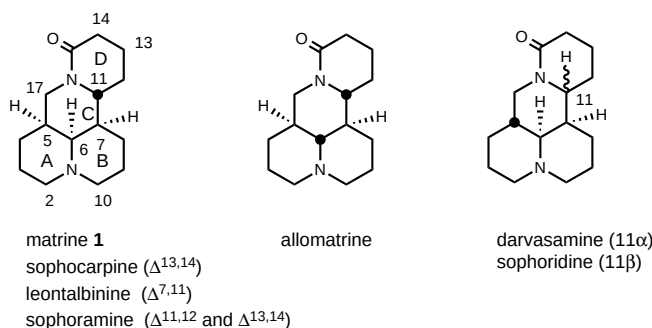


Figure 1. Some alkaloids of the matrine family.

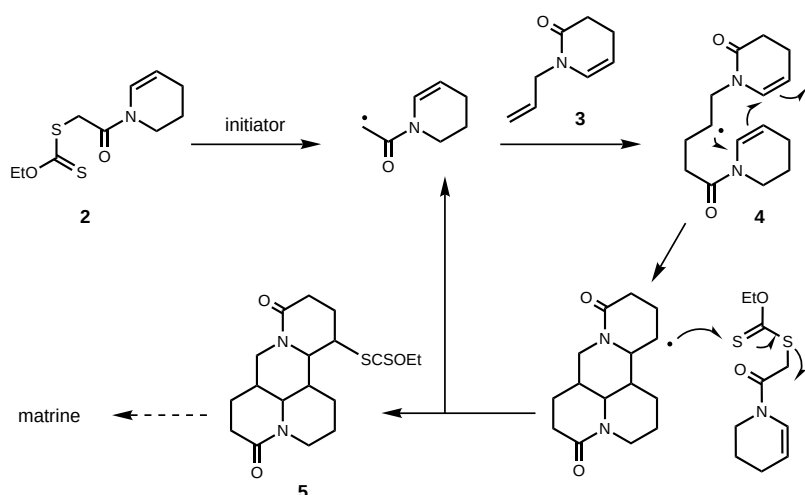
and darvasamine) differ only in the relative stereochemistry at the ring junctions; others contain one or more double bonds (leontalbinine, sophoramine) or a hydroxyl group (sophoranol or 5α-hydroxymatrine). Matrine has been claimed to have antiulcerogenic and anticancer activities, but information on these biological aspects is still scant.^[1] Here we describe a short, convergent synthesis of (±)-matrine involving a radical cascade reaction of a xanthate as the key step.

The three earlier total syntheses of matrine^[2] rely on traditional ionic chemistry; the most recent by Chen and co-workers^[2a] is biomimetic in its conception and is based on an

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Scheme 1. Radical cascade reaction for the one-step construction of the matrine skeleton.

elegant intramolecular Mannich reaction. In contrast, our approach (Scheme 1), hinges on the possibility of building the tetracyclic framework by two consecutive radical cyclizations. Six-membered ring closure via radical intermediates is usually slower and therefore more difficult to accomplish than the formation of five-membered rings.^[3] Earlier work on simpler bicyclic perhydroquinolizidines by Beckwith et al.^[4] revealed that premature reduction can occur in competition with the desired cyclization when the radical is generated with tributyltin hydride; slow (syringe pump) addition of the stannane was necessary. We hoped to avoid such a shortcoming by exploiting the inherently long lifetime of radicals created by the xanthate transfer process.^[5]

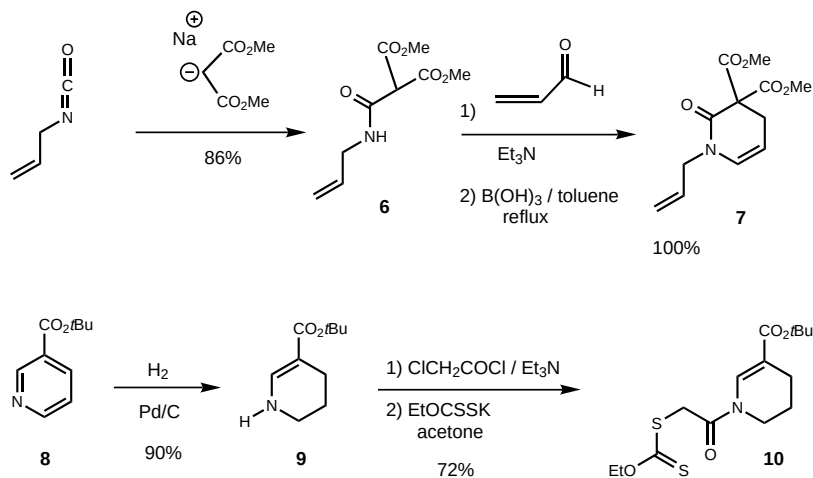
Initially, the most direct route to matrine seemed to conduct the radical cascade starting with the two relatively unsubstituted substrates **2** and **3**, exactly as shown in Scheme 1. However, in a preliminary study, **2** and **3** were prepared and tested with little success: Neither the regiochemistry (the radical derived from xanthate **2** did not selectively attack the terminal double bond in **3** and even appeared to react with the double bond in its own precursor **2**) nor the relative stereochemistry could be controlled. Complex mixtures were thus invariably obtained. But even if these difficulties were overcome, we would still be faced by the issue of selectively reducing the lactam in ring A of adduct **5** without affecting the lactam in ring D. In view of the very close similarity of the two lactams, this was certainly not a trivial matter. After some further model studies, a better route which addressed most of these problems eventually emerged.

First, the olefinic partner **7** was selected. The two geminal ester functionalities should protect the carbonyl group of the lactam against reduction later in the synthesis and shield the endocyclic double bond to a certain extent, making it less susceptible to radical attack. Its synthesis was straightforward (Scheme 2): Addition of the anion of dimethyl malonate to commercially available allyl

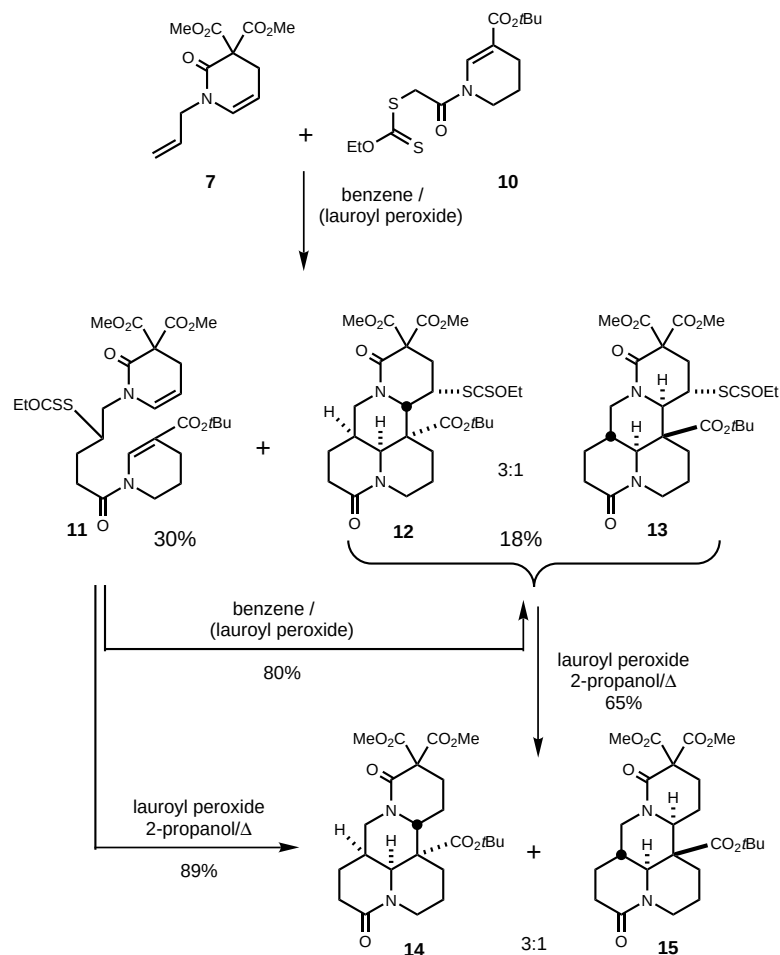
isocyanate cleanly gave amide **6**. The reaction of malonate anions with isocyanates was studied by Dieckmann et al. early this century,^[6a] but has not found much use since despite its obvious importance.^[6b] Amide **6** smoothly underwent Michael addition to acrolein in the presence of triethylamine, and the intermediate aminal was dehydrated without prior purification by heating with boric acid in toluene to afford the desired cyclic enamide **7** in 86% overall yield. The xanthate component **10** was also easily prepared in 64% overall yield from *tert*-butyl nicotinate (**8**) through catalytic hydrogenation to enamine **9**,^[7] chloroacetylation, and finally reaction with potassium ethyl xanthate in acetone (Scheme 2).

We now examined the key radical cyclization. Heating a mixture of **7** (3 equiv) and **10** (1 equiv) in benzene (0.3M in **10**) in the presence of a small amount of lauroyl peroxide as the initiator gave three major compounds: the two tetracyclic derivatives **12** and **13** in a combined yield of 18% (in a ratio of 3:1 in favor of **12**, which has the relative stereochemistry of matrine; **13** has the allomatrine skeleton) and the bicyclic intermediate **11** (30%); the radical arising from the first addition transferred a xanthate group before undergoing cyclization (Scheme 3). Since some starting xanthate (15–20%) was recovered, the corrected yield for the various adduct is in fact a little higher. Compound **11** is itself a xanthate, and merely reexposing it to lauroyl peroxide converted it into the same mixture of the two tetracyclic isomers **12** and **13** in 80% yield. This is an enormous advantage of the xanthate transfer method: The radical can always be regenerated in order to force an otherwise reluctant cyclization, unlike the organotin hydride process where reduction of the radical by the stannane is fast and irreversible.

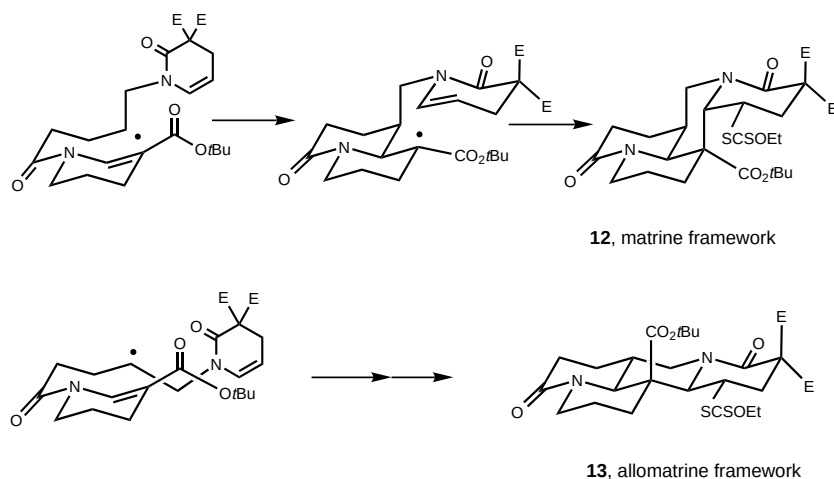
Four new bonds (including the quite difficult *intermolecular* C–C bond) and five contiguous chiral centers have thus been created in one operation with reasonable efficiency and fair stereoselectivity. It is the first cyclization that provides the stereochemistry shown in Scheme 4. The transition state with



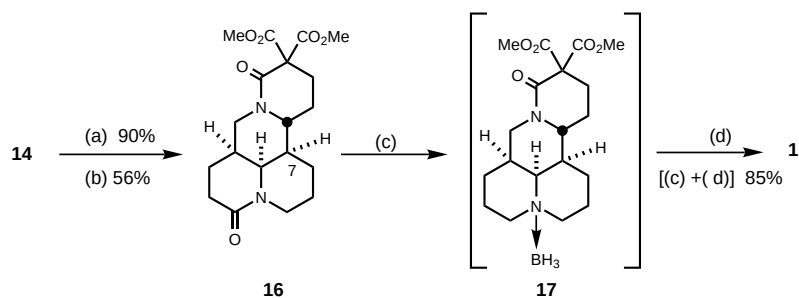
Scheme 2. Synthesis of precursors **7** and **10** for the cascade radical reaction.



Scheme 3. Key radical cascade reaction and reductive cleavage of the xanthate group.



Scheme 4. Stereochemistry of the radical cyclization.



the pseudo-axial disposition of the side chain is slightly less congested than the alternative with a pseudo-equatorial conformation, even though the latter would ultimately lead to the thermodynamically more stable all-*trans* allomatrine structure. The difference between the energies of the two transition states must be small, since the ratio of the two isomeric products is only 3:1. The relative configurations were determined by NMR spectroscopy, especially in relation to a model adduct for which an X-ray structure was secured, and eventually confirmed by the final conversion into matrine. The transfer of the xanthate in the last propagation step takes place reversibly to give the least hindered, thermodynamically more stable, equatorial xanthate group at C-12.

Although reductive cleavage of the xanthate group can be effected with tributylstannane^[8] or “nickel boride” (formed in situ from NiCl₂ and NaBH₄),^[9] we elected to use a combination of lauroyl peroxide and isopropyl alcohol.^[10] Portion-wise addition of lauroyl peroxide (total 1.3 molar equiv) to a solution of the mixture of tetracyclic adducts **12** and **13** at reflux afforded the corresponding derivatives **14** and **15** in 65% yield and in the same 3:1 ratio (Scheme 3). The advantage of this method is that hydrogen atom transfer from isopropyl alcohol is relatively slow, and exposure of the uncyclized intermediate **11** to the same reaction conditions provided the cyclized and reduced mixture of **14** and **15** directly and in excellent yield (89%, Scheme 5).

Chromatographic separation of **14** and **15** is easier than that of the xanthate precursors and was carried out preparatively at this stage. The remaining steps consisted of removing the extra functionalities present in **14**. Treatment with trifluoroacetic acid caused selective cleavage of the *tert*-butyl ester group at C-7 in 90% yield. The free carboxylic acid was then reductively removed with the ester method by Barton et al.^[11] to give intermediate **16** in an overall yield of 56%. Not unexpectedly, delivery of the hydrogen atom from the thiol took place from the least hindered convex face (Scheme 4). Finally, reduction of the lactam in ring A was accomplished cleanly with BH₃·Me₂S in THF; the lactam in ring D was completely protected by the two

Scheme 5. Final steps of the synthesis. a) CF₃CO₂H, CH₂Cl₂; b) (COCl)₂, CH₂Cl₂; *N*-hydroxy-4-methylthiazolinethione, Et₃N; *tert*-dodecanethiol, cyclohexane, reflux, (cat. azobisisobutyronitrile); c) BH₃·Me₂S, THF; d) 2M HCl, reflux.

neighboring ester groups. The resulting crude tertiary amine, which could be isolated as the borane complex **17**, was simply heated with dilute hydrochloric acid to effect both hydrolysis and decarboxylation of the geminal diester moiety. ($\pm$)-Matrine was obtained as the hydrochloride salt in 85 % overall yield. The ^1H and ^{13}C spectra (400 MHz) of the free base in deuterated benzene was identical to those described by Chen et al.^[2a]

The short, convergent approach to matrine we implemented here highlights the utility of several radical processes, especially the cascade reaction mediated by the xanthate group. In principle, the *tert*-butyl ester group can be replaced by a bulkier group to improve selectivity or, perhaps even better, by a chiral amide unit, which would allow an asymmetric synthesis of matrine and its congeners.^[12]

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Micelle-Bound Metalloporphyrins as Highly Selective Catalysts for the Epoxidation of Alkenes**

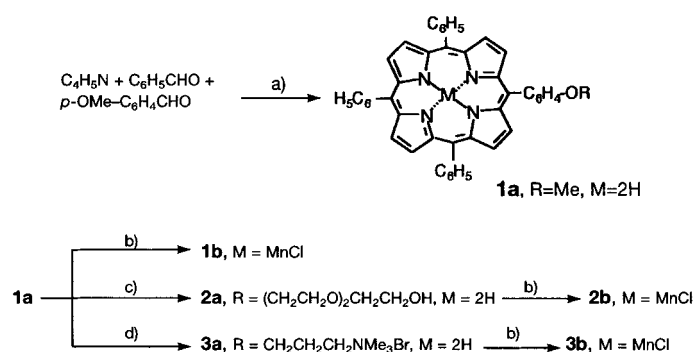
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The synthesis and the study of metalloporphyrins as catalysts for the oxidation of organic substrates is an active area of research.^[1] Much effort has been devoted to the construction of systems able to mimic the activity of metalloenzymes such as the family of cytochrome P₄₅₀ dependent monooxygenases. Their reactivity, in terms of turnover number, and regio- and stereoselectivity, can be finely modulated by the presence of substituents on the macrocycle. Encouraging results were obtained when the reactions were performed in the ordered microenvironment offered by vesicles, liposomes, and monolayers,^[2] and when dendritic polymers were introduced along the periphery of the pyrrolic macrocycle.^[3] Guilard et al. reported recently on the synthesis and the spectroscopic characterization of some metalloporphyrin derivatives that are able to form micellar aggregates.^[4] The use of an organized medium^[5] is known to strongly affect the rate and the selectivity of many organic reactions^[6] as well as some metal-catalyzed reactions.^[7] With this aim we began a study on the synthesis and the reactivity of porphyrin derivatives bearing a suitable, appended functionality making them soluble in the micellar phase.^[8] We report here the results obtained in the application of these porphyrins as catalysts for the epoxidation of selected alkenes carried out in the presence of surfactants.

Porphyrin **1a** was synthesized and demethylated according to literature methods (Scheme 1).^[9] Williamson coupling of the intermediate 5-(*p*-hydroxyphenyl)-10,15,20-triphenylporphyrin with triethyleneglycol monochloride and 1-bromopropyl-3-trimethylammonium bromide gave the porphyrins **2a** and **3a**, respectively, in good yield. The metalloporphyrins **1b**, **2b**, and **3b** were obtained by standard procedures,^[10] purified by column chromatography and crystallization, and characterized (^1H NMR, UV/Vis, and FAB-MS). Detailed experimental procedures along with the spectroscopic and analytical data will be reported elsewhere. The metalated porphyrins **2b** and **3b** are fairly soluble in aqueous media.

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Scheme 1. Synthesis of porphyrins **1a–3a** and **1b–3b**. a) $\text{CH}_3\text{CO}_2\text{H}$, Δ , 6 h, 15 %; b) $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$, DMF, 80°C , 3 h, 87 %; c) BBr_3 , CH_2Cl_2 , 0°C , 12 h, 85 %; $\text{ClCH}_2\text{CH}_2(\text{OCH}_2\text{CH}_2)_2\text{OH}$ (2.5 equiv), KOH, DMF, 80°C , 12 h; dilute HCl, 65 %; d) BBr_3 , CH_2Cl_2 , 0°C , 12 h, 85 %; $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{NMe}_3\text{Br}$ (3 equiv), K_2CO_3 , THF/MeCN 1:1, 20°C , 5 d; dilute HCl, 70 %.

Micellar phase solutions of the porphyrin derivatives were prepared by injection with 1,4-dioxane and sonication.^[2b] The incorporation of the macrocycles into the micellar phase upon dissolution was followed by ^1H NMR and UV/Vis spectroscopy. The inclusion of the porphyrins **1a**, **2a**, and **3a** in D_2O /surfactant solutions (Brij 35 and CTAB) causes, as expected, broadening of the proton signals.^[11] Typical changes in the UV/Vis spectra of the porphyrins in the presence of surfactants were also observed, confirming the inclusion of the macrocycles into the micellar phase. Coordination of an additional axial ligand (e.g. imidazole) to the metallomacrocycle embedded inside the micellar assemblies was ascertained by monitoring the UV/Vis spectrum (Table 1).^[12]

Table 1. Spectroscopic data of porphyrins incorporated in aqueous micellar phase.

Porphyrin	Absorptions ^[a] λ_{max} [nm]					
1b ^[b]	380	400	422	468 (Soret)	567	601
1b ^[c]	383	400	423	470 (Soret)	571	603
1b ^[d]		402		472 (Soret)		635
1b ^[e]	386	407		472 (Soret)		635
1b ^[f]	394			472 (Soret)		635
2b ^[g]	381	401	420	469 (Soret)	568	601
2b ^[c]	384	404		468 (Soret)	571	605
2b ^[d]	376	403		471 (Soret)	578	616
3b ^[g]	382	403	422	470 (Soret)	568	602
3b ^[c]	385	403	419	471 (Soret)	571	604
3b ^[f]	381	406		472 (Soret)	585	622

[a] [Porphyrin] = 1×10^{-5} M. [b] In methanol. [c] 1×10^{-2} M Brij 35. [d] 1×10^{-2} M Brij 35, 5×10^{-3} M imidazole. [e] 1×10^{-2} M CTAB. [f] 1×10^{-2} M CTAB, 5×10^{-3} M imidazole. [g] In water.

Epoxidation of olefins such as cyclooctene, cyclohexene, and 1-octene in the presence of NaClO and an excess of imidazole (the axial ligand) proceeded smoothly at room temperature to give the corresponding epoxides. Blank experiments carried out without catalysts yielded the chlorohydrin derivatives as major products (Table 2). When the reaction is conducted in the presence of the surfactant, conversion is much higher than when the reaction is performed in water/ethanol and water/dioxane, media that

Table 2. Epoxidation of alkenes with NaClO in micellar phase.^[a]

Entry	Catalyst	Medium	Substrate	Yield [%]
1	1b	Brij 35	cyclooctene	26
2	1b	CTAB	cyclohexene	< 5
3	1b	Brij 35	1-octene	25
4	2b	CTAB	cyclooctene	24
5	2b	Brij 35		85
6	2b	^[b]		25
7	2b	Brij 35	cyclohexene	10
8	2b	CTAB		5
9	2b	Brij 35	1-octene	48
10	3b	CTAB	cyclooctene	8
11	3b	Brij 35		25
12	3b	^[c]		23
13	3b	CTAB	cyclohexene	96
14	3b	Brij 35		15
15	3b	^[c]		< 5
16	3b	CTAB	1-octene	< 5
17	–	Brij 35	cyclooctene	0 ^[d]
18	–	CTAB	cyclohexene	0 ^[d]
19	–	Brij 35	1-octene	0 ^[d]

[a] In a typical reaction NaClO solution (100 μL of a 1 M solution; 100 μmol), which was buffered to roughly pH 10.5 by addition of solid NaHCO_3 , was added in 10 μL aliquots over 2 h to 2 mL surfactant solution ($1-3 \times 10^{-2}$ M) containing the porphyrin catalyst (1 μmol), imidazole (20 μmol), and olefin (10 μmol). An internal standard (*n*-decane or *n*-dodecane) was added, and an aliquot of the reaction mixture (100 μL) was removed, quenched with methanol (200 μL) to disrupt the micellar aggregates, filtered from the precipitated salts, and analyzed by GC and GC-MS. Runs were duplicated and were reproducible within 5 %. [b] 1,4-dioxane/water 1/1 v/v. [c] EtOH/water 1/1 v/v. [d] Chlorohydrin is formed along with some 1,2-diol.

reproduce the polarity of the aqueous interface of CTAB and Brij 35, respectively. Another striking feature of the reaction is the large influence exerted by the nature of the micellar phase on the chemoselectivity of the epoxidation. With catalyst **3b** in the presence of CTAB, for example, the epoxidation of cyclohexene is nearly quantitative, whereas the yield of the epoxide dramatically drops in the case of cyclooctene. An opposite trend is evident in the case of the system **2b**/Brij 35, which converts cyclooctene efficiently but cyclohexene only modestly. This could be ascribed to the different location of the substrate in the micelles. The less hydrophobic cyclohexene, which is located close to the aqueous interface, can better interact with the cationic porphyrin **3b** located in the same region.^[13] In the case of the neutral amphiphilic porphyrin **2b**, which is located in a more hydrophobic region of Brij 35 aggregates, optimal interaction is possible only with the more hydrophobic eight-membered ring. The same explanation holds for the results obtained with 1-octene. These results are in agreement with earlier studies which pointed out the crucial role played by olefin hydrophobicity in electrophilic halogenation reactions.^[14] In experiments with “crossed systems” (**2b**/CTAB and **3b**/Brij 35) and with the nonspecifically reacting **1b** low yields of epoxides were observed which were similar to those obtained in the absence of surfactant. This is possibly due to the less than optimal interaction between the catalyst and the surfactant, since the two have polar heads of different nature. The solubilities of porphyrins **2b** and **3b** in the neutral and the cationic surfactants could also play a role. Further experi-

ments are needed to fully understand the intimate nature of the interactions involved. Moreover, the relevance of the result obtained with 1-octene in Brij 35—epoxidation in up to 48 % yield—must be pointed out. These results compare very well with those reported for reactions carried out with simple porphyrins,^[15] which underlines the value of our system. Olefins such as 1-octene, cyclooctene, and cyclohexene could be oxidized with NaClO in homogeneous medium to give good yields of the epoxides only in the presence of polyhalogenated or tailor-made metalloporphyrins.

Finally, in the presence of micellar aggregates the catalysts showed remarkable stability toward the degradative action of NaClO. In fact, under the conditions used for the epoxidation less than 5 % degradation had occurred (UV/Vis) even after a reaction time of two days.^[16]

The catalytic system reported here may be a good mimic for the enzyme-catalyzed oxidation reaction, owing to its high stability and its high degree of selectivity with regard both to the substrate and the formation of epoxides. Further studies aimed at the construction of more robust macrocycles suitable for use with stronger oxidants on a wider range of substrates are underway.

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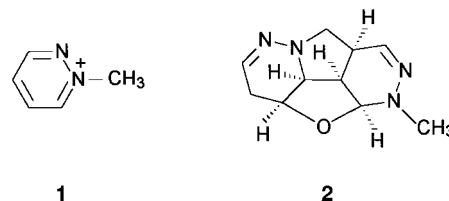
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A New Tetracycle from Dimerization of the *N*-Methylpyridazinium Ion in Aqueous Solution**

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Dedicated to Professor David A. Buckingham on the occasion of his 60th birthday

During an investigation into OD[−]-catalyzed H–D exchange in the *N*-methylpyridazinium ion (**1**), we observed that in aqueous alkaline solution this species stereospecifically forms the tetraazafluorene **2**.^[1] Despite an extensive literature



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search we could find no reference to dimerization of related *N*-alkylazinium or diazinium cations, nor has a tetracycle possessing the structural features of **2** been reported. However, 1,3-dipolar cycloaddition of acetylenic compounds to pyridazinium ylides has long been a recognized route to azaindolizines,^[2] and certain *N*-ethyltriazinium ions are known to dimerize to tricyclic hexaazaphenanthrenes.^[3] Remarkably, no fewer than four separate and consecutive processes are observed when dimerization of **1** is monitored with ¹H NMR spectroscopy (D₂O solution, 25.0 °C), and a study of these has allowed the mechanism of formation of **2** to be described in detail.

The tetracycle is rapidly formed upon treatment of **1** as its I[−] or ClO₄[−] salt with strong alkali at room temperature. Thus, in a one-pot synthesis, the I[−] salt of **1** affords **2** in 58% recovered yield^[4] when the reaction is carried out in aqueous 1M NaOH at room temperature and worked up after 15 min. The structure of **2** was initially assigned with a combination of COSY, HETCOR, and NOE spectroscopic methods and was later confirmed by X-ray crystallography. The structure of one of the four independent molecules contained in the asymmetric unit (Figure 1) shows that the all-*cis* ring junctions

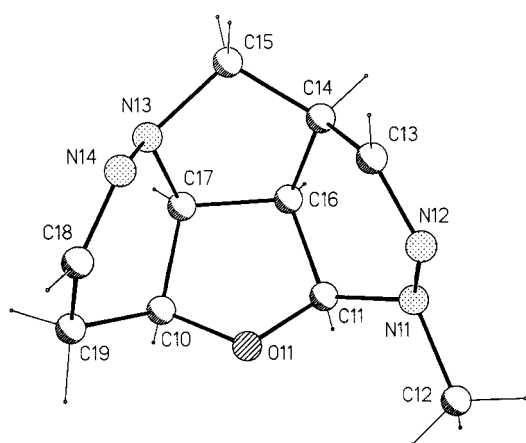
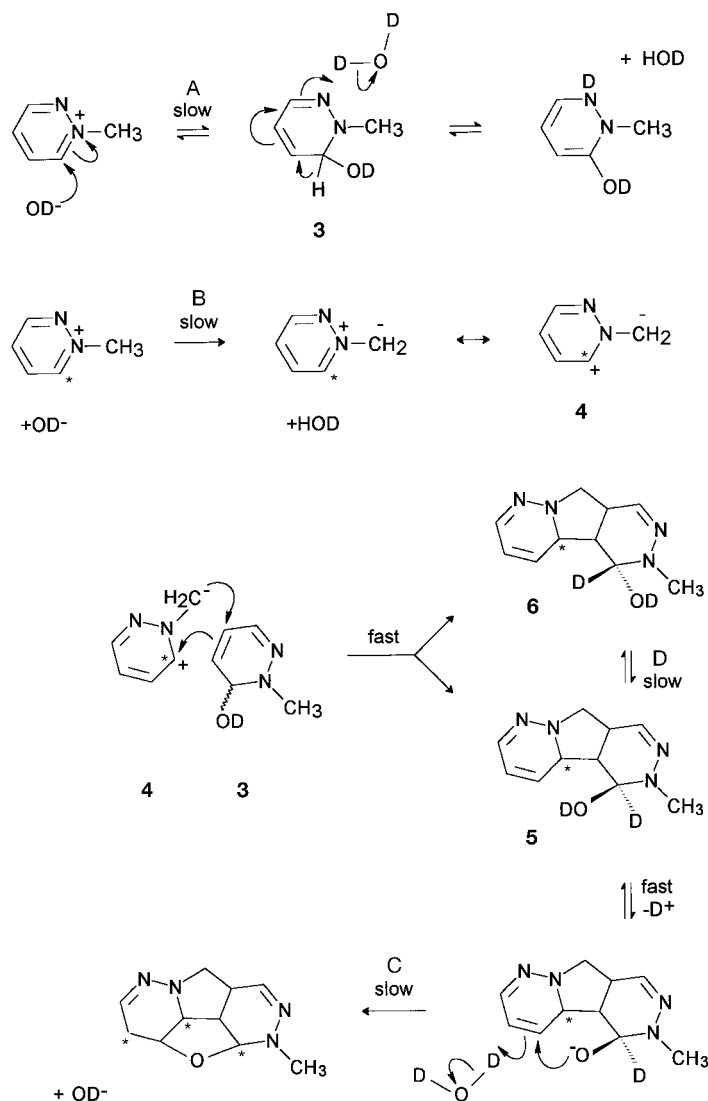


Figure 1. Molecular structure of **2** with atom-numbering scheme.

result in a molecule with a well-defined cavity (diameter ca. 4 Å, depth 2 Å). All hydrogen atoms except those of the CH₃ group lie on the exterior surface of the molecule.

The available evidence is consistent with dimerization by the processes shown in Scheme 1. The first reaction visible by ¹H NMR spectroscopy for **1** in alkaline D₂O is H–D exchange at the *ortho* position (H-6, δ = 9.67; equilibrium A in Scheme 1), which ultimately accounts for deuterium incorporation at C₁₁ and C₁₇ in **2** (numbering of atoms according to the crystal structure). Exchange appears to involve attack of OD[−] at the *ortho* carbon atom (intermediate **3**), with subsequent hydrogen transfer facilitated by participation of the non-methylated nitrogen atom in a concerted process.

The second reaction is readily followed for pD > 11.5, where the remaining proton signals of **1** at δ = 9.48 (1H, d), 8.56 (2H, m), and 4.66 (3H, s) decay in concert with simultaneous appearance of a plethora of new resonances.



Scheme 1. Mechanism for the formation of **2** in D₂O. When not denoted explicitly as D, sites with incorporation of deuterium atoms are labeled with an asterisk.

A major distinguishing feature of this process is the large primary kinetic isotope effect observed when the CH₃ group of **1** is replaced by CD₃. The observed rate constants at pD 12.30 are $k_{\text{H(obs)}} = (5.42 \pm 0.16) \times 10^{-4} \text{ s}^{-1}$ and $k_{\text{D(obs)}} = (8.06 \pm 0.19) \times 10^{-5} \text{ s}^{-1}$, respectively, hence $k_{\text{H}}/k_{\text{D}} = 6.7 \pm 0.6$. Thus, deprotonation of the methyl group of the reactant is rate determining for this step (step B in Scheme 1). Among the NMR signals that appear as a consequence of the second process are two N-Me singlets at δ = 2.77 and 2.85, corresponding to diastereomers **5** and **6** ([**5**]:[**6**] = 1.5:1). Formation of these species occurs via intermediates **3** and **4** in a step that necessarily occurs faster than ylide reprotonation, since no deuterium incorporation is seen in either the methyl group or the C₁₅ methylene group of the final product. The efficient scavenging of **4** by **3** is quite remarkable, since the latter never accumulates to a level that is detectable.

Figure 2 shows changes in the intensities of the N-Me signals at pD = 12.65 as a consequence of the second, third, and fourth reactions. The third process reaches an advanced

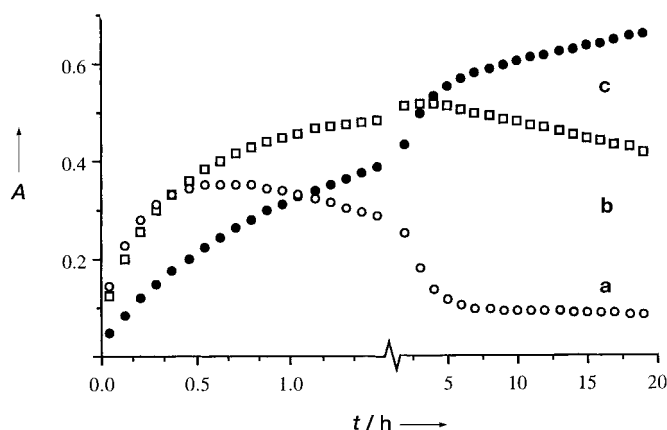


Figure 2. Changes in intensity (peak area *A*) as a function of time for the N-Me signals at $\delta = 2.77$ (a, $\circ$), 2.85 (b, $\square$), and 2.90 (c, $\bullet$) during dimerization of **1** in D_2O (ClO_4^- salt, 7.38 mg in 0.80 mL of 0.50 M phosphate buffer, $pD = 12.65$).

stage before the second is fully complete and is apparent through the growth of an additional N-Me resonance at $\delta = 2.90$. This increase occurs at the expense of the signal at $\delta = 2.77$ and corresponds to direct formation of **2** from deprotonated **5** (step C, Scheme 1). The reaction occurs with incorporation of deuterium at the adjacent carbon atom, which labels the C_{19} methylene group of **2**. The fourth process is a very slow conversion of **6** into **2**, as seen in the decay of the resonance at $\delta = 2.85$ as the signal at $\delta = 2.90$ increases in intensity (Figure 2). This reaction probably involves an inversion at carbon to give **5**, and cyclization as described above (step D, Scheme 1).

That **1** dimerizes so readily is certainly due to a fortuitous combination of steric and electronic factors not duplicated in other N-alkylated heterocycles.^[5] The ability to add OH^- is clearly an important ingredient, since **3** emerges as a vital intermediate. Steric constraints may be responsible for a 10^2 -fold reduction in dimerization rate when CH_3 in **1** is replaced by CH_3CH_2 ; however, the fact that electron donation deters ylide formation could also play a role. Whatever the exact nature of the influences, they lead to a new type of heterocycle in which a complex array of rings is assembled with a high degree of stereoselectivity.

Experimental Section

2: A solution of the I^- salt of **1** (170 mg) in H_2O (10 mL) was treated with NaOH (0.40 g, 10 mmol), and the solution was allowed to stand for 15 min. The aqueous phase was then saturated with NaCl and extracted with $CHCl_3$ (5×10 mL). The organic phase was decolorized with charcoal and evaporated, and the residue was crystallized from $CHCl_3$ /pentane to yield 46 mg (58%) of white crystals that slowly turn yellow on exposure to light. Elemental analysis calcd for $C_{10}H_{14}N_4O$: C 58.25, H 6.80, N 27.18; found: C 58.02, H 7.20, N 27.38; ^1H NMR (300 MHz, $CDCl_3$, $25^\circ C$, TMS): $\delta = 2.03$ (ddd, $^3J(H,H) = 16.5, 3, 2$ Hz, 1 H, $H_{19}\beta$), 2.41 (brdd, $^3J(H,H) = 10, 6$ Hz, 1 H, H_{17}), 2.43 (ddd, $^3J(H,H) = 16.5, 5, 3$ Hz, 1 H, $H_{19}\alpha$), 2.98 (s, 3 H, CH_3), 3.44 (ddd, $^3J(H,H) = 10, 8, 7$ Hz, 1 H, H_{16}), 3.44 (dd, $^3J(H,H) = 12.5, 6$ Hz, 1 H, $H_{13}\beta$), 3.86 (d, $^3J(H,H) = 12.5$ Hz, 1 H, $H_{15}\alpha$), 4.00 (dd, $^3J(H,H) = 8, 6$ Hz, 1 H, H_{14}), 4.11 (m, half-width = 14 Hz, 1 H, H_{10}), 4.78 (d, $^3J(H,H) = 7$ Hz, 1 H, H_{11}), 6.80 (dt, $^3J(H,H) = 5, 2$ Hz, $^4J(H,H) = 1.5$ Hz, 1 H, H_{18}), 7.11 (s, 1 H, H_{13}); ^{13}C NMR (75 MHz, $CDCl_3$, $25^\circ C$, TMS): $\delta = 23.8$ (C_{19}), 34.5

(C_{17}), 43.7 (CH_3), 48.7 (C_{16}), 62.2 (C_{15}), 66.4 (C_{14}), 68.3 (C_{10}), 87.8 (C_{11}), 136.2 (C_{18}), 148.3 (C_{13}).

NMR spectra (^1H , ^{13}C) were recorded at $25.0 \pm 0.5^\circ C$ with a Varian VXR-300 NMR spectrometer. Rate constants for reactions at constant pD were obtained from peak areas with least-squares fitting routines for simple first-order or consecutive first-order situations as appropriate. Values of the rate constants were independent of substrate concentration (3.5–15 mg in 0.80 mL of buffered D_2O solution). The pD values were determined with a Radiometer pHM 82 pH meter. Calibration for measurement in D_2O solution was accomplished by the method of Fife and Bruice;^[6] $pD = pH(\text{measured}) + 0.36$ ($25.0^\circ C$).

Crystal data for colorless blocks grown from 1-butanol: crystal dimensions $0.70 \times 0.60 \times 0.20$ mm; triclinic; space group $P1$; $a = 8.6390(10)$, $b = 10.490(2)$, $c = 12.391(2)$ Å, $\alpha = 99.080(10)$, $\beta = 96.500(10)$, $\gamma = 113.880(10)^\circ$, $V = 994.2(3)$ Å³; $Z = 4$; $\rho_{\text{calcd}} = 1.378$ Mg m⁻³; $T = 168(2)$ K; $2\theta_{\text{max}} = 45^\circ$, $MoK\alpha$ radiation ($\lambda = 0.71073$ Å); ω scans; 2513 measured reflections, 2513 independent reflections, 2513 refined reflections; absorption correction not applied; structure solution by direct methods (SHELXS-97);^[7] refinement by full-matrix least squares on F^2 (SHELXL-97);^[8] 245 parameters; 3 restraints; $wR2 = 0.2350$ for all data and a conventional $R1 = 0.0856$ for 2220 reflections with $I > 2\sigma I$; largest difference electron density peak and hole 0.502 and -0.444 e Å⁻³. 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-100734. 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).

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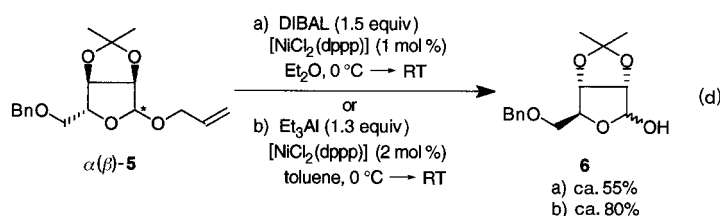
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Table 2. [NiCl₂(dppp)]-catalyzed deallylation of diethers.

Entry	Substrate R	Solvent	Product	Yield [%] ^[a]
1	3a	<i>t</i> BuMe ₂ Si	4a	92
2	3b	4-MeOC ₆ H ₄	4b	95
3	3c	benzyl	4c	95
4	3d	allyl	4d	51
5	3e	prenyl	4e	80
6	3f	MOM	4f	90
7	3g	THP	4g	89
8	3h	acetyl	4h	73
9	3i	pivaloyl	4i	85
10	3j	benzoyl	4j	80

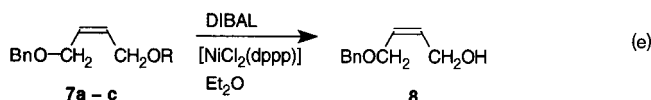
[a] Yield after SiO₂ column chromatography. [b] Reaction was carried out with DIBAL (1.5 equiv) and [NiCl₂(dppp)] (1 mol %) at 0 °C → RT, 2 h. [c] Reaction was carried out with NaBH₄ (4.0 equiv) and [NiCl₂(dppp)] (4 mol %) at 0 °C → RT.

hemiacetal mixture **6**, in which the the acetonide functionality is intact, by selective deallylation and spontaneous epimerization [Eq. (d)]. However, the reaction was found to proceed



much better when triethylaluminum was used in place of DIBAL, because the hemiacetal functionality is more stable with the former reagent. Although ester functionalities (acetyl, pivaloyl, and benzoyl) are not incompatible with DIBAL as a reagent, when the ester substrates **3h–j** were treated with NaBH₄ in THF/EtOH the corresponding hydroxy esters **4h–j** were obtained in good yields (Table 2, entries 8–10).

Chemoselective cleavage of the allyl functionality was also demonstrated by the reaction of the allyl ethers of allyl alcohols [Eq. (e), Table 3]. Thus, the reaction of allyl (*Z*)-4-benzyloxy-2-butenyl ether (**7a**) occurred selectively at the



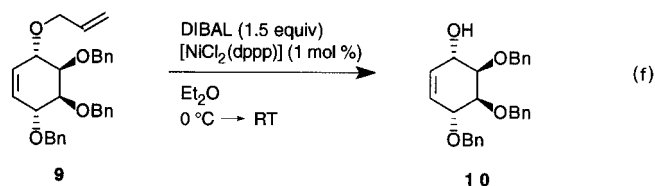
nonsubstituted allyl end to give the corresponding allyl alcohol **8a** in good yield. Facile chemoselective cleavage at the nonsubstituted allyl end was also observed with the secondary allylic substrate **9** to give the secondary allylic

Table 3. [NiCl₂(dppp)]-catalyzed deallylation of diallyl ethers.

Entry	Substrate	R	<i>t</i> [h]	Product	Yield [%] ^[a]
1	7a	allyl	2 ^[b]	8a	71
2	7b	prenyl	12 ^[b]	8b	0 ^[c]
3	7c	benzyl	12 ^[b]	8c	0 ^[c]

[a] Yield after SiO₂ column chromatography. [b] Reaction was carried out in Et₂O with DIBAL (1.5 equiv) and [NiCl₂(dppp)] (1 mol %) at 0 °C → RT. [c] Starting material was recovered unchanged.

alcohol **10** in 93 % yield [Eq. (f)]. On the other hand, no reaction occurred with either prenyl and benzyl (*Z*)-4-benzyloxy-2-butenyl ethers **7b** and **7c**, respectively, under the same conditions (Table 3).



The present study offers an extremely facile and selective deallylation procedure for a variety of allyl ethers and also confirms that the reaction proceeds by nickel-catalyzed hydroalumination–elimination. Because of its simplicity and chemoselectivity, this procedure will undoubtedly extend the use of allyl groups for the protection of a variety of hydroxyl compounds.

Experimental Section

To a stirred solution of **1a** (100 mg, 0.6 mmol) and [(dppp)NiCl₂] (3 mg, 6 μmol) in Et₂O^[10] (2 mL) under argon was added dropwise DIBAL (1.5 M in toluene, 600 μL, 0.9 mmol) at 0 °C. The mixture was stirred for 5 min at the same temperature and then for 2 h at room temperature. The mixture was diluted with Et₂O (3 mL), quenched by addition of H₂O (600 μL) and, after stirring for 1 h, dried directly over MgSO₄, filtered through a Celite pad, and concentrated under reduced pressure to leave the crude product, which was chromatographed on silica gel (3 g, Et₂O/hexane 1/4 v/v) to give pure **2a** (68 mg, 90 %).

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The Total Synthesis of Spirotryprostatin A**

Scott D. Edmondson and Samuel J. Danishefsky*

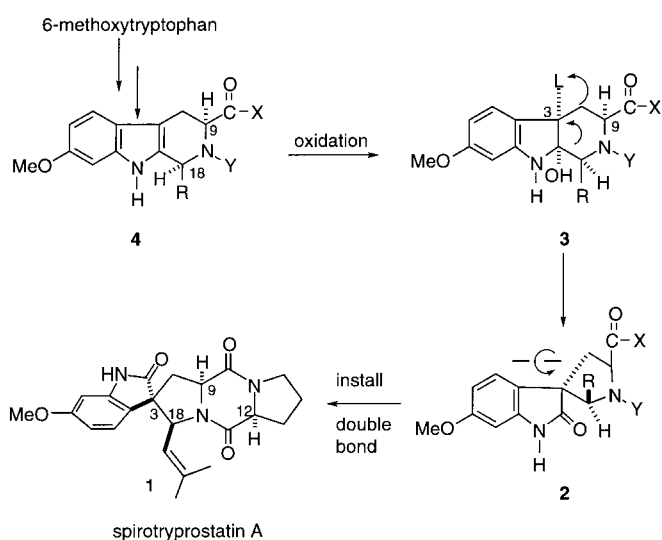
A growing number of alkaloids, formally derivable from L-tryptophan, that bear an additional pyrrole ring in the context of a diketopiperazine system, display a range of biological profiles resulting in cell cycle modulation.^[1] Our laboratory has particularly focused on those members of this class that also carry prenyl or "reverse prenyl" substituents. As a prelude to multidisciplinary investigations of structure–activity relationships (SAR) and the mode of action of these compounds, we have concerned ourselves with their total synthesis. To date, we have described the total syntheses of amauramine, the ardeemins, gypsetin, and tryprostatin B.^[2]

In this context our attention was drawn to the family of spiroindolinones reported in 1996, which are exemplified by spirotryprostatin A (**1**) (see Scheme 1).^[3] This compound and its dehydrocongener spirotryprostatin B^[4] are isolated from the fermentation broth *Aspergillus fumigatus* and manifest cell cycle inhibition at the G2/M phase with IC₅₀ values in the micromolar range. We began our research into this intriguing subgroup with a program directed toward a total synthesis of **1** and report herein the realization of this goal.

In all the members of the spirotryprostatin family the side chain is a 2-methylprop-1-enyl function, except in tryprostatin B, which bears a 3-methylbut-2-enyl group. Also requiring close attention was the fashioning of the spiro linkage of the pyrrole and indolinone sectors, as well as the correct relative stereochemistry between the spiro carbon, C3, and the side chain at C18, in the context of the L-tryptophan and L-proline related centers C9 and C12, respectively.

Our strategy relied on the construction of a β -carboline of the type **4** (Scheme 1). The precise timing for presentation of the diketopiperazine ring was not decided at the planning level. At an appropriate stage we would devise means for oxidation of the indole system ($\rightarrow$ **3**). Given the overall need for oxidative rearrangement, it seemed likely that structures **4**, **3**, and **2** would contain a virtual rather than an actual double bond.

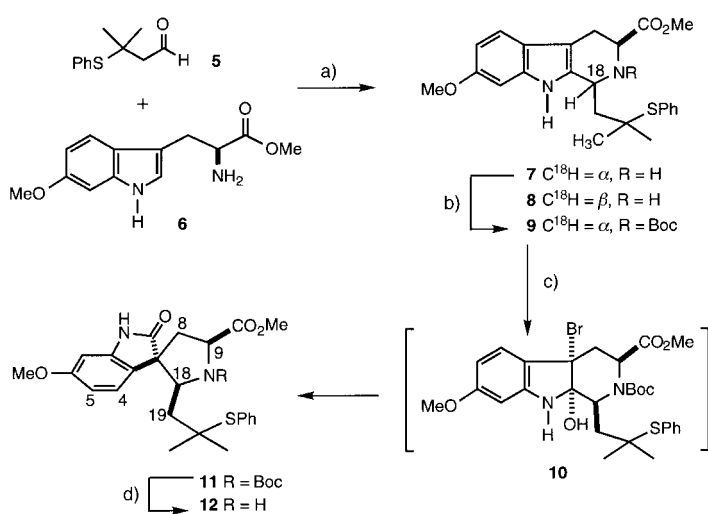
Implementation of the required absolute and relative stereochemistry required for a synthesis of **1** seemed to be feasible under the broad logic of Scheme 1. Thus, maintenance of the L configurations of the proline and tryptophan building blocks would dictate the stereochemistry of the diketopiperazine structure. The eventual stereochemistry of



Scheme 1. Synthetic strategy for spirotryprostatin A (**1**). X, Y = diketopiperazine unit or groups from which one can be generated; L = leaving group; R = group from which the 2-methylprop-1-enyl group can be generated.

the 2-methyl-1-propenyl function at C18 arises from its relationship to the two "fixed" centers at C9 and C12. The stereochemical connectivity between C18 and C3 would follow from the sense of oxidation of the indole double bond and the anticipated inversion of the configuration at C3 in the rearrangement step.

Our synthesis commenced with a Pictet–Spengler reaction of aldehyde **5** with the 6-methoxytryptophan derivative **6** (Scheme 2).^[5] As would be expected, the desired *cis* product **7** was favored at the kinetic level, albeit in only a 2:1 ratio.^[6] In light of the extensive and scholarly research of Cook et al., it was not surprising that under more forcing equilibrating conditions (HCl, MeOH, Δ , 24 h), **8**, the apparent thermodynamic product, prevailed.^[7] Amine **7** was readily protected as its *tert*-butylcarbamate derivative ($\rightarrow$ **9**). Treatment of **9** with



Scheme 2. Synthesis of the spiro framework. a) CH₂Cl₂, CF₃CO₂H, molecular sieves (4 Å), 0 $\rightarrow$ 20 °C, 88%; b) Boc₂O, CH₃CN, Et₃N, Δ , 84%;^[11] c) NBS, THF, H₂O, HOAc, 46%;^[11] d) CF₃CO₂H, CH₂Cl₂, 93%. Boc = *tert*-butoxycarbonyl; NBS = *N*-bromosuccinimide.

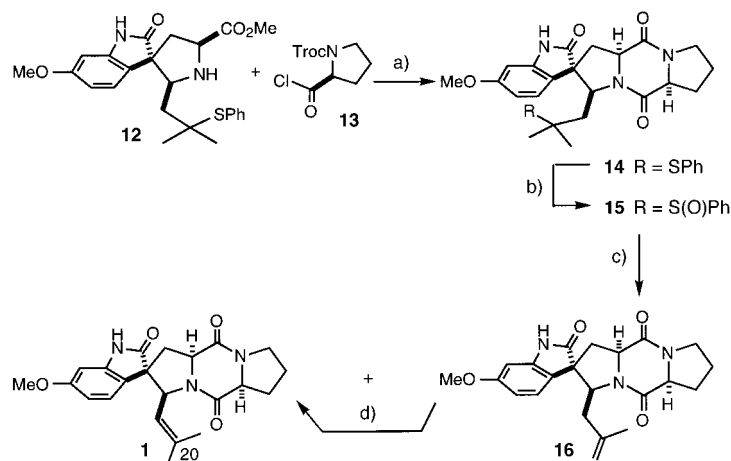
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N-bromosuccinimide in THF containing aqueous acetic acid afforded an oxindole, which was tentatively formulated as **11**. We surmised that the oxindole would have arisen from rearrangement of a bromohydrin derivative, which we presumed would have the structure shown in **10**.^[8] The stereochemistry of the series could be confirmed by detailed NMR analysis only after cleavage of the Boc function.^[9] This transformation was accomplished through the action of trifluoroacetic acid on **11** ($\rightarrow$ **12**).^[10]

In the next stage the diketopiperazine linkage was introduced. Toward this end, we prepared the *N*-protected prolinyl acid chloride **13** (Scheme 3).^[12] Coupling of **12** and **13** was



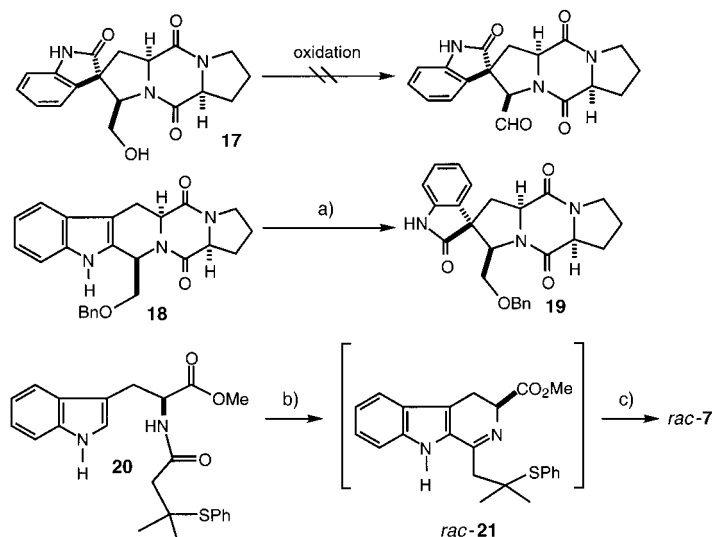
Scheme 3. Synthesis of spirotryprostatin A (**1**). a) CH_2Cl_2 , Et_3N ; Zn , NH_4Cl , H_2O , THF, MeOH, 68%; b) NaIO_4 , H_2O , MeOH; c) PhCH_3 , Δ ; 80% over two steps; d) $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$, EtOH, Δ , 41%. Troc = 2,2,2-trichloroethoxycarbonyl.

accomplished with triethylamine in methylene chloride. Zinc-mediated cleavage of the 2,2,2-trichloroethoxycarbonyl (Troc) group also induced diketopiperazine formation, leading to compound **14** in 68% yield.^[13] Thus, under these carefully defined conditions the thiophenyl group on the tertiary carbon in the side chain had been sustained through a remarkably diverse series of steps. The time was now at hand to effect its elimination. Clearly, the whole undertaking was at considerable risk since elimination could produce directly either of two olefinic products (Δ^{19} or Δ^{20}). Another concern was that of rapid isomerization of the double bond en route to a Δ^{18} "enamide" type of structure. In the event, sulfide **14** was oxidized with sodium metaperiodate to give the sulfoxide **15**, which was pyrolyzed in toluene under reflux to afford a separable mixture of spirotryprostatin A (**1**) and **16** (2.6:1) in 80% yield. Remarkably, isomerization of **16** with rhodium trichloride afforded **1** in 40% yield without further isomerization to the enamide.

The synthetically derived spirotryprostatin A (**1**) was identical to the naturally occurring material by comparison of its high-field ^1H NMR and ^{13}C NMR with corresponding spectra of the natural product. Moreover, the high-resolution mass spectrum of the synthetic product independently confirmed its molecular formula. We note that the optical rotation of synthetic **1** ($[\alpha]_{20}^D = -116.2^\circ$) differs substantially from that reported by Osada et al.^[3] ($[\alpha]_{26}^D = -34.0^\circ$). Since, in

principle, every chiral center of **1** is susceptible to epimerization, it is conceivable that during its isolation naturally occurring **1** had undergone substantial racemization. Alternatively, the discrepancy may also reflect the fact that only small, inhomogeneous samples of **1** were isolated from natural sources.

It is well to point out features of several alternative modalities which had to be set aside but are nevertheless of possible future interest. Thus, chemistry very similar to that described here was used to synthesize compound **17** (Scheme 4). However, all attempts to obtain the corresponding aldehyde (which appeared suitable for introduction of the



Scheme 4. Further investigations. a) NBS, THF, H_2O , HOAc; b) POCl_3 , C_6H_6 , Δ ; c) NaBH_4 , MeOH, 0°C . Bn = benzyl.

2-methylprop-1-enyl group) were unsuccessful. Also of note is the dependence of the stereochemistry of oxidation of the indole system on the presence of the diketopiperazine ring. For instance, with compound **18**, which contains this unit, oxidative rearrangement gave rise to **19**, a C3 epimer of the desired series. Additionally, we have attempted to attain a fully satisfying solution for control over the required *cis* relationship between C9 C18 by controlling the stereochemistry in the rearrangement substrates **7** and **9**. To this end, compound **20** was synthesized from tryptophan methyl ester. Bischler–Napieralski cyclization of **20** afforded **21**, which upon reduction with sodium borohydride provided **7**. Unfortunately, however, this compound was obtained in racemic form.^[14] Thus, while the required *cis* relationship between C9 and C18 can now be fashioned stereospecifically, the solution involves unacceptable forfeiture of enantiocontrol.

We would hope to improve upon the synthesis of **1** by productive incorporation of these or related refinements. Nonetheless, the total synthesis presented herein already delivers spirotryprostatin A in 12% overall yield. Now that the problem of the availability of this drug has been solved, studies directed toward its chemistry and its biology can be instituted in earnest.

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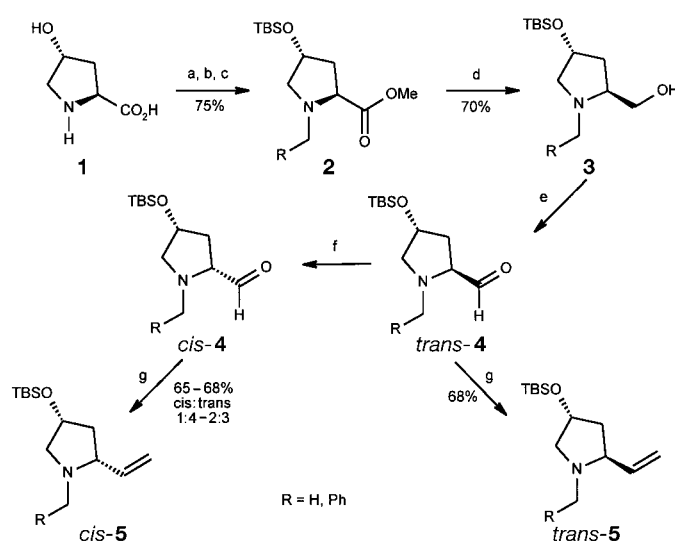
Unusual Diastereoselection in the Synthesis of Nine-Membered Ring Lactams and Conformation-Controlled Transannular Reactions to Generate Optically Active Indolizidinones**

Alexander Sudau and Udo Nubbemeyer*

Nine-membered ring lactams (“azoninones”) of defined constitutions and configurations had been synthesized from vinylpyrrolidines by a zwitterionic aza-Claisen rearrangement.^[1, 2] The highly ordered chairlike transition state^[3] of the [3,3] sigmatopic rearrangement always induced the complete 1,3-chirality transfer from an (*E*)-allylamine to the corresponding γ,δ -unsaturated lactam.^[1, 3] Furthermore an almost complete simple diastereoselection was operative^[2, 3] resulting from a defined (*Z*)-enolate geometry in the hypothetical zwitterionic intermediate. A diastereoselective transannular reaction then converted the azoninones into indolizidinones.^[2]

Here we report on the 1,4-chirality^[3] transfer of the zwitterionic rearrangement induced by the defined enolate geometry, which had been sparsely investigated up to now. Terminally unsubstituted allylamines served as reactants, and the azoninones so formed were used as the key intermediates in the synthesis of chiral indolizidinones.

As starting compounds we chose the optically active *N*-benzyl- and *N*-methylvinylpyrrolidines *trans*-**5** and *cis*-**5**, which were generated from 4-*trans*-hydroxy-L-proline (**1**) in six steps (Scheme 1).



Scheme 1. Synthesis of the vinylpyrrolidines. a) SOCl_2 , MeOH, reflux, 6 h; b) 98 % HCO_2H , 37 % CH_2O , reflux, 7 h or PhCHO, NaBH_3CN , MeOH, 60°C , 2 d; c) TBSCl, imidazole, CH_2Cl_2 , 20°C , 12 h; d) DIBAL, Et_2O , 0°C , 5 h; e) $\text{C}_2\text{O}_2\text{Cl}_2$, DMSO, Et_3N , CH_2Cl_2 , -60°C , 2 h; f) cat. base, CH_2Cl_2 , 20°C , 1 d;^[12] g) $[\text{Ph}_3\text{PCH}_3]^+\text{I}^-$, *n*-BuLi, THF, -78°C to 20°C , 16 h.

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After esterification,^[4] **1** was subjected to a reductive amination either with formaldehyde (Clarke–Eschweiler)^[5] or with benzaldehyde.^[6] The hydroxyl group was then protected as a silyl ether^[7] with *tert*-butyldimethylsilyl chloride (TBSCl) to generate the *N*-methyl- or the *N*-benzylaminoesters **2**, respectively. Reduction^[8] with DIBAH to the alcohols **3** and subsequent Swern oxidation^[9] led to the aldehydes *trans*-**4**, which were converted by a Wittig olefination with methylenetriphenylphosphorane^[10, 11] into vinylpyrrolidines *trans*-**5**. Leaving the aldehyde *trans*-**4** as it was at room temperature led to a partial epimerization of the C-2 formyl groups; this method thus afforded *cis*-vinylpyrrolidines *cis*-**5** after separation of the diastereomers.^[12]

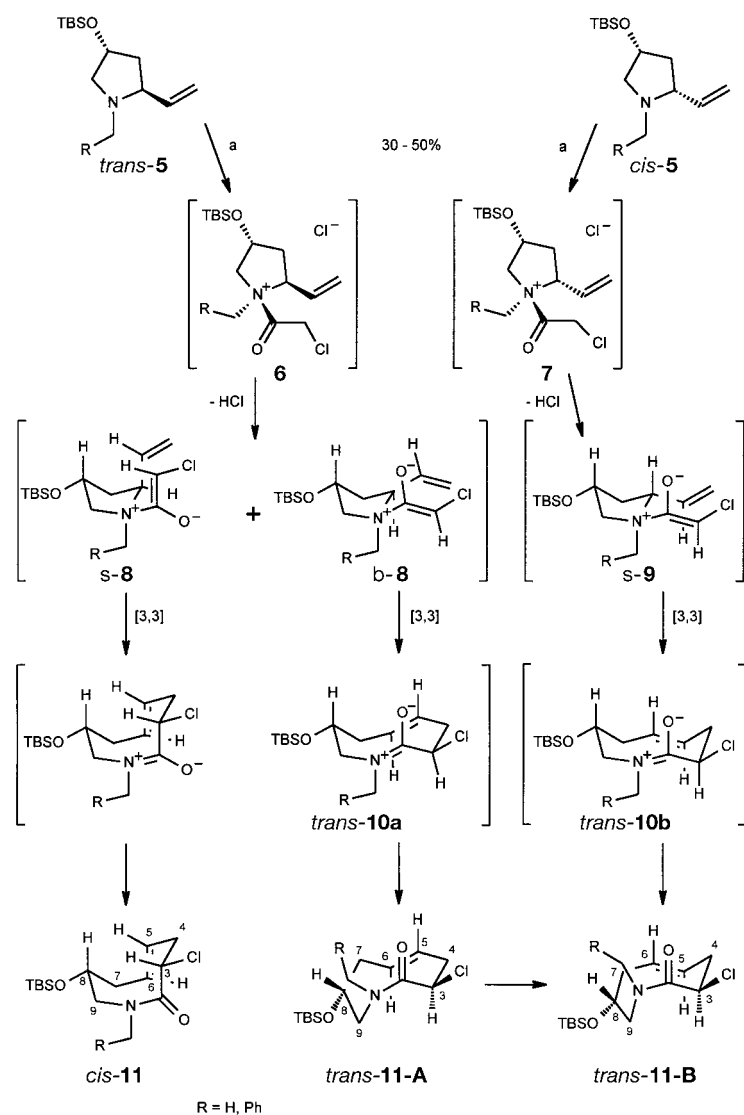
Under standard conditions^[1, 2] the vinylpyrrolidines **5** were treated with chloroacetyl chloride in chloroform in presence of trimethylaluminum (Scheme 2). The reactions of both *trans*- and *cis*-vinylpyrrolidines **5** gave good yields of the corresponding azoninones (*trans*-**11**) configured *trans* with respect to positions 3 and 8. Only the rearrangement of the *N*-

benzylpyrrolidine *trans*-**5** led to the formation of a small amount of the 3,8-*cis* diastereomer *cis*-**11** as a by-product (*cis*-**11**:*trans*-**11** 1:5).^[13] The diastereomers were separated by preparative HPLC, and the relative configurations of the stereogenic centers were proved beyond doubt by NOE analysis.^[13, 14]

The formation of the 3,8-disubstituted lactam *trans*-**11** from vinylpyrrolidine *trans*-**5** was characterized by a conspicuous change of its conformation: right after the isolation of the product a 3,8-*trans*-configured azoninone with the defined conformation *trans*-**11-A** was identified. The NOE analysis indicated the proximity of protons H-3, H-6, and H-9 α . If the product was kept neat or in solution (CDCl₃, MeCN, etc.) at room temperature for 3–5 days, a complete change of the conformation to *trans*-**11-B** was observed. Now the NOE analysis proved the proximity of protons H-3, H-5, and H-9 α :^[14] the 3,8-*trans* configuration was maintained. The rearrangement of the vinylpyrrolidine *cis*-**5**, however, directly afforded the lactam with the stable conformation *trans*-**11-B**; no molecular relaxation could be detected.^[14] The *N*-methyl and *N*-benzyl compounds behaved quite similarly. The **A** and **B** conformations of the major lactam *trans*-**11** (R = Ph) differed unequivocally from the minor diastereomer *cis*-**11** (R = Ph) isolated from this reaction (the spectroscopic data are summarized in Table 1).

Fundamentally the reaction of the two diastereomeric allylamines **5** to the same product **11** might have been caused by passing a common transition state. On the other hand ¹H and ¹³C spectroscopic analyses gave evidence of two defined diastereomeric transition states **8** and **9**.^[15] Another explanation for the observations could be as follows: In the first step of the reaction two acylammonium salts **6** and **7** were diastereoselectively generated bearing the acyl group in *anti* position to the bulky silyl substituent. Such primary active species were investigated in the *N*-methyl series (R = H).^[16] After deprotonation to form the hypothetical zwitterions **8** and **9** the enolates should be *Z*-configured as all amide enolates.^[17] The arrangement in a chairlike transition state^[18] conformation **s-9** with minimized 1,3-diaxial repulsions led, after rearrangement, to *trans*-**10b** and isomerization of the amide bond directly to lactam *trans*-**11-B**. The generation of a chair-like conformation from zwitterion **s-8** was apparently hindered by severe repulsive interactions (1,3-strain). Therefore the system rearranged preferentially via the alternative boat-conformation **b-8**,^[19] which is normally known to be disfavored in acyclic reactions. After sigmatropic rearrangement to *trans*-**10a** and isomerization of the amide bond, lactam *trans*-**11** with the less stable conformation *trans*-**11-A** was formed as the primary isolated product. The change towards the more stable lactam with the conformation *trans*-**11-B** was caused by molecular relaxation.^[20]

Recent investigations^[2] have shown that defined configured 3,4-difunctionalized azoninones under-



Scheme 2. Zwitterionic aza-Claisen rearrangement. a) ClCH₂COCl, Me₃Al, CHCl₃, K₂CO₃, 0°C, 1 d.

Table 1. Spectroscopic data of **11** (R = Ph), and **12–14**.^[a]

cis-**11**: IR: $\tilde{\nu}$ = 1645 (C=O), 1451, 1421, 1260 cm⁻¹; MS (60°C): *m/z*: 393 [*M*⁺], 378, 358, 336, 302, 246, 91, 73; ¹H NMR: δ = 7.25–7.35 (m, 5H; Ar), 6.04 (ddd, ³*J* = 16, 10, 5, 1H; H-6), 5.44 (ddd, ³*J* = 16, 12, 4, 1H; H-5), 5.14 (d, ²*J* = 15, 1H; CH₂Ar), 5.02 (dd, ³*J* = 4, 2, 1H; H-3), 4.64 (ddd, ²*J* = 15, ³*J* = 9, ⁴*J* = 1, 1H; H-9 α), 4.08 (d, ²*J* = 15, 1H; CH₂Ar), 3.91 (m, 1H; H-8), 2.97 (d, ²*J* = 15, 1H; H-9 β), 2.80–2.65 (m, 3H; H-7 β , CH₂-4), 2.12 (ddd, ²*J* = 12, ³*J* = 12, 9, 1H; H-7 α), 0.83 (s, 9H; *t*BuSi), 0.04 (s, 3H; MeSi), 0.02 (s, 3H; MeSi); ¹³C NMR: δ = 169.8 (s), 137.4, 131.9 (d), 131.0 (d), 129.1, 127.7, 127.6, 71.6 (d), 65.1 (d), 56.2 (t), 51.3 (t), 43.6 (t), 36.8 (t), 26.3 (q), 18.3 (s), –4.4 (q)

trans-**11-A**: ¹H NMR: δ = 7.25 (m, 5H; Ar), 5.76 (ddd, ³*J* = 15, 11, 3, 1H; H-6), 5.44 (ddd, ³*J* = 16, 9, 6, 1H; H-5), 5.05 (d, ²*J* = 14, 1H; CH₂Ph), 4.84 (dd, ³*J* = 10, 8, 1H; H-3), 4.17 (d, ²*J* = 15, 1H; CH₂Ph), 4.05 (m, 1H; H-8), 3.55 (dd, ²*J* = 16, 10, 1H; H-9 α), 3.01 (dd, ²*J* = 15, ³*J* = 4, 1H; H-9 β), 2.90 (m, 1H; H-4 α), 2.54 (ddd, ²*J* = 17, ³*J* = 10, 6, 1H; H-4 β), 2.28 (m, 1H; H-7 α), 2.09 (ddd, ²*J* = 17, ³*J* = 11, 5, 1H; H-7 β), 0.81 (s, 9H; *t*BuSi), –0.01 (s, 3H; MeSi), –0.07 (s, 3H; MeSi); ¹³C NMR: δ = 169.8 (s), 136.8, 131.2 (d), 130.8 (d), 128.7, 128.0, 127.9, 66.5 (d), 55.3 (d), 51.8 (t), 49.4 (t), 39.2 (t), 37.12 (t), 25.7 (q), 17.9 (s), –4.8 (q), –5.0 (q)

trans-**11-B**: IR: $\tilde{\nu}$ = 1644 (C=O), 1451, 1421, 1260 cm⁻¹; MS (60°C): *m/z* = 393 [*M*⁺], 378, 358, 336, 302, 246, 91, 73; ¹H NMR: δ = 7.2–7.3 (m, 5H; Ar), 5.67 (ddd, ³*J* = 16, 10, 6, 1H; H-5), 5.34 (ddd, ³*J* = 15, 11, 3, 1H; H-6), 5.22 (d, ²*J* = 15 Hz, 1H; CH₂Ar), 4.50 (dd, ³*J* = 12, 3, 1H; H-3), 4.09 (d, ²*J* = 15, 1H; CH₂-Ar), 4.01 (m, 1H; H-8), 3.62 (dd, ²*J* = 14, ³*J* = 9, 1H; H-9 α), 2.97 (d, ²*J* = 14, 1H; H-9 β), 2.60–2.80 (m, 3H; H-7 β , CH₂-4), 2.02 (ddd, ²*J* = 12, ³*J* = 12, 9, 1H; H-7 α), 0.81 (s, 9H; *t*BuSi), 0.02 (s, 3H; MeSi), 0.00 (s, 3H; MeSi); ¹³C NMR: δ = 169.6 (s), 136.3 (s), 131.2 (d), 130.1 (d), 128.6 (d), 127.9 (d), 127.6 (d), 69.5 (d), 56.2 (d), 54.3 (t), 49.7 (t), 42.8 (t), 40.1 (t), 25.6 (q), 17.8 (s), –4.5 (q), –4.9 (q)

12: IR: $\tilde{\nu}$ = 1644 (C=O), 1578, 1458, 1434, 1388, 1280, 1249 cm⁻¹; MS (150°C): *m/z*: 459 [*M*⁺], 444, 402, 302, 244, 210, 170; ¹H NMR: δ = 7.40 (m, 2H; *o*-Ar), 7.00–6.90 (m, 3H; *m*-, *p*-Ar), 4.00 (dd, ³*J* = 9, 6, 1H; H-6), 3.84 (dddd, ³*J* = 6, 6, 6, 1H; H-2), 3.55 (dd, ²*J* = 12, ³*J* = 6, 1H; H-3 α), 3.37 (dd, ²*J* = 12, ³*J* = 7, 1H; H-3 β), 3.05 (ddd, ³*J* = 10, 10, 5, 1H; H-8 α), 2.53–2.4 (m, 2H; H-7 α , H-8), 2.20–2.05 (m, 2H; H-1 β , H-7 β), 1.47 (ddd, ²*J* = 13, ³*J* = 10, 8, 1H; H-1 α), 0.92 (s, 9H; *t*BuSi), –0.02 (s, 3H; MeSi), –0.03 (s, 3H; MeSi); ¹³C NMR: δ = 164.2 (s), 136.3 (d), 129.5 (d), 125.8 (d), 125.9 (s), 68.8 (d), 61.8 (d), 54.1 (d), 53.9 (t), 42.0 (t), 40.7 (t), 40.7 (d), 22.7 (q), 17.9 (s), –4.9 (q), –5.0 (q)

13: IR: $\tilde{\nu}$ = 1663 (C=O), 1578, 1448, 1364, 1253 cm⁻¹; MS (150°C): *m/z*: 459 [*M*⁺], 444, 402, 302, 244, 210, 170, 134, 73; ¹H NMR: δ = 7.50–7.45 (m, 2H; *o*-Ar), 7.05–7.00 (m, 3H; *m*-, *p*-Ar), 4.03 (dd, ³*J* = 4, 1.5, 1H; H-6), 3.86 (dd, ³*J* = 5, 5, 1H; H-2), 3.72 (dd, ²*J* = 13, ³*J* = 5, 1H; H-3 β), 3.62 (ddd, ³*J* = 11, 11, 5, 1H; H-8 α), 3.42 (d, ²*J* = 14, 1H; H-3 α), 3.25 (ddd, ³*J* = 11, 11, 3, 1H; H-8), 2.23 (ddd, ²*J* = 15, ³*J* = 2, 2, 1H; H-7 β), 2.11 (dd, ²*J* = 13, ³*J* = 4, 1H; H-1 α), 1.48 (ddd, ²*J* = 15, ³*J* = 13, 5, 1H; H-7 α), 1.07 (ddd, ²*J* = 12, ³*J* = 12, 4, 1H; H-1 β), 0.91 (s, 9H; *t*BuSi), –0.03 (s, 3H; MeSi), –0.06 (s, 3H; MeSi); ¹³C NMR: δ = 162.9 (s), 136.4, 129.4, 128.7, 126.1, 68.4 (d), 61.7 (d), 56.5 (d), 55.0 (t), 42.9, 39.9, 36.5, 25.8 (q), 18.0 (s), –4.9 (q)

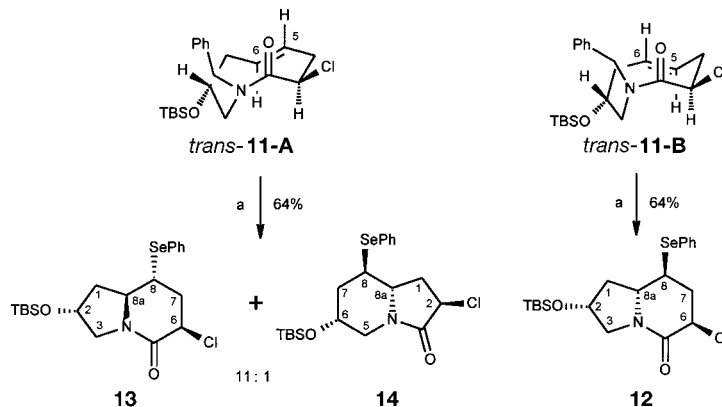
14: IR: $\tilde{\nu}$ = 1714 (CO) 1578, 1472, 1435, 1257 cm⁻¹; MS (150°C): *m/z*: 459 [*M*⁺], 444, 402, 244, 210, 73; ¹H NMR: δ = 7.56–7.50 (m, 2H; *o*-Ar), 7.35–7.26 (m, 3H; *m*-, *p*-Ar), 4.34 (dd, ³*J* = 8, 3, 1H; H-2), 4.03–3.93 (m, 2H; H-5 α , H-6), 3.60–3.50 (ddd, ³*J* = 11, 7, 7, 1H; H-8 α), 3.22–3.10 (m, 1H; H-8), 2.75 (d, ²*J* = 12, 1H; H-5 β), 2.23 (ddd, ²*J* = 15, ³*J* = 6, 2, 1H; H-1 β), 2.32–2.25 (m, 1H; H-1 α), 2.25–2.15 (m, 1H; H-7 α), 1.68 (m, 1H; H-7 β), 0.81 (s, 9H; *t*BuSi), 0.02 (s; MeSi), –0.03 (s; MeSi); ¹³C NMR: δ = 135.7, 129.1, 128.4, 65.1 (d), 58.9 (d), 53.8 (d), 46.5 (t), 40.6, 39.6, 36.7, 25.5 (q)

[a] IR: (KBr/film). MS: EI, 70 eV. ¹H NMR: 270 MHz, CDCl₃, 20°C, TMS, *J* in Hz. ¹³C NMR: 67.9 MHz, CDCl₃, 20°C. Experimental details: Ref. [2]; other spectroscopic data: Refs. [14, 22, 24].

went regio- and diastereoselective ring contractions to indolizinones. Apparently, the rigid conformation of the lactams involved caused the formation of a single product in high yield. Since the 3,8-disubstituted lactam (R = Ph) exists either in the relatively long-lived conformation *trans*-**11-A** immediately after the rearrangement of lactam *trans*-**5** or in

the stable conformation *trans*-**11-B**, we could study the selectivity of the ring contraction.

Under standard conditions^[2, 21], the treatment of the stable conformation *trans*-**11-B** of 3-chlorolactam (R = Ph) with phenylselenanyl chloride in acetonitrile at room temperature led to the formation of the single regio- and diastereomerically pure indolizidinone **12** (Scheme 3, Table 1). The relative



Scheme 3. Transannular reaction. a) PhSeCl, MeCN, 20°C, 3 h.

configurations of the new stereogenic centers were proved by NOE analysis, and the position of the phenylselenanyl substituent was determined by HETCOR (heteronuclear correlation).^[22] The analogous reaction of conformation *trans*-**11-A** (R = Ph) took an alternative regio- and stereochemical course: Instead of the generation of the known indolizidinone **12**, two further bicycles, **13** and **14**, were formed in an 11:1 ratio (see Table 1). The structural analysis was again achieved by HETCOR and NOE analyses.^[22]

The results indicated that the particular conformation of lactam *trans*-**11** directed the regio- and the diastereoselectivity of the transannular reaction. In contrast to processes following the Curtin–Hammett Principle,^[23] the activation energy for the conformational relaxation appeared to be much higher than that of the reaction! The different relative arrangement of the π -systems (amide and olefin) caused a relatively stable facial chirality: the electrophile (PhSe⁺) always attacked the free face of the olefin (that is, the face unhindered by the ring).

The zwitterionic aza-claisen rearrangement of 2-vinylpyrrolidines to the γ,δ -unsaturated lactams proceeded with a high 1,4-chirality transfer. Relative to well-known acyclic Claisen rearrangements an unusual diastereoselectivity in the reaction of amine *trans*-**5** and the usual stereochemistry in the reaction of *cis*-**5** both led to azoinone *trans*-**11** with identical olefin and amide geometries. However, the initial conformations (**A** and **B**) differed with respect to the relative orientation of the π -systems. The relaxation from the kinetically generated conformation *trans*-**11-A** into the thermodynamically stable *trans*-**11-B** required a significantly higher activation energy than the transannular reactions. In contrast to the dictates of the Curtin–Hammett Principle, lactam *trans*-**11** allowed defined reactions depending on the predominant conformation. The facial chirality of the nine-membered ring could be used to generate defined stereogenic

centers in the indolizidinones by means of the ring contraction. Further investigations into the scope and limitations of the diastereoselective transannular reaction are in progress.

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An Enzyme-Labile Linker Group for Organic Syntheses on Solid Supports**

Bernd Sauerbrei, Volker Jungmann, and Herbert Waldmann*

Combinatorial chemistry has proven to be a new and valuable method for the rapid identification and further development of compounds with a predetermined profile of properties, not only for drug discovery but also for asymmetric catalysis.^[1] In the majority of the cases combinatorial syntheses are carried out on solid supports. Once the desired compounds are constructed they have to be released from the supports selectively and without attack on the synthesized structures through cleavage of a suitable anchor group (linker). Combinatorial synthesis gives access to a multitude of different classes of compounds with a wide range of stability under the conditions of the releasing reactions. Therefore the development of broadly applicable linkers

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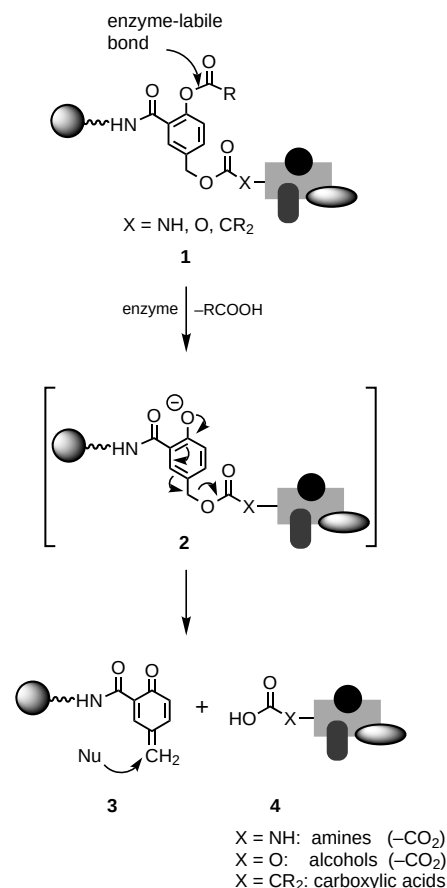
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allowing for selective cleavage of the synthesized products from the polymeric support under mild conditions (preferably at pH 7 and room temperature) is of particular importance. In many cases biocatalyzed transformations have opened up advantageous alternatives to classical chemical approaches, since enzymatic reactions often proceed under very mild conditions and with pronounced chemo-, regio-, and stereo-selectivity.^[2] The use of enzyme-labile anchor groups could also provide new opportunities for combinatorial chemistry and solid-phase synthesis. However, a broadly applicable enzyme-labile linker has not yet been developed.^[3] We now report that the 4-acyloxy-3-carboxybenzyloxy group can be employed advantageously as an enzyme-labile linker for solid-phase syntheses. The compounds built up at this anchor group can be released by means of an enzyme-initiated fragmentation.

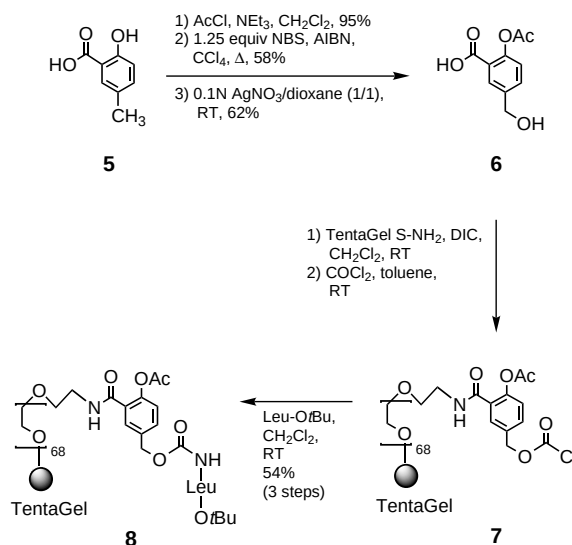
For the design of an enzyme-labile linker we have drawn from our experience in the development of enzymatically removable protecting groups.^[4] The anchor group was constructed in such a way that a) it contains a functional group that is recognized and attacked by the biocatalyst, that b) cleavage of the enzyme-labile bond yields an intermediate that undergoes a spontaneous fragmentation, thereby releasing the desired compound,^[5] and that c) a further functional group for attaching the linker to the solid support is present. The realization of this principle is shown in Scheme 1. The linker is attached through a carboxyl group as an amide to the solid phase ($\rightarrow$ 1). It contains an acyl group, for example an acetate, which can be cleaved by lipases or esterases. A phenolate is thus generated ($\rightarrow$ 2), which fragments to give a quinone methide 3 and releases the desired compound 4, a product of, for example, combinatorial synthesis. The quinone methide remains bound to the solid phase and is trapped there by water or an additional nucleophile. In this way amines (bound as urethanes), alcohols (bound as carbonates), and carboxylic acids (bound as esters) can be detached from the polymeric carrier. The substrate specificity of the enzyme guarantees that only the intended ester is cleaved, and the mild conditions of the biocatalyzed transformations ensure that the compounds built up on the solid phase remain intact during the cleavage. Furthermore the linker is constructed in such a way that the variable part of the substrates is remote from the site of the biocatalyst's attack. This guarantees that the substrate tolerance of the enzyme in the cleaving reaction is not restricted by interfering electronic or steric interactions of the protein with the different substrates generated by combinatorial synthesis.

For the synthesis of the linker, building block 5-methylsalicylic acid (5) was first O-acetylated, then the methyl group was converted into a benzyl bromide with *N*-bromosuccinimide (NBS), and the bromide was finally hydrolyzed to the benzyl alcohol by treatment with AgNO₃ solution (Scheme 2).

The polymeric support selected for the subsequent transformations on the solid phase was TentaGelS-NH₂, a polystyrene resin onto which terminally NH₂-functionalized oligoethyleneglycol units had been grafted.^[6] Its polar surface and the fact that it is well solvated in aqueous solution are particularly advantageous properties that should facilitate the enzymatic cleavage of the linker. After activation with



Scheme 1. Principle for the development of the enzyme-labile 4-acyloxybenzyloxy linker groups. The solid support is represented by a shaded sphere; the target compounds constructed by combinatorial synthesis are shown schematically (rectangles, circles, ovals, ellipses).

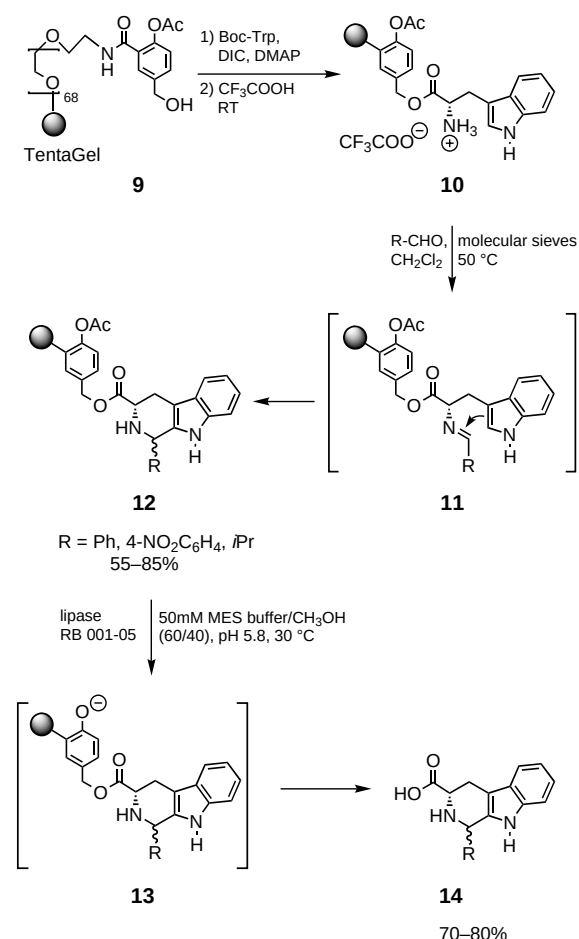


Scheme 2. Synthesis of linker 6 and its attachment to TentaGelS-NH₂. AIBN = 2,2'-azobisisobutyronitrile, DIC = diisopropylcarbodiimide, Leu = leucine, RT = room temperature.

diisopropyl carbodiimide (DIC) the carboxylic acid 6 was coupled to the polymer, and the benzylic alcohol was then converted into the chloroformic acid ester 7 by treatment with phosgene. Thus, an activated intermediate is generated to

which a broad variety of amines and alcohols can be attached. Carboxylic acids can already be coupled to the polymer-bound benzyl alcohol **9** (see Scheme 3). In order to determine the best conditions for the enzyme-initiated fragmentation of the anchoring group, leucine *tert*-butyl ester was linked to **7** to give the urethane **8**.^[7] Several commercially available lipases and esterases were investigated for the enzyme-initiated fragmentation of the linker. By far the best results were achieved with lipase RB001-05 (Recombinant Biocatalysis, Diversa, San Diego, USA). This biocatalyst detaches leucine *tert*-butyl ester at pH 5.8 und 40 °C in 0.05 M morpholinoethane sulfonic acid (MES) buffer/methanol (60/40), in other words, under very gentle conditions. The amino acid ester was isolated in 73 % yield. Lipase from *Mucor miehei* also catalyzes this reaction under similarly mild conditions (0.1 M NaH₂PO₄ buffer, pH 6, 37 °C); however, the product was obtained in lower yield (50 %).

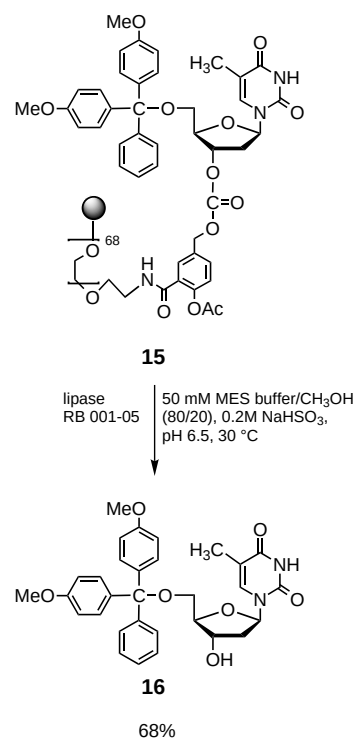
The applicability of the enzyme-labile anchor group to multistep transformations on the solid phase, which are for instance relevant to the generation of libraries in pharmaceutical research, was proven by the synthesis of tetrahydro- β -carboline by means of the Pictet–Spengler reaction^[8] and their subsequent enzyme-mediated release (Scheme 3). To



Scheme 3. Solid-phase synthesis of tetrahydro- β -carboline and subsequent detachment ($\rightarrow$ **14**) by enzyme-initiated fragmentation of the anchor group. Boc = *tert*-butoxycarbonyl, Trp = tryptophan, DMAP = 4-dimethylaminopyridine.

this end, the benzylic OH group of the TentaGel-S-NH₂ bound linker **9** was first esterified with Boc-L-tryptophan, and the Boc group was then removed by treatment with trifluoroacetic acid. The support-bound tryptophan **10** was then condensed with aliphatic and aromatic aldehydes at 50 °C in the presence of molecular sieves to give imines **11**, which under these reaction conditions cyclized immediately to the tetrahydro- β -carboline. Starting from **9** the heterocyclic amines **12** were thus formed in 55–85 % yield.^[7] The Pictet–Spengler adducts could also be released from the polymeric support under very mild conditions by lipase-initiated fragmentation of the anchor group. Upon treatment of **12** with lipase RB001-05 at pH 5.8 in an MES buffer/methanol mixture (60/40) the enzyme selectively attacked the acetate incorporated into the linker and converted it into the corresponding phenolate ($\rightarrow$ **13**), which then fragmented spontaneously. By means of this enzyme-mediated dissection of the anchor group the desired tetrahydro- β -carboline **14** were released in 70–80 % yield.^[9] The result that the enzymatic fragmentation of the linker occurs already at pH 5.8 is not a foregone one. In the nonenzymatic cleavage of 4-acyloxybenzyloxy groups the pH has to be raised to at least 10–11 to deprotonate the corresponding phenol and thereby induce its conversion into the quinone methide.^[10, 11] Active participation of the enzyme in the fragmentation, for example by means of basic amino acid side chains in or close to the active site, is therefore very probable.

To further prove the broad applicability of the enzyme-labile anchor group the polymer-bound chloroformic acid ester **7** was coupled with the very acid-labile 5'-*O*-dimethoxytrityl(DMT)-protected thymidine (NaH, THF). Treatment of the resulting immobilized nucleoside **15** with lipase RB001-05



Scheme 4. Detachment of DMT-protected thymidine from the polymeric support by enzyme-initiated fragmentation of the anchor group.

at pH 6.5 initiated the fragmentation of the linker and released the DMTr-protected thymidine **16** from the solid support under gentle conditions (Scheme 4).

The results demonstrate that the 4-acetyloxybenzyloxy linker allows for the detachment of amines (like leucine *tert*-butyl ester), carboxylic acids (like the tetrahydro- β -carboline **14**), and alcohols (like the protected nucleoside **16**) from the polymeric support under very mild conditions (pH 5–7, room temperature) and with complete selectivity. The results are not only relevant to combinatorial chemistry, they also indicate that enzymes in general may be valuable reagents for transformations on solid supports.^[12]

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Novel Distorted Pentagonal-Pyramidal Coordination of Anionic Oxodiperoxo Molybdenum and Tungsten Complexes**

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There is currently much interest in the preparation of new polyoxo(peroxo)metalates for homogeneous catalysis^[1] and heterogeneous systems^[2] in order to understand the chemistry of surface species and the nature of the catalytically active sites of transition metal containing molecular sieves or other materials. While studying oxidation reactions with mesoporous materials,^[1m] which are potentially interesting catalysts and/or catalyst supports,^[3] we became interested in comparing anionic or neutral oxoperoxo complexes with those that can be formed on silica and/or alumina. From studies on systems of aqueous $[\text{MoO}_4]^{2-}$ and $[\text{Mo}_7\text{O}_{24}]^{6-}$ solutions and silica, it is known that Mo^{VI} uptake by SiO_2 is relatively low over the entire pH range, except for a small increase at pH 2 or lower owing to the formation of $[\text{SiMo}_{12}\text{O}_{40}]^{4-}$ ions, which can partially desorb into solution.^[4] Furthermore, silica (BET specific surface area 263 m^2g^{-1}) and molybdenum- (or tungsten-) oxoperoxo species interact in aqueous acidic medium to form surface peroxo species with characteristic IR bands $\tilde{\nu}_{\text{O-O}}$ near 870 cm^{-1} ($\tilde{\nu}_{\text{O-O}}$ is expected to be in the range of 845–885 cm^{-1}).^[1] These observations suggest that it might be possible to synthesize oxoperoxo-heterosiloxanes involving the various functionalities on the silica surface (i.e., lone

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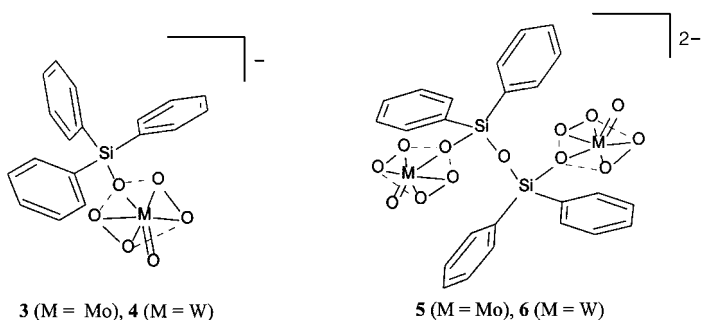
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(free) geminal silanols and vicinal silanols from siloxane bridges).

Several unsuccessful attempts to prepare heterosiloxanes of molybdenum or tungsten by conventional methods have been reported.^[5] However, compounds containing Mo–O–Si moieties are formed by the reaction of sodium triphenylsilanolate with the dimethylformamide complex of $[\text{MoO}(\text{OH})_2\text{Cl}_2]$.^[6] As far as silanediols are concerned, the eight-membered metallasiloxane $[(t\text{Bu})_2\text{SiO}_2\text{Mo}(=\text{O})_2]_2$, which may be considered as a model for metal oxides supported on silica surfaces, was isolated by Roesky et al.^[7] With the dilithium salt $[\text{LiOSi}(t\text{Bu})_2]_2\text{O}$ and MoO_2Cl_2 , the twelve-membered cyclic molybdenum(vi) siloxane, $[\text{MoO}_2(\text{OSi}(t\text{Bu})_2\text{OSi}(t\text{Bu})_2\text{O})_2]$ was prepared.^[8] The two molybdenum centers are bridged by two disilanolato moieties.

Diphenylsilanediol ($\text{Ph}_2\text{Si}(\text{OH})_2$) and 1,1,3,3-tetraphenyldisiloxane-1,3-diol ($[\text{Ph}_2\text{Si}(\text{OH})]_2\text{O}$) tend to undergo self-condensation in reactions with metal derivatives; on the other hand, tris(neopentyl)nitridomolybdenum(vi) reacts with Ph_3SiOH or $[\text{Ph}_2\text{Si}(\text{OH})]_2\text{O}$ at 60 °C to yield imidotris(neopentyl) complexes.^[9] Recently, two anionic polyoxoperoxo species $(\text{PPh}_4)_2[\text{Ph}_2\text{SiO}_2\{\text{M}_2\text{O}_2(\mu\text{-O}_2)_2(\text{O}_2)_2\}]$ ($\text{M} = \text{Mo}, \text{W}$) were synthesized in high yield by simple procedures involving $\text{Ph}_2\text{Si}(\text{OH})_2$, $\text{H}_2\text{O}_2/\text{H}_2\text{O}/\text{EtOH}$, $\text{MO}_3 \cdot \text{H}_2\text{O}$, and PPh_4Cl .^[10] These compounds were proposed as models for neutral $\{\text{M}_2\text{O}_2(\mu\text{-O}_2)_2(\text{O}_2)_2\}$ units grafted on silica surface through geminal silanol groups. Thus, organosilanols can be used to model silica-supported metal – oxo(peroxo) species; the novel anionic species may be synthesized by nondemanding reactions involving the various silanol groups of silica-based materials.

The reactions of triphenylsilanol (Ph_3SiOH , **1**) and $[\text{Ph}_2\text{Si}(\text{OH})]_2\text{O}$ (**2**) with an aqueous solution of $[\text{MO}(\text{O}_2)_2 \cdot (\text{H}_2\text{O})_2]$ ($\text{M} = \text{Mo}, \text{W}$) lead to mononuclear anionic diperoxo species **3** and **4** and dinuclear complexes **5** and **6**, respectively,



in fair to nearly quantitative yields. The new molybdenum- and tungsten – siloxane complexes were fully characterized by elemental analysis, vibrational and ^{29}Si NMR spectroscopies, and single-crystal X-ray diffraction studies.^[11] The molecular structure of the complex anions **3** ($\text{M} = \text{Mo}$) and **4** ($\text{M} = \text{W}$) are shown in Figure 1.

The metal center in **3** and **4** is surrounded by one silanolato ligand ($\text{C}_6\text{H}_5\text{SiO}$) and two peroxo groups that are side-bound in a η^2 fashion. An interesting feature of these very unusual anionic complexes is the slightly distorted pentagonal-monopyramidal configuration of the six-coordinate Mo (or W)

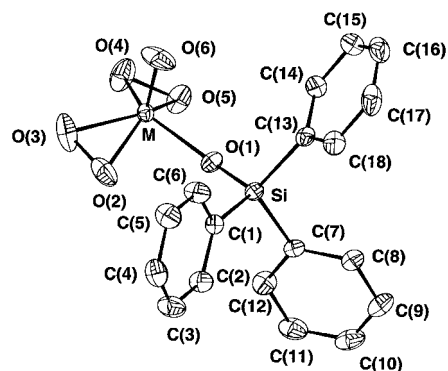


Figure 1. CAMERON representation^[22] of $[\text{Ph}_3\text{SiO}\{\text{Mo}(\text{O}_2)_2\}]^-$ showing the atom-labeling scheme. Selected bond lengths [Å] and angles [°] for **3** ($\text{M} = \text{Mo}$) [**4** ($\text{M} = \text{W}$)]: M–O(1) 1.933(4) [1.925(4)], M–O(2) 1.886(6) [1.898(8)], M–O(3) 1.895(6) [1.892(7)], M–O(4) 1.920(5) [1.925(7)], M–O(5) 1.907(5) [1.897(6)], M–O(6) 1.680(4) [1.690(6)], O(2) – O(3) 1.407(9) [1.38(1)], O(4) – O(5) 1.421(7) [1.422(9)], Si–O(1) 1.617(4) [1.616(5)], Si–C(1) 1.872(6) [1.882(8)], Si–C(7) 1.860(5) [1.860(7)], Si–C(13) 1.869(6) [1.851(7)]; O(1)–M–O(2) 84.6(3) [84.2(3)], O(1)–M–O(5) 84.2(2) [84.7(3)], O(3)–M–O(4) 87.4(3) [88.0(3)], O(2)–M–O(3) 43.7(3) [42.8(3)], O(4)–M–O(5) 43.6(2) [43.7(3)], Si–O(1)–M 145.4(3) [147.8(3)].

atom, since molybdenum(vi) or tungsten(vi) centers are seven-coordinate in most oxodiperoxo complexes;^[12] there have only been two previous reports of compounds containing six-coordinate metal centers that describe an oxodiperoxo vanadate (1^-).^[13] The coordination of two-electron donor ligands L (usually H_2O , hexamethylphosphoramide (HMPA), etc.) does not occur, although water was not excluded from the recrystallization solvent.

The axial position is occupied by an oxo ligand with a normal M–O bond length.^[12] The M atoms are not located in the mean basal plane defined by the O atoms of the two peroxo groups and the silanolato group (deviation 0.55 [0.56] Å for Mo(1) [W(1)]; ca. 0.38 Å in a seven-coordinate complex). The oxygen atoms are 0.15 [0.16] Å from the mean basal plane. The Si–O and Si–C bond lengths are similar to those in metallasiloxanes.^[14] The O–O bond lengths in the peroxo groups (1.38 (1) and 1.423 (9) Å) for **4** correspond to published values,^[12] but are significantly shorter than those in $[\text{AsO}_4\{\text{W}_2\text{O}_2(\mu\text{-O}_2)_2(\text{O}_2)_2\}]^{3-}$ (1.45 (2)–1.56 (2) Å);^[15] such long bonds seem to be essential for the easy transfer of active oxygen to olefinic substrates.

The reaction of **2** with $[\text{MoO}(\text{O}_2)_2(\text{H}_2\text{O})_2]$ in aqueous H_2O_2 leads to the dianionic species **5**, in which the two Mo atoms are also coordinated by six oxygen atoms in a pentagonal monopyramidal arrangement (Figure 2). Each girdle (basal plane) is generated again by two peroxo groups and one oxygen atom of the $(\mu\text{-OSiPh}_2\text{OSiPh}_2\text{O})$ ligand. One of the O–O bonds is 1.353 (8) Å long and amongst the shortest reported.^[12] The oxygen atoms that define the mean basal plane are coplanar to within 0.16 Å. The apical position of the girdle axis is occupied by the terminal oxo ligand O^{2-} . As for the octahedral coordination in polyoxometalates, the Mo atoms are displaced by 0.58 Å towards the oxo ligand. One side of the anion is related to the other by an inversion center at O(7). The coordination environment about the silicon atoms is tetrahedral. An analogous complex was synthesized

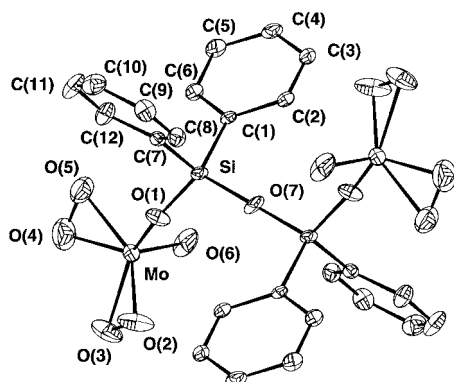


Figure 2. CAMERON representation^[22] of $[(\text{Ph}_2\text{SiO}[\text{MoO}(\text{O}_2)_2])_2\text{O}]^{2-}$ (**5**) showing the atom labelling scheme. Selected bond lengths [Å] and angles [°]: Mo–O(1) 1.925(3), Mo–O(2) 1.907(5), Mo–O(3) 1.915(4), Mo–O(4) 1.840(6), Mo–O(5) 1.876(6), Mo–O(6) 1.697(4), O(2)–O(3) 1.439(7), O(4)–O(5) 1.353(8), Si–O(1) 1.600(3), Si–C(1) 1.863(4), Si–C(7) 1.856(5), Si–O(7) 1.609(1); O(1)–Mo–O(2) 84.5(2), O(1)–Mo–O(5) 84.1(2), O(3)–Mo–O(4) 85.7(3), O(2)–Mo–O(3) 44.2(2), O(4)–Mo–O(5) 42.7(3), Si–O(1)–Mo 150.7(2).

with $\text{WO}_3 \cdot \text{H}_2\text{O}$, but crystals suitable for an X-ray crystal structure determination could not be obtained. Comparison of the $\tilde{\nu}_{\text{O-O}}$ and $\tilde{\nu}_{\text{Si-O}}$ vibrations (IR and Raman) in the solid state and in solutions of MeCN suggests that the overall structure of the four anions is conserved in solution.

The Mo^{VI} and W^{VI} oxoperoxo complexes **3–6** are also active species in olefin oxidation and form epoxides as primary products; slight heating (optimum 40–60 °C) is necessary to activate these anionic species. In all cases, the extent of increasing activity of homogeneous (" $\text{H}_2\text{O}_2/\text{H}_2\text{O}/t\text{BuOH}$ ") or phase-transfer catalysis systems depends on the silicon-based auxiliary anion. The replacement of phenyl by alkyl groups favors the reaction, as does use of phase-transfer agents with long alkyl chains (C_{16} – C_{18}). The yields and turnover numbers of the reaction depend inter alia on the $[\text{M}]:[\equiv\text{Si-O ligand}]:[\text{onium salt}]$ ratio; it is important to avoid a large excess of the latter.^[1c, 16] Spectroscopic data (Raman and/or NMR) show that the complexes are recovered without any change if excess H_2O_2 is used. Work is currently in progress to optimize conversions and selectivities and to compare the complexes with analogues in the chemistry of grafted silica surfaces and mesoporous materials.^[1m]

In the solid state most of the diperoxo and some monoperoxo complexes are pentagonal-bipyramidal species. In solution, based on ab initio calculations^[17] and spectral data, a distorted octahedral arrangement is favored. The work reported here shows that other structural types can be stabilized in the solid state and in solution for molybdenum and tungsten compounds as they are for anionic oxo(diperoxo)vanadium(v) species.^[13]

Experimental Section

$[\text{Ph}_2\text{Si}(\text{OH})_2]\text{O}$ (**2**) was synthesized as described in reference [18].

$(\text{Ph}_4\text{P})_2\text{-3}$ [$(\text{Ph}_4\text{P})\text{-4}$]: MoO_3 (0.72 g, 5 mmol) [$\text{WO}_3 \cdot \text{H}_2\text{O}$ (1.25 g, 5 mmol)] was added to a 30 % solution of hydrogen peroxide (4 mL, 35 mmol). After 1 h at 60 °C the solution was cooled to room temperature [followed by centrifugation (15 min at 2000 rpm)] and then slowly added to a solution of **1** (1.38 g, 5 mmol) in ethanol (16 mL). NaOH (5 M, 1 mL) was added

dropwise, and the solution stirred for 45 min. The complex anion was then precipitated by slow addition of PPh_4Cl (1.87 g, 5 mmol) in ethanol (2 mL). The pale yellow [white] solid was isolated by filtration, washed with water and Et_2O , and then dried under air. Yield = 85 % [87 %]; correct elemental analysis.

$(\text{Ph}_4\text{P})_2\text{-5}$ [$(\text{Ph}_4\text{P})_2\text{-6}$]: MoO_3 (0.36 g, 2.5 mmol) [$\text{WO}_3 \cdot \text{H}_2\text{O}$ (0.62 g, 2.5 mmol)] was treated with a 30 % solution of hydrogen peroxide (2 mL, 17 mmol). After 1 h at 60 °C cooling of the solution [followed by centrifugation (15 min at 2000 rpm)] and dropwise addition of a solution of **2** (0.52 g, 1.25 mmol) in ethanol (4 mL) and of NaOH (5 M, 1 mL) gave a solution, which was stirred for 45 min. Slow addition of PPh_4Cl (0.94 g, 2.5 mmol) in ethanol (1 mL) gave a pale yellow [white] precipitate, which was treated as above. Yield = 95 % [60 %]; correct elemental analysis.

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1617, $\lambda = 71.069$ pm, $T = 293$ K, $\mu(\text{Mo}_{\text{K}\alpha}) = 0.462$ mm $^{-1}$, crystal dimensions $0.4 \times 0.3 \times 0.25$ mm ^{3} , $2 \leq 2\theta \leq 50^\circ$; of 7153 measured reflections, 6525 were unique; 462 parameters refined in full matrix, $R1 = 0.039$ with 3411 reflections ($I > 3\sigma(I)$), $wR2 = 0.041$, $w = 1$, min./max. residual electron density $-290/480$ e nm $^{-3}$. (Ph $_4$ P)-4: C $_{42}$ H $_{35}$ O $_6$ PSiW, $M_r = 878.644$, monoclinic, space group $P2_1/c$ (no. 14); $a = 1089.2(2)$, $b = 1744.0(4)$, $c = 1989.7(3)$ pm, $\beta = 100.05(1)^\circ$, $V = 3.722(2)$ nm ^{3} , $Z = 4$, $\rho_{\text{calcd}} = 1.57$ Mg m $^{-3}$, $F(000) = 1747$, $\lambda = 71.069$ pm, $T = 293$ K, $\mu(\text{Mo}_{\text{K}\alpha}) = 3.29$ mm $^{-1}$, crystal dimensions $0.25 \times 0.25 \times 0.15$ mm ^{3} , $2 \leq 2\theta \leq 56^\circ$; of 7144 measured reflections, 6519 were unique; 462 parameters refined in full matrix, $R1 = 0.032$ with 4031 reflections ($I > 3\sigma(I)$), $wR2 = 0.037$, $w = 1$, min./max. residual electron density $-910/790$ e nm $^{-3}$. (Ph $_4$ P)-5: C $_{72}$ H $_{60}$ O $_{13}$ P $_2$ Si $_2$ Mo $_2$, $M_r = 1443.261$, monoclinic, space group $P2_1/c$ (no. 14); $a = 1305.0(2)$, $b = 1560.2(3)$, $c = 1676.9(6)$ pm, $\beta = 103.90(2)^\circ$, $V = 3.314(1)$ nm ^{3} , $Z = 2$, $\rho_{\text{calcd}} = 1.45$ Mg m $^{-3}$, $F(000) = 1469$, $\lambda = 71.069$ pm, $T = 293$ K, $\mu(\text{Mo}_{\text{K}\alpha}) = 1.025$ mm $^{-1}$, crystal dimensions $0.5 \times 0.6 \times 0.2$ mm ^{3} , $2 \leq 2\theta \leq 56^\circ$; of 8624 measured reflections, 7973 were unique; 503 parameters refined in full matrix, $R1 = 0.045$ with 4724 reflections ($I > 3\sigma(I)$) and $wR2 = 0.047$, $w = 1$, min./max. residual electron density $-640/870$ e nm $^{-3}$. The data were collected on a Enraf-Nonius CAD4 four circle diffractometer (ω - 2θ scans). All measurements were made at room temperature; two standard reflections showed no significant variation in intensity. Corrections were made for Lorentzian and polarization effects; an extinction correction was also applied;^[19] an empirical absorption correction on the basis of Ψ scan data was introduced. The structures were solved by direct methods (SHELXS-86 program)^[20] and subsequent Fourier difference techniques. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were found on difference Fourier maps; their positions were not refined and they were given one overall isotropic thermal parameter. Refinements were carried out by minimizing the function $\sum w(|F_o| - |F_c|)^2$, where F_o and F_c are the observed and calculated structure factors (program CRYSTALS).^[21] 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-100828. 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).

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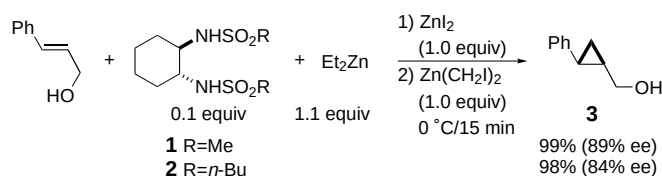
Solution and Solid-State Studies of a Chiral Zinc–Sulfonamide Complex Relevant to Enantioselective Cyclopropanations**

Scott E. Denmark,* Stephen P. O'Connor, and Scott R. Wilson

Sulfonamide derivatives of chiral amines and diamines have recently emerged as an important class of auxiliaries and catalysts in enantioselective transformations.^[1] Chiral sulfonamides serve admirably as ligands for a number of different metals and have been employed in a wide variety of synthetically useful reactions, for example, cyclopropanation (Zn),^[2] addition of dialkylzinc to aldehydes (Ti),^[3–6] Mukaiyama aldol reaction (lanthanides),^[7] enantiotopic group differentiation (Li),^[8] Diels–Alder reactions (Al),^[9] and enantioselective allylation of aldehydes (B).^[10] In each of these systems, it is generally assumed that the metal is covalently bound to sulfonamide nitrogen atoms. Indeed, Corey et al. have provided an X-ray crystal structure of a chiral diazaaluminolide prepared from *N,N'*-(1,2-diphenylethylene)bis(trifluoromethanesulfonamide) and trimethylaluminum, which clearly shows that the aluminum atom is bound in just such a manner.^[11] Our interest in this area derives from the demonstration that chiral bis(sulfonamide)s which, when pretreated with diethylzinc, are effective catalysts for the enantioselective cyclopropanation of allylic alcohols.^[12] Herein we provide reaction data, elemental analyses, spectroscopy studies, and an X-ray crystal structure in support of a catalyst structure which, among other interesting features, contains a zinc atom bound to both sulfonamide nitrogen atoms.

Although our previous studies have shown (*R,R*)-*N,N'*-cyclohexane-1,2-diylbis(methanesulfonamide) (**1**) to be the optimal cyclopropanation catalyst (Scheme 1), we selected the analogous and equipotent bis(*n*-butanesulfonamide) **2** for these structural studies owing to its superior solubility (e.g. in CH $_2$ Cl $_2$: **1**: ≈ 1 mg mL $^{-1}$ CH $_2$ Cl $_2$; **2**: > 40 mg mL $^{-1}$).

We first established the chemical composition of the catalyst, which according to earlier studies requires the combination of **1** with diethylzinc.^[12c] Therefore, a solution of **2** in dichloromethane was treated with diethylzinc (1.0 equiv, room temperature), and the solvent removed in



Scheme 1. Bis(sulfonamide)-catalyzed enantioselective cyclopropanation.

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vacuo. The resulting off-white powder provided a correct elemental analysis (C, H, N, S, Zn)^[13] for the formula C₁₄H₂₈N₂O₄S₂Zn, which corresponds to the simple zinc salt of **2** (i.e., [Zn²⁺(**2**–2H)^{2–}]). That deprotonation at the sulfonamide nitrogen atom had occurred was confirmed by ¹H NMR spectroscopy. A comparison of the spectra acquired before and after the addition of diethylzinc (1.0 equiv) to **2** in CDCl₃ showed clearly that the sulfonamide NH protons (δ = 4.78) had disappeared (Figure 1a and b). Interestingly, the

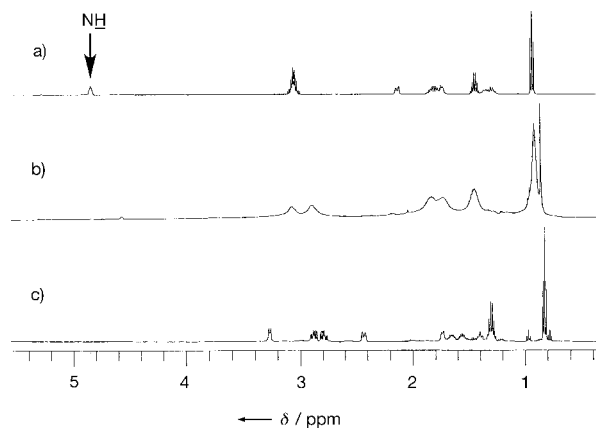
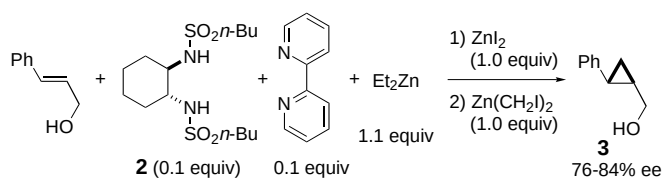


Figure 1. ¹H NMR spectra of a) **2**, b) **2** + Et₂Zn (1.0 equiv), c) **2** + Et₂Zn (1.0 equiv) + bipy (1.0 equiv).

remaining signals became very broad, which suggested that the zinc–sulfonamide species was aggregated. Furthermore, the solution had gelled within 15 min of the addition of diethylzinc, thus providing additional evidence that the zinc–sulfonamide species was strongly self-associating. The gel could be solubilized by the addition of pyridine (2 equiv), 1,10-phenanthroline (1 equiv), or 2,2'-bipyridyl (bipy, 1 equiv). The ¹H NMR spectrum of [Zn²⁺(**2**–2H)^{2–}] which had been treated with one equivalent of bipy displayed very sharp resonances (Figure 1c). Presumably, the bidentate ligand was capable of disrupting the intermolecular zinc–sulfonamide interactions to give a monomeric complex.

Having demonstrated that deprotonation of **2** to form a zinc complex proceeds efficiently under the chosen reaction conditions, we next sought to establish that [Zn²⁺(**2**–2H)^{2–}] is a kinetically significant species. Therefore, the zinc–sulfonamide complex was formed from **2** (0.1 equiv) and diethylzinc (0.1 equiv) under the same conditions as for the NMR experiment, and this solution was then added to ethylzinc cinnamyl alcoholate followed by the addition of zinc iodide (1.0 equiv) and di(iodomethyl)zinc (1.0 equiv). The product cyclopropane **3** was formed rapidly with 83% *ee*. This verified that the active form of the sulfonamide must be the deprotonated species produced upon treatment of **2** with diethylzinc.

In addition, we also demonstrated that the zinc–sulfonamide moiety remains intact and catalytically active upon complexation with bipy. Two different protocols were used to generate this species (Scheme 2). In the first reaction, all three components (cinnamyl alcohol, **2**, and bipy) were combined prior to treatment with diethylzinc. The product was obtained with the same selectivity (84% *ee*) as in the absence of bipy (see Scheme 1). In the second reaction, [Zn²⁺(**2**–2H)^{2–}]



Scheme 2. Cyclopropanation with **2** in the presence of bipy.

(0.1 equiv) was formed separately and then treated with bipy (0.1 equiv). The solution of this preformed ternary complex ([Zn²⁺(**2**–2H)^{2–}(bipy)]) was then used for the cyclopropanation of cinnamyl alcohol. The product was obtained with a slightly lower enantiomeric excess (76% *ee*). Taken together, these experiments reveal that [Zn²⁺(**2**–2H)^{2–}] retains its catalytic activity upon complexation with bipy, and that bipy is a weakly competitive ligand for the catalyst in place of the substrate and reagents in the cyclopropanation.

The most compelling evidence concerning the nature of the zinc–sulfonamide species is provided by the solid-state structure (Figure 2).^[14] Single crystals of [Zn²⁺(**2**–2H)^{2–}(bipy)] suitable for X-ray diffraction analysis

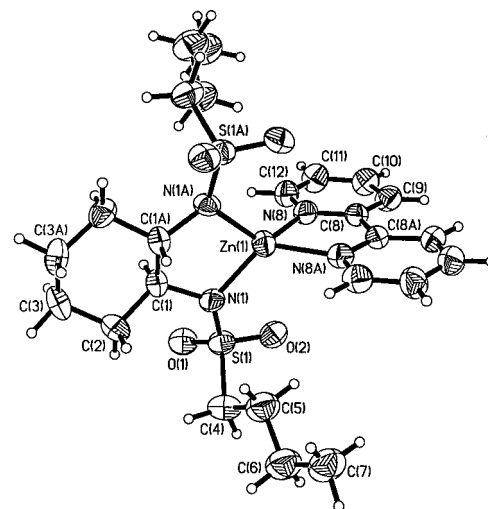


Figure 2. SHELXTL representation of the crystal structure of [Zn²⁺(**2**–2H)^{2–}(bipy)] (35% thermal ellipsoids). Selected bond lengths [Å] and angles [°]: Zn(1)–N(1) 1.942(8), Zn(1)–N(8) 2.047(8), S(1)–N(1) 1.569(7), S(1)–O(1) 1.461(8), S(1)–O(2) 1.446(8); N(1)–Zn(1)–N(1A) 85.8(4), N(8)–Zn(1)–N(8A) 80.0(5), N(1)–Zn(1)–N(8) 124.8(3), N(1)–Zn(1)–N(8A) 123.4(3), Zn(1)–N(1)–S(1) 119.8(4); torsional angles [°]: C(4)–S(1)–N(1)–Zn(1) 119.0(10), S(1)–C(4)–C(5)–C(6) –161(2).

could be obtained by treatment of racemic **2** in CHCl₃ with diethylzinc (1.0 equiv) and then bipy (1.0 equiv) at room temperature followed by cooling to –20 to –25 °C.^[15] The compound crystallized as a tris(chloroform) solvate.

The crystal structure confirmed that the zinc atom is bonded to both sulfonamide nitrogen atoms. The Zn–N bond lengths are both 1.942(8) Å, as the molecule resides on a twofold symmetry axis. The distances between zinc and the bipy nitrogen atoms are 2.047(8) Å; the four nitrogen atoms around zinc form a highly distorted tetrahedron. The sulfonamide N–Zn–N angle is contracted from the ideal tetrahedral angle of 109.5° to 85.8(4)°, whereas the N–Zn–N angle for the

bipy ligands is 80.0(5)° owing to the long Zn–N bonds in each of the two five-membered rings. Another noteworthy feature is the pyramidal nature of the sulfonamide nitrogen atoms (sum of angles at N 352.3°). This places the sulfonyl groups in pseudo-equatorial orientations and clearly results from the minimization of nonbonded interactions with the cyclohexane backbone. The differential disposition of the sulfonamide groups plays a critical role in our model for asymmetric induction.^[12c]

The chelation of zinc by the Lewis basic bipy nitrogen atoms suggests that the active catalyst may function in solution as a divalent Lewis acid. With our transition state model^[12c] for the enantioselective cyclopropanation, we propose that the coordination sites at the zinc atom of $[\text{Zn}^{2+}(\mathbf{2}-2\text{H})^{2-}]$ are occupied by the oxygen atom of the alkoxide and the zinc-bound iodine atom of the reagent, iodomethylzinc iodide. The crystal structure of $[\text{Zn}^{2+}(\mathbf{2}-2\text{H})^{2-}(\text{bipy})]$ and the data described herein provide additional support for this dual mode of action of a zinc-containing Lewis acid. The simultaneous coordination of two reactive species, namely the substrate ethylzinc alkoxide and the reagent iodomethylzinc iodide, by the zinc atom in $[\text{Zn}^{2+}(\mathbf{2}-2\text{H})^{2-}(\text{bipy})]$ implies that it acts as a focal point, or organizational center, and at the same time enhances the reactivity of the reagent by virtue of the electron-deficient and geometrically distorted zinc atom.

The structure of the active species in any catalytic process is difficult to guarantee. This is particularly true for a heterogeneous reaction of this complexity with many components, and $[\text{Zn}^{2+}(\mathbf{2}-2\text{H})^{2-}]$ may represent a precatalyst. Nevertheless, taken together with the results from previous studies, we can now formulate a more coherent picture for the nature of the substrate^[12c] as well as the structures of the reagent^[12d] and the catalyst in these enantioselective cyclopropanations.

Experimental Section

2: To a solution of (*R,R*)-1,2-cyclohexanediamine (1.097 g, 9.6 mmol) and triethylamine (2.92 g, 28.9 mmol) in CH_2Cl_2 (30 mL) at 0°C was added *n*-butanesulfonyl chloride (3.92 g, 25.0 mmol). The reaction mixture was warmed to room temperature and stirred for 12 h. The mixture was then cooled to 0°C, and aqueous H_2SO_4 (3.0 N, 30 mL) was added. Extraction of the aqueous layer with CH_2Cl_2 (3 × 20 mL), drying of the combined extracts (MgSO_4), and in vacuo concentration followed by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 19/1) and crystallization from hexane/ CH_2Cl_2 provided 2.98 g (8.4 mmol, 87%) of **2** as a white crystalline material. M.p. 137.0–138.0°C; ^1H NMR (500 MHz): δ = 4.78 (d, *J* = 6.8, 2H, NH), 3.06 (m, 6H, HC(1), $\text{H}_2\text{C}(4)$), 2.15 (d, *J* = 12.4, 2H, $\text{H}_{\text{eq}}\text{C}(2)$), 1.79 (m, 6H, $\text{H}_{\text{ax}}\text{C}(2)$, $\text{H}_2\text{C}(5)$), 1.46 (m, 4H, $\text{H}_2(6)$), 1.32 (m, 4H, $\text{H}_2\text{C}(3)$), 0.95 (t, *J* = 7.3, 6H, $\text{H}_3\text{C}(7)$); ^{13}C NMR (125 MHz): δ = 57.42 (C1), 53.84 (C4), 34.58 (C2), 25.60 (C5), 24.63 (C3), 21.54 (C6), 13.59 (C7); MS (EI): *m/z* (%): 354 (M^+ , <1), 96 (100); IR: $\tilde{\nu}$ = 3279 (s), 2957 (s), 2943 (s), 2922 (s), 1451 cm^{-1} (s); TLC *R*_f 0.30 ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 49/1); elemental analysis calcd for $\text{C}_{14}\text{H}_{30}\text{N}_2\text{O}_4\text{S}_2$ (354.53): C 47.43, H 8.53, N 7.90, S 18.09; found: C 47.69, H 8.49, N 7.97, S 18.04.

$[\text{Zn}^{2+}(\mathbf{2}-2\text{H})^{2-}]$: To a solution of **2** (753 mg, 2.12 mmol) in CHCl_3 (20 mL) at 0°C was added diethylzinc (218 mL, 1.00 equiv), and the solution allowed to warm to room temperature. After about 10 min the solution became somewhat viscous, and a white, powdery precipitate formed. The contents of the flask were cooled in a liquid N_2 bath, and a vacuum (≈ 0.1 mm) was applied overnight. As the liquid N_2 was allowed to evaporate, the solvent was distilled into a liquid N_2 trap to leave an off-white powdery solid. This material was sealed under vacuum and transferred to a dry box. Samples were weighed and sealed in tin capsules for C, H, N elemental analysis and in aluminum capsules for S and Zn elemental

analysis: calcd for $\text{C}_{14}\text{H}_{28}\text{N}_2\text{O}_4\text{S}_2\text{Zn}_1$ (417.89): C 40.24, H 6.75, N 6.70, S 15.34, Zn 15.65; found: C 40.39, H 6.91, N 6.66, S 14.88, Zn 15.83.

$[\text{Zn}^{2+}(\mathbf{2}-2\text{H})^{2-}(\text{bipy})]$: To a solution of **2** (355 mg, 1.00 mmol) in CHCl_3 (8.0 mL) in a 35-mL two-neck round-bottom flask fitted with a rubber septum and a ground glass gas inlet adapter but no stirrer was added diethylzinc (104 mL, 1.02 equiv) at room temperature. This was done while gently swirling the flask to mix the contents. After about 10 min the solution became very viscous. A solution of 2,2'-bipyridyl (156 mg, 1.00 equiv) in CHCl_3 (2.0 mL) was added, and the flask swirled to mix the contents. The solution was no longer viscous upon complete addition of the 2,2'-bipyridyl solution. After cooling at –20 to –25°C in a freezer, in the absence of light, a large amount of colorless, long, thick needlelike crystals had formed. The crystals could be redissolved at 0°C and reformed upon subsequent cooling to –20 to –25°C for several hours. A single crystal was removed and quickly mounted in a stream of N_2 at –70°C.

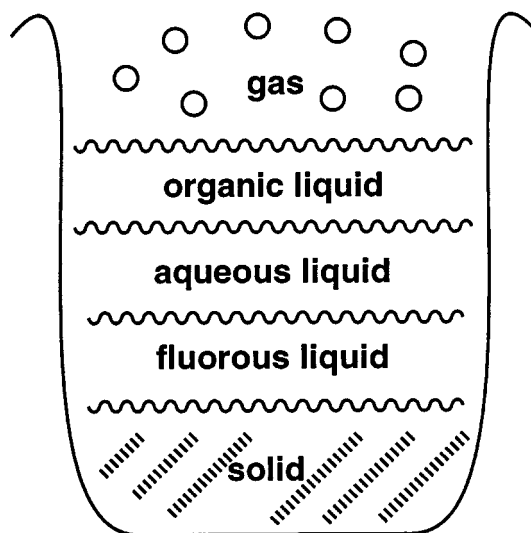
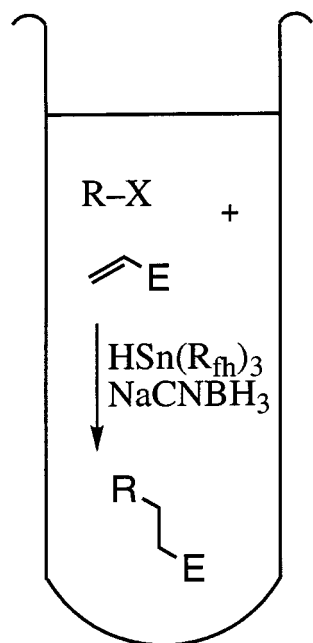
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Keywords: asymmetric catalysis • cyclopropanations • sulfonamides • zinc

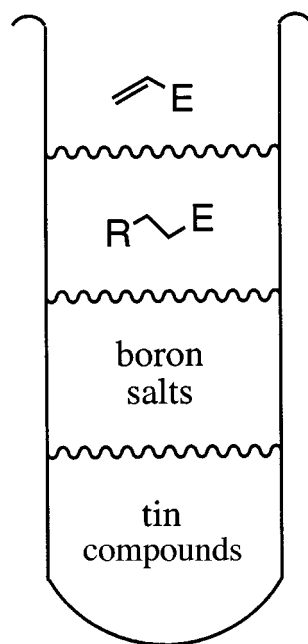
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reaction



"orthogonal phases"
for purification at workup level

workup phase
 separation



desired product in
a unique phase from
all other reaction components

Strategy-Level Separations in Organic Synthesis: From Planning to Practice

Dennis P. Curran*

The yield and practicality of every reaction are limited by the ability to separate and recover the final pure product from the reaction mixture. Said another way, synthesis and separation are inseparable. However, over the years mainstream synthetic organic chemistry has tended to divorce synthesis from separation by treating separation as a technical issue. Advances in the field of separation have enabled modern synthetic chemists to contemplate and then synthesize molecules of remarkable complexity. At the same time, the power of modern separations has instilled a complacency in some. The expectation is that we can separate anything these days. However, separation advances notwithstanding, this expectation is no more realistic than the expectation (held by some outside the synthesis community) that we can

synthesize anything we desire. On the process-chemistry front, we are expected not only to synthesize the desired compound, but to synthesize it cheaply, efficiently, and safely. Furthermore, with the advent of combinatorial chemistry, synthesizing *anything* isn't good enough anymore, we are expected to synthesize *everything*—and quickly! To meet these high expectations, synthetic chemists have begun to formulate strategic plans at the beginning of a synthesis. In these plans synthesis dictates separation, and molecules in the final reaction mixture are designed to virtually separate themselves when processed in a purification stage. The best laid plans allow products to be isolated by using simple workup techniques such as evaporation, extraction, and filtration. There is an emerging field at the interface of

synthesis and separation, and though it is firmly rooted in the past the field is anything but old-fashioned. A unified basis for strategic separation planning is constructed by bringing together under a single umbrella a number of results from apparently disparate areas such as acid–base chemistry, solid-phase synthesis, fluorous synthesis, and others. A vision for the future forms in which reactions and separations are remarried and work together to help meet the demanding expectations that the field of organic synthesis faces in its ever more challenging quest to produce useful chemical entities.

Keywords: combinatorial chemistry • fluorous synthesis • solid-phase synthesis • synthesis design

1. Introduction

1.1. Purification in Synthesis

The discipline of organic synthesis is essential to progress in many fields, and is therefore one of the core disciplines in chemistry. During the second half of this century, synthetic strategies and techniques have rapidly advanced,^[1] and this has resulted in the discovery and characterization of millions of organic molecules of all sizes. However, the number of known organic compounds still pales in comparison to the diversity that is offered by structures based on the element carbon. The need for new organic molecules of relatively small size (relative molecular weights in the range 250–750) is especially acute in the pursuit of new drugs. In response to this

need, the emerging disciplines of combinatorial synthesis and automated organic synthesis are beginning to provide new compounds at a greatly accelerated pace.^[2] In this arena, speed is of the essence.

At the other end of the spectrum from discovery is the production of molecules that have useful functions. Here, the development of the safest, least expensive, and most environmentally friendly synthetic route possible is widely recognized as an important goal. Supporting both discovery and production work in organic synthesis is a large component of basic research in areas such as the synthesis of natural and unnatural products, the development of new synthetic methods, and the study of reaction mechanisms. This research continues to transform the field of synthesis by providing increasingly powerful strategies, reactions, and techniques to make even the most sophisticated of organic molecules.

Despite these sweeping changes in our ability to conduct and also to analyze reactions, one crucial aspect of synthesis has not been affected much over the last decades: purification. The initial purification of an organic reaction mixture by

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“workup” has changed little over the past 50 years. Subsequent purification by crystallization, distillation, chromatography, or other methods are fundamentally similar now to 20 years ago, although there have been notable improvements in these purification techniques, especially in the area of chromatography.

Indeed, the whole purification process is regarded as a technical one in the field of synthesis. Aspects of purification rarely emerge in the experimental sections of papers, and authoritative books on synthesis say little or nothing about purification. Synthesis, as we know, is about reactions and strategies for conducting reactions in sequence. There are strategies for making molecules, for chemo-, regio-, and stereoselectivity, for protecting groups, and for other aspects of the synthesis process. However, it would seem that there are no strategies for purification—one simply conducts a reaction and then tries the available purification techniques to see which work and how well.

The advent of combinatorial chemistry and automated parallel synthesis is beginning to change the way synthesis is done. Combinatorial and parallel syntheses demand simple purification methods, and this demand has exposed huge gaps in the available techniques. These gaps are now being filled by promoting purification from a technical concern to a strategy-level concern. In other words, the plan for a reaction or sequence of reactions specifically takes into account separation at the design stage. Although rarely phrased in strategic terms, separation design is not new. The use of volatile or water-soluble reagents, acid–base extractions, and more recently solid-phase synthesis are all examples of designed separation. However, the field has lied fallow for sometime until recently, and existing applications—such as acid–base extractions—are so well established that they are almost treated as isolated techniques rather than as components of a larger strategy.

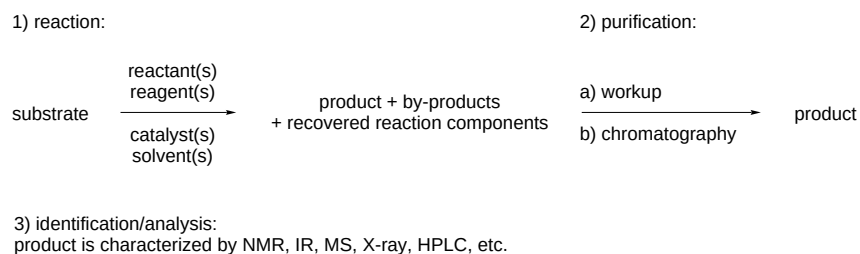
The purpose of this article is to provide guidelines for strategy-level separation planning, to show how these guidelines are now being implemented in practice, and thus to expedite work in this fast-moving field. This is not a review about combinatorial chemistry,

about which many excellent reviews already exist.^[2] Nor is it a review about solid-phase synthesis; solid-phase synthesis and allied techniques will be integrated into the big picture of separation planning. Thorough reviews are already available in the area of solid-phase synthesis,^[3] and the citations in this paper are selected solely for illustration. Likewise, the use of water-soluble reaction components is commonplace and is not extensively reviewed here. Other areas are at an earlier stage of development, and an effort is made to be more complete in referencing.

1.2. Stages in the Development of a Step in Organic Synthesis

The synthesis of an organic molecule of any size generally proceeds through a planned sequence of steps in which an initial starting material (substrate) is converted into a product by means of a chemical reaction. The product of the first reaction then becomes the substrate for the second reaction, and so on until the target product is made. Strategies to plan the sequence of steps for the synthesis of an organic molecule are now very sophisticated.^[1] Although those of us who write the journal articles and books like to focus on reactions, those who do the experiments are quick to recognize that there is more to synthesis than reactions.

Each step in a synthetic sequence can usually be subdivided into three stages: reaction, purification, and identification/analysis (Scheme 1). The reaction stage consists of treating the substrate with appropriate reactants, reagents, or catalysts^[4] under suitable conditions (temperature, sometimes pressure, light, etc.) to effect the transformation to the desired



Scheme 1. Stages of a step in an organic synthesis.



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product. Most reactions are conducted in the liquid phase with the aid of one or more solvents.

In the purification stage, the desired product is separated from any by-products and remaining reaction components. By-products can be obligatory, as with the remnants of a reactant consumed in the reaction (for example, Ph_3PO from a Wittig reaction), or they can result from undesired reaction pathways of the substrate or another reaction component. In the identification/analysis stage, the structure of the product is typically secured by spectroscopic and/or X-ray crystallographic means, and the purity of the product is ascertained by spectroscopic and/or chromatographic techniques. This three-stage classification is somewhat loose (for example, analysis can and often does take place at any of the three stages), but it is still representative of the majority of synthetic steps.

In modern organic synthesis, the purification stage is frequently subdivided into two sections: workup and chromatography. The workup stage uses simple phase-separation techniques such as extraction, filtration, and evaporation to make crude separations. The subsequent chromatographic stage is a more recent introduction that has greatly increased the power of organic synthesis by allowing the separation of organic compounds from other organic compounds based on various sophisticated types of phase partitioning. However, chromatography can be an expensive and time-consuming proposition, and chemists who make large quantities of organic compounds have always tried to use the time-honored techniques of distillation and crystallization or other simple methods in place of chromatography.^[5] Purification is often the most costly stage in terms of time and resources.

2. Planning Separation Strategies

2.1. The Goal

The ultimate goal in organic synthesis is represented by Paul Wender's notion of an "ideal synthesis".^[6] Taking this to the limit, I provide the following paraphrase of an ideal synthesis: You mix inexpensive, commercially available starting materials in the required stoichiometries and get the pure final product in quantitative yield. At this extreme case, the purification stage disappears; nothing is added to the "reaction mixture" except components that wind up in the final product. Wender's actual definition is more realistic, and allows for things such as catalysts—which immediately reintroduces the need for the purification stage since the catalyst must be separated from the product. However it is framed, the notion of an ideal synthesis represents a valuable "grail" for the synthesis community by exposing the fact that even though synthesis has come a long way, there is still a very long way to go. Phenomenal recent and future progress in reaction chemistry notwithstanding, there is no immediate prospect of the development of this chemistry to the point where it eclipses the need for a purification stage in most transformations.

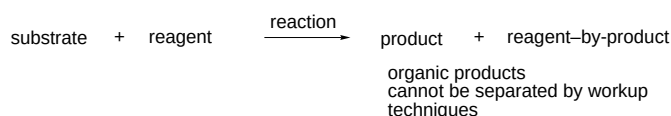
Planning for purification at the strategy level is based on the following goal for the "ideal purification": The product should be separated into a different phase from everything else that is

present in the final reaction mixture. When this goal is met, the reaction mixture can be quickly subjected to one or more simple phase-separation techniques to provide a pure product. This is a time-honored goal that is only implemented occasionally.^[5] For example, acylation of an amine with an acid chloride followed by a series of simple acid–base extractions provides the product amide (neutral phase) free from any unchanged amine (acid phase) or acid chloride (hydrolyzed to the acid and in the base phase). These simple notions will be generalized below to the concept of purification by "phase switching."

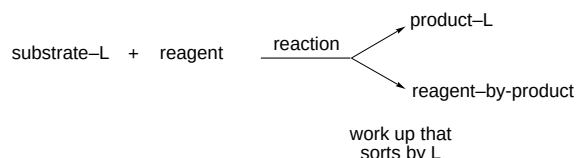
With this goal, separation at the strategy level becomes an exercise in "phase planning". This begins with the recognition that all molecules have a "natural" phase into which they will generally partition in a simple phase separation. Most molecules of interest in synthesis are "naturally" organic. We use the term organic here and throughout the rest of the article in a more restricted sense than the standard definition: Molecules are "organic" with respect to a phase-separation technique if they end up in the organic liquid phase. In other words, for a liquid–liquid extraction between diethyl ether and 1N HCl, the amide and the acid are organic (they partition to the ether phase) whereas the amine is basic (it partitions to the acid phase). In the case of an extraction with diethyl ether and 1N NaOH, the amide and the amine are organic, but the acid is not. The natural phase of a molecule must therefore be specified with reference to a given phase-separation technique. This qualitative behavior is quantified by a partition coefficient. In this section, we take the unrealistic view that all the partition coefficients are 100% into the natural phase. A more realistic view of partition coefficients is given in Section 3, which deals with the "practice".

In principle, the natural phase of any molecule with respect to a given separation can be modified by a process that we call "phase labeling".^[7] The basic notion is shown in Scheme 2, where L is some type of chemical-phase label that can be attached to any reaction component before (Scheme 2),

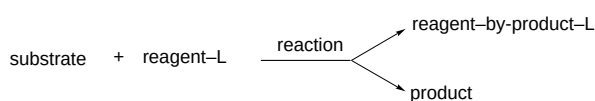
basic reaction



substrate attached to phase label L



reagent attached to phase label L

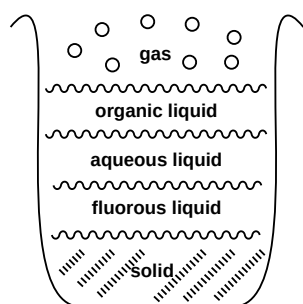


Scheme 2. Separation by phase labeling.

during, or after a reaction. For example, the attachment of a protected amino acid to a polymer support renders this naturally “organic” compound and all its subsequent reaction products in a “solid” with respect to the phase-separation technique of filtration. Phase labeling is a chemical process, so the attachment that alters the phase of the amino acid in the purification also can have profound consequences not only at the purification stage but also at the reaction and identification/analysis stages. Solid-phase synthesis provides an extreme example of this; the labeled substrates are generally insoluble at all times. While this facilitates separation, it can complicate reaction, identification, and analysis. Ideally, phase labeling should allow simple separations without compromising the reaction, identification, and analysis stages of a synthetic step.

2.2. The Simple Phase-Separation Techniques

Four phases are commonly used in simple workup-level purification techniques: the gas phase, the organic liquid phase, the aqueous liquid phase, and the solid phase. These four phases are orthogonal to each other (Scheme 3) as well as



phase label	phase	separation technique
none	organic	evaporation, extraction, filtration
ionized group	aqueous	liquid–liquid or solid-phase extraction
insoluble polymer	solid	filtration
soluble polymer	solid	precipitation–filtration
highly fluorinated group	fluorous	liquid–liquid or solid-phase extraction

Scheme 3. A simplified view of mutually immiscible phases that can be separated by evaporation, extraction, or filtration.

to the fifth, less commonly used fluororous liquid phase.^[8] Each of these phases can be separated from any other in simple and very general ways.

Since the natural phase of a compound can be specified only with reference to a phase-separation technique, phase planning starts with the techniques. Most of the simple phase-separation techniques are well known to organic chemists and are based on partitioning between gas, liquid, and solid phases. Essentially all separation techniques involve some kind of phase separation, but the scope here is restricted to simple workup-level techniques.

Evaporation partitions a mixture into volatile and non-volatile compounds. It is routinely used to separate solvents from crude or purified reaction components, and has limited utility for separating volatile from nonvolatile reaction components. Its use is restricted to a small range of “naturally volatile” compounds since there is no general method to “label” compounds as volatile by a chemical process.

Filtration partitions a mixture into a solid and a liquid phase. In classical organic synthesis, a filtration follows a crystallization (or, more generally speaking, a precipitation); the precipitation creates two phases that are separated by the filtration. Many of today’s modern solid phase synthesis techniques dispense with the precipitation event since the polymer-bound substrates never dissolve in the first place.

Extraction partitions a mixture into two (or more) liquid phases. The process is routinely conducted with the aid of volatile solvents, and evaporation then follows extraction to separate the nonvolatile components from the solvent. Two types of extractions are important for purification of reaction mixtures: liquid–liquid extraction and solid–liquid extraction. Liquid–liquid extractions predate the field of organic synthesis and have remained an integral part of most workup procedures for more than a century. Yet only three types of liquid–liquid extractions are common: A mixture is partitioned between an organic solvent and an aqueous phase that is either neutral, acidic, or basic. Simply said, an organic–aqueous extraction partitions a mixture into organic and inorganic (or better, water-soluble) fractions. Basic components can be extracted into acid and vice versa, forming the basis of the “phase switch” by acid–base extraction described above.

There are a number of organic phases that are immiscible (for example, hexane is not miscible with either acetonitrile or methanol), and these pairs can be used in extractions. These “exotic” extractions have limited utility at this point, although the concept of phase labeling could possibly be applied to extend their usefulness. However, there is one class of exotic extractions that does have significant potential. It has been known for half a century that perfluorocarbon (and some very highly fluorinated) liquids are immiscible with water and many common organic solvents.^[9, 10] Some properties of two common fluorocarbon solvents are summarized in Scheme 4. In a simple view, highly fluorinated solvents and compounds that partition into them form a separate phase called the “fluorous phase”,^[8, 11] in which organic and inorganic compounds have little or no tendency to dissolve. Therefore, phase labeling a compound or subset of compounds as fluororous is all that is required for a successful extraction.

The presence of three mutually immiscible liquid phases rather than two has a number of consequences. First, more types of extractions are possible since there are now seven basic types of two-phase extractions (one organic–fluorous, three organic–aqueous, and three fluororous–aqueous; the aqueous phase can be either neutral, acidic, or basic) and three types of three-phase extractions (organic–fluorous–aqueous). Each of these ten extractions provides its own set of separation capabilities.

Related to liquid–liquid extraction is the technique of solid-phase extraction (SPE). Though only now becoming



perfluoromethylcyclohexane

- $M_r = 350$
- bp = 76°C
- $\rho \approx 1.8 \text{ g cm}^{-3}$

immiscible with

- EtOAc
- CH₂Cl₂
- H₂O
- CH₃CN

partially soluble in

- Et₂O, THF
- CCl₄

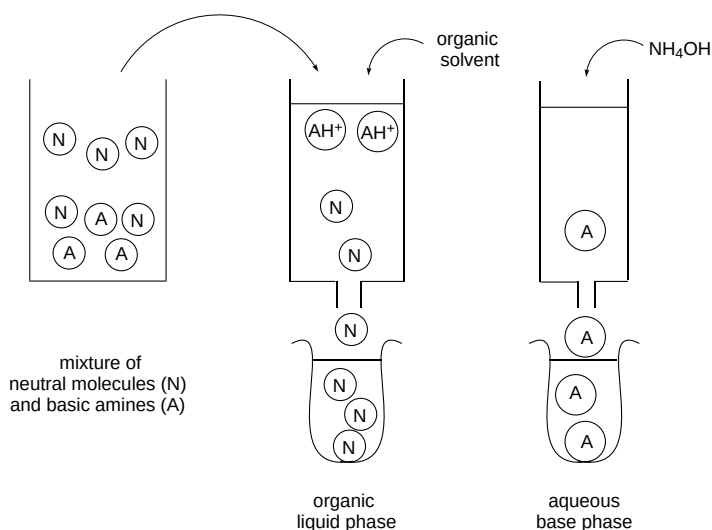
perfluorohexanes (FC-72 3M)

- bp $\approx 56^\circ\text{C}$
- mixture of isomers, mostly linear
- $M_r = 338$
- $\rho \approx 1.8 \text{ g cm}^{-3}$

Scheme 4. The fluorous phase. Perfluorocarbons are nonpolar, nontoxic, and immiscible with many common organic solvents or water.

popular in synthesis, it has been a staple in analytical chemistry for some time. The technique sits on the fence between filtration and extraction, but we classify it here as an extraction since it functions in many ways like a liquid–liquid extraction and since it frequently provides the separated reaction mixture in two liquid phases.

Solid-phase extractions are popular in chemical analysis. For example, in the analysis of compound mixtures (e.g. of organic amines) a solid-phase extraction analogous to an acid–base extraction is often conducted. A mixture containing the amine or amines to be analyzed is injected onto an acidic ion-exchange column (Scheme 5). The amines are



Scheme 5. Schematic representation of a solid-phase extraction.

affixed onto the column by protonation by the supported acid. Elution with a suitable organic solvent then quickly removes all the organic (neutral) impurities. Subsequent elution with a basic solvent then provides a second liquid phase containing the amines, which are then further analyzed. In this “prepurification” process, the amines are “extracted” from the first eluent onto the solid phase of the column as salts, and then extracted back off with a second eluent.

Currently, the potential for preparative purification by solid-phase extraction is largely untapped. In execution, solid-

phase extractions resemble filtrations, and they are probably easier to conduct in parallel than liquid–liquid extractions. However, the advantages are more than technical. Solid-phase extractions can in principle provide better separations than liquid–liquid extractions. As the separation by solid-phase extraction becomes poorer and poorer, the “extraction” becomes at some point a “chromatography.”

This transition is roughly analogous to the conversion of a separation by “evaporation” into a “distillation” as the boiling points of two liquids converge. The goal of a solid-phase extraction is often to use a phase label to control the extraction behavior. The partition-

ing of compounds onto and off of the column is determined not by the structure of the compounds themselves but by whether they contain a phase label or not. Rephrased in chromatography terms, all compounds ideally have retention factors (R_f values) of 1 or 0 (with or without the label). Among other applications, SPE may be useful in the combinatorial synthesis of aggregate mixtures of soluble molecules,^[12] which are now generally used without purification.^[13]

The above description of phases and techniques is not exhaustive. Present challenges in the field including developing new ways to use common separation techniques as well as harnessing other separation techniques for strategic separation purposes. In the case of the latter, the allied methods of dendrimer synthesis and size-exclusion chromatography will be highlighted below as examples.

2.3. Features of Phase-Separation Techniques

The overwhelming popularity of solid-phase synthesis has led to frequent discussions about the advantages of solid-phase methods over traditional methods, and there are indeed significant advantages. However, there has been little clear discussion about which of these advantages are associated with solid–liquid separations and which with solid–solid separations. Yet the difference is crucial, since features of solid–liquid separations are shared in principle by all phase-separation techniques, whereas solid–solid features are unique.

The basic feature of all the above methods is a simple separation technique, be it evaporation, extraction, or filtration. Likewise, excess reaction components of any type can be used with impunity in any reaction that meets the conditions of phase isolation. This oft-sited feature of solid-phase synthesis is by no means unique: All methods in which the substrate and the product are in the same phase can afford pure products at the end of a reaction, provided that the reaction occurs in quantitative yield based on the substrate and that none of the other reaction components or by-products derived therefrom is in the same phase as the product.

There are, however, powerful features associated with solid-phase synthesis that are not shared by other methods and that are directly attributable to solid–solid separations. Particles of any kind can be separated from one another by a

variety of triaging procedures. Indeed, arguably the most famous separation process of all time is a solid–solid separation: Pasteur resolved tartaric acid by sorting the enantiomeric crystals with tweezers under a microscope. The now popular technique of “split synthesis” is also based on a solid–solid separation.^[2, 3, 14] Each bead in a synthesis contains a single compound and can be physically separated from every other bead. Although split synthesis shares the solid–solid separation features of the resolution of tartaric acid, it also requires the polymer, which in effect serves as an “internal reaction vessel” to hold a group of attached substrates together.

Split-synthesis techniques^[14] then rely on three separate features: 1) The solid–liquid (and solid–gas) separations allow excess reagents to be used and provide for easy separation of products from other reaction components, 2) the solid–solid separation provides separation of one product (bead) from another, and 3) the chemical attachment of multiple substrate copies to the polymer provides enough product per bead for detection and analysis. This third feature is crucial, but it does not rely on phase separation.

Solid–solid separations and chemical attachment also provide unique features that can be collected under the term “site isolation”. For example, in Rebek’s famous three-phase test (Scheme 6a),^[15] a reactive intermediate such as acetyl

some extent also from substrates on the same bead. Solid–solid separations prevent functional groups on different particles from reacting with each other, but effective molarity^[17] retards functional groups on the same particle from reacting with each other.

2.4. The “Strategy” in Strategy-Level Separation Planning

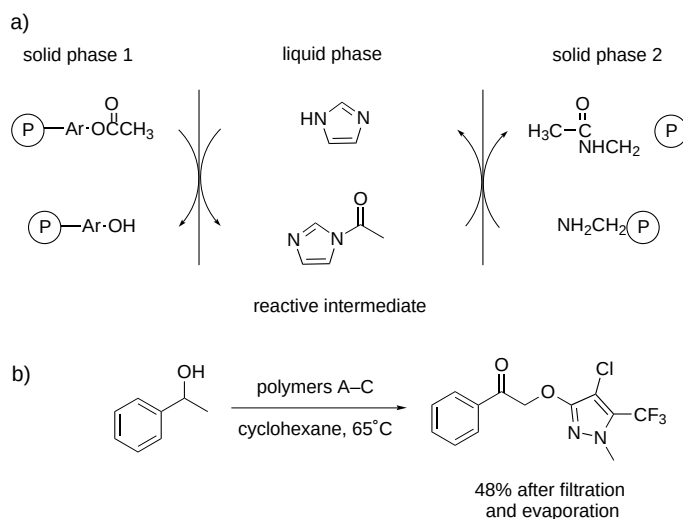
To reach the goal of isolating the product in a unique phase requires that separation be promoted from its current “technical” status to a strategy-level concern. In other words, synthetic chemistry dictates separation, and the planning of each step in a reaction sequence incorporates a designed strategy for purification. In the area of parallel synthesis, the separation strategy should be identically applicable across all members of the library. Strategic planning of separations is an exercise in matching separation techniques with the natural and labeled tendencies of all the expected components of the final reaction mixture. Additional levels of planning are associated with how and when phase labels are attached and detached (phase switching), and what other roles phase labels are required to play (as protecting groups or directors of stereo-, regio-, or chemoselectivity).

Exploiting the natural tendencies of molecules in simple phase-separation techniques formed the basis for the earliest separations, and this time-honored approach can still be used for classes of reactions that pair nonvolatile organic substrates with volatile or water-soluble reaction components. Separations for such reactions are already trivial, but these types of reactions are relatively uncommon. The development of phase-labeling techniques is now making the goal of applying simple workup-level separation techniques a reality for many more kinds of reactions.

2.5. Methods of Phase Labeling

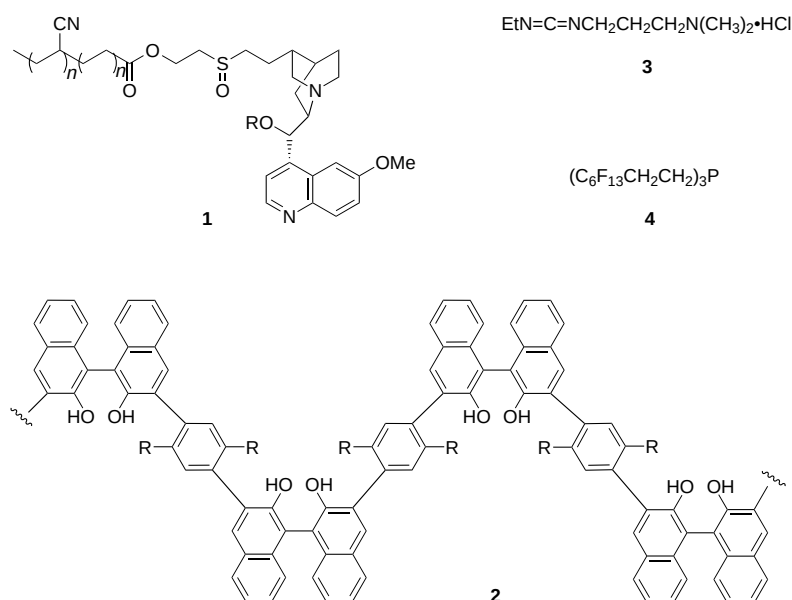
The natural phase of any type of reaction component can be overridden by attachment to a phase label, or changed by a chemical process such as polymerization. We provide below a loose classification of phase labels taken largely from solid-phase synthesis. The basic concepts can be extended to any kind of phase-separation technique.

Permanent labeling: Reaction components such as reagents, catalysts, and additives that are not transferred to the final organic product of a reaction sequence can be rendered permanently solid, fluorosoluble, or acid/base-soluble. The resulting modified reagents find use in any area of synthesis, because they facilitate purification of the reaction product as well as recovery of the labeled reaction component for reuse. A number of techniques for doing this are well appreciated.^[5] For example, an organic reagent can be rendered solid either by attaching it to a polymer backbone,^[18] as in the case of the asymmetric dihydroxylation catalyst **1** (Scheme 7),^[19] or by fashioning a polymer of the reagent itself, as illustrated by the polymeric binaphthol (BINOL) derivative **2**.^[20] Similarly, many standard reagents now have water-soluble (or acid- or base-soluble) variants: Water-soluble *N*′-(3-dimethylamino-



Scheme 6. a) An example of the three-phase test; no reaction occurs between solid phases in the absence of imidazole. b) Simultaneous multistep synthesis with polymer reagents; polymer A: poly(4-vinylpyridinium dichromate), oxidizes (secondary) alcohols to ketones; polymer B: perbromide on Amberlyst A-26, brominates ketones; polymer C: Amberlite IRA-900 ((4-chloro-1-methyl-5-trifluoromethyl)-1*H*-pyrazol-3-ol), displaces bromide.

imidazole is released from one polymer into solution and trapped on another polymer. In a related way, otherwise incompatible reagents can be mixed. For example, polymeric reagents can coexist and simultaneously operate on substrates in solution without reacting with each other (Scheme 6b).^[16] These effects again result from solid–solid separations. Finally, especially in more rigid polymers, attached substrates are isolated not only from substrates on another bead but to



Scheme 7. Representative examples of permanently labeled reagents and catalysts: a catalyst with a polymer backbone (**1**), an integral polymer catalyst (**2**), a water-soluble reagent (**3**), and a fluororous reagent (**4**).

propyl)-*N*-ethylcarbodiimide (EDCI, **3**) can often be substituted for an organic carbodiimide in dehydrations,^[21] and phosphane **4** can be viewed as a fluororous version of a standard trialkylphosphane.^[8]

Temporary labeling: When instead reaction substrates and products are labeled, the labeling must be temporary because the initial and final products are organic. Temporary attachments can be accomplished in a number of different ways, two of which are illustrated in Scheme 8. In the simplest version, labels are attached and detached at the same site. Such a strategy resembles closely the standard use of protecting groups in many cases, as in solid-phase synthesis. Attachment

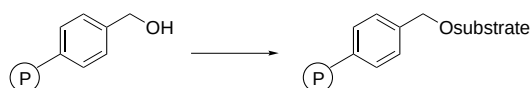
2.6. Establishing Different Phase Behavior at the Reaction and Purification Stages

It is frequently desirable for reaction components to exhibit different phase behaviors at the reaction and purification stages. Although biphasic reactions are purposefully used to advantage for some kinds of reactions, it is more common to conduct reactions that (ideally) occur in a homogeneous liquid phase. In contrast, at least two phases are required for any kind of separation. In solid-phase synthesis with insoluble polymers, it is not possible to establish a homogeneous liquid phase. This

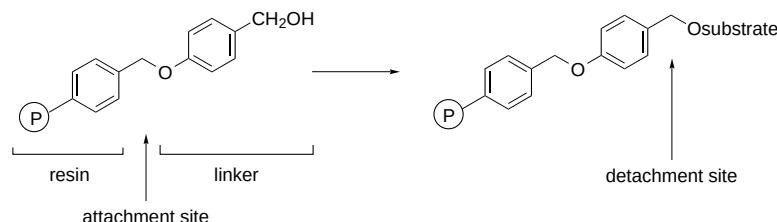
problem is being overcome by designing polymers that better mimic solution behavior and by developing reaction conditions that are optimized for solid–liquid reactions.

In most other applications not involving insoluble polymers, it is often possible to establish homogenous reaction conditions and then to cause a phase separation during purification. Because the phase behavior of a compound depends on both the compound and the phase-separation technique, a phase separation can be accomplished either by changing the technique or changing the compound. In perhaps the simplest example, the reaction itself converts a soluble substrate into an insoluble product, and a solid–liquid separation occurs. Product precipitation is highly sought after in process chemistry but has limited generality. Precipitations of specific compounds are also commonly effected by changing solvents or temperatures.

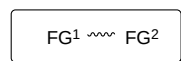
one-point attachment: hydroxymethylpolystyrene



two-point attachment: Wang resin



general linker

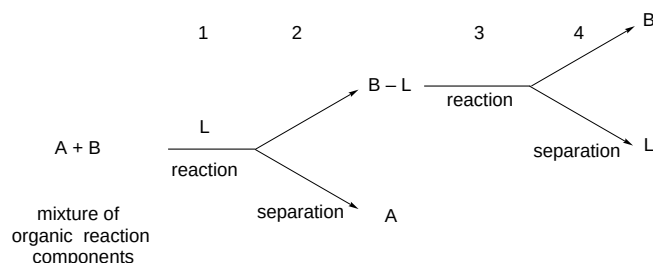


FG¹ to phase tag
FG² to substrate, reactant, etc.

Scheme 8. Examples of temporary labeling in solid-phase synthesis.

The use of soluble polymers represents a much more general approach to the problem of separation by precipitation or filtration. Some polymers are soluble under certain reaction conditions (solvent, temperature, etc.), but can be precipitated by changing the solvent or conditions.^[22g, 23] When these polymers are used as phase labels, the precipitation can be controlled by the polymeric phase label and not by the labeled substrate or reagent. Fluorous approaches can also provide for one phase at the reaction stage and two phases at the separation stage either by alternative heating and cooling or by using different solvents at each stage.^[8] Indeed, techniques based on soluble polymers and fluorous compounds are often classified together under the term “liquid-phase synthesis”. However, since soluble polymers, fluorous tags, and the like are used for separation and not for synthesis, we prefer to classify these techniques according to their different phase behavior in separation.

It is also possible to switch the phase of one or more reaction components in a designed fashion, so that they become separable from another component or subset of components from which they were previously inseparable. We call this technique “phase switching” (Scheme 9). As men-



Scheme 9. Stages in phase switching: 1) selective labeling of a component B with a label L (by protonation, deprotonation, conjugation to a polymer, fluorous group, etc.); 2) phase separation based on the presence or absence of L; 3) and 4) removal of L and repeated separation (only if isolation of B is required).

tioned above, phase switching can be as simple as an acid–base extraction. Here, the phase-switching “event” is the chemical protonation or deprotonation of a base or an acid.

Complementing this classical technique are new methods based on chemoselective reactions of reaction components to attach or remove phase labels such as polymers or fluorous groups. The attachment/removal can be accomplished before the reaction, as a direct result of the reaction, or after the reaction. Any reaction component can be subjected to phase switching to effect purification. Probably the most powerful types of phase switches involve reaction products; if the product can be selectively switched into a unique phase, it can be isolated in pure form independent of the absolute yield of the reaction.

3. Strategy-Level Separation—Practice

3.1. Classification of Purification Schemes

The various purification strategies listed in the following are classified by whether or not phase switches are involved,

and are further sorted by the natural phase (at the separation stage) of the substrate and/or product of a reaction as “organic synthesis”, “solid-phase synthesis”, “fluorous synthesis”, etc. This classification is based on the notion that there are two fundamentally different strategies to effect a phase separation of a homogeneous reaction mixture: 1) The reaction conditions (solvent, temperature, etc.) can be modified to effect a partition, and 2) one or more components of the reaction mixture can be chemically modified to change the phase behavior of the mixture with respect to a given phase-separation process. In the classification scheme, acid–base extractions and related techniques are listed as phase switches, and protonation or deprotonation becomes the phase-switching event.

3.2. Fundamental Methods Not Involving Phase Switches

In most synthetic applications, the natural phase of the substrates and products of a multistep synthesis is either never changed or changed only at the beginning and the end of a sequence. This results then in a relatively small number (at present) of fundamental ways to conduct organic synthesis. The choice of a fundamental method for a synthesis is made at the highest level of strategic planning. Indeed, until the advent of solid-phase synthesis, the “choice” of a fundamental method was essentially made by default since it was not recognized that there were any choices. For lack of a better name, standard methods based on “unlabeled” substrates and products are classified under the umbrella of “organic synthesis”, where the term “organic” refers again to small organic molecules that generally partition into the organic liquid phase. Other methods are classified according to the nature of the label that is attached to the substrate at the outset. The features of each method at the reaction, the purification, and the identification/analysis stages of a synthetic step will be briefly evaluated.

3.2.1. Organic Synthesis

The original and still by far the most common fundamental strategy is to directly use organic molecules themselves. During the course of a sequence of reactions, intermediate products are chemically modified for all sorts of purposes including setting up subsequent bond-forming reactions, protecting reactive functional groups, and controlling stereo- and regioselectivity. However, they are not modified in a general way to change their phase behavior.

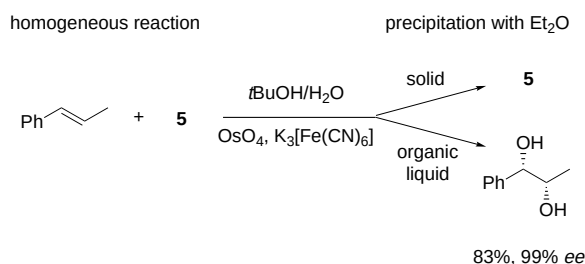
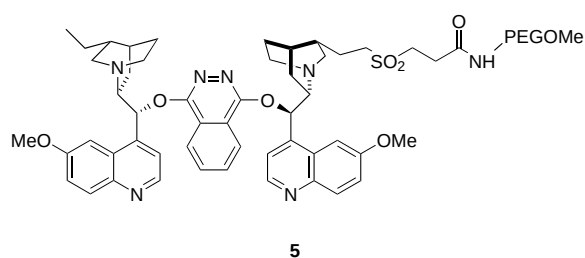
Backed by decades of intensive research and continuous improvements,^[1] traditional organic synthesis is very strong at the reaction stage. It is also strong with respect to identification and analysis; there are many powerful spectroscopic and chromatographic methods that specifically address small organic molecules. However, traditional organic synthesis is weak at the purification stage—it is an exception rather than the rule that a single nonvolatile organic compound is present at the end of a reaction. The separation of one nonvolatile organic compound from another often requires chromatography, because most organic molecules partition together into

the organic liquid phase in any of the simple phase-separation techniques.

Although early methods for combinatorial synthesis were almost exclusively based on solid-phase techniques, “solution-phase” methods that use standard organic molecules as substrate and products are now making a comeback. In these methods, phase planning dictates that other additives to a reaction of a small organic molecule are chosen such that they all partition into a phase other than the organic liquid phase.^[11]

Methods based on the gas phase (with volatile additives) and the aqueous phase (with inorganic or water-soluble additives) are well recognized by all practitioners, but are not covered here. Likewise, polymer-bound reagents have been used for more than two decades^[22] and are becoming increasingly popular. In addition to allowing simple purification by filtration, these reagents can be used simultaneously (Scheme 6b). Furthermore, the reagents need not be polymer-bound; any type of insoluble solid will do. Heterogeneous metal catalysts, clay catalysts, and zeolites are examples of other types of insoluble solids that can promote reactions and then be separated from products by filtration.^[5b]

Reagents attached to “soluble polymers” represent an especially useful class, because they can be made soluble at the reaction stage but precipitated at the purification stage by a change in solvent or temperature.^[22g] The most popular and useful reagents to date in this class are bound on polyethylene glycol ethers (PEG).^[23] PEG polymers arise from polymerization of ethylene oxide, and are available in varying molecular weights; they then have differing phase characteristics. PEG with a relative molecular weight (M_r) of 2000 to 20000 is soluble in many organic solvents, but can be precipitated by adding diethyl ether. A variety of reagents and catalysts are now available conjugated to PEG;^[23] a representative example is shown in Scheme 10. The PEG-conjugated catalyst for asymmetric dihydroxylation (AD) provides superior results in representative Sharpless AD reactions, and is readily separated from the products and

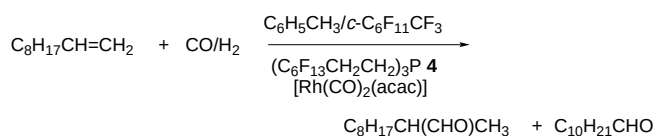


Scheme 10. A Sharpless AD catalyst tagged to a soluble PEG polymer.

recovered for reuse by precipitation.^[24] Dendritic reagents may also offer interesting capabilities.^[25]

Compared to other areas, the use of fluorous reagents to facilitate separations in traditional organic synthesis is in its infancy. It remains to be seen whether these methods will grow to complement more established alternatives. However, they do offer a significant potential advantage over methods based on polymer labeling or acid–base chemistry: The functionality present in the fluorous labels is highly inert and should therefore be stable under a wide range of reaction conditions.

Horváth and Rábai introduced “fluorous biphasic catalysis” by preparing the fluorous phosphane **4** and using it in the hydroformylation reaction shown in Scheme 11.^[8] The reaction is conducted in a biphasic system of toluene and

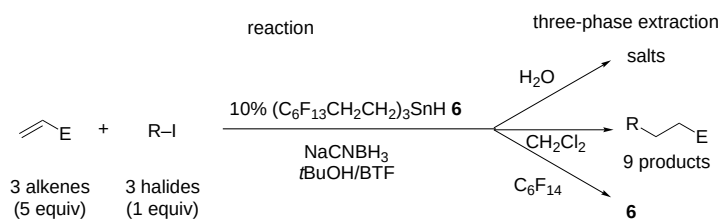


Scheme 11. Fluorous biphasic catalysis. acac = acetylacetonate.

perfluoromethylcyclohexane, and upon completion the two phases are separated. The hydroformylation products are recovered by evaporation of the toluene phase. There is no need to evaporate the perfluoromethylcyclohexane; the fluorous catalyst remains in this phase and can thus be reused in a subsequent reaction. A number of other catalysts for fluorous biphasic reactions have also been introduced, and the general strategy appears to have excellent potential.^[8b, 26]

For more traditional syntheses including combinatorial applications, the use of immiscible phases in the reaction stage is often not desirable. Homogeneous reaction phases can be obtained upon use of organic solvents (such as ethers) that have a good dissolving power for fluorous compounds or upon use of miscible organic and fluorous solvents. Certain solvent pairs that are immiscible at room temperature become miscible on warming, and this is proving very useful for reactions with fluorous catalysts.^[8b, 26d,f] Alternatively, one of the best ways to dissolve organic and fluorous compounds together is with “hybrid solvents”. These are simply organic solvents that contain a few fluorine atoms; examples include benzotrifluoride (*aaa*-trifluorotoluene, C₆H₅CF₃), 4-chloro- and 3,4-dichlorobenzotrifluoride, and trifluoroethanol.

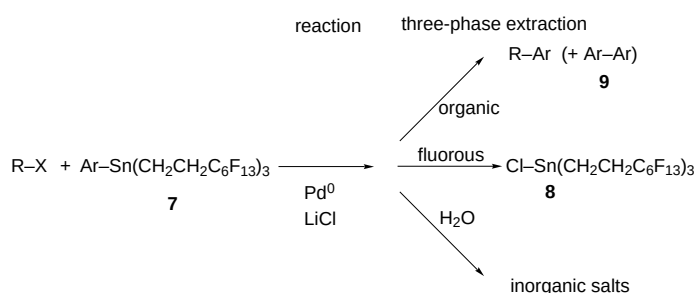
Scheme 12 shows the synthesis of a small library of radical-addition products formed in parallel Giese reactions mediated by fluoride-containing **6**.^[27] This tin hydride is used in catalytic



Scheme 12. Fluorous reagents/catalysts: catalytic reactions of the fluorous tin hydride **6**.

amounts with sodium cyanoborohydride as the coreductant. Related reactions do not succeed in organic solvents such as benzene (because the tin hydride is insoluble) or fluorosolvents such as perfluorohexane (because the organic reactants are insoluble), but proceed smoothly in benzotrifluoride. In the case of the catalytic transformations, *tert*-butanol is added as a cosolvent to aid the dissolution of the sodium cyanoborohydride. At completion of the reaction, the reaction mixture is evaporated (which removes excess alkene) and partitioned between water, an organic solvent, and a fluorosolvent in a three-phase extraction. The aqueous layer containing the inorganic salts is discarded, whereas evaporation of the organic and fluorosolvent layers gives the corresponding products. Nine different organic products are obtained in reasonable yield and excellent purity from the organic phases. Since the fluorosolvent product is the starting tin hydride in all cases, the fluorosolvent phases can be combined and evaporated to provide **6** for reuse.

In the above small library, **6** behaves as a catalyst and the sodium cyanoborohydride as a reagent; together they provide a constant component (a hydrogen atom) to each product. The fluorosolvent version of the Stille coupling (Scheme 13)



Scheme 13. Fluorous reactants: the Stille coupling.

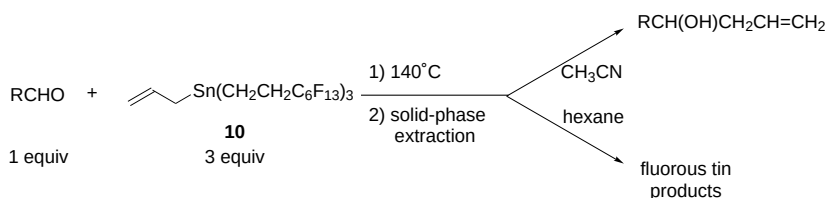
provides an example for the synthesis of a small library with use of a collection of fluorosolvent reactants **7**.^[28] Unlike reagents, reactants provide a variable piece of a library.^[4] In this case, the Stille coupling detaches the aryl ring from the fluorosolvent label to provide an organic product. The reactions are conducted with standard catalysts and ligands in DMF or DMF/THF. The starting tin reagents are not completely soluble in warm DMF, but do dissolve to some extent, and the reactions appear to become homogenous over several hours. Interestingly, LiCl is essential for rapid and clean Stille couplings of fluorosolvent tin reagents.

Reaction mixtures are again purified by three-phase extraction, and the obligatory by-product from the tin reagent, fluorosolvent tin chloride **8**, is recovered in excellent yield. In reactions such as this, the labeled reactant can be used in excess provided it is effective in forcing the partitioning of the tin reagent into the fluorosolvent phase. Extraction experiments show that the starting tin reagents **7** do partition very well into fluorosolvent solvents. However, analysis of the product mixture also shows that there is no aryltin reagent left

at the end of the reaction. Furthermore, about the same yield of Stille coupled product is obtained with 1.1 equivalents of tin reagent as with 3 equivalents. In general it follows that for reactions in which the fluorosolvent reactant is consumed the label need only be of sufficient size and fluorine content to force the obligatory by-product into the fluorosolvent phase; the partitioning of the starting reagent is unimportant.

In addition to the unavoidable tin chloride by-product, there is a side product of these reactions, biaryl **9**, which results from the homocoupling of **7**. This product is “organic” with respect to a fluorosolvent–organic liquid–liquid extraction and cannot be separated from the cross-coupled products by nonchromatographic methods. This is a general problem that is not unique to fluorosolvent chemistry: When a side product is formed that detaches a reagent, reactant, or catalyst from its label, it is usually organic and passes through the phase-separation process with the desired organic product. In the case at hand, the problem was solved by optimizing the reaction conditions; addition of a copper salt or conduction of the reaction under microwave conditions (or both) suppress the formation of the homocoupled product.^[29] The use of microwave techniques has the added benefit of reducing the reaction time to just a few minutes.

Allylations can be conducted under standard conditions with the allyl tin reagent **10** either thermally without solvent or with a standard catalyst in benzotrifluoride.^[30] In the first case reaction mixtures (Scheme 14) were purified by standard liquid–liquid extraction and by a new technique, fluorosolvent solid-phase extraction. This uses “fluorous reverse-phase silica gel”,^[31] which can be prepared by the standard silylation procedures that are used to prepare normal reverse-phase silica gel; our silica was silylated with $\text{ClSi}(\text{Me})_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$. In the solid-phase extraction, the crude reaction mixture is loaded directly onto the fluorosolvent column, which is then eluted with acetonitrile. Organic compounds cannot interact with the



Scheme 14. Purification by fluorosolvent solid-phase extraction. The solid-phase extraction is conducted with fluorosolvent reverse-phase silica (silica– $\text{OSiMe}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$).

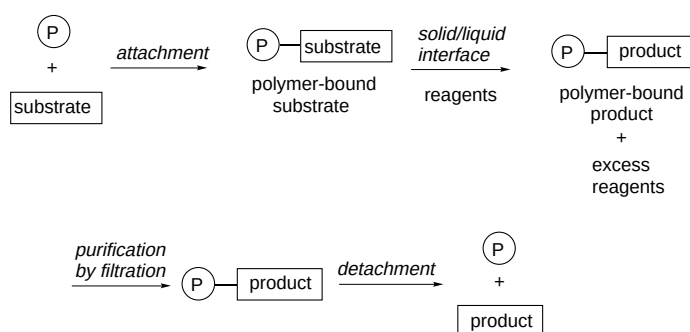
column and are eluted instantly. On the other hand, the same general, nonspecific interaction that allows one fluorosolvent compound to dissolve in another helps to hold the fluorosolvent tin reagents firmly to the column. However, this interaction is shattered by elution with a fluorosolvent solvent (or even a very nonpolar organic solvent such as hexane), and the tin fraction then elutes immediately.

Currently, Hindsgaul and co-workers are introducing the complementary technique of reverse solid phase extraction.^[32] These and related techniques for solid-phase extraction provide technically simple yet substantive and general separations across a range of processes (see below).

3.2.2. Solid-Phase Synthesis

Solid-phase synthesis was the first fundamental strategic alternative to traditional organic synthesis from the standpoint of phase planning, and is still the only one of demonstrated generality. Techniques for solid-phase synthesis have exploded from their origins in peptide and oligonucleotide synthesis to encompass the synthesis of libraries of small molecules^[2, 3] and, very recently, natural products.^[33] Since the general approach is now familiar to most practicing chemists, no specific examples are provided here; we simply summarize the strategy within the larger picture of phase planning.

Schematic representations such as that in Scheme 15 are often used to reduce solid-phase synthesis to its bare bones. A small organic molecule is initially attached through a



Scheme 15. Solid-phase synthesis with polymer-bound substrates.

covalent bond to a polymer or another form of solid support. This is a phase-labeling event, and the substrate and all products until detachment are then fixed as solids in any solid–liquid (or solid–gas) separation. Most applications make use of insoluble polymers, and reactions are then conducted at the solid–liquid interface with a large excess of other reaction components. The use of these excesses is crucial in solid-phase synthesis since reactions can be more difficult to drive to completion. The purification of reaction mixtures from solid-phase syntheses is the essence of simplicity, and generally involves filtration to separate the insoluble products from soluble reaction components.

Purification is thus the overriding strength of solid-phase synthesis. In contrast to traditional syntheses of small molecules, however, solid-phase synthesis presents problems at the reaction stage owing to inhomogeneity. Additional constraints are added at the identification and analysis stage, because polymer-bound substrates are mixtures of large macromolecules. Standard chromatographic techniques provide no information on polymer-bound substrates. Whereas spectroscopic techniques such as IR and NMR can be used to great advantage, experiments are rarely easy to execute and sometimes do not provide as much information on polymer-bound substrates as they do on small organic molecules.

Like synthesis with insoluble polymers, the attachment of substrates to soluble polymers such as PEG is an outgrowth of polypeptide synthesis. Gravert and Janda have shown that this method has many attractive features for the synthesis of

libraries.^[23] In addition to their ability to be dissolved at the reaction stage, PEG-bound substrates tend to be easier to identify than other polymer-bound substrates. The PEG substrates are bound only to the end(s) of the linear polymer, and since the end of one polymer is pretty much like the end of another, the molecules often behave like they are single entities even though they are not. For example, many PEG-labeled substrates give well-resolved, readily interpretable NMR spectra. Only the small region in the vicinity of the signal for the PEG methylene group is obscured. However, like fluororous synthesis described below, PEG-supported synthesis sacrifices the features of solid–solid separations and cannot be used for “one-bead, one-compound” split-synthesis techniques.

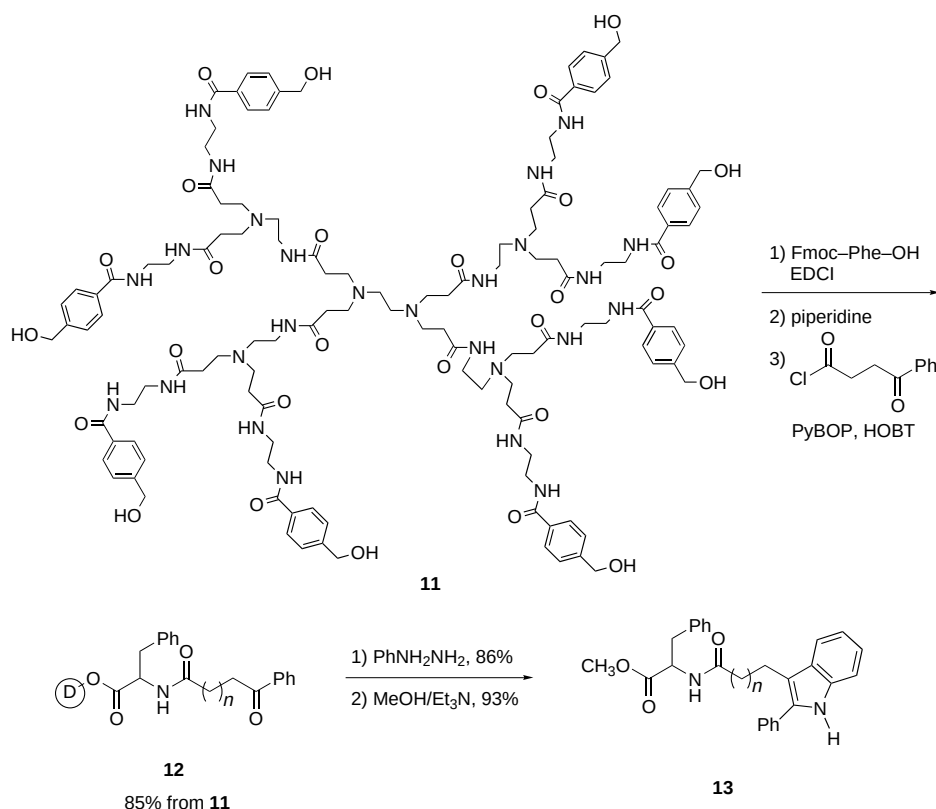
The rapid and overwhelming embrace of solid-phase synthesis as a mainstream technique speaks volumes for purification. In the early 1990s, organic chemists deemed it easier to solve the reaction, identification, and analysis problems in solid-phase synthesis than to solve the purification problems in the synthesis of small molecules. That collective decision—conscious or unconscious—has resulted in the development of solid-phase synthesis into a valuable mainstream method that is improving at a rapid pace.

3.2.3. Dendrimer Synthesis

Recently introduced by Kim and co-workers at Merck,^[34] the technique of dendrimer synthesis allies labeling of substrates by dendrimers with size-exclusion chromatography. In size-exclusion chromatography, a suitable support is charged with a mixture to be purified and then eluted with a solvent. Smaller molecules are retained better by the column, while larger molecules move faster. In dendrimer synthesis, the technique is used in a crude way to separate large molecules from small ones, and the purification tends to resemble a filtration more than a chromatographic separation.

The features of the technique are illustrated in Scheme 16 for the Fisher indole synthesis; purification is accomplished at each stage by size-exclusion chromatography. The starting dendrimer **11** was prepared by conjugation of a first-generation poly(amidoamine) (PAMAM) Starburst dendrimer^[35] to a hydroxymethylbenzoic acid linker. Acylation first with 9-Fmoc-phenyl alanine (Fmoc = 9-fluorenyloxycarbonyl) and then with 4-benzoylbutyric acid provides the substrate **12** for Fisher indole synthesis. Reaction of this substrate with phenylhydrazine followed by detachment from the linker provides the product **13** in excellent yield and purity.

Dendrimer synthesis has attractive features at all stages of the synthesis process. At the reaction stage, standard solution reaction conditions for the synthesis of small molecules should often be directly applicable, as dendrimers are generally soluble molecules. At the purification stage, size-exclusion chromatography provides a simple method to separate dendritic from non-dendritic molecules. At the identification and analysis stage, dendrimer synthesis is attractive because the products, while rather high in molecular weight, are still single entries^[36] that are readily soluble. Although many standard chromatographic techniques are not applicable, the dendritic products are amenable to the same types of



Scheme 16. Dendrimer synthesis with the Starburst dendrimer **11**, which has linkers ready for eight substrates. PyBop = 1-benzotriazolylxytripyrrolidinyphosphonium hexafluorophosphate; HOBT = 1-hydroxy-1*H*-benzotriazole.

spectroscopic analysis that are conducted for small molecules. Even mass spectra can be obtained by using the electrospray method. Finally, the “loading level” of substrates on a dendrimer is much higher than typical polymer loadings.

Split synthesis with dendrimers provides mixtures of compounds that can be analyzed or characterized in several ways. Kim and co-workers illustrated this with a 3×3 split-mix synthesis of 27 indoles in which the three variable components were the amino acid, the keto acid, and the arylhydrazine (Scheme 16). The final result was three mixtures of indoles that each contained one hydrazine fragment connected to the nine possible combinations of the other two fragments. Like with solid-phase synthesis, each individual dendrimer in any mixture (ideally) contains eight copies of the same indole. However, there is no way to capitalize on this at present since one dendrimer cannot be conveniently separated from another.

3.2.4. Fluorous Synthesis and Multilayer Reaction Schemes

The most recent addition to the list of fundamental synthesis techniques is fluorous synthesis, which we introduced in early 1997.^[37] The approach is conceptually similar to solid-phase synthesis (especially the soluble variants such as PEG chemistry) and dendrimer synthesis. A substrate is attached to a fluorous phase label that has sufficient fluorine content to draw the labeled substrate and its subsequent products into the fluorous phase in a suitable separation technique. To date, we have only used fluorous–organic

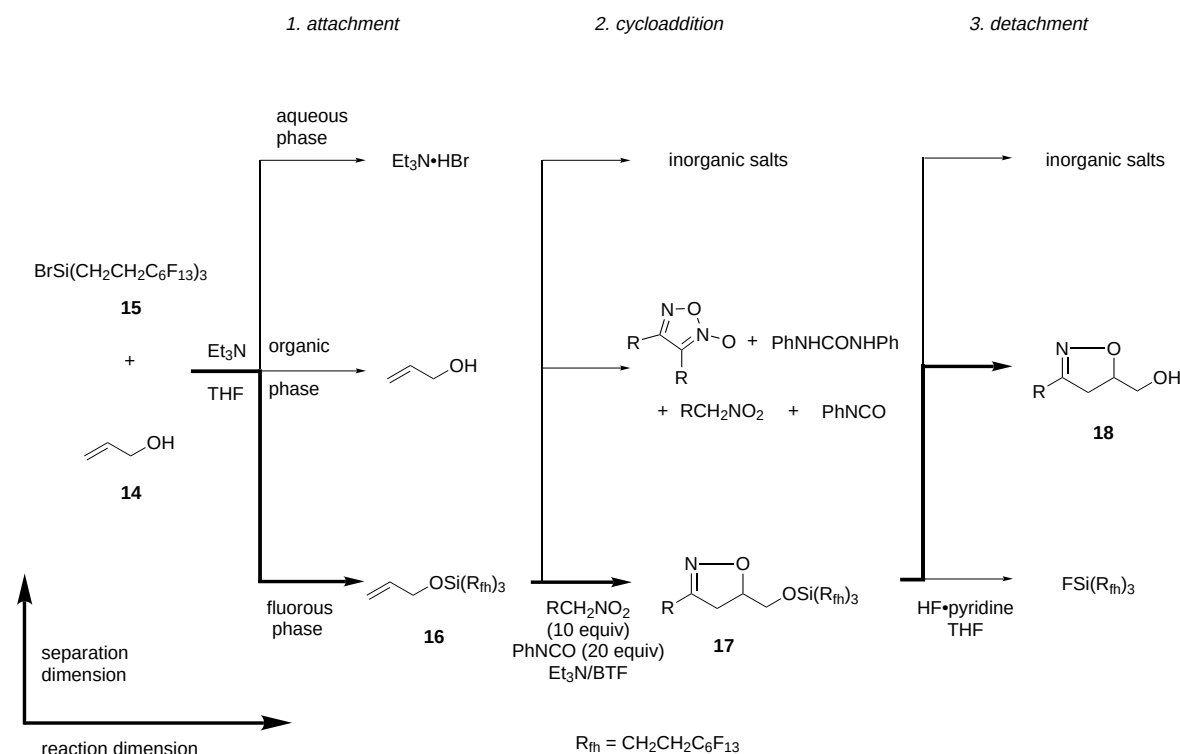
liquid–liquid extractions, but we expect the fluorous solid-phase extraction will be applied to advantage in due course. The substrate is then subjected to one or more reactions prior to removal of the fluorous label to give the desired small molecule.

The technique was first demonstrated with the synthesis of a series of isoxazoles and isoxazolines. These were initially prepared by the traditional method with isolation and chromatographic purification of all intermediates, and then the sequence was repeated on selected samples with purification only by fluorous–organic extraction (Scheme 17). Introduced in Scheme 17 is a “multilayered” organic reaction scheme that is intended to augment the traditional approach to writing schemes that places everything across a single line. The traditional scheme for notation of reactions is readily adapted to visualizing “two-phase” reactions such as poly-

mer synthesis (solid–liquid filtration) and dendrimer synthesis (dendrimer/non-dendrimer filtration). In these two-phase methods, it is common to write substrates and products in front of and behind arrows, while reagents and other additives are written above and below arrows. This naturally separates, say, the final solid-phase reaction components from the final liquid-phase products. However, things start to become less clear when more than two phases are involved or phase switching is used.

Multilayer schemes like that in Scheme 17 divide the reaction and purification stages of a process into two different dimensions. In Scheme 17, the reaction dimension is horizontal. Purification then occurs in the vertical dimension, and a layer is drawn for each type of product. The lines in boldface track the progress of the target products. The reaction mixtures in Scheme 17 are all purified by three-phase extractions with water, an organic solvent, and a fluorous solvent. Each horizontal line represents the contents of one of the phases at the end of every step. In some of the schemes below, reagents will be written adjacent to the vertical arrows; these signify reagents that are added during or after the reaction to effect a phase switch of one or more of the components. These types of multilayer schemes are readily adaptable to the diverse array of purification methods, and help with both planning and visualization of the separation scheme.

The “organic” allyl alcohol **14** is rendered fluorous by silylation with the highly fluorinated silyl halide **15** (Scheme 17). The excess alcohol used to drive the reaction to completion (based on the tag) is removed into the organic



Scheme 17. Fluorous synthesis illustrated in a multilayer reaction scheme.

layer of the ensuing three-phase extraction. Nitrile oxide cycloaddition is then conducted by the Mukaiyama method with very large excesses of a nitro compound (10 equiv) and phenyl isocyanate (20 equiv). This ensures a quantitative yield of fluorous isoxazoline **17** (based on the precursor **16**). All unchanged reagents and side products derived therefrom are in the organic or aqueous phases. Desilylation of **17** returns the final product **18** to the organic phase in the last three-phase extraction.

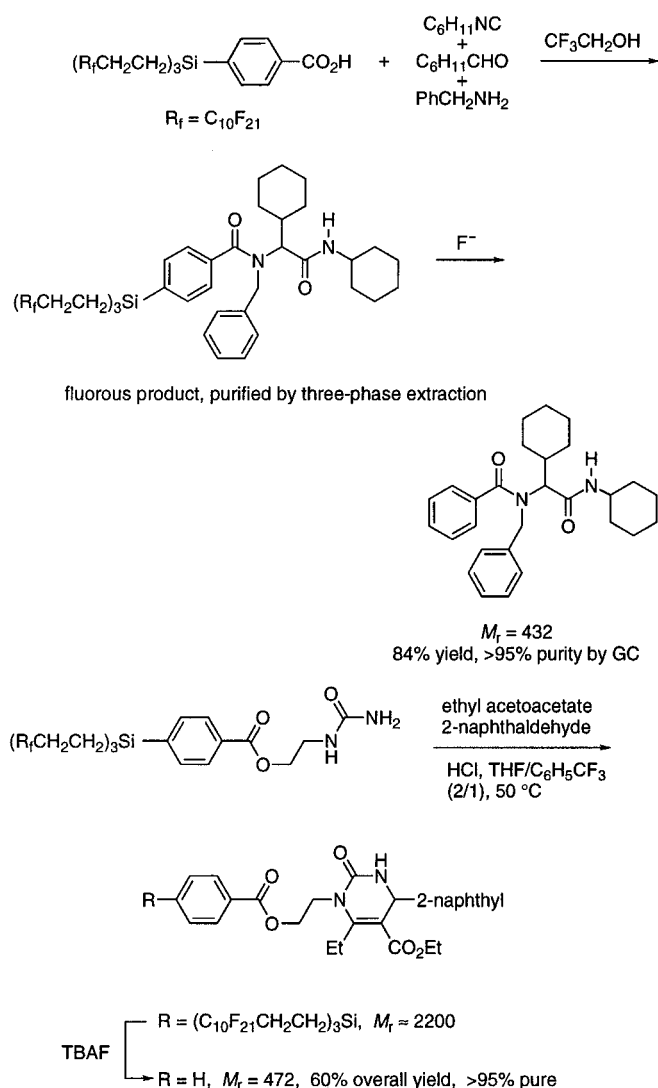
This nitrile oxide cycloaddition requires protection of the alcohol (which would otherwise react with the phenyl isocyanate). This might normally be accomplished with a trialkylsilyl ether; however, in this route all the intermediates on the fluororous (lower) level in Scheme 17 are organic and must be separated from all the other organic products on the organic (middle) level.

The silyl bromide **15**, containing 39 fluorine atoms, has been used to render small organic molecules ($M_r < 200$) fluorous with respect to liquid–liquid extractions, but larger molecules begin to partition into the organic phase. However, the use of labels with more fluorine atoms favors partitioning of even relatively large molecules into the fluorous phase. For example, the fluorous acid and urea shown in Scheme 18 were subjected to Ugi and Biginelli reactions, respectively.^[37a,c] In both cases, very large excesses of organic components were used, and the organic components that had not (or only partially) reacted were separated from the desired fluorous products by liquid–liquid extraction. Final desilylation of the fluorous products then provided the organic Ugi and Biginelli products shown. A number of other products in the molecular-weight range of about 300–500 were synthesized by these procedures.

While there is still much to be learned before fluorous synthesis can be applied more generally, it does offer a number of attractive features that should stimulate research in this area. At the reaction stage, fluorous synthesis offers the potential for homogeneous reactions to be conducted under standard conditions, although solvents must sometimes be adapted to ensure that all reactions components are sufficiently soluble. For example, in the nitrile oxide cycloaddition in Scheme 17 benzotrifluoride was used in place of a standard solvent such as benzene or toluene, whereas in the Ugi reaction in Scheme 18 trifluoroethanol was used in place of methanol or ethanol.

In the purification stage, the fluorous label allows tagged molecules to be separated from untagged molecules by liquid–liquid or solid-phase extraction. However, the nature of the tag is substantially different from the polymers and dendrimers used to date. Perfluoroalkyl chains are much more stable under organic reaction conditions than most polymers and dendrimers, and the tagging strategy resembles the protection of functional groups. Therefore, fluorous labels are generally expected to expand, rather than contract, the range of reaction conditions to which a labeled substrate can be exposed. Although linkers may be useful for some applications, they are generally not needed. Like protecting groups, the fluorous labels are attached and detached at the same site. This makes recycling of the labels convenient.

At the identification and analysis stage, fluororous substrates resemble small organic molecules much more closely than with the other techniques. Although their relative molecular weights are high (1000–2500), the substrates in fluororous synthesis are all soluble entities that can be identified and analyzed by the full battery of techniques for small molecules.



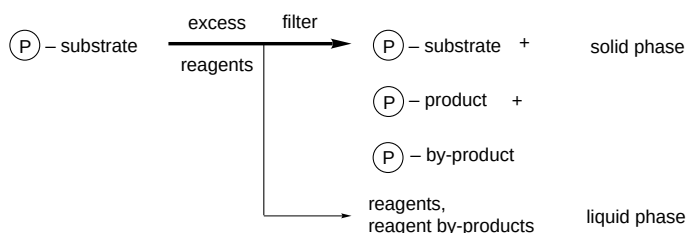
Scheme 18. Fluorous Ugi and Biginelli reactions.

With the exception of spin–spin coupling to nearby nuclei, the fluorine atoms are silent; the ^1H and ^{13}C NMR spectra of the fluorous substrates in Schemes 17 and 18 resemble standard protected organic molecules. Owing to the volatility of organofluorine compounds, electrospray methods are not needed to obtain mass spectra; standard electronic impact and chemical ionization techniques suffice, and both low- and high-resolution spectra can be obtained.

Potential advantages also accrue because fluorous synthesis links a single substrate to a label, as opposed to most other methods which attach multiple substrates per label. Reactions can be followed by thin-layer chromatography, and products can be analyzed by HPLC or other standard techniques (but generally not gas chromatography). Although fluorous techniques are designed to minimize purification, standard chromatographic purification of fluorous compounds is still possible. Polymers cannot generally be purified beyond washing. While it may be possible to purify dendrimers in reactions that do not occur in quantitative yield (based on a bound substrate), the purification is pointless because each individual dendrimer would itself contain a mixture of bound products.

3.3. Phase-Switching Techniques

There are two well-recognized problems with using any single fundamental method of synthesis continuously for a sequence of reactions: 1) Reagents and reactants having the same natural phase as the substrate cannot be used, and 2) reactions must occur in quantitative conversion and yield (based on the substrate). The first problem is most acute for traditional organic synthesis; despite active research there are currently not nearly enough reaction components (polymer, fluorous, dendritic, etc.) available to contemplate a complex multistep synthesis starting with a soluble organic molecule without adding or forming another organic molecule besides the desired product. The second problem is more insidious and cuts across all areas. It is illustrated in Scheme 19 for polymer-bound substrates. If a



Scheme 19. The Achilles heel of one-phase synthesis (illustrated with polymers).

polymer-bound substrate is left unchanged in a given reaction, it cannot be separated from the polymer-bound product; if the polymer-bound substrate is consumed but gives two products, these cannot be separated from each other. The problem is similar for soluble and insoluble polymers and dendrimers. When substrates and products are organic or fluorous, the separation is often possible by chromatography, but the whole point of the synthesis design is to render this unnecessary.

These two problems are solved by the technique of phase switching. To address the first problem, phase switching of reactants, reagents, or by-products therefrom (in other words, anything but substrates and products) is used. This provides methods to separate substrate and products from other reaction components. If the reaction occurs in quantitative yield and the phase switch succeeds, the product is isolated in pure form. The second problem is addressed by phase switching of substrates or products derived from substrates. These techniques are more powerful because they permit the isolation of pure products in reactions that do not occur in quantitative yield. This is attractive for library synthesis because even “optimized” reaction conditions are unlikely to provide quantitative yields and conversions for hundreds of different reaction partners.

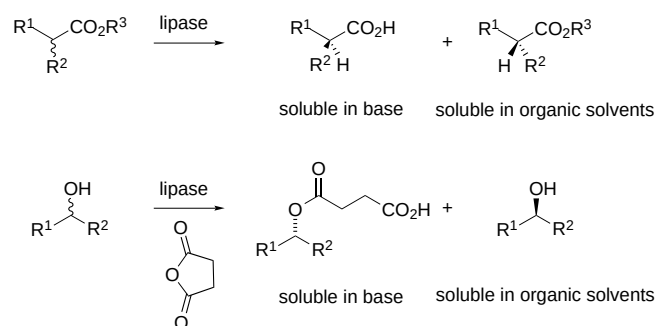
A number of techniques of phase switching are summarized below and organized according to the form of “nonorganic” phase from or into which a given product or subset of products is switched. Emphasis is placed on the use of linkers which allow phase switches to occur indirectly.

3.3.1. Acid–Base Chemistry

Acid–base extractions have long been used for workup-level purifications, but have changed very little until recently.

As mentioned above, the phase switch of an acid–base extraction is accomplished by protonation or deprotonation. This ionization step frequently transfers molecules from the organic to the aqueous phase in a liquid–liquid extraction. Acid–base chemistry is not generally thought of as providing substantive purifications, but recent results show that the power of acid–base purification extends well beyond its traditional bounds.

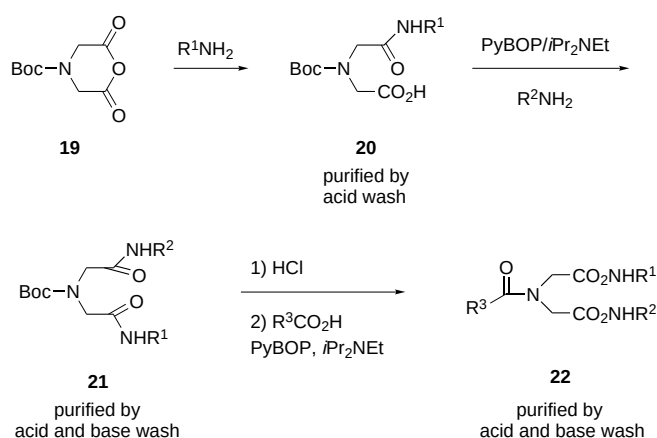
A classical example of an acid–base switch is shown in Scheme 20. Hydrolysis of a racemic mixture of esters with a lipase provides an acid from one enantiomer while leaving the



Scheme 20. Enantioselective acid–base phase switches.

other substantially unchanged.^[38] In highly efficient kinetic resolutions of this type, the two products can be isolated in enantiomerically pure form by a suitable acid–base extraction. When ionizable functionalities are not directly involved, they can be “linked” to the process in question to effect a phase switch. For example, enzyme-catalyzed acylation of racemic alcohols typically provides two organic products, a recovered alcohol and an ester. However, if the esterifying reagent is something like succinic anhydride, the process of acylation links an acid group selectively to one of the products.^[39] An acid–base extraction then separates the products into organic-soluble and water-soluble fractions based on the stereoselection in the acylation step. In both of these simple examples, the separation is directly coupled to the prior chemistry; the enantioselective reactions dictate the phase switch. In the subsequent examples, chemoselection is commonly used.

In seminal work on solution-phase synthesis of libraries of individual, pure compounds, Boger and co-workers prepared a number of “universal” dipeptide mimetics.^[40] A representative example of the approach is shown in Scheme 21. Template **19** is allowed to react with a first amine used in excess to form the acid amide **20**. Purification by acid extraction causes the excess amine to switch phases to the aqueous layer in an organic–aqueous extraction, and pure **20** can be obtained from the organic phase. Coupling with a second amine in the presence of PyBOP reagent is the next step. Sequential acid and base extractions remove leftover amine, PyBOP and associated by-products to leave pure amide **21** in the final organic phase. Acid-promoted cleavage of the *tert*-butoxycarbonyl (Boc) groups, renewed coupling with an acid in the presence of PyBOP, and acid–base washing provides the final compounds **22**.

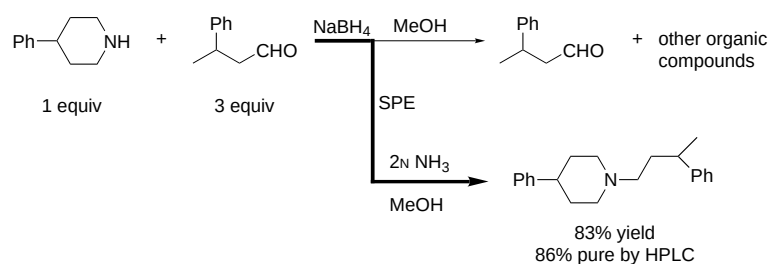


Scheme 21. Parallel synthesis of soluble organic products with purification by acid–base extraction.

In this sequence the acid–base extractions are used to remove reagents (PyBOP) and by-products derived therefrom as well as variable reactants (acids and amines) that are used in excess to drive reactions to completion and unchanged starting materials that are ionizable. The actual products are retained in the organic phase at all times, presumably because the reactions proceed in such high yields that purification of these products by phase switching is not needed. However, some of the products are ionizable and could at least in principle be purified by a suitable acid–base technique. This approach dictates that everything that is added to the substrate either is water-soluble or can be made so by protonation or deprotonation; it has been used to make libraries of over 1000 compounds in tens to hundreds of milligram quantities in excellent crude purities (typically > 90 %).

Research groups at Lilly,^[41] Signal,^[42] Monsanto,^[43] Bristol Myers,^[44] Roche,^[45] and Argonaut^[46] have recently reported examples in which solid-phase extraction replaces liquid–liquid extraction as the separation technique for executing acid–base switches. Solid-phase extractions are easier to automate and conduct in parallel than liquid–liquid extractions, and possible complications with emulsions are avoided. Furthermore, not all ionized organic compounds partition out of an organic liquid phase and into an aqueous phase, but methods for solid-phase extraction should still at least provide some measure of separation of neutral molecules from ionized ones. Details about the technique of solid-phase extraction were illustrated in Scheme 5. In general, the ionized component is retained on the column during the first pass to provide a neutral fraction. When the desired product is neutral, the columns can then simply be discarded (at least in small-scale work). When the desired product is an ionic species, it must then be eluted from the column in a second pass with a suitable complementary eluent. For example, a solution of ammonia could be used to elute an amine from an acidic ion-exchange resin, or acetic acid could be used to elute an acid from a basic resin.

An example of an ion-exchange process is shown in Scheme 22. The straightforward reaction and purification sequence has been used at Lilly^[41] to make hundreds of



Scheme 22. Solid-phase extraction on an acidic ion-exchange column.

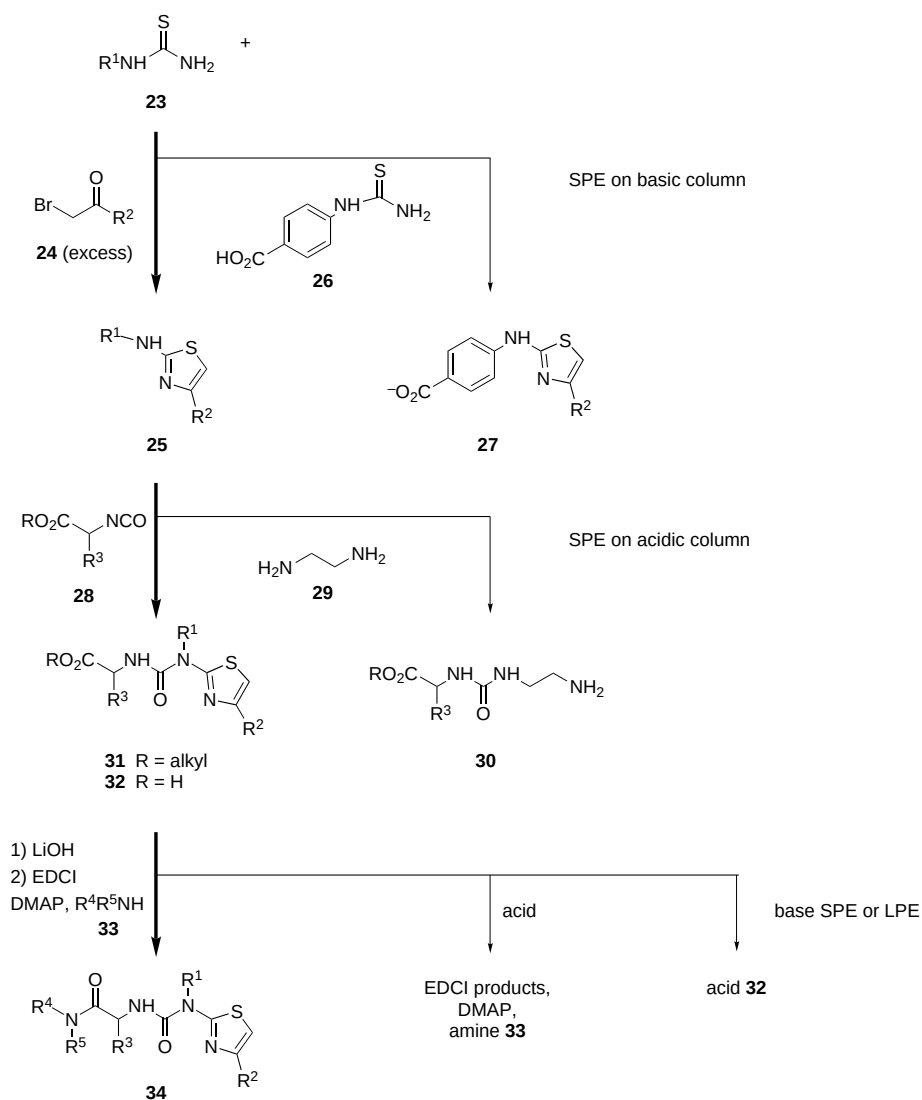
secondary and tertiary amines by an assortment of different alkylation reactions. Purities typically range from 85 to 95 % or better. Other groups have related comparable successes in different reactions.^[42–46]

The separation of two nonionizable reaction components can be accomplished by a linking strategy. In the example in Scheme 22, the ionizable group was introduced in one of the original reaction components. However, it can also be conjugated after the reaction by adding a suitable linker (scavenger) that will react quickly and chemoselectively with the target functional group (or groups).^[41, 43] Once again, the chemistry dictates the separation. Scheme 23 shows a four-step library synthesis that features solid-phase extractions at three steps and a linking strategy in two of these steps.^[45] A multilayer scheme is used with reactions in the vertical direction and separations in the horizontal direction. Reaction of thiourea **23** with excess bromomethyl ketone **24** provides thiazole **25**. Excess thiourea **26** was then added at the end of the reaction to convert the neutral bromoketone **24** into the acidic thiazole **27**, which was removed by solid-phase extraction. In the subsequent coupling of **25** with isocyanate **28**, the excess isocyanate was linked after the reaction to ethylene diamine **29**, and the resulting amino urea **30** was separated from the desired product **31** by solid-phase extraction. The hydrolysis that follows is a classical example of a purification that requires only removal of inorganic by-products, and this is accomplished by liquid–liquid extraction (not shown). Finally, the acid **32** is coupled with excess amine **33** in the presence of EDCI (**3**). Purification by suitable acid–base techniques leaves **34** as the only organic compound.

An attractive feature of the linker strategy is that suitable linkers

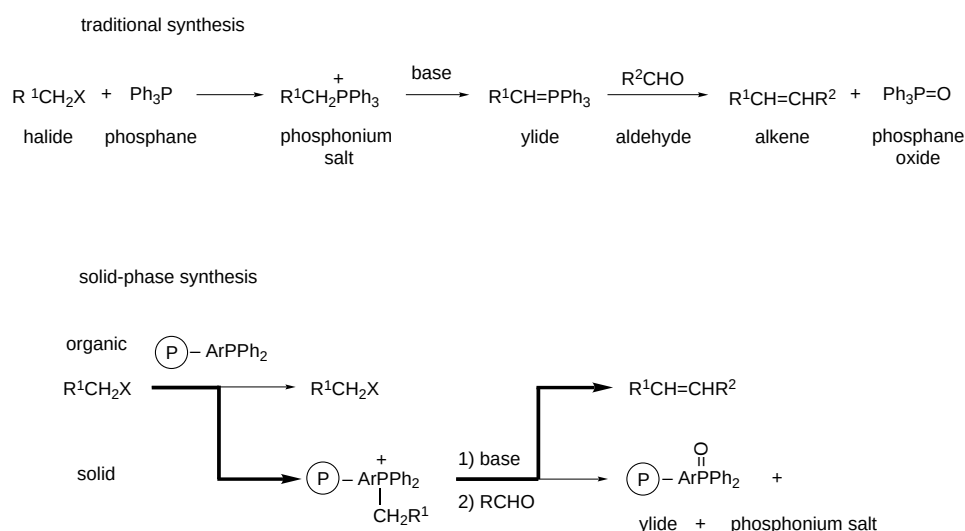
can be added to capture any type of reaction component, including one or more of the starting materials or a known (or expected) by-product. Thus, pure products can be obtained from reactions that do not occur in quantitative yield. From the standpoint of purification, the most attractive method is to link the product itself. Provided this can be done selectively and the separation technique succeeds, a pure product is isolated independent of the yield of the reaction or the nature of the by-products.

Although the use of linkers dramatically extends the generality of acid–base switches, there are still limitations. The molecule (or molecules) being separated must be stable to brief exposure to moderate or strong acid, base, or both. Furthermore, it (they) cannot have any ionizable functionalities that are complementary to the purification techniques. A library that is being freed of amines, for example, cannot have any members that are ionized by acid. Like the other methods discussed below, acid–base methods sometimes involve a “double phase switch”. An amine, for example, is



Scheme 23. Purification by solid-phase extraction with linkers.

transferred to the aqueous phase by protonation and back to the organic phase by deprotonation. There are then two opportunities for purification, but acid–base chemistry capitalizes almost exclusively on the first phase switch in terms of purification; the second is simply to recover the product that was transferred. The polymer (solid) and fluorous switches described below follow analogously from the principle of acid phase switches, but they have unique attractive features that allow them to both supplement and complement acid–base switches.



Scheme 24. Comparison of the traditional Wittig reaction with the solid phase switch variant.

3.3.2. Solid Phase Switches

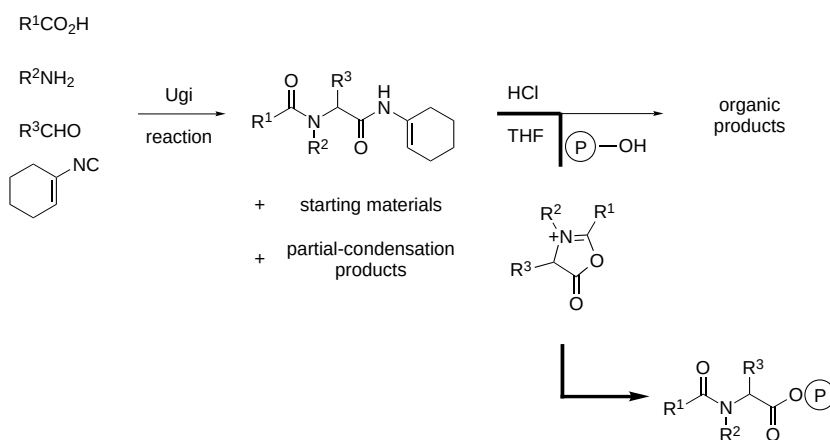
In traditional solid-phase synthesis, a substrate is attached to the linker and then processed through a sequence of steps prior to detachment. Although the attachment and detachment steps are switches to and from the solid phase, they rarely exhibit substantive features of purification. However, these features can be expressed by attaching reaction components to the solid phase during a reaction or detaching them from the solid phase after completion of a reaction. A number of these features were recognized in the early days of solid-phase synthesis, and some pioneering experiments have been summarized by Hodge under the name of “fishing out”.^[22e]

The Wittig reaction was one of the first C–C bond forming reactions to be studied on the solid phase,^[47] and it nicely exemplifies some of the attractive features of solid phase switches. A standard solution Wittig reaction is shown in the top part of Scheme 24. Assuming that the aldehyde is the limiting reagent that provides the alkene product in quantitative yield, the alkene must still be separated from triphenylphosphane oxide and any unchanged triphenylphosphane, ylide or phosphonium salt, and halide. A successful solid-phase synthesis provides for all these separations.

Reaction of an organic halide with a polymer-bound phosphane provides the intermediate phosphonium salt, which can be separated from unchanged halide by filtration because the substrate is switched from organic to solid. The solid-phase Wittig reaction then switches the substrate from solid back to organic. The bound reagent and all its derivatives (phosphane, phosphonium salt, ylide, phosphane oxide) are solids throughout and are readily separated from the organic product. However, the process also

allows the separation of one of the organic substrates (the halide) from the organic product (the alkene) because of the intervening double phase switch. The intermediate oxyphosphonium salt can also be separated from any unchanged aldehyde by filtration. The reaction nicely illustrates the power of a reaction designed such that the phase of an intermediate product is different from that of the starting and final products. In such a process, a reaction component is drawn out of one phase, physically transferred away from it to effect purification, and then allowed to react with another reaction component of the same phase as the original phase. The “three phase test” (see Scheme 6a) bridges two solid-phase components by a liquid-phase component, whereas the Wittig reaction bridges two liquid-phase components by a solid-phase component.

With a technique dubbed “resin capture”, Armstrong and co-workers conducted Ugi reactions in solution and then captured the products on the solid phase by acylation (Scheme 25).^[48] While one of the components could have been (and indeed has been^[31]) linked to the solid phase prior to the Ugi reaction, the resin-capture



Scheme 25. Resin capture of Ugi reaction products: a solid phase switch that selectively targets products.

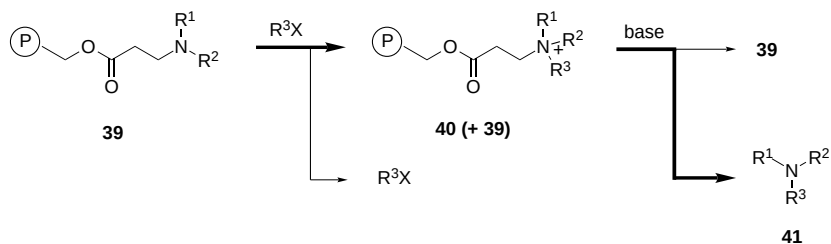
strategy allows the complex multistep Ugi reaction to occur in solution, while simpler, more rapid reaction (acylation) is forced to occur at the solid–liquid interface.

An especially attractive feature of this process is that it does not target any one of the original reaction components; the whole Ugi product is required for acylation. Thus, pure products can be obtained in nonquantitative reactions. In contrast, standard solid-phase variants of the Ugi reaction require quantitative yield (based on the solid-phase component) to provide pure products. Since the process in Scheme 25 requires an initial cyclization for subsequent switching to the solid phase to take place, it is the logical reversal of “cyclative cleavage” (cleavage of a component from a solid phase that is induced by cyclization of the component, see below). It is also analogous to the acid–base applications described in Section 3.3.1 and fluorous phase switches in Section 3.3.3; since the alcohol trapping agent bears a polymer rather than an ionizable group, a filtration is called for rather than an acid–base (or fluorous–organic) extraction.

It was recognized early on in solid-phase synthesis that cyclative cleavage had the unusual feature of providing pure final products after resin capture in reactions sequences that had not occurred in quantitative yields. A typical example of a cyclative cleavage is shown in Scheme 26.^[49] Only products **37**, in which the amino acid **35** and the isomer **36** were incorporated in the synthesis sequence, will be removed from the solid phase in the final step. In a broader sense, cyclative cleavage is an example of a solid-organic phase switch. As with the resin-capture process described above, the selectivity of this technique relies on the following: Only the intermediate that contains the multiple components of the product reacts further. The message is clear: the more chemoselective a phase-switching process is for the product as opposed to impurities, the better. Processes that target a single functional group in one of the starting components are still valuable, because they allow the switching of organic soluble reaction components to other phases, but processes that target features unique to the product are even more valuable.

Cyclative cleavage is not the only way to trigger a selective solid–organic switch. Morphy and co-workers described the

solid-phase synthesis of tertiary amines (Scheme 27).^[50a] Quaternization of the resin-bound amine **39** provides the salt **40**, which is then freed from the resin in a selective phase

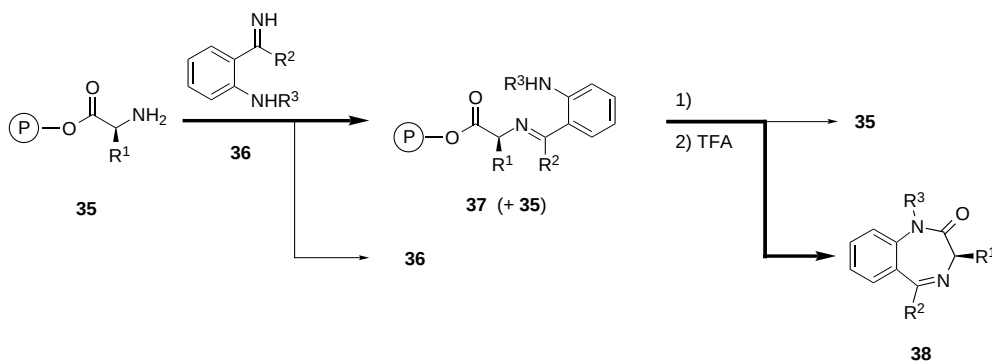


Scheme 27. A solid–organic switch that targets ammonium salts.

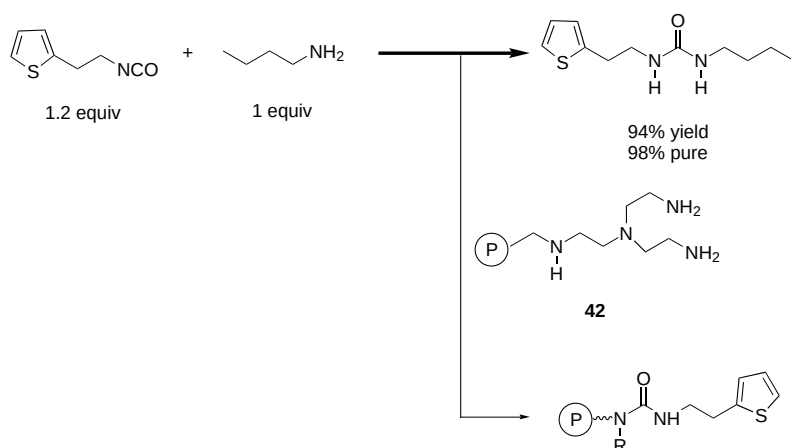
switch by β -elimination to give **41**. This process targets quaternary ammonium salts **40**, and other impurities such as tertiary amines **39** resulting from incomplete *N*-alkylation are left on the solid phase. Another very recent example of a solid–organic switch was provided by Ito and Ogawa. They loaded two monosaccharides onto a polymer and then cut them off with concomitant linking to each other to make a disaccharide with a β -mannose linkage.^[50b]

A solid phase switch can be conducted without ever binding a target product to a polymer.^[4f, 4b, 51] Solid phase switches that remove excess reagents, reactants, and by-products are only just emerging, but it is already evident that these are among the simplest and therefore most powerful techniques. For example, polymeric acid chlorides can function as general traps for nucleophiles, whereas polymeric amines can function as traps for electrophiles. An example from the work of Booth and Hodges is shown in Scheme 28.^[51] In a design that borrows from dendrimers, polymeric primary diamine **42** was prepared in order to double the quenching capacity of standard aminomethyl polystyrene resin. Resin **42** can be used to remove isonitriles, acid chlorides, and other reactive electrophiles used in excess. The process occurs in a batch mode and is therefore even simpler to execute than solid-phase extraction. A quenching resin is added to a reaction mixture, and, after allowing time for the phase switch to complete, the reaction is filtered and the product is isolated by evaporation of the organic phase.

Solid phase switches of all sorts will benefit from the use of linkers. As in the acid–base chemistry, one end of the linker



Scheme 26. Cyclative cleavage, an example of a selective solid–organic phase switch. TFA = trifluoroacetic acid.

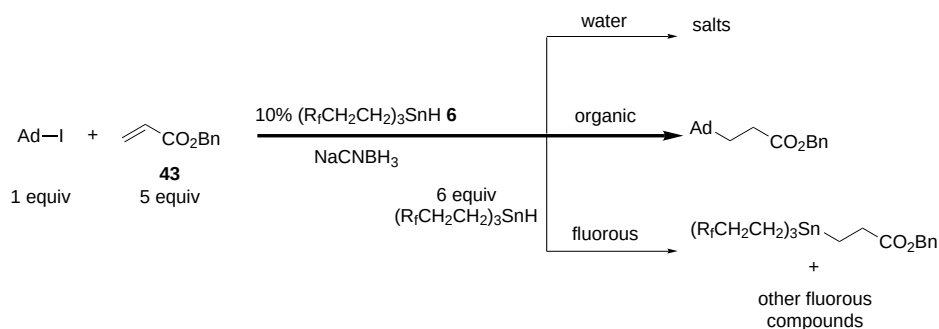


Scheme 28. Polymer-supported quenching: removal of impurities by organic–solid switching.

targets the functionality to be purified. Furthermore, the other end targets a complementary functional group or combination of groups in the polymer. This allows the use of a simple, rapid (biphasic) reaction to conjugate to the polymer. Also, by varying one end of the linker, a relatively large number of quenching processes can be conducted with just a few types of polymers. In traditional solid-phase synthesis, the linker is connected to the polymer and then the organic compounds is connected to the linker. However, mixing and matching of the order of these steps introduces valuable new options for both synthesis and separation.

3.3.3. Fluorous Phase Switches

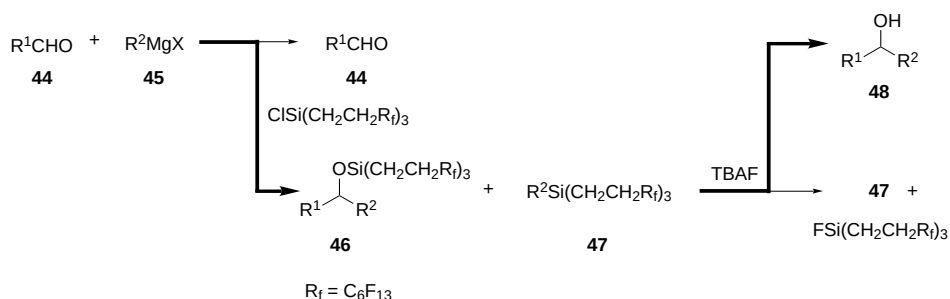
Fluorous phase switches can in principle be designed based on any of the elements outlined above by replacing the polymer or ionizable functional groups with a fluorous group. For example, we executed the fluorous quench shown in Scheme 29 for removing excess alkenes by hydrostannation.^[52] This is an extension of the process given in Scheme 12, in which an excess of volatile alkenes was used and then removed by evaporation. In Scheme 29, an excess of non-volatile alkene **43** is used, and additional fluorous tin hydride



Scheme 29. Quenching by hydrostannation with a fluorous reagent. Ad = adamantyl.

6 is added at the end of the reaction to consume the unchanged alkene **43**. Fluorous–organic extraction then provides the pure products in the organic phase. The process is generalizable to any reaction as long as the products do not react with the tin hydride and alkenes are involved that do.

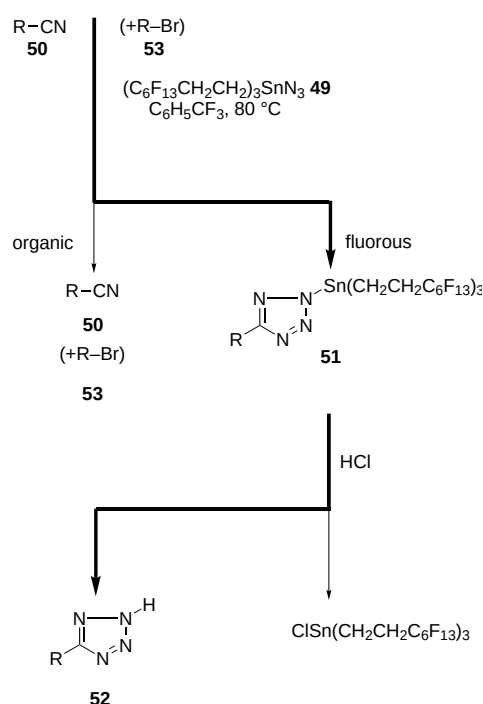
We also introduced a number of simple fluorous switches that exhibit interesting separation features and are generalizable to other methods. For example, the standard Grignard reaction shown in Scheme 30 can be coupled with a silylation of the intermediate alkoxide by the fluorous silyl ether. The resulting organic–fluorous–organic



Scheme 30. A double phase switch (organic–fluorous/fluorous–organic). TBAF = tetrabutylammonium fluoride.

“double switch” resembles in many ways an acid–base extraction. However, unlike acid–base processes, the act of switching from fluorous back to organic is not the reverse of going from organic to fluorous. In other words, each phase switch is a distinct event with its own purification opportunities based on chemoselection. An example is a reaction with excess aldehyde **44**. After silylation and separation, the excess aldehyde **44** is removed in the organic phase, and the conversion from fluorous ether **46** to organic alcohol **48** by desilylation with fluoride provides no additional purification. However, when the Grignard reagent **45** is used in excess, the second step effects the purification: **46** is converted into **48**, but **47** remains fluorous. For reactions that are incomplete (as in Scheme 30), both steps effect independent separations. In short, well-planned double switches can be especially powerful.

Scheme 31 provides a simple example of how a reagent, in this case fluorous azide **49**, can provide purification of the target compound based on chemoselection. Reaction of three equivalents of nitrile **50** with the azide **49** provides tetrazole **51** in the fluorous phase, and excess nitriles are left behind in the organic phase in a fluorous–organic liquid–liquid extraction. Unlike the silylation in



Scheme 31. Use of fluororous **49** as reagent and label.

Scheme 30 or the resin capture in Scheme 25, this process does not separate the reaction at hand from the labeling step. Only azides (or more generally, products formed by reaction with **49** and retaining the tin) are labeled as fluororous in the process. This, and indeed any process that switches the phase of the desired product, has the feature of being able to “correct” prior purification problems in a synthesis. For example, if the nitrile **50** was made from a bromide **53** and that prior alkylation was incomplete, a mixture of a nitrile and bromide would result (because both are organic). However, for the ensuing tetrazole synthesis, there is no need to separate this mixture since the bromide **53** does not react with azide **49**. This shows the power of phase switches of products as opposed to that of any other reaction component. As parallel syntheses become longer and more complex, occasional phase switches of products will become key features of purification planning.

4. Summary and Outlook

This review makes the case that purification is a strategy-level concern that should be addressed in the planning stage of any synthesis. From the purification standpoint, the “ideal synthesis” is designed such that only simple separation techniques such as evaporation, filtration, and extraction are needed for separation. A basis for phase planning is presented by bringing together a number of apparently disparate concepts and results. At the most fundamental level, many of the concepts that have been used in acid–base chemistry, polymer synthesis, and the more recently introduced methods of dendrimer synthesis and fluororous synthesis are more or less interchangeable. Multilayer reaction schemes are introduced

to facilitate the phase planning and to illustrate a number of the more powerful techniques. These techniques are often designed such that reaction chemistry dictates separation.

A number of the techniques call for excess reagents coupled with the addition of quenching reagents, and these are inherently wasteful from the standpoint of “atom economy”. Such applications are targeted primarily towards parallel and combinatorial synthesis, where the scales are small and it is time rather than “atoms” that is being economized. However, many of the other techniques are applicable across the whole field of synthesis from discovery to production. Even “wasteful” techniques such as quenching to remove by-products might still be more economical on a production scale than other alternatives for purification. The best techniques provide not one but two or more products in separate phases at the end of a phase-separation scheme. One of the products is of course the target of the synthesis, while the other is a catalyst or some form of a recovered reagent that can be reused at a later date.

Many of the existing techniques and concepts of strategic purification need to be extended and generalized to reach their full potential. For example, the quenching techniques were illustrated with amide chemistry, but the quenching approaches outlined above are more fundamental and can be applied to a range of organic syntheses by allying them with suitable reaction chemistry. The use of linkers, which heretofore played mostly a specialized role to connect substrates to polymers at the beginning of a solid-phase synthesis, is especially ripe for development in conjunction with new phase switches. Phase-switching techniques that involves substrates, intermediates, or products have much untapped potential; with suitable planning and execution they can be used to provide pure products from sequences of reactions that do not occur in quantitative yields. This is important in library synthesis, where it may be more efficient from the standpoint of time simply to design an effective synthesis and purification scheme than to optimize all reaction conditions. Especially prized are phase switches that are coupled with one or more steps in the synthetic sequence or that target functionalities present only in one set of products.

This review offers four general strategies for rendering erstwhile organic molecules “nonorganic” with respect to a given phase-separation technique in a process called phase labeling: acid–base, solid, dendrimer, and fluororous. Surely there are other fundamental ways to accomplish this, and the identification of these ways is a valuable goal. For example, Ramage et al. attached heptacyclic analogues of Fmoc to amino acids in peptide synthesis, and then separated labeled from unlabeled peptides by absorption of the former on porous graphitized carbon.^[53] In principle, this technique could be generalized beyond peptide synthesis. Likewise, the recent use by Hindsgaul et al. of long hydrocarbon tags to label carbohydrates and effect polar/apolar separations over reverse-phase silica may also represent a generalizable approach.^[32]

The design of new methods couples a suitable label with a given separation technique, which in the ideal case separates molecules into fractions based on the presence or absence of the label. Along these lines, techniques based on molecular

recognition appear ripe for development. For example, one could view fluororous solid-phase extraction as a case of (very nonspecific) molecular recognition in which a fluorinated tag (guest) is recognized by the bonded phase of the column (host). More selective techniques making use of smaller labels would be useful. In this view, the labeling process begins to resemble affinity chromatography.

The yield in any given reaction sequence is limited not only by the efficiency of the chemical process or processes, but also by the ability to recover the desired product from the reaction mixture after each process. Ideally, the reaction mixture is the pure product, but this idealized scenario is and will continue to be extremely rare. Along with all the other accepted features, well-planned syntheses should incorporate designed strategies for separation that provide pure products and simultaneously minimize time (for discovery-oriented syntheses) as well as cost and waste (for production-oriented syntheses).

I am very grateful to the talented and enthusiastic students and postdoctoral fellows in my group who have taken up the challenge of fluororous chemistry, especially the pioneers in 1995: Dr. Sabine Hadida, Dr. Masahide Hoshino, and Dr. Armido Studer. I also warmly thank Professors Anders Hallberg, Marty Newcomb, Tara Meyer, Ilhyong Ryu, and Peter Wipf and their co-workers for their invaluable collaborative efforts. The ideas in this article took shape in part as a result of stimulating discussions with several industrial groups investigating parallel synthesis; I thank Dr. John Saunders (CombiChem), Dr. John Hodges (Parke-Davis), and Dr. Steven Kaldor (Lilly) for sharing their problems, ideas, and results. Finally, I am most grateful to the National Institutes of Health and the National Science Foundation as well as Parke-Davis, CombiChem, and OxyChem for providing research funds.

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to the diversity of the products. Multiple “reactants” are used in a combinatorial synthesis and these provide variable groups of atoms to the product library when allowed to react with single or multiple substrates. The collective term “reaction components” is used to describe all of these classifications.

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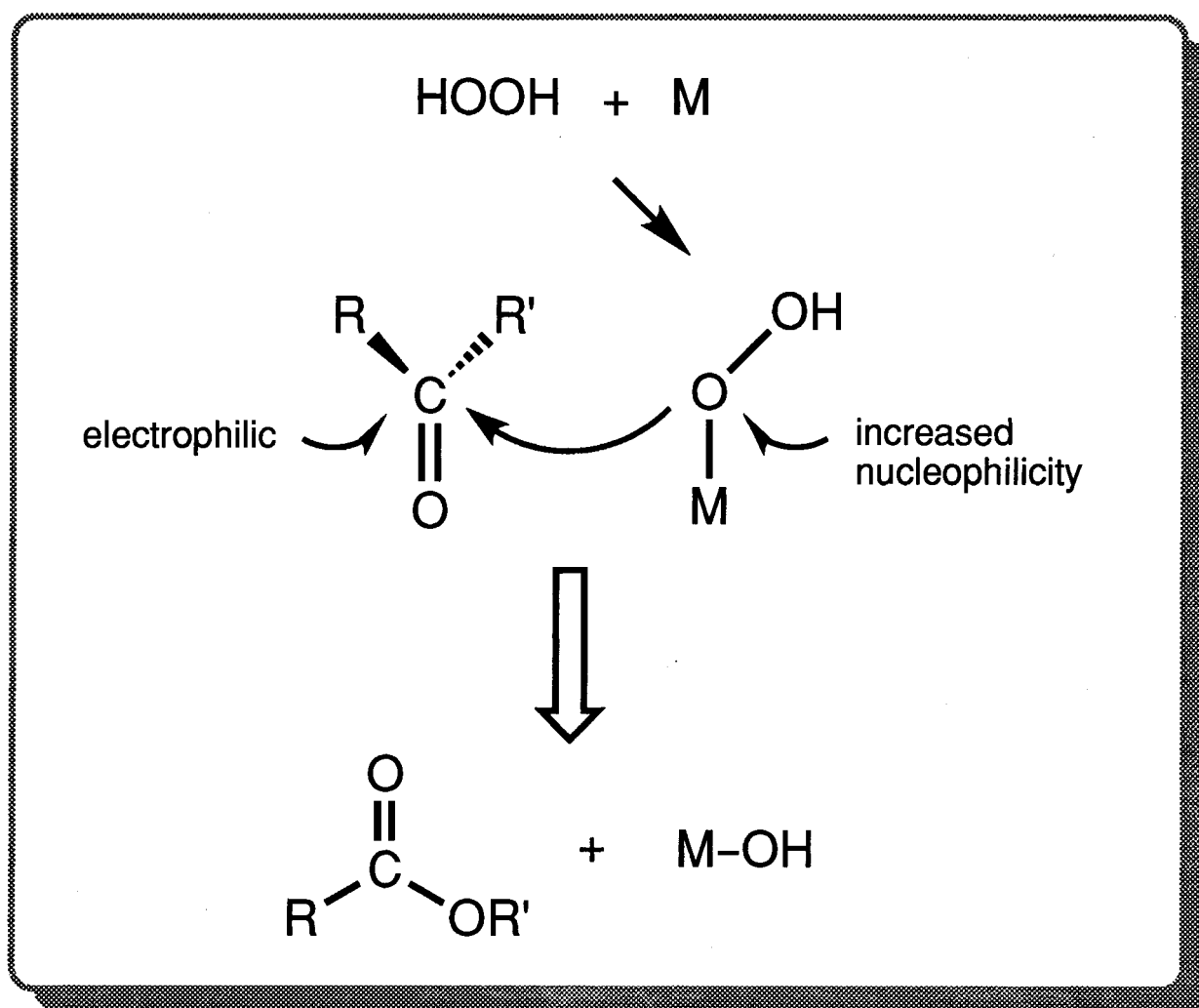
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537. Adolf Baeyer und Victor Villiger: Einwirkung des Caro'schen Reagens auf Ketone.

[Vorläufige Mittheilung aus dem chemischen Laboratorium der Akademie der Wissenschaften zu München.]

(Eingegangen am 27. December.)

H. Caro¹⁾ hat im vergangenen Jahre gefunden, dass die Salze der Ueberschwefelsäure durch Zusammenbringen mit concentrirter



Almost 100 years lie between the first publication on the Baeyer–Villiger oxidation (1899) and the modern variants of this reaction that are catalyzed by transition metal compounds.

Transition Metal Catalysis in the Baeyer–Villiger Oxidation of Ketones

Giorgio Strukul*

In memory of Fulvio Di Furia (1944–1997)

Increased ecological awareness and increasing restrictions are forcing the chemical industry worldwide to redesign some production lines in order to comply with the protection of the environment. In particular, industrial organic chemistry often makes use of multistep synthetic methods in which the amount of useful product is largely outweighed by the amount of by-products that need disposal. In this context catalytic methods capable of simplifying the synthetic procedures or the use of cleaner reagents is in principle more environmentally friendly than stepwise stoichiometric transformations. This review deals with an organic reaction (the Baeyer–Villiger oxidation) that is

widely used in a variety of synthetic applications and the attempts that have been made over the years to make the reaction catalytic, particularly in association with a typically “green” oxidant such as hydrogen peroxide. The initial section summarizes briefly the general features of the Baeyer–Villiger oxidation with peracids that have made it so successful in organic synthesis. The next section emphasizes the use of hydrogen peroxide as oxidant and the number of transition metal systems based on Pt, Re, and Ti that so far have proved successful for the catalytic reaction. The mechanistic principles (in particular the need for a nucleophilic peroxygen) are compared with

those of the stoichiometric reaction with peracids. The use of dioxygen as oxidant in the presence of sacrificial aldehydes and transition metal catalysts is reviewed. Finally, the systems capable of performing the transformation in both an enantiospecific and an enantioselective fashion are discussed. This analysis provides some useful strategies for the future development of new catalytic systems in this reaction.

Keywords: Baeyer–Villiger oxidation • homogeneous catalysis • ketones • oxidations • transition metals

1. Introduction

The Baeyer–Villiger oxidation of ketones is a reaction of major synthetic interest in organic chemistry with a large range of possible applications spanning such diverse areas as the synthesis of antibiotics and steroids, the synthesis of pheromones for agrochemistry, the synthesis of monomers for polymerization, etc. Over the years, the whole subject has been reviewed several times,^[1] either in specific reviews^[1a,f] or in the more general context of organic oxidations.^[1b–e] The versatility of this reaction in synthetic organic chemistry is witnessed by the observation that the most recent of these reviews published by Krow^[1f] includes more than 1000 references.

In contrast to this wealth of purely organic chemistry, the attempts to apply transition metal catalysis to this important organic transformation have met with only moderate success and have never been reviewed. Indeed, catalytic methods may

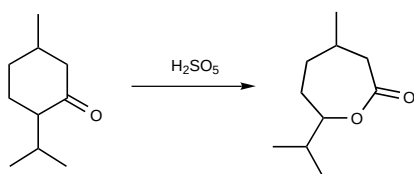
have a number of advantages over their stoichiometric counterparts, ranging from the simplification of the operational conditions, to the use of cheaper reactants and the minimization of waste products. These benefits make them more attractive for practical applications both economically and also ecologically in the context of developing more environmentally friendly methods of production.

In this review, the use of transition metal catalysts for the Baeyer–Villiger oxidation will be analyzed critically in an attempt to understand the basic requirements for successful catalysis and set some possible guidelines for future developments in this field.

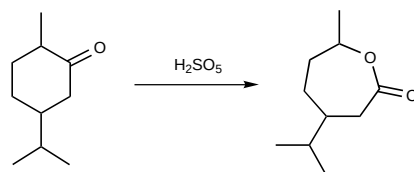
2. Historical Background

The Baeyer–Villiger reaction owes its name to the pioneering work of Adolf Baeyer and Victor Villiger who reported, almost a century ago, the possibility of converting cyclic ketones into lactones with a peroxy acid as oxidant.^[2] The reactions studied by Baeyer and Villiger in 1899 were the oxidations of menthone and tetrahydrocarvone to the corresponding lactones [Eqs. (1) and (2)]. For this purpose these

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(1)



(2)

authors used the most powerful oxidant known at that time, monopersulfuric acid, the synthesis of which had been accomplished the year before by Caro^[3] by mixing together equivalent amounts of potassium persulfate, concentrated sulfuric acid, and water [Eq. (3)].



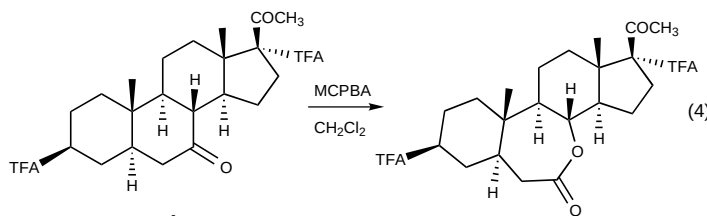
2.1. Properties of the Baeyer–Villiger Oxidation

The Baeyer–Villiger oxidation of ketones, as it is practised nowadays, has a number of intrinsic advantages that have made it so successful in synthetic organic chemistry:

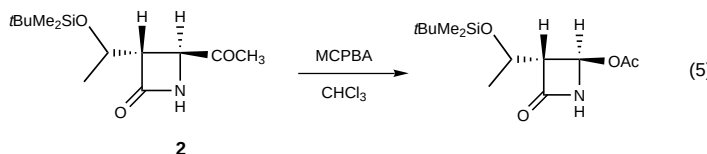
- It tolerates the presence of many functional groups in the molecule. For example, even in unsaturated ketones the oxidation with peracids occurs generally at the carbonyl group, provided the carbon–carbon double bond is not conjugated.
- The regiochemistry of the reaction can be normally controlled by reference to the scale of migratory aptitude for different groups, although there are cases (for example the bicyclic systems) in which various stereoelectronic aspects can influence the regioselectivity of the oxygen insertion.
- It is generally stereoselective, which implies that migrating chiral carbon atoms retain their absolute configuration also in the product ester.

- A wide variety of peroxy acids can be used as oxidants for the reaction.

Two examples that summarize the above points are shown in Equations (4) and (5). Pregnan-7,20-dione (**1**), a precursor of 7-oxyprogesterone, reacts only at the C-7 carbonyl,^[4] and the acyl-substituted β-lactam **2**, an intermediate in the synthesis of carbapenem antibiotics, is converted exclusively into the corresponding acetate.^[5] Both reactions proceed almost



(4)



(5)

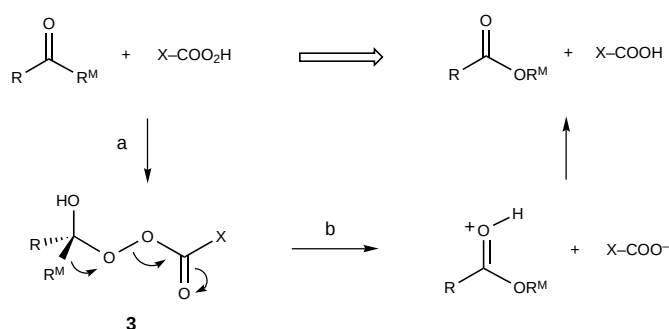
exclusively at the indicated carbonyl group despite the presence of other potentially oxidizable functional groups and with retention of configuration at the migrating carbon atom.

2.2. Mechanism

The mechanism of the Baeyer–Villiger oxidation was first studied by Criegee^[6] about 50 years ago and, in its general features, has remained essentially the same. As shown in Scheme 1, the stepwise process consists of an initial nucleophilic attack of the peroxy acid at the carbonyl carbon (step a) to form an intermediate species (**3**) known as the Criegee adduct. This step is followed by the migration of one of the alkyl groups onto the peroxy oxygen and the concomitant release of the carboxylate anion (step b). Of these, step b is the more important in determining the properties of the overall reaction.

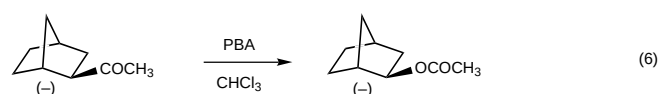


G. Strukul was born in Padua, Italy, in 1946. He graduated from the University of Padua in 1970 and, after serving in the army, was appointed assistant at the University of Venice in 1972, where he spent all his academic career, interrupted by a two year period (1976–1977) at the University of British Columbia (UBC), Vancouver, as postdoctoral fellow with Brian R. James and a visiting professorship at UBC in 1981. He became associate professor in 1983. His research interests include homogeneous catalysis with late transition metals, applications of catalysis to the solution of some environmental problems, and catalytic oxidations with hydrogen peroxide as oxidant on which he published a monograph in 1992.



Scheme 1. Mechanism of the Baeyer–Villiger oxidation of ketones. R^M denotes the migrating group.

The migration step is, in fact, concerted, as was suggested for the first time by Berson and Suzuki in 1959^[6] [Eq. (6); PBA = perbenzoic acid], which accounts for the selectivity of



the reaction, and also rate-determining in the vast majority of cases. The latter point is consistent with the general observation that the reaction rate is increased by the presence of electron-withdrawing substituents on the peroxy acid, which make its conjugate base a better leaving group. For example, peroxotrifluoroacetic acid (PTFAA) is known to be a better oxidant than peracetic acid (PAA), and *m*-chloroperbenzoic acid (MCPBA) is better than perbenzoic acid. Also consistent with a rate-determining step b is the ability of electron-donating substituents in the migrating group to facilitate the rearrangement.

These observations are consistent with the well-known scales of migratory aptitude (*t*-alkyl > cyclohexyl > *s*-alkyl > benzyl > phenyl > *n*-alkyl > cyclopentyl > methyl) and reactivity of the oxidant (TFPAA > monopermaleic acid > mono-*o*-perphthalic acid > 3,5-dinitroperbenzoic acid > *p*-nitroperbenzoic acid > MCPBA ≈ performic acid > PBA > PAA ≫ H_2O_2 > *t*BuOOH). The reactivity scale is related to the strength of the conjugate acid of the leaving group.

3. Hydrogen Peroxide as Oxidant

Some of the above peracids are commercially available. In general, they are prepared from the corresponding acids and concentrated hydrogen peroxide under acid catalysis. In the past the use of 90% H_2O_2 as reagent for the synthesis of peracids was rather common. More recently, the withdrawal of 90% H_2O_2 from the market because of its highly explosive properties has forced the use of the commercially available 70% H_2O_2 ; however, only lower grade peracids can be prepared.

The most powerful oxidants that are also strong acids require the use of a buffer in the Baeyer–Villiger oxidation to avoid transesterification. In addition, at the end of the

Baeyer–Villiger reaction the spent carboxylic acid is separated and discarded. This procedure, while normally viable in common laboratory practice, especially with peracids that are commercially available, is hardly acceptable for large-scale industrial operations. The alternative could be the use of the spent carboxylic acid to regenerate the peracid, but again this additional operation would imply additional costs.

While the use of peracids results in the ultimate consumption of hydrogen peroxide as primary oxidant, its direct use in the Baeyer–Villiger oxidation may have a number of advantages:

- It simplifies greatly the workup to allow the use of simpler reaction conditions and avoid the separation of the carboxylic acid.
- It has a higher active oxygen content (defined as the % active oxygen with respect to the molecular weight), which is economically advantageous as chemicals are sold by weight. For example, the active oxygen content of H_2O_2 is 47%, of PAA 21%, and of TFPAA 9.2%.
- As a consequence, it produces a lower amount of by-product (water) and is the most environmentally friendly among peroxidic oxidants.

All the above points have important economic implications that make hydrogen peroxide very attractive for industrial applications. Indeed, chemical industries are facing increasing costs to clean their off-streams, and it can be easily predicted that some productions will have to be redesigned to comply with regulations for the protection of the environment.

On the other hand, hydrogen peroxide has also disadvantages with respect to organic peracids:

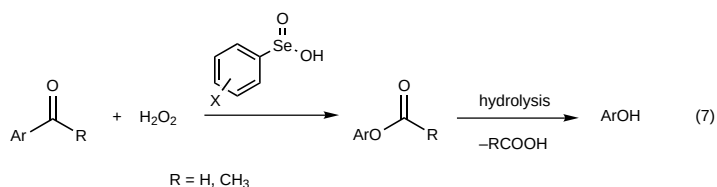
- Water is always present either as a co-solvent or in any case as a reaction product. Hydrolysis of the ester products may result, and incompatibility with the solvent/substrate system may hamper the substrate/oxidant interaction.
- It has a lower stability towards radical decomposition.
- It is kinetically more inert and requires the use of a suitable catalyst.

3.1. Early Catalytic Work

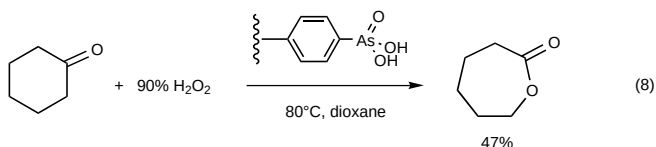
The use of acid or base catalysis with H_2O_2 as oxidant in the Baeyer–Villiger oxidation has been known for a long time.^[1a] However, it is limited to strained cyclic ketones such as cyclobutanones or bicyclo[2,2,1]hepten-2-ones,^[8] so the success of the reaction is more due to the reactivity of the substrate rather than that of the oxidant. Other early attempts to create catalytic systems tried generating peracids *in situ*.

The easy reaction between substituted benzeneselenenic acids and 30–90% hydrogen peroxide has been exploited to produce the corresponding peracids, which were successfully employed for the conversion of aromatic aldehydes and ketones into phenols by hydrolysis of the corresponding formates or acetates [Eq. (7)].^[9] The major drawback of this system is that 30% H_2O_2 can be used only with the easily oxidizable aldehydes, while ketones require the no longer commercially available 90% H_2O_2 .

Similarly, arsenated polystyrene resins catalyze biphasic and triphasic Baeyer–Villiger oxidations of ketones in

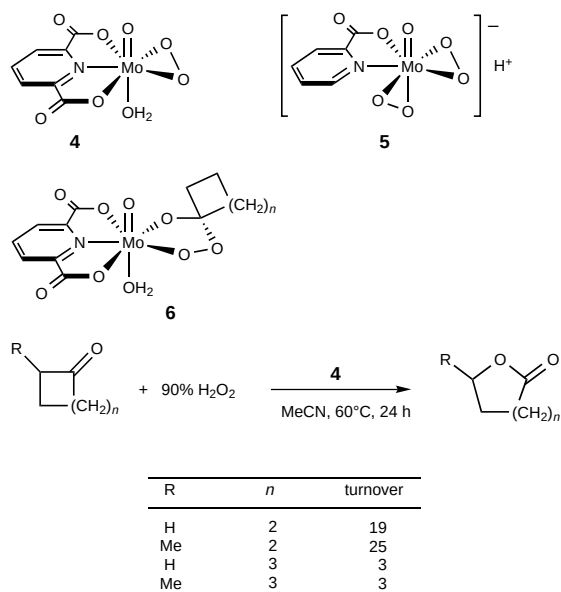


methanol, dioxane, or chloroform with 30 % or 90 % H_2O_2 at 80°C .^[10] The use of water-miscible solvents could not avoid extensive hydrolysis of the product ester, particularly when 30 % H_2O_2 was employed as oxidant. The problem was partly circumvented either by using 90 % H_2O_2 [Eq. (8)] or in a



triphasic system with chloroform as solvent. Under these conditions, water-immiscible cyclic ketones can yield the corresponding lactones with good selectivities.

The first report of transition metal catalysis in the Baeyer–Villiger oxidation of cyclic ketones is due to Mares and co-workers, who reported in 1978 the use of picolinato and dipicolinato Mo^{VI} peroxy complexes (**4** and **5**) as catalysts and 90 % H_2O_2 as oxidant (Scheme 2).^[11] Complexes **4** and **5** can



Scheme 2. Oxidation of cyclic ketones catalyzed by Mo^{VI} complexes.

be easily prepared from the corresponding oxo compounds by reaction with hydrogen peroxide.^[12] Molar turnovers ranged from poor to moderate, thereby reflecting the difficulty to bring together two electrophiles such as the carbonyl carbon and the peroxygen in the peroxometallacyclic species **6** proposed by the authors to be the crucial intermediate.

This system has been recently reinvestigated by Campes-trini and Di Furia,^[13] who failed to observe the stoichiometric reaction between the peroxomolybdenum complex **4** and cyclopentanone, as one would expect if **4** was the actual oxidant. To explain the occurrence of the catalytic reaction when H_2O_2 was present, these authors suggested the likely involvement of acid catalysis as a consequence of the strong acidic character of peroxomolybdenum(vi) complexes such as **4**.^[14] Interestingly, an equivalent amount of sulfuric acid instead of **4** resulted in the same catalytic activity.^[13]

3.2. The Platinum System

The above results on the molybdenum system seem to suggest that, as the point of attack for oxygen transfer (the carbonyl carbon) is electrophilic in nature, the search for an efficient catalyst for the Baeyer–Villiger oxidation will have to be directed towards complexes capable of increasing the nucleophilicity of hydrogen peroxide. Indeed, the platinum dioxygen complex $[(\text{PPh}_3)_2\text{Pt}(\text{O}_2)]$ has long been known to interact easily with ketones to give stable peroxometallacyclic insertion products.^[15] The driving force for the reaction has been recognized to be the nucleophilic attack of the peroxy moiety on the electrophilic carbonyl carbon (Scheme 3).



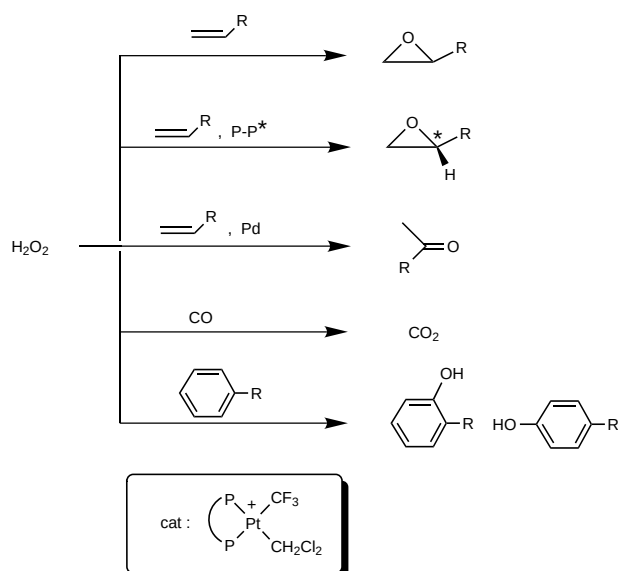
Scheme 3. Basic principle of the oxygen transfer to ketones by a peroxy complex of Pt^{II} . N = nucleophile, E = electrophile.

Unfortunately, the insertion complex is very stable, and no oxidation products evolve.

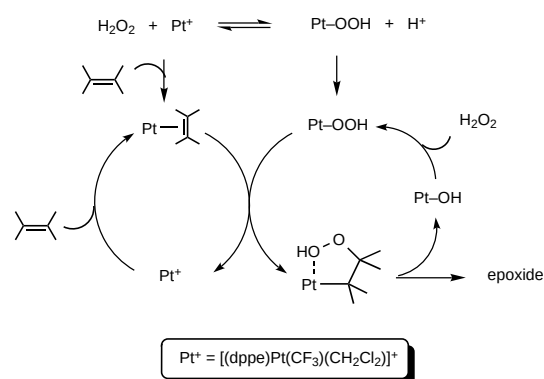
Since 1979 we have been studying the interaction of a variety of square-planar, *cis* complexes of the type $[(\text{P}-\text{P})\text{Pt}(\text{CF}_3)\text{X}]$ ($\text{P}-\text{P}$ = various diphosphanes; $\text{X} = \text{CH}_2\text{Cl}_2$, OH) with H_2O_2 and *t*BuOOH to yield stable peroxy compounds with the aim of increasing the nucleophilicity of the peroxygen through coordination.^[16] Evidence on the extent of polarization of the $\text{Pt}-\text{O}$ bond,^[16c, 17] and hence on the nucleophilic nature of the coordinated peroxygen, was found through NMR spectroscopy by analyzing the $^1J_{\text{PPt}}$ coupling constant between Pt and the P donor *trans* to the peroxy oxygen and from the whole body of reactivity displayed by these complexes.

Over the years, this class of compounds proved very profitable as catalysts for a variety of oxidation reactions with hydrogen peroxide as oxidant (Scheme 4): these include the epoxidation of terminal olefins,^[18] including the enantio-selective version,^[19] the ketonization of terminal olefins with a Pd cocatalyst,^[20] the oxidation of carbon monoxide,^[21] and the direct hydroxylation of aromatics.^[22]

The mechanistic principle by which these catalysts operate^[23] is shown in Scheme 5 for the epoxidation of olefins. The two catalytic cycles operate simultaneously and evidence the bifunctional role played by Pt, which increases the electro-



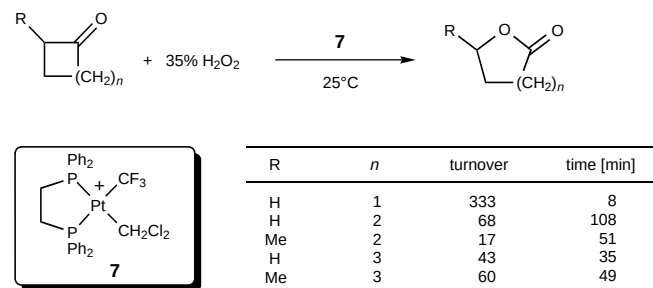
Scheme 4. Summary of Pt^{II} -catalyzed oxidation reactions with hydrogen peroxide.



Scheme 5. Mechanism of the Pt^{II} -catalyzed epoxidation of olefins with hydrogen peroxide. dppe = ethane-1,2-diylbis(diphenylphosphane).

philic character of the substrate (olefin) on one hand and the nucleophilic character of hydrogen peroxide on the other.

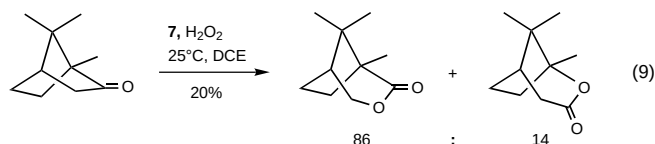
The use of $[(\text{dppe})\text{Pt}(\text{CF}_3)(\text{CH}_2\text{Cl}_2)]\text{BF}_4$ (**7-BF₄**) for the Baeyer–Villiger oxidation was successfully tested at room temperature for a variety of simple cyclic ketones^[24] with 35 % H_2O_2 . As is shown in Scheme 6, this system, which represents the first unambiguous example of transition metal catalysis applied to the Baeyer–Villiger oxidation, is more efficient



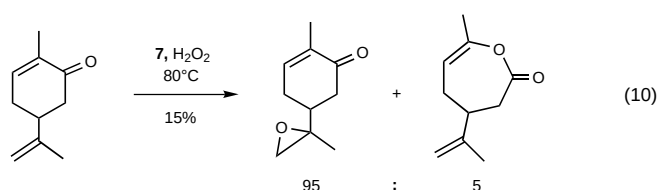
Scheme 6. Catalytic activity of complex **7** in the oxidation of cyclic ketones.

than the molybdenum-based one and allows operation under considerably milder conditions.

Catalyst **7** was found to be inactive in the oxidation of acyclic ketones, even highly substituted ones such as methyl-*tert*-butylketone, while it behaves similarly to peracids in promoting the oxidations of substituted cyclic ketones such as menthone or camphor [Eq. (9); DCE = 1,2-dichloro-

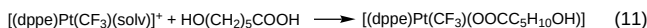


ethane].^[25] Other than with peracids, unsaturated ketones first undergo epoxidation and then Baeyer–Villiger oxidation [Eq. (10)]. The chemoselectivity can be quite high, and this

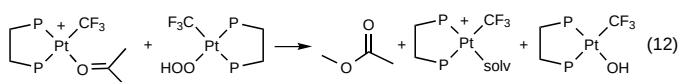


class of catalyst proved successful for the (even asymmetric) epoxidation of α,β -unsaturated ketones.^[26]

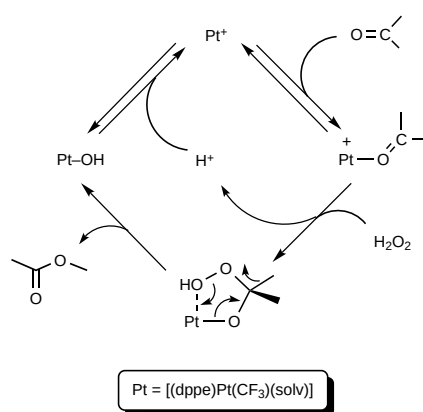
Catalyst **7** tends to deactivate as the oxidation proceeds, thereby limiting the maximum achievable turnover. This deactivation was associated to the presence of small amounts of hydroxycarboxylic acid arising from lactone hydrolysis, which can easily react with **7** to produce a no longer catalytically active carboxylate derivative [Eq. (11)].^[25]



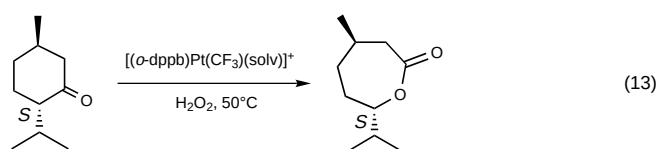
The mechanism of the reaction^[25] is shown in Scheme 7 and differs from the epoxidation reaction (Scheme 5) as far as the nature of the oxidant is concerned. Although $[(\text{dppe})\text{Pt}(\text{CF}_3)(\text{OOH})]$ can be a possible oxidant, as was demonstrated by successfully performing the stoichiometric reaction shown in Equation (12), the actual oxidant of the catalytic reaction was



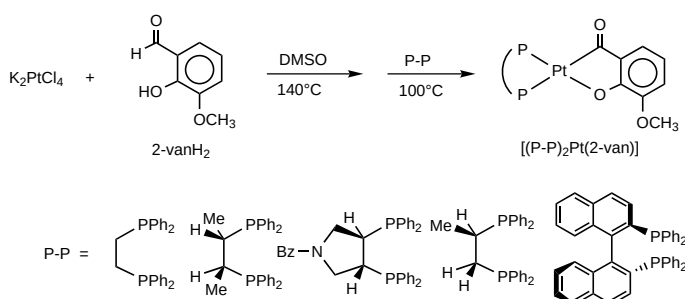
found to be free H_2O_2 (Scheme 7). The catalyst behaves essentially as a Lewis acid, capable of increasing the electrophilic character of the carbonyl carbon, and indeed the quasi peroxometallacyclic intermediate bears strong similarities with the Criegee intermediate, with Pt^+ instead of H^+ . However, the peculiar role of Pt seems to be rather to provide an easy pathway for the exit of the poor HO^- leaving group through coordination, thereby giving the system the driving force necessary to break down the quasi peroxo-

Scheme 7. Mechanism of the oxidation of ketones catalyzed by **7**.

metallacyclic intermediate and yield products. Again, the analogy with step b of the Baeyer–Villiger oxidation with peracids (Scheme 1) in determining the overall reactivity of the process is remarkable. Even more so, it was found in the case of menthone that the reaction proceeds with retention of configuration at the migrating carbon atom [Eq. (13), *o*-dppb = *o*-bis(diphenylphosphanyl)benzene].



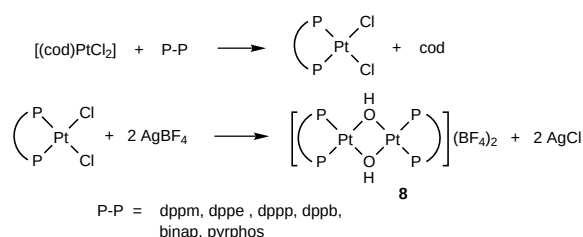
Other Pt species containing electron-withdrawing ligands capable of mimicking the effect of the CF₃ ligand were studied. Complexes of the type [(P–P)Pt(2-van)] (P–P = various diphosphanes; 2-van = 2-vanillin dianion) were synthesized following the general method outlined by Pregosin and co-workers (Scheme 8).^[27] These complexes that,



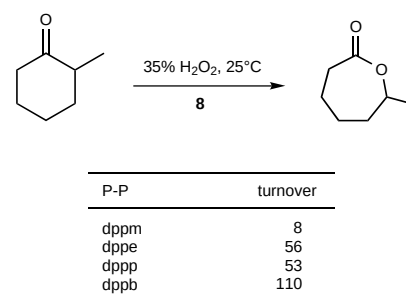
Scheme 8. Synthesis of [(P–P)Pt(2-van)] complexes. Bz = benzyl.

per se, are catalytically inactive can be promoted with the addition of one equivalent of a strong non-coordinating acid and can perform the catalytic oxidation of a series of simple cyclic ketones.^[28] Studies on the evolution of these platinum(II) compounds under acidic conditions has led to the identification of a class of known bridging hydroxy complexes that proved interesting catalysts for the Baeyer–Villiger oxidation of ketones.^[29]

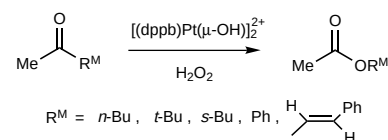
The synthesis of this class of complexes (Scheme 9) was reported for the first time in 1972 by Bushnell et al.,^[30] however, in about 25 years they have been scarcely studied because they are hardly reactive. The synthetic route outlined in Scheme 9 that was originally reported only for PPh₃

Scheme 9. Synthesis of [(P–P)Pt(μ-OH)]₃⁺ complexes. dpmm = methanediylbis(diphenylphosphane); dppe = propane-1,3-diylbis(diphenylphosphane); dppb = butane-1,4-diylbis(diphenylphosphane); binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl; pyrphos = 3,4-bis(diphenylphosphanyl)pyrrolidine.

derivatives has been employed by several authors for the preparation of homologous compounds containing a variety of diphosphanes. Interestingly, the ability of **8** to promote the Baeyer–Villiger oxidation with hydrogen peroxide is dependent on the size of the diphosphane–platinum ring,^[31] as was demonstrated for a series of homologous complexes on the substrate methylcyclohexanone (Scheme 10). The most active

Scheme 10. Effect of the diphosphane P–P in the oxidation of methylcyclohexanone catalyzed by **7**.

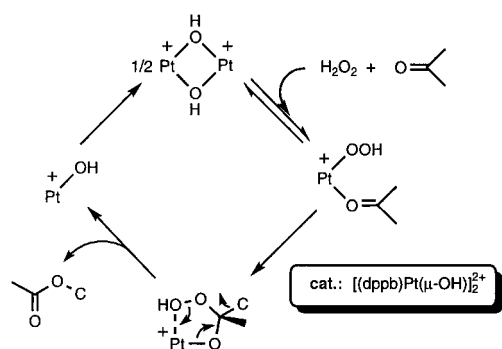
catalyst [(dppb)Pt(μ-OH)]₂²⁺ was also reactive towards a series of acyclic ketones,^[31] thus representing the first example of transition metal catalysis (Scheme 11). The reactivity



Scheme 11. Catalytic oxidation of acyclic ketones.

observed indicates the scale of migratory aptitude *tert*-alkyl > vinyl > *s*-alkyl > phenyl > *n*-alkyl and parallels the reactivity known with peracids as oxidants (see above).

The oxidation of methylcyclohexanone was also studied kinetically and suggested the mechanism of reaction shown in Scheme 12.^[31] The dimeric complex first opens by the action

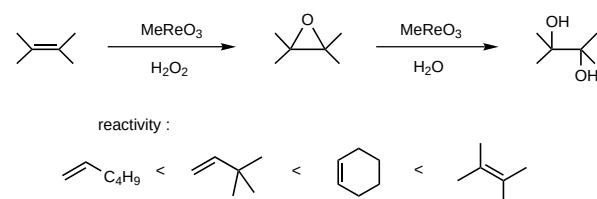


Scheme 12. Mechanism of the oxidation of ketones catalyzed by $[(\text{dppb})\text{Pt}(\mu\text{-OH})]_2^{2+}$.

of hydrogen peroxide and the ketone, followed by the apparently crucial step of an intramolecular nucleophilic attack of the hydroperoxy ligand on the coordinated ketone. The high activity of $[(\text{dppb})\text{Pt}(\mu\text{-OH})]_2(\text{BF}_4)_2$ relative to the homologous diphosphane derivatives could be due to a better ability to promote the initial dissociation equilibrium because of a larger P–Pt–P bite angle.

3.3. The Methyltrioxorhenium (MTO) Catalyst

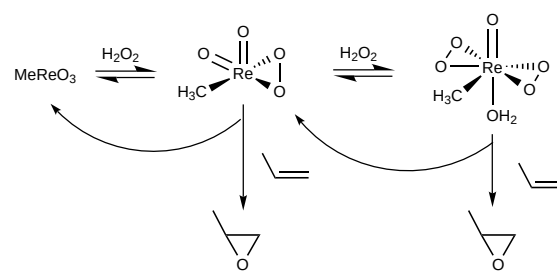
MTO is a simple and easily accessible organometallic oxide, the synthesis of which was reported by Herrmann and co-workers.^[32] MTO is a useful catalyst for oxidation reactions with hydrogen peroxide as oxidant including the oxidation of Baeyer–Villiger. Again, the discovery that cyclic ketones could be easily converted into lactones stemmed from previous work on the epoxidation of olefins.^[33] It was observed that a variety of simple internal and cyclic olefins could be easily epoxidized at temperatures ranging from -10 to 70°C , although in some cases the reaction proceeds further, yielding the diol as the major oxidation product (Scheme 13).



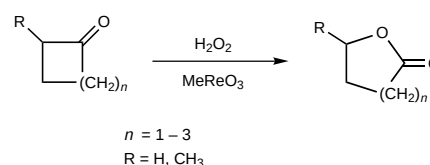
Scheme 13. Epoxidation of olefins catalyzed by $[\text{MeReO}_3]$.

Hydrogen peroxide is activated through the formation of mono- and bisperoxides,^[34] which are the actual oxidants capable of transferring oxygen to olefins (Scheme 14). The reactivity observed^[35] and a careful kinetic study of the reaction^[36] have demonstrated that oxygen transfer occurs by nucleophilic attack of the olefin on an electrophilic peroxy oxygen via an intermediate “butterfly” transition state, as seems to be the general case for d^0 transition metal systems.^[37]

So it was surprising that MTO is also involved as catalyst in the Baeyer–Villiger oxidation of cyclic ketones with hydrogen peroxide (Scheme 15) via the same reactive peroxy

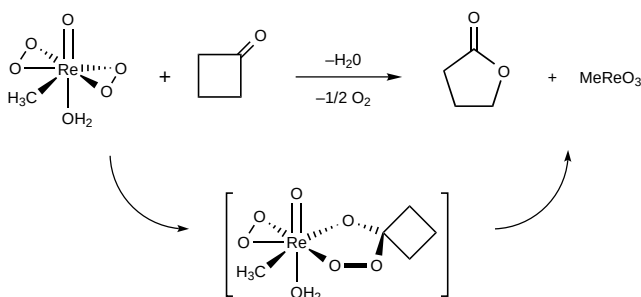


Scheme 14. Mechanistic pathway for the epoxidation of olefins catalyzed by $[\text{MeReO}_3]$.



Scheme 15. Oxidation of cyclic ketones catalyzed by $[\text{MeReO}_3]$.

intermediates.^[38] The reaction was suggested to proceed through the formation of an intermediate peroxometallacyclic species (Scheme 16), and to account for the reactivity



Scheme 16. Mechanistic pathway for the oxidation of cyclobutanone catalyzed by $[\text{MeReO}_3]$.

observed the authors suggested that the peroxy oxygen atoms are nucleophilic on the basis of the following observations:^[38]

- ^{17}O NMR spectroscopy indicated the existence of inequivalent peroxy oxygens as should be expected by their relative position with respect to the equatorial methyl ligand. The observation of an uncommonly intense IR stretching at 877 cm^{-1} led to the conclusion that the O–O bond was substantially polarized;
- a solvent-dependent nucleophilic character was observed by reaction with thianthrene-5-oxide.

3.4. Titanium Silicalite (TS-1)

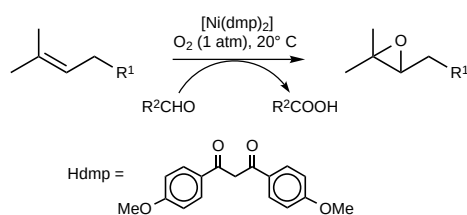
In the last decade, titanium silicalites have emerged as the major breakthrough in the use of H_2O_2 as oxidant in industrial organic chemistry.^[39] The catalyst TS-1, in particular, is presently in use in the large-scale industrial production of diphenols, cyclohexanone oxime, and propylene oxide. Other reactions accomplished on a laboratory scale are the selective epoxidation of olefins and diolefins, the selective oxidation of

primary alcohols to aldehydes and secondary alcohols to ketones, and the hydroxylation of aromatic and aliphatic compounds.^[40] However, only very recently has the first example of Baeyer–Villiger oxidation been reported.^[41]

The oxidation of cyclohexanone and acetophenone can be accomplished at 80°C with modest turnovers that increase moderately upon addition of a free acid. The selectivity to ester is generally below 50 %, and the hydroxycarboxylic acid (or phenol and acetic acid) are the major by-products. Other products are the hydroxyketone, the diketone, and products arising from further hydroxylation of the aromatic ring, where present.^[41] The modest activity observed seems in agreement with the nature of the actual oxidant, which is believed to be a surface Ti^{IV} (electrophilic) peroxy species;^[40] in this respect TS-1 is similar to the old Mo^{VI} catalyst.^[11]

4. Dioxygen as Oxidant: the Mukaiyama System

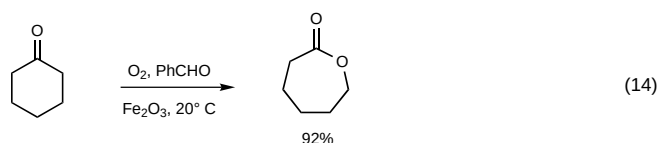
In 1991 Mukaiyama and co-workers described the use of sacrificial aldehydes for the aerobic epoxidation of olefins in the presence of Ni complexes as catalysts (Scheme 17).^[42] This



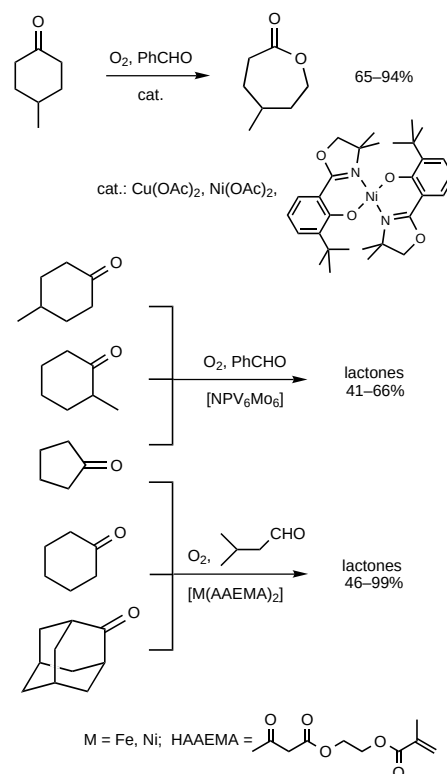
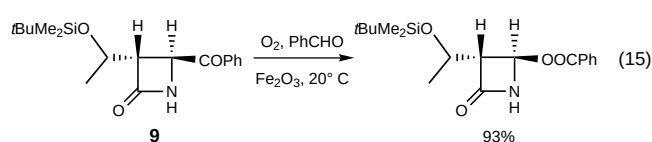
Scheme 17. Principle of the Mukaiyama system.

report followed some earlier patents by, among others, Union Carbide, and Mitsubishi Kasei,^[43] and exploits the easy autoxidation of aldehydes to promote the in situ formation of peroxy acids. This system has been highly successful in the promotion of the aerobic oxidation of a variety of substrates including olefins,^[44] aldehydes,^[45] silyl enoethers,^[46] lactams,^[47] and alkanes,^[48] and has proved useful for the Baeyer–Villiger oxidation of ketones as well.

So Fe_2O_3 catalyzes the oxidation of cyclohexanone and other cyclic ketones to the corresponding lactones in high yields [Eq. (14)], but also the conversion of the benzoyl- β -



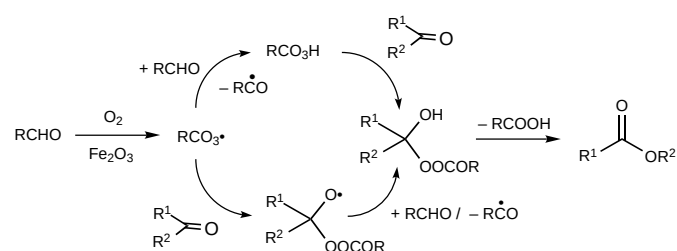
lactam **9** into the corresponding benzoate ester with complete retention of configuration [Eq. (15)].^[49] Similar results have been obtained for substituted cyclohexanones and cyclopentanone on use of β -diketonato complexes,^[50] a Schiff-base derivative of Ni^{II} ,^[50] or even polyoxometalates^[51] (Scheme 18). Polymerizable β -diketonato complexes of nick-



Scheme 18. Examples of oxidation of cyclic ketones with the Mukaiyama system.

el, iron, and cobalt have been also used for the oxidation of adamantanone, cyclohexanone, and cyclopentanone (Scheme 18).^[52] Attempts to oxidize open-chain ketones such as benzophenone or *tert*-butylmethylketone were unsuccessful.^[52]

A mechanistic interpretation of the Fe_2O_3 -catalyzed oxidation has been proposed by Murahashi (Scheme 19).^[49] The catalyst is suggested to be involved merely in the promotion of the easy autoxidation of benzaldehyde to produce perbenzoic acid in situ, in a way that is identical to the well-known industrial synthesis of acetic acid.^[53] Once formed, perbenzoic acid (or its peroxy radical) performs the Baeyer–Villiger oxidation with no intervention of the catalyst. This view,



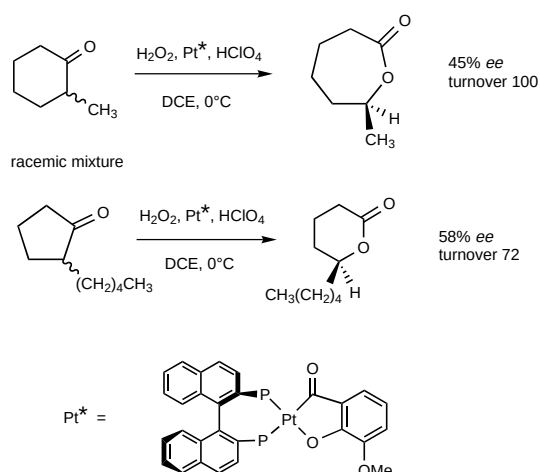
Scheme 19. Mechanistic pathway for the oxidation of ketones with the Mukaiyama system.

which appears the most obvious one, seems in agreement with the observation that, with Fe_2O_3 as catalyst, open-chain ketones can be oxidized [Eq. (15)]^[49] and with the fact that with benzaldehyde the reaction can proceed even in the absence of catalyst.^[54] However, in all other systems reported above and based on more elaborate catalyst formulation, only cyclic ketones are reported to be oxidized in contrast with the known reactivity for an in situ produced peroxy acid. This observation and the fact that the system has been modified successfully to accomplish the Baeyer–Villiger enantioselective transformation (see Section 5) seem to suggest that the metal may also be actively involved in the oxygen transfer step, although how is still unclear.

5. Asymmetric Oxidation

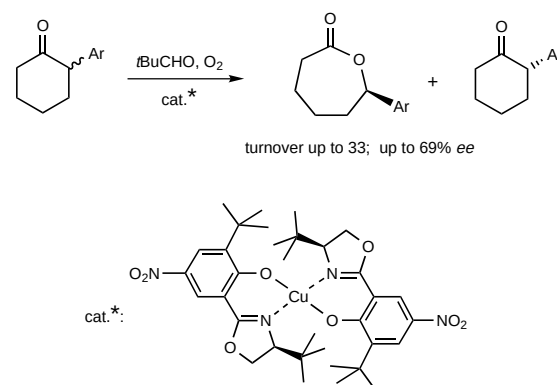
The use of microorganisms in the asymmetric Baeyer–Villiger oxidation of ketones has been known for several years and has been recently reviewed.^[55] Whole cell cultures^[56] or purified enzymes^[57] extracted from the *Acinetobacter* bacteria family have allowed the preparation chiral lactones with optical purity higher than 98 %.

Recently, the first two examples of transition metal catalysis for the Baeyer–Villiger oxidation were published independently and almost simultaneously by Gusso et al.^[28] and by Bolm et al.^[58] In both cases the reaction was the kinetic resolution of racemic ketones through enantiospecific conversion into chiral lactones. The former studies were based on the use of Pt complexes modified with chiral diphosphanes and hydrogen peroxide as oxidant. Optimization of the catalyst structure^[28, 29] led to the conversion of a series of racemic cyclohexanones and cyclopentanones into chiral lactones related to pheromones and fragrances with an *ee* of up to 58 % (Scheme 20). The latter studies^[58] were based on a



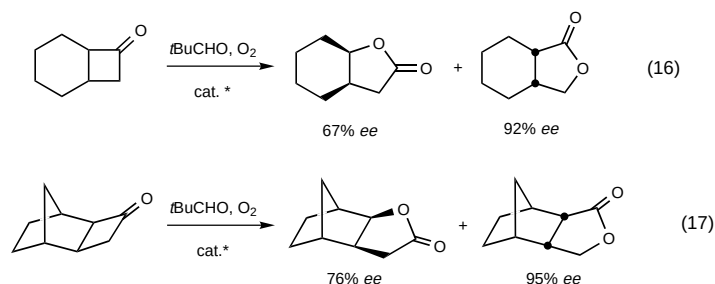
Scheme 20. Enantiospecific oxidation of ketones catalyzed by chiral platinum complexes. DCE = 1,2-dichloroethane.

modified Mukaiyama system consisting of a chiral copper complex (Scheme 21), pivalaldehyde, and oxygen as the primary oxidant. Racemic aryl-substituted cyclohexanones could be oxidized to the corresponding enantiomerically

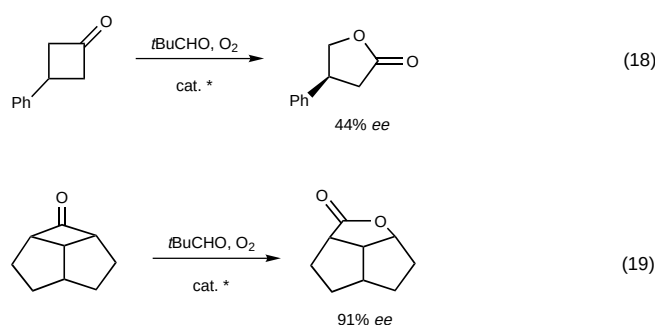


Scheme 21. Enantiospecific oxidation of ketones catalyzed by chiral copper complexes.

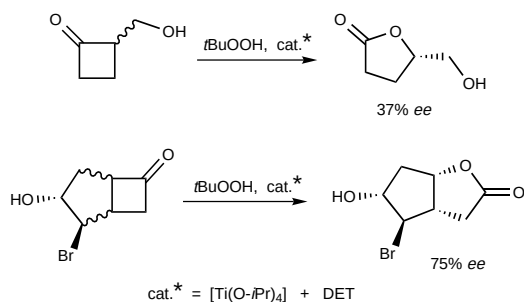
enriched lactones with an *ee* of up to 69 %. No enantiospecificity was observed with homologous Ni complexes, while the use of other sacrificial aldehydes resulted in lower *ee*'s. The steric and electronic properties of the ligand influence the activity and enantiospecificity of the catalysts. Better yields and *ee*'s were obtained with the *p*-nitro-substituted complexes rather than their unsubstituted counterparts. Substituents less bulky than *t*Bu in the arene resulted in much poorer chemical yields (< 10 %).^[58] The same catalyst system was extended to the oxidation of a variety of racemic substituted cyclobutanones, which again led to a kinetic resolution yielding chiral lactones with better *ee*'s [Eqs. (16) and (17)].^[59]



The first example of enantioselective Baeyer–Villiger oxidation has been very recently reported by Bolm with the same catalyst system in the oxidation of prochiral ketones.^[60] Substituted cyclobutanones afforded the corresponding butyrolactones [Eqs. (18) and (19)] with an asymmetric induction up to 91 % *ee*. Unfortunately, the system seems unable to oxidize ketones other than cyclobutanones.^[60]



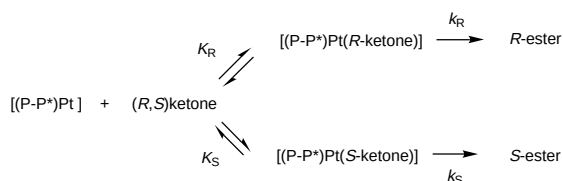
Similar results have been recently reported also by Lopp et al. (Scheme 22) with the Sharpless catalyst ($[\text{Ti}(\text{O}-i\text{Pr})_4] + \text{diethyltartrate}$) and $t\text{BuOOH}$ as oxidant.^[61] Yields are



Scheme 22. Enantiospecific oxidation of cyclobutanones catalyzed by Sharpless reagent. (DET = diethyltartrate).

moderate, but the reaction cannot be considered catalytic in a true sense, as more catalyst than substrate was present in the reaction mixture. Again, only substituted cyclobutanones could be oxidized, probably reflecting the inadequacy of Ti^{IV} (a d^0 transition metal center) to bring about the reaction.

A possible mechanistic interpretation for the asymmetric induction in these systems seems relatively easy in the case of the Pt system for which the general mechanism of reaction has been studied (Schemes 7 and 12). Clearly, the asymmetric transformation occurs by formation of diastereomeric Pt(ketone) intermediates (formed by the chiral Pt complex in the presence of a racemic ketone), followed by a stereoselective oxygen transfer step. A schematic view of this kinetic resolution process is indicated in Scheme 23. A similar



Scheme 23. Basic principle of kinetic racemate resolution with chiral Pt complexes.

interpretation could well apply to the Ti case, assuming for the Baeyer–Villiger oxidation a reaction mechanism similar to that known for the epoxidation of allylic alcohols.^[62] Unfortunately, no interpretation can be proposed for the most interesting case reported by Bolm,^[60] the only one in which a real asymmetric induction is observed, and the only mechanistic interpretation for the overall reaction suggested by Murahashi (Scheme 19) is clearly inadequate.

6. Summary and Outlook

Transition metal catalysis in the Baeyer–Villiger oxidation of ketones is still a challenging issue, as the reaction mechanism is to some extent elusive, and the number of transition metal systems capable of efficient catalysis is very

limited. In this respect, it seems significant that versatile catalyst families, such as metalloporphyrins, that in the last two decades have been extensively studied and have proved successful in a wide variety of oxidation reactions, have been so far unable to catalyze the Baeyer–Villiger oxidation.

As this review has tried to demonstrate, the possible successful catalysts will have to be able to increase the nucleophilic character of the peroxy oxygens of the oxidant and, at the same time, assist the leaving group to depart from the “reactive intermediate” involved in the catalysis, as in the Criegee intermediate suggested for the organic transformation.

From a synthetic point of view, the use of chiral transition metal catalysts appears to be the only promising alternative to catalysis by microorganisms for the synthesis of esters with (medium) high optical purity in the enantioselective transformation. In order to compete with organic synthesis, the scope and applications of the transition metal catalyzed Baeyer–Villiger oxidation will have to be improved. In this respect a major breakthrough will be the finding of really efficient catalysts capable of promoting the oxidation of acyclic ketones to the corresponding esters.

I wish to thank the National Research Council and the Ministry of Education and Scientific Research of Italy for financial support of this work. I am deeply indebted to my colleagues and co-workers whose names are cited in the references for their invaluable intellectual and experimental contribution. Finally I would like to acknowledge the late Professor Fulvio di Furia, an eminent organic chemist and unforgettable friend, to whom I have dedicated this review.

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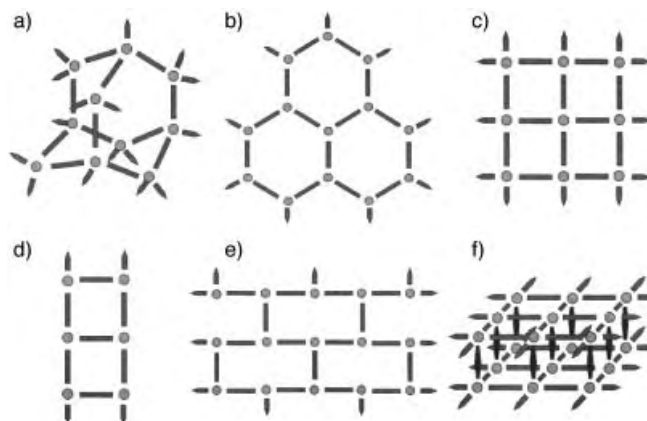
From Disymmetric Molecules to Chiral Polymers: A New Twist for Supramolecular Synthesis?

Michael J. Zaworotko*

The term “crystal engineering” was first coined in 1971 in the context of photochemistry in the organic solid state, and referred specifically to topochemical control of reaction pathway and product stereochemistry.^[1] However, despite the promise and challenge offered by crystal engineering (i.e. the control and prediction^[2] of solid-state structure), this area did not begin to flourish until the past decade.^[3, 4] Recent interest has been sparked not so much by the desire to predict crystal structures but rather the realization that supramolecular synthesis of new classes of functional solid is a natural consequence of successful crystal engineering.

Organic networks, sustained by directional noncovalent interactions,^[3] and coordination polymers,^[4] sustained by coordinate covalent bonds, represent the two primary classes of compound currently being investigated by crystal engineers. The two areas have thus far developed largely apart from each other, however, a paper in the previous issue of *Angewandte Chemie* suggests that this situation might soon change.^[5] A synthetic strategy that potentially offers intricate control over the architecture of coordination polymers is detailed by Ranford, Vittal and Wu, namely the generation of an architecture with use of noncovalent hydrogen bonds and subsequent condensation to form a covalent polymer with the same basic architecture.

Coordination polymers offer great potential in the context of new classes of microporous^[6] and/or magnetic materials.^[7] The primary strategy employed is quite simple: propagate a known coordination geometry with a rigid linear bifunctional spacer ligand. This strategy has resulted in a number of obvious motifs for open-framework coordination polymers (Scheme 1), some of which are rare or even unprecedented in naturally occurring solids.^[8] Furthermore, such compounds can be prepared in one-pot reactions by simply mixing the metal moiety with the bifunctional spacer ligand in the appropriate stoichiometry. Ligands that are suitable for the generation of such structures vary quite substantially in terms of length and chemical type; these include cyanide,^[9a] pyrazines,^[9b] and longer ligands such as 4,4'-bipyridine and



Scheme 1. A schematic representation of several of the simpler network architectures exhibited by coordination polymers. Nodes are metal moieties, and ligands are represented by rods: a) diamondoid, b) honeycomb, c) square grid, d) ladder, e) brick, f) octahedral.

derivatives.^[10] However, there are two major drawbacks to this simple synthetic approach: the problems of interpenetration^[11] and supramolecular isomerism/polymorphism^[12] have not yet been overcome, and the number of architectures is limited.

Ranford et al. describe an alternative two-step approach to the construction of networks that depends on the outer sphere of a complex and its ability to self-assemble. The complex $[\{Zn(sala)(H_2O)_2\}] \cdot 2H_2O$ (**1**, $H_2(sala) = N$ -(1-hydroxybenzyl)-L-alanine), exists as discrete dimers (Figure 1) which self-assemble because of complementary hydrogen bonding between hydrogen-bond donors on one of its faces (the coordinated aqua ligand and the N–H moiety of the sala ligand) and the carboxylate moiety of the sala ligand of an adjacent molecule. This supramolecular synthon sustains an unusual architecture: helical hydrogen-bonded chains (Figure 2a) which are held together by cross-linking (Figure 3a). Interestingly, there are also solvate water molecules that are hydrogen bonded in the helical channels, and the channels are aligned parallel to one another. Clearly, the structure of **1** is favorably disposed towards loss of the coordinated aqua ligands and retention of the overall architecture. Indeed, the proximity of the aqua ligands to the uncoordinated carboxylate moieties and the existence of the helical channels facilitate loss of all water molecules and generation of

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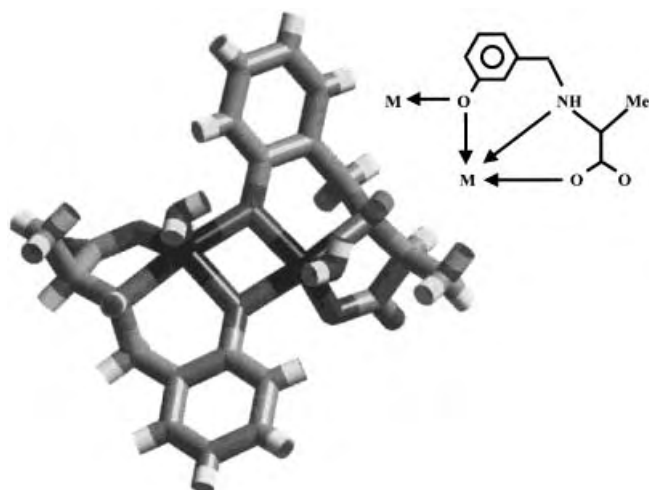


Figure 1. Stick model of compound **1** and its monomeric unit (above right). The hydrogen-bond donor groups are oriented above the plane of the molecule, whereas the acceptor groups point below the plane.

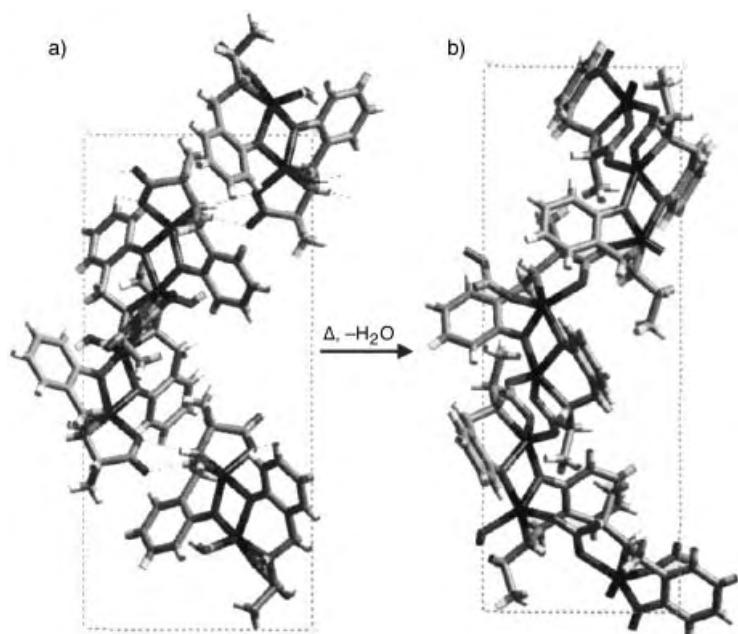


Figure 2. The helical chain architecture exhibited by compounds **1** and **2** viewed parallel to the crystallographic *c* axis.

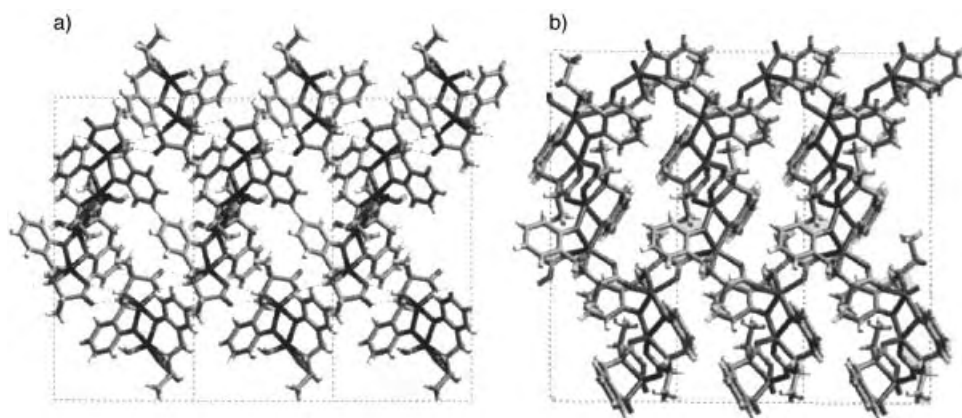


Figure 3. The structures of compounds **1** and **2** viewed along the crystallographic *ac* plane. Guest water molecules lie in the channels of compound **1**.

[[Zn(sala)_n]] (**2**). The three-dimensional coordination polymer **2** has an architecture that is very similar to that of **1** (Figures 2b and 3b) with covalent bonds between the Zn center and the oxygen atom of the carboxylate group.

Notwithstanding the novelty of the structures of **1** and **2**, the ultimate significance of the conversion of **1** into **2** probably lies in its implications beyond coordination chemistry and porosity. In principle, these compounds could represent a new synthetic paradigm: supramolecular synthesis by direct conversion of noncovalent networks into covalent polymers. Indeed, the potential for building two-dimensional and three-dimensional organic polymers with controlled architecture has already been discussed by Ermer,^[13] and interest in second or outer-sphere complexation is on the rise.^[14] In summary, there are several salient features of the new work:

- 1) A two-step approach to the construction of coordination polymers based upon manipulation of outer-sphere interactions between discrete complexes has been delineated.
- 2) This approach eliminates the common problems of supramolecular isomerism and interpenetration.
- 3) Chiral porous solids are reported.
- 4) The implications of the new work extend beyond the boundaries of coordination chemistry and porous solids since the same strategy should work equally well in organic and organometallic systems and could be applied to other bulk properties, especially polarity and magnetism.

In conclusion, it is worth noting that Schmidt's seminal work that defined the concept of crystal engineering remains particularly relevant and topical even after almost three decades.^[1] This particular facet of crystal engineering, supramolecular synthesis of new solids, now appears ready to bear fruit.

Keywords: coordination polymers • crystal engineering • hydrogen bonds • porosity • topochemistry

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Induced Chemical Defense in Plants**

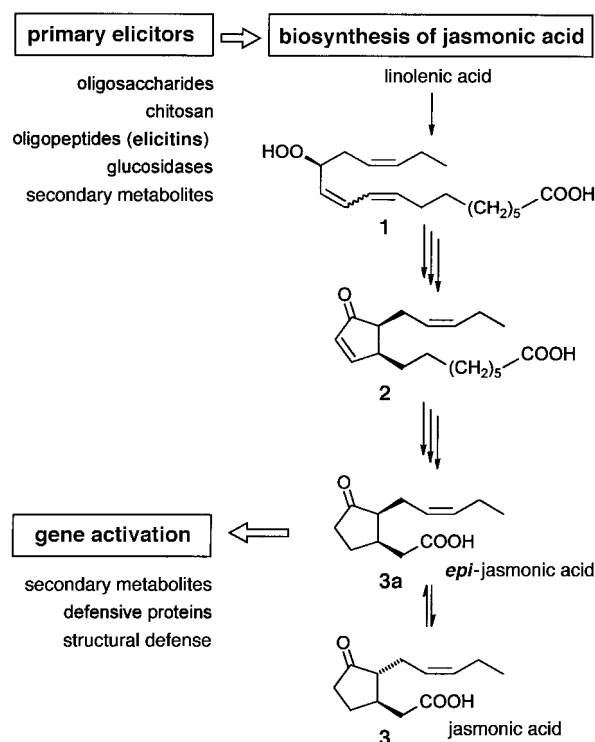
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The chemical defense of plants has been a most fascinating topic of natural product chemistry since its early beginnings. To date, a large number of secondary metabolites have been identified including alkaloids, anthocyanins, flavonoids, and terpenoids, which are thought to have ecological functions related to plant defense against microbial, fungal, or herbivorous attack.^[1] Additionally, several plant species have been shown to produce defensive proteins such as proteinase inhibitors.^[2]

While many of the defensive compounds in plants are formed constitutively, recent results show that plants have highly sophisticated regulation mechanisms that control the production of defensive secondary metabolites or proteins. A growing number of examples demonstrates that the biosynthesis of defensive compounds may be induced by damage from pathogens or herbivores.^[3] These induced plant defense reactions can be local, but very often extend systemically through the plant; that is, they are not limited to the site of damage.

The induced synthesis of defensive compounds, especially when the response of the plant is systemic, must rely on highly effective signaling systems that mediate a quick response to microbial or herbivorous attack. Although the understanding of

defense systems in plants is still limited, and the signaling pathways may vary among plant species, recent results suggest a general underlying pattern for plant self-defense mechanisms (Scheme 1). Depending on the nature of the attacking



Scheme 1. General pattern of signaling systems involved in induced plant defense reactions and biosynthesis of jasmonic acid (3).

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pathogen, compounds from various classes of natural products have been found to function as the primary elicitors that activate the plant's signaling system. These can be oligosaccharide fragments generated from both plant or fungal cell walls,^[4] small proteins (elicitors) secreted by infesting fungi,^[5] secondary metabolites, or enzymes such as β -glucosidases in the saliva of herbivorous insects.^[6]

While there is a high degree of chemical diversity among the primary elicitors, defensive signaling in plants seems to rely on at least one common group of signal transducers. For a large number of species from different plant families it has been shown that recognition of the primary elicitors eventually induces the biosynthesis of jasmonic acid (**3**) or methyl jasmonate.^[7] In plants jasmonic acid is produced from linolenic acid in a series of steps (the octadecanoic pathway) as described by Vick and Zimmermann (Scheme 1).^[8] After lipoxidation, the intermediate (13*S*)-hydroperoxy-9,11,15-octadecatrienoic acid (**1**) is converted into 12-oxophytodienoic acid (**2**), which itself shows strong activity as a phytohormone. Reduction of **2** followed by three β -oxidation cycles finally leads to jasmonic acid (**3**).

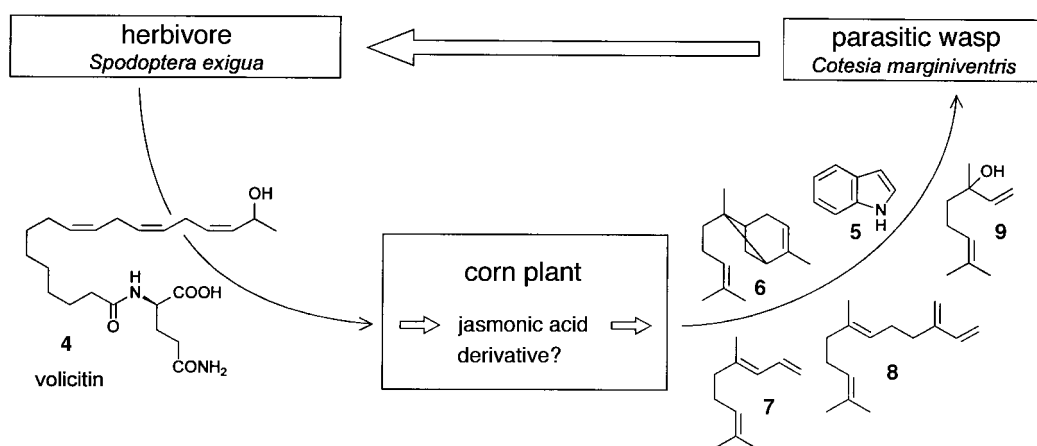
In the next step of the signal-transduction chain, the jasmonic acid derivatives trigger the specific responses of the plant to the attacking pathogen or insect. For example, jasmonates induce genes encoding proteinase inhibitors, antifungal proteins, and enzymes involved in the biosynthesis of defensive secondary metabolites.^[7] Thus, in addition to their well-established functions as regulators of plant growth and development,^[9] jasmonates play a key role as phytohormones or signal transducers in the defense-signaling systems of plants.

So far, investigations of herbivore-induced chemical defense in plants have focused mainly on direct interactions between plant and herbivore. Recent studies have now demonstrated that plant response to herbivoral attack may include interaction with a third trophic level: Herbivore-damaged plants actively attract insect parasitoids or predators. Corn (*Zea mays*), for example, responds to injury inflicted by a caterpillar (*Spodoptera exigua*) with a systemic emission of a characteristic blend of volatile compounds, which attracts females of a parasitic wasp (*Cotesia margin-*

iventris), a natural predator of these caterpillars (Scheme 2).^[10] Several components of this volatile mixture, including indole (**5**) and terpenoids **6–9**, are emitted only when the oral secretions of the herbivore comes into contact with damaged plant tissue, and are absent when the plants are just mechanically wounded. Furthermore, the timing of emission of these volatile compounds corresponds to the period of day when the parasitic wasps are foraging for their hosts. The plants are thus able to distinguish between mechanical wounding and damage caused by insects. Similar tritrophic interactions have been described for species from various other plant families, including cotton (*Gossypium hirsutum*),^[11] beans (*Phaseolus lunatus*),^[6] or cabbage (*Brassica oleracea*).^[12] Tumlinson et al. showed that in cotton, the characteristic components emitted, indole (**5**) and terpenoids **7–9**, are synthesized de novo upon insect attack.^[11] Therefore, elicitors present in the oral secretions of the feeding insects activate at least two different biosynthetic pathways. Until recently the nature of these primary elicitors was largely unknown. Hopke et al. have shown that in some plant species a mixture of β -glucosidases, when applied to freshly wounded leaves, induced the emission of volatile compounds.^[6] Since β -glucosidases are also present in the oral secretions of many herbivores, it was concluded that β -glucosidases may represent one group of primary elicitors.

Recently Alborn et al. demonstrated that *N*-(17-hydroxylinolenyl)-L-glutamine (volicitin, **4**), isolated from oral secretions of *Spodoptera exigua*, acts as an elicitor of volatile emission in corn (Scheme 2).^[10] Volicitin, presumably derived from linolenic acid, represents the first example of a secondary metabolite from insects that acts as an elicitor of a defensive reaction in plants. Its presence in the oral secretion of the caterpillars is not related to diet, and it thus appears to be produced de novo by the insect. Whether compounds related to **4** are present in the oral secretions of other insects and whether **4** acts as an elicitor of the defense reactions in other plant species remains unknown.

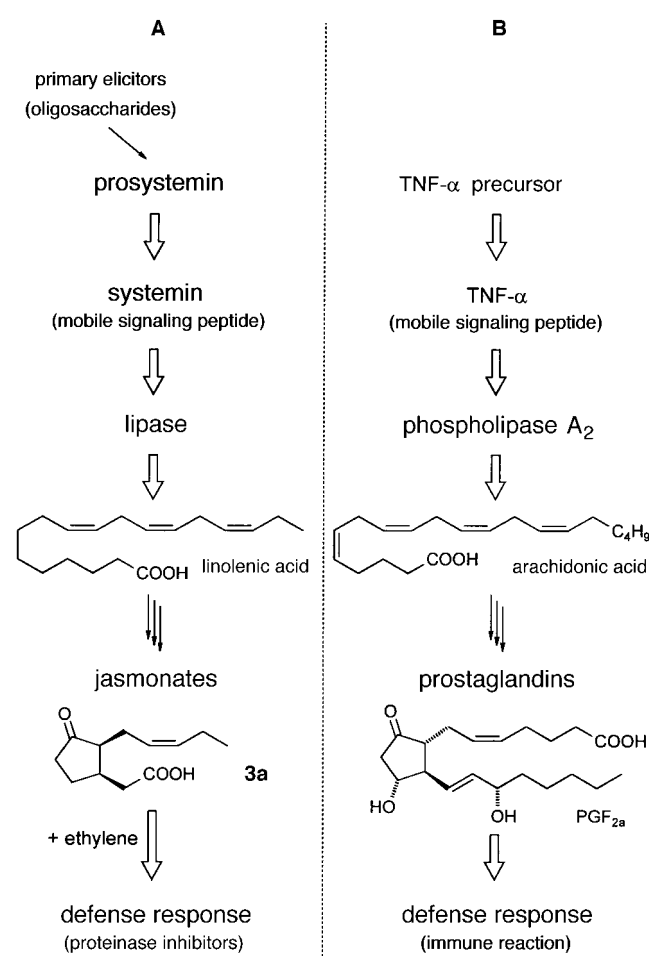
The signal-transduction pathways within the corn plant that lead from the recognition of volicitin to the systemic emission of volatile compounds have been only partially elucidated. As in the case of defensive reactions in other plant species,



Scheme 2. Chemical signals in the tritrophic interaction between corn (*Zea mays*), herbivore (*Spodoptera exigua*), and parasitic wasp (*Cotesia marginiventris*). The absolute configuration at position 17 in volicitin (**4**) has not yet been determined.

jasmonic acid derivatives appear to play an important role. Interestingly, in many plant species *N*-jasmonoyl amino acids ("amino acid conjugates" of jasmonic acid) act as highly active phytohormones.^[7d] Since jasmonic acid is produced from linolenic acid, Alborn et al. proposed that an elicitor such as volicitin (that is, an octadecatrienoate conjugated to an amino acid) may be involved with the octadecanoic pathway in the herbivore-damaged corn plant.^[10]

Although defensive reactions of plants appear to be induced by jasmonic acid derivatives, jasmonates may not generally represent the systemic signal that travels through the plant and induces defense reactions in its undamaged parts.^[13] Interestingly, in one of the most extensively investigated defense mechanisms, the systemic response of tomato plants to herbivore attack, a polypeptide factor was established as the systemic signal (Scheme 3 A).^[2, 14]



Scheme 3. A: Defense signaling in tomatoes in response to wounding (simplified).^[2, 14] B: Analogies in the defense signaling systems of animals.

Tomato plants (*Lycopersicon esculentum*) respond to wounding with a systemic production of proteinase inhibitor proteins (PINs), which interfere with the digestive systems of the attacking herbivores, reducing the availability of essential amino acids and retarding the growth and development of the herbivores.^[2] In this case, oligosaccharides from the plant cell

walls act as primary elicitors. However, these oligosaccharides can induce the production of PINs only locally at the sites of pathogen attack, and therefore do not represent the systemic signal which induces the defense reaction in other parts of the plant. Finally, Pearce et al. showed that the systemic reaction is induced by a mobile polypeptide made up of 18 amino acids (systemin), which is produced from a precursor with 200 amino acids (prosystemin) at the sites of wounding.^[2b] Systemin travels to distal leaves, where it induces the biosynthesis of jasmonic acid; this then triggers the biosynthesis of PINs. Recently Bowles et al. showed that jasmonic acid activates the PIN genes only in the presence of ethylene.^[15] Whether ethylene is directly induced by the mobile signal systemin is not clear, yet ethylene and jasmonic acid influence each other's level in the plant and together act to regulate PIN gene expression.^[15]

The biochemical mechanisms involved in the activation of jasmonic acid biosynthesis by systemin remain largely unknown. In the model proposed by Ryan et al. systemin activates a lipase in receptor cell membranes, resulting in the release of linolenic acid and thus the production of jasmonic acid and finally the activation of the PIN genes (Scheme 3 A).^[14]

The important role that jasmonates and other intermediates of the octadecanoic pathway play as signal transducers in the defense signaling systems of plants seems to parallel the role of the structurally related prostaglandins, which have key functions in the response of animals to parasitic or pathogenic attack (Scheme 3 B).^[14] While in plants jasmonic acid is produced from linolenic acid by the octadecanoic pathway, in animals important signal transducers such as the prostaglandins are synthesized from arachidonic acid. Plant and animal defense signaling may show even further analogies. The systemic induction of jasmonate biosynthesis in plants by phloem-transported polypeptides such as systemin may correspond to the activation of prostaglandin biosynthesis in animals by the polypeptide cytokine tumor necrosis factor α (TNF- α) transported in blood.^[16] TNF- α triggers the activation of a phospholipase, which releases arachidonic acid from cell membranes. This is analogous to the activation of a lipase in tomatoes by systemin, which leads to the release of linolenic acid. Further investigations of the intracellular biochemical mechanisms including identification of the lipase and the mode of its activation are needed to prove whether these analogies of plant and animal defense signaling are significant.

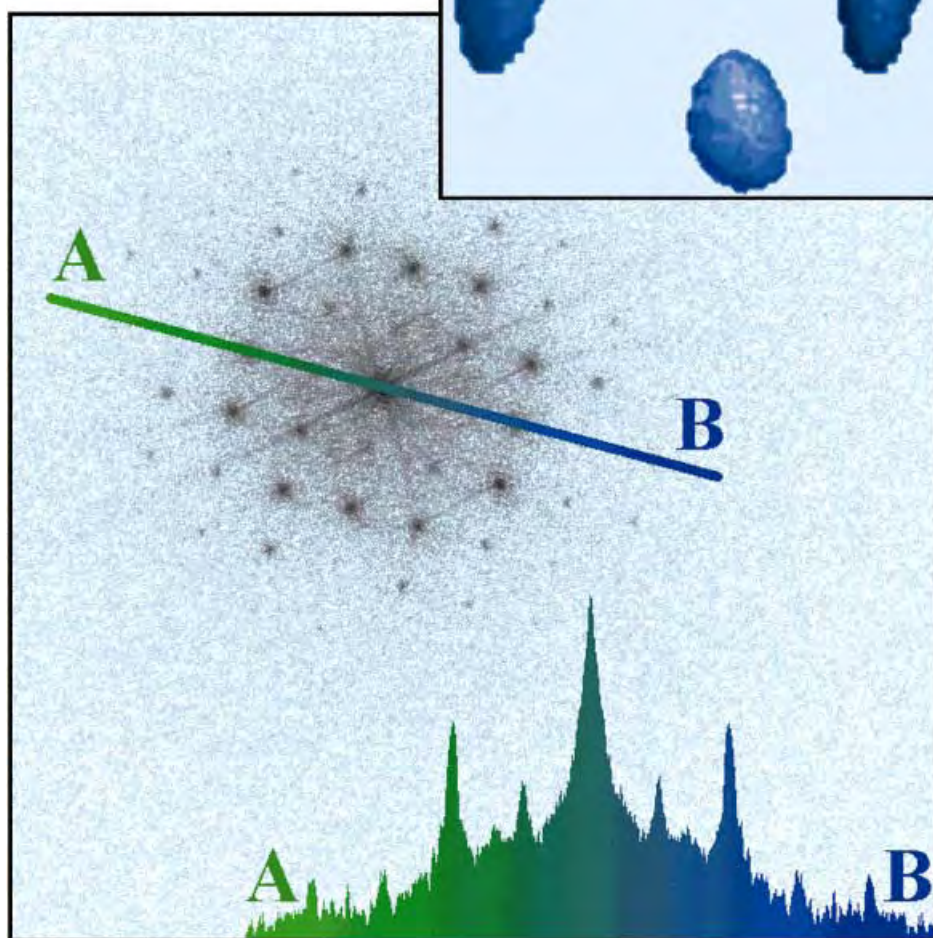
Although the underlying signaling pathways have only partially been revealed, it is apparent that the regulatory systems of chemical defense in plants show a high degree of complexity and sophistication. In addition to the defense strategies discussed here, several other mechanisms of inducible plant defense have been described, including a response known as "systemic-acquired resistance", in which plants can become immune to attack by a wide range of fungal, bacterial, or viral pathogens after surviving an initial infestation.^[3] Moreover, it seems likely that only a small fraction of plant defense mechanisms has so far been discovered.

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The crystal structure of colloidal Pd_3P was determined from high-resolution transmission electron microscopy images. A three-dimensional image of the structure (picture top right, viewed along $[001]$) was calculated by combining data from the Fourier transforms of the images (bottom left).



The positions of both the palladium (blue) and the phosphorus atoms (red) could be determined. More information about this new possibility in structure elucidation is provided by Bovin et al. on the following pages.

The First Structure Determination of Nanosized Colloidal Particles of Pd₃P by High-Resolution Electron Microscopy**

Anna Carlsson, Takeo Oku, Jan-Olov Bovin,*
Reine Wallenberg, Jan-Olle Malm, Günter Schmid, and
Thomas Kubicki

The determination of the crystal structures of materials whose particle size is intermediate between those of clusters and colloidal particles is important, since their chemical and physical properties are structure-dependent. Nanosized crystalline particles are used in many important areas, such as catalysis, vapor deposition of metals, photoelectronics, solar cells, and powder metallurgy. Future developments in the fields of lasers, magnetic disks, photocells, and quantum devices will exploit the quantized electron energy levels of clusters. Single crystal X-ray diffraction, which is the most common technique for structure determination, is of very limited applicability for collecting data from nanosized crystalline particles. A combination of high-resolution transmission electron microscopy (HRTEM) images, recorded with the electron beam along different crystallographic directions, and selected-area electron diffraction (SAED) data is more useful for structure determination of very small crystals. Recent developments in recording images with a linear gray scale, by using slow-scan CCD cameras (CCD = charge-coupled device), allow quantitative evaluation of micrographs. Many previous structure determinations from HRTEM images used data that contained information on two dimensions and were recorded along one short axis of the unit cell.^[1,2] The atomic positions along the short axis were deduced from geometrical and chemical considerations. A full three-dimensional reconstruction that combines HRTEM images from several crystallographic directions is preferable.^[3] Here we show how HRTEM images were used for the first time to determine the positions of the palladium and phosphorus atoms in the crystal structure of colloidal Pd₃P particles with a size range of 15–20 nm.

The solid-state structure of Pd₃P has been determined by X-ray diffraction.^[5] The compound crystallizes in the space group *Pnma* ($a = 0.5980$, $b = 0.7440$, $c = 0.5164$ nm) and has the same structural type as cementite Fe₃C^[6] and Pd₃B.^[7] From hundreds of HRTEM images, 23 that were recorded parallel to crystallographic directions with low indices and exhibited high resolution were selected and subjected to image processing. Image simulations showed that multiple diffraction in these palladium-containing particles starts to affect the relative amplitudes of the reflections at a crystal thickness

exceeding 5–7 nm.^[8] In our case we assumed that the particles were approximately spherical and that only close to the edge of the crystal would the crystal thickness lie below this range. Therefore, the particle core was excluded from the image-processing procedure by masking. The resulting images resemble the perspective view of a pitted olive; two examples are shown in Figure 1. For image processing, 23 images from

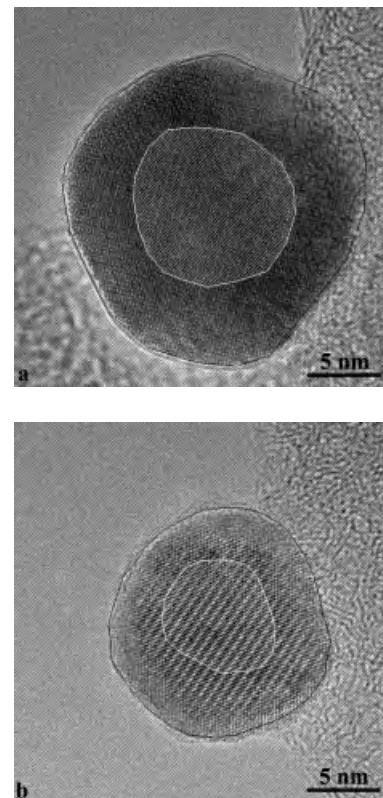


Figure 1. HRTEM images of two colloidal particles, recorded with the electron beam parallel to [010] (a) and [011] (b). The central part of the particles is masked out to avoid multiple-scattering effects in image processing.

17 particles, which were recorded with the electron beam parallel to the directions [100], [010], [110], [011], and [113], were selected. Image processing was performed with the Semper software of the company Synoptics. Each image was Fourier transformed (see Figure 2) and corrected for the effect of the contrast transfer function (CTF) of the objective lens. The focus of the microscope was estimated from the Fourier transform of amorphous material present on the surface of the particles. A full correction was performed with a Wiener filter.^[9] Images of several particles and images recorded at different foci showed identical measured phases after focus correction (0 or π , since the structure is centrosymmetric). Amplitudes and phases with a signal-to-noise ratio greater than or equal to 3 were extracted from the focus-corrected Fourier transforms. The variation in amplitudes between different images of the same direction was typically around 30%. The origin was shifted to the correct phase origin of the projection, and the symmetry of the projection was imposed on the amplitudes and phases. The symmetry was chosen in accordance with the space group *Pnma* of the

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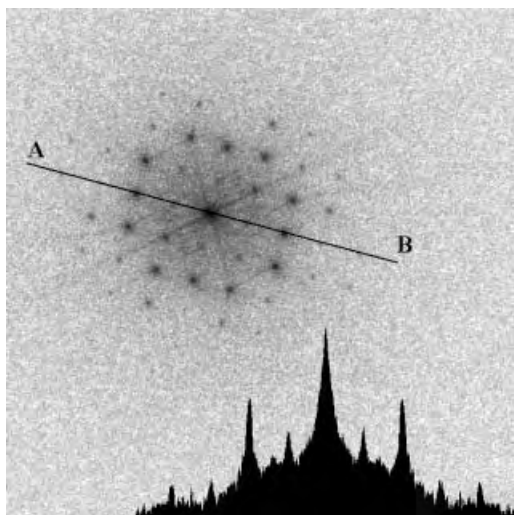


Figure 2. Fourier transform of the HRTEM image of a particle recorded along [010]. A line scan (along A–B) is shown bottom right.

bulk phase of Pd_3P , which also agreed with the lattice parameters and symmetry of the images, as determined by measuring the phase differences after imposition of the symmetry. The amplitudes and phases obtained from several images and directions were scaled together and combined. Thus from 26 unique reflections, 17 with a resolution of 0.17 nm were obtained (Table 1). The three-dimensional

Table 1. Structure factors used in the inverse Fourier transform.

h	k	l	$F/10^5$
0	0	2	2.49
0	1	1	–0.221
0	2	2	1.57
1	0	1	0.450
1	0	2	–3.69
1	1	1	0.160
1	1	2	–1.65
1	2	1	–0.136
1	2	2	–1.87
2	0	0	–1.14
2	0	1	–3.02
2	0	2	–1.36
2	1	1	–3.00
2	2	0	0.959
2	2	1	0.777
3	0	1	–3.90
3	1	1	0.750

crystal potential (structure) was finally calculated by an inverse Fourier transform. The positions of the palladium and phosphorus atoms were directly determined from the positions of the peaks in the three-dimensional image (Figure 3).

The palladium atoms are located in the positions ($x=0.04$, $y=0.25$, $z=0.88$) and ($x=0.21$, $y=0.04$, $z=0.35$) and are comparable to the palladium atom positions in the X-ray structure ($x=0.03$, $y=0.25$, $z=0.87$) and ($x=0.18$, $y=0.06$, $z=0.34$).^[5] Note, however, that the atomic positions in a small particle are not necessarily the same as in the bulk structure. The deviations between the positions determined by X-ray

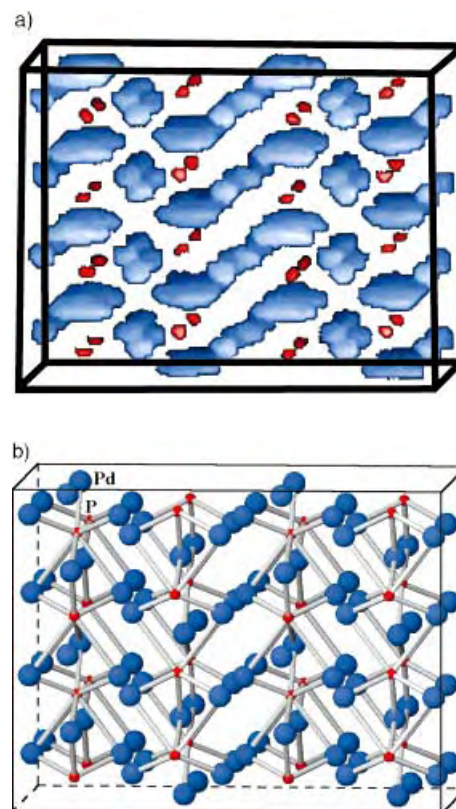


Figure 3. Three-dimensional depictions of the structure of Pd_3P . a) Calculated by inverse Fourier transform. b) Structural model calculated from Figure 3a.

diffraction and those obtained by electron microscopy are 0.017 nm and 0.027 nm. The P atom is located in center of the triply capped trigonal prism of Pd atoms and has the coordinates $x=0.84$, $y=0.25$, $z=0.35$. In the X-ray crystal structure, the P atom occupies the position $x=0.88$, $y=0.25$, $z=0.46$. The P centers cannot be as precisely localized as the Pd centers, because of the relatively low electron-scattering power of phosphorus. The difference in the P positions of the two structures is 0.060 nm. The Pd–P distances in the triply capped trigonal prism lie between 0.203 and 0.299 nm (0.231–0.314 nm in the structure determined by X-ray diffraction). The Pd–Pd distances within the trigonal prism lie in the range 0.306–0.331 nm; hence, the trigonal prism in the colloidal particles is more regular than that in the crystals (Pd–Pd 0.278–0.322 nm). The regular polyhedron and the chemically reasonable bond lengths further support this structure determination. Attempts were made to repeat the determination without masking out the core of the particles, but due to severe multiple scattering, no clear peaks were found in the inverse Fourier transform.

Experimental Section

The compound $\text{Pd}_4\text{B}_6\text{Cl}(\text{PBu}_3)_4$ ^[4] was used as the precursor for the colloidal particles and was heated under vacuum on an activated-carbon support (ca. 2 wt % Pd) to temperatures between 350 and 950 °C. The palladium clusters, which had an initial size of 2 nm, coalesced and reacted when the temperature was increased. At 850 °C formation of carbon nanocapsules was observed. The size distribution of the particles subjected to higher temperatures was broad, but the majority of the particles were in the size

range of 10–30 nm. Nanoprobe EDXS and EELS analysis revealed a composition of Pd₃P for most of the particles. Above 500°C the initial 2 nm clusters reacted only with the phosphorus atoms of the ligand shell, since neither boron nor carbon could be detected in the larger particles. The samples containing the palladium phosphide colloids were supported on lacy carbon film on a copper grid and investigated in a JEM-4000EX electron microscope, which was operated at 400 kV and a structural resolution of about 0.16 nm ($C_s = 1.0$, $C_c = 2.5$ mm, spread of focus about 60 Å, and semiconvergence angle 0.50 mrad). The crystal structure images were recorded at magnification of about 300 000 × (3.4 pixels per 1.7 Å) with a slow-scan CCD camera (Gatan 694). Two particles imaged along different directions are shown in Figure 1. All images were recorded in the linear range of the CCD camera (0–12 000 gray levels). The particles are too small to be oriented by stage tilting when the microscope is in diffraction mode, so correctly aligned particles must be sought among randomly oriented particles.

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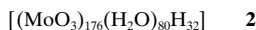
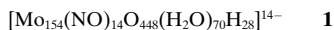
Formation of a Ring-Shaped Reduced “Metal Oxide” with the Simple Composition $[(\text{MoO}_3)_{176}(\text{H}_2\text{O})_{80}\text{H}_{32}]^{14-}$

Achim Müller,* Erich Krickemeyer, Hartmut Bögge, Marc Schmidtman, Christian Beugholt, Paul Kögerler, and Canzhong Lu

Dedicated to Professor Heribert Offermanns on the occasion of his 60th birthday

Two years ago, we reported on the ring-shaped polyoxometalate ion **1**.^[1a–c] We have now succeeded in obtaining crystals which contain an even larger ring-shaped cluster formed by a conservative self-organization process. Remark-

ably, it represents a simple reduced, protonated, and hydrated molecular metal oxide, built up from 176 molybdenum and 608 oxygen atoms.^[2] Based upon the number of metal atoms, it seems to be the largest discrete inorganic species characterized by single-crystal X-ray structure analysis.^[3] Its large cavity (diameter 2.3 nm) opens new perspectives for host–guest and supramolecular chemistry.



After acidifying an aqueous solution of lithium molybdate (about 1M) followed by reduction with tin(II) chloride at room temperature, dark blue rhombic-bipyramidal crystals (crystal class *mmm*) of a compound containing cluster **2** precipitate together with chemically identical amorphous material from the dark blue reaction mixture. The blue compound contains cluster **2** together with additional, partly disordered lattice components (crystal water as well as small amounts of Li⁺ and Cl[−] ions; see Experimental Section). The compound was characterized by elemental analyses, cerimetric titration of the formal number of Mo^V centers, thermogravimetric analysis (to determine the crystal water content), bond valence sum calculations (to determine the number and position of protonated oxygen atoms as well as the formal number of Mo^V centers^[4]), spectroscopic methods (IR, Raman, UV/Vis and NIR spectroscopy), EHMO calculations, and single-crystal X-ray structure analysis.^[5]

Remarkably, **2** shows the stoichiometry of a protonated reduced molecular molybdenum trioxide with coordinated H₂O ligands. Despite the significantly different properties of **1** and **2**, a structural comparison shows striking similarities. According to a related building-block scheme for the cluster types $[\{\text{Mo}_2\}\{\text{Mo}_8\}\{\text{Mo}_1\}]_n \equiv [\{\text{Mo}_2^{\text{VI}}\text{O}_5(\text{H}_2\text{O})_2\}\{\text{Mo}_8^{\text{VI/V}}\text{XO}_{25}(\text{OH})_2(\text{H}_2\text{O})_3\text{Mo}^{\text{VI/V}}\}]_n$, **1** can be formulated as a tetradecamer (with $n = 14$ and $\text{X} = \text{NO}$) and **2** as a hexadecamer (with $n = 16$ and $\text{X} = \text{O}$; Figure 1).^[1b, 6–8] This confirms that the {Mo₈} units, connected by building units of the type {Mo₁} and {Mo₂} in **1** and **2**, represent a special type of building block that occurs in several polyoxometalate structures.^[1a,b, 6–8] A more detailed structural comparison of both systems shows that the inner regions of the rings, which are mainly built up by {Mo₂} units, are less tightly bound in **1**. This causes the rings to be slightly domed in the corresponding regions and can—upon decreasing the negative charge of the ring—easily lead to a release of {Mo₂}²⁺ groups with further consequences for the reactivity in the case of **1**.^[7, 8] Further unusual condensation reactions in the case of **2** can occur at the relatively tightly bound {Mo₂} groups result in the formation of polyoxometalate fragments in the inner regions of the rings. These condensations lead to the formation of structures with a kind of “hubcap” caused by a novel type of molecular growth. In general however, the growth of polyoxometalates by condensation is only observed if the overall ion charge increases with a concomitant, approximately constant charge per molybdenum center. This ensures the solubility of the clusters and prevents not only the molecular units from forming the oxidic solid (showing translational

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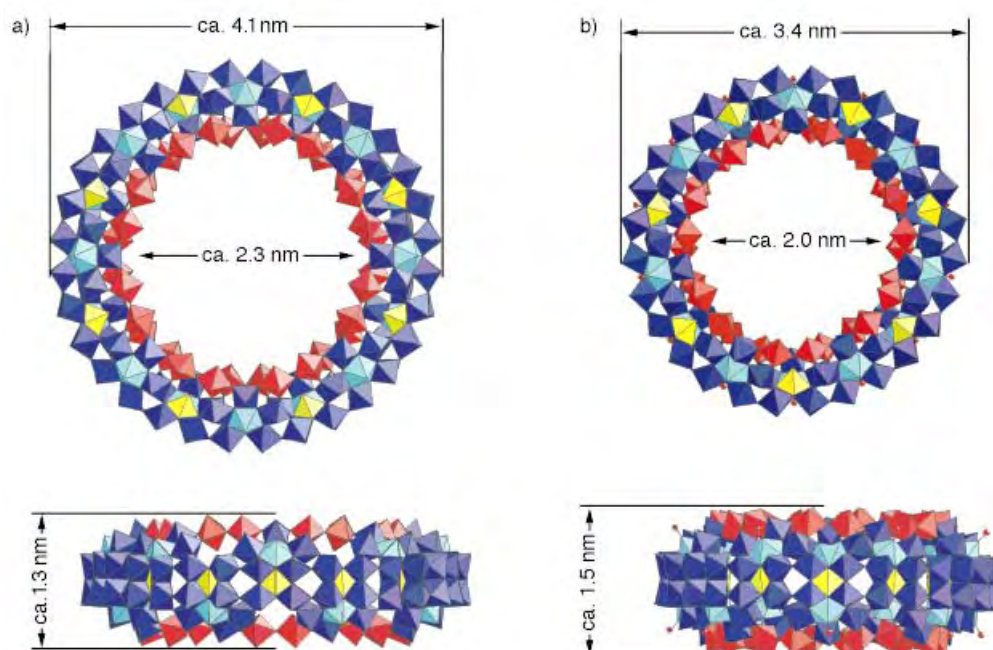


Figure 1. a) Polyhedral representation of the structure of **2** (view along the approximate C_8 axis (top) and perpendicular to it (bottom)). Compound **2** consists of sixteen $\{Mo_8\}$ units (blue, with a central pentagonal MoO_7 bipyramid in light blue), which are linked by the sixteen units of the $\{Mo_2\}$ type (red) as well as sixteen $\{Mo_1\}$ units located at the equatorial ring plane (yellow). b) Polyhedral representation of **1** (top: view from the top; bottom: side view) to show the structural similarities and differences: The ring of **2** is distinctly less thick than that in **1** because of the smaller ring tension and looser bonding in the flexible $\{Mo_2\}$ groups.

invariance) but also hydrolysis to smaller species or uncontrolled linking. In the special case considered here, however, the solubility in protic solvents is achieved by the extremely hydrophilic surface of the cluster, arising from the presence of numerous water and hydroxyl ligands.

A comparison of the electronic structures of **1** and **2** calculated by EHMO methods^[9] shows a clear ordering of the molybdenum-centered molecular orbitals in the HOMO region for both ring systems. A first set of 14 (for **1**) or 16 (for **2**) molecular orbitals, which contain mainly (around 90 %) 4d orbitals of the 56 (or 64) molybdenum atoms located on the peripheral near equatorial positions^[8] (mainly, in agreement with the results of the bond valence sum calculations of the molybdenum atoms with corresponding values between 5 and 6^[4]), is followed by an energetically separated second set of molecular orbitals. This second set of orbitals contains contributions of increasing energy stemming from 4d orbitals of molybdenum atoms located in the central cluster regions. The energetic structuring of the considered molecular orbitals is strongly dependent on the protonation of the species (that is, the number of hydroxyl groups). With respect to the given degree of protonation (28 OH and 70 H_2O in **1** or 32 OH and 80 H_2O ligands in **2**) the EHMO calculation favors a charge of 14⁻ for **1** and zero for cluster **2**. These charges correspond to 28 or 32 Mo^V centers, respectively. Thus in both cases the first set of mainly molybdenum-centered MOs is fully occupied resulting in a distinct HOMO–LUMO separation. The exchange of the $\{MoNO\}^{3+}$ (in **1**) by $\{MoO\}^{4+}$ groups (in **2**) in the $\{Mo_8\}$ units scarcely influences the predominantly Mo^V -centered frontier orbitals, as expected,

but influences considerably the ion's charge with substantial consequences (see above as well as references [7, 8, 10]). Our calculation shows that the $\{MoNO\}^{3+}$ -centered molecular orbitals, which due to their energy do not interact with other molecular orbitals, are concentrated around an energy level of about -12 eV.

A general problem arises with the characterization of these types of compound.^[12] Since the spectroscopic data (for example, vibrational spectra^[13, 14]) and the analytical data do not differ significantly, extremely large clusters can in principle often only be distinguished from similar large clusters of the same type (but with a different number of building blocks) by single-crystal X-ray structure analyses or, as in

the present case, by the crystal shape. In an earlier article about molybdenum blue, this problem was addressed as follows:^[14a] “Principally, also the presence of different and larger ring-shaped species with the general composition $\{(MoO_3)_m(H_2O)_nH_p\}^{x-}$ cannot be totally excluded, neither by X-ray powder diffraction nor by IR and Raman spectroscopy alone.” In this context, it is interesting that the new cluster **2**, which belongs to the class of the soluble molybdenum-blue compounds, indeed possesses the composition $\{(MoO_3)_m(H_2O)_nH_p\}$ (here with $m = 176$, $n = 80$, $p = 32$), which has been predicted to be characteristic for this type of compound.^[14a, 17]

If the intention is to create ever larger species, the fundamental question is whether the present type of cluster synthesis in polyoxometalate chemistry leads to a dead end. This question is difficult to answer. Under normal preparative conditions, extremely large clusters of the type in question according to our present knowledge, preferentially form amorphous materials that cannot be characterized unambiguously (see also reference [15]). Though the relationship between certain reaction conditions and the size of emerging clusters is not yet understood in detail, the requirements for the formation of extremely large systems like **2** are observed to be very low pH values and high molybdate concentrations. In this context, the influence of the cluster charge (or the degree of reduction) on the growth process, for instance due to a successive exchange of $\{MoNO\}^{3+}$ by $\{MoO\}^{4+}$ groups, represents an interesting aspect for further research. Our aim for the future is to concentrate on the simplification of the syntheses in order to get uniform crystalline material in high yields and reasonable time.

Experimental Section

2 · ca. 400 H₂O · ca. 20 Li⁺ · ca. 20 Cl⁻: Li₂MoO₄ (4.50 g, 25.9 mmol; Johnson Matthey) was dissolved in H₂O (25 mL) as far as possible, and HCl (14.8 mL of a 10% solution) was then added to the stirred reaction mixture, which nearly led to the complete dissolution of the lithium molybdate. Finely ground SnCl₂ · 2H₂O (p.a.; 0.61 g, 2.7 mmol, an amount theoretically sufficient for the reduction of 20% of the Mo^{VI} to Mo^V centers) was then added in small portions while stirring, whereby a dark blue precipitate formed. The reaction mixture was stored at 20°C in a wide-necked 100 mL Erlenmeyer-flask covered by a watch glass without further disturbance (to facilitate the crystallization) for about six weeks. Dark blue rhombic-bipyramidal crystals of the above-mentioned composition precipitated. In addition to less crystalline or amorphous material (see ref. [15]) minor amounts of dark blue pinacoidal^[16] and rhombic plates^[16] were formed subsequently, due to the lower molybdate concentrations in the reaction medium as material precipitates. Furthermore, a small amount of a colorless precipitate of a salt containing the [Mo₃₆O₁₁₂(H₂O)₁₆]⁸⁻ anion was formed. The rhombic-bipyramidal crystals were separated mechanically in the mother liquor, washed several times with the filtered mother liquor and dried on filter paper in air (yield: ca. 0.2–0.3 g corresponding to 4–6% relative to the initial molybdate quantity). The mechanical separation is necessary as the rhombic-bipyramidal crystals, which lose some of their crystal water upon storage in air, do not differ sufficiently in solubility from the pinacoidal and rhombic plates.^[17]

Characterization of **2** · ca. 400 H₂O · ca. 20 Li⁺ · ca. 20 Cl⁻: Cerimetric titration yields 32 ± 2 Mo^V per formula unit. Elemental analyses: ca. 0.4% Li and ca. 2.0% Cl.^[12] Thermogravimetry: ca. 20% weight loss or ca. 400 H₂O. Some characteristic bands in IR (KBr pellet, prepared under argon): $\tilde{\nu}$ [cm⁻¹]: 1616 (m, δ (H₂O)), ca. 991(sh) 972(m), 911(w–m) (ν (Mo=O)), ca. 820(sh) 742(s), ca. 675(sh) 632(s), 558(s). Solid-state Vis/NIR spectrum (KBr pellet, in transmission): λ [nm]: ca. 700 and ca. 1000 due to intervalence charge-transfer transitions.

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- [3] Cf. K. Wassermann, M. H. Dickman, M. T. Pope, *Angew. Chem.* **1997**, *109*, 1513–1516; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1445–1448.
- [4] I. D. Brown in *Structure and Bonding in Crystals, Vol. II* (Ed.: M. O'Keeffe, A. Navrotsky), Academic Press, New York, **1981**, pp. 1–30.
- [5] Space group *Cmcm*; $a = 53.317(4)$, $b = 31.146(2)$, $c = 66.830(4)$ Å, $V = 110979(12)$ Å³; $Z = 4$; solved with direct methods, $R = 0.104$ for 22845 independent reflections ($F_0 > 4\sigma(F_0)$); (Siemens)AXS-Smart diffractometer (173240 reflections obtained at –100°C of 1271 records, which cover 0.3° in ω each, $2\theta_{\max} = 45^\circ$). The crystals of **2** were taken directly out of the mother liquor and measured immediately to prevent weathering through loss of crystal water. The measurements of individual crystals always led to the same result. The structure was solved with the programme SHELXS-96 and refined with the programme SHELXL-93 (G. M. Sheldrick, University of Göttingen, **1996** and **1993**). Further details of the structure investigations 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 number CSD-408508.
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- [7] The formulation based on the building blocks {Mo₂}, {Mo₈} and {Mo₁} is useful for the following reasons: In the ring of **1**, defects in the {Mo₂}²⁺ units can easily be produced, for example, by a formal exchange of {MoNO}³⁺ → {MoO}⁴⁺. The resulting decrease of the cluster charge supports the repulsion of the {Mo₂}²⁺ units. The defects obviously favor a linking of the rings to chains^[8a] and layer structures^[8b] but generally speaking cause a change in reactivity.
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- [9] The EHMO calculations are based on the positions of the atoms obtained from the X-ray structure analysis. Standard atomic parameters of the program were used (G. A. Landrum, YAeHMOP 2.0: “Yet Another Extended Hückel Molecular Orbital Package”; URL: <http://overlap.chem.cornell.edu/yaehmop>). The positions of the H atoms were obtained on the basis of bond valence sums of the oxygen positions by molecular modeling calculations (generic UFF-plus force-field) using the CERIU 3.2 software (CERIU 3.2, Molecular Simulations, Cambridge **1993**).
- [10] The reduction of aqueous molybdate solutions with hydroxylamine,^[11a] which is important in this context, has been known for about 100 years and has often been described misleadingly in the literature. It leads preferentially to the formation of {MoNO}³⁺ units^[11b] and in general to polynuclear molybdates.^[11c,d] In addition to the formation of the {MoNO}³⁺ group, hydroxylamine can also give rise to the reduction of further molybdenum centers.^[1a] The {MoNO}³⁺ groups can be linked by molybdate fragments^[11d] but also under special conditions by sulfide/polysulfide ions,^[11c] which in both cases results in the formation of polynuclear chalcogenomolybdates. The synthesis and a relatively good characterization of the large, red polyoxomolybdate cluster [Mo₃₆(NO)₄O₁₀₈(H₂O)₁₆]¹²⁻ was most likely carried out already in 1931.^[11e] On the other hand, the structure of the yellow precipitate (an important starting material^[11e]) which is always formed at the initial phase of the reaction between molybdate and hydroxylamine, has not yet been characterized. Obviously, it is a polymolybdate with “(NO)” groups, but containing no (reduced) Mo centers.^[11f] Our investigations show that hydroxylamine is *not* essential for the synthesis of the considered type of ring species. However, the possible substitution steps of the type {MoNO}³⁺ ↔ {MoO}⁴⁺, as pointed out above, can have major consequences for the reaction pathways.^[8]
- [11] a) K. von der Heide, K. A. Hoffmann, *Z. Anorg. Chem.* **1896**, *12*, 279–292; V. Kohlschlüter, K. A. Hoffmann, *Justus Liebigs Ann. Chem.* **1898**, *307*, 323; Übersicht: E. Lassner, *J. Less Common. Met.* **1968**, *15*, 143–150; b) see, for example, A. Müller, S. Sarkar, *Angew. Chem.* **1977**, *89*, 189–190; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 183–184; *ibid.* **1977**, *89*, 479–480 or **1977**, *16*, 468–469; A. Müller, W. Eltzner, S. Sarkar, H. Bögge, P. J. Aymonino, N. Mohan, U. Seyer, P. Subramanian, *Z. Anorg. Allg. Chem.* **1983**, *503*, 22–36, and references therein; c) see, for example, A. Müller, W. Eltzner, H. Bögge, S. Sarkar, *Angew. Chem.* **1982**, *94*, 555–556; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 535–536; A. Müller, W. Eltzner, N. Mohan, *ibid.* **1979**, *91*, 158–159 or **1979**, *18*, 168–169; d) P. Gouzerh, Y. Jeannin, A. Proust, F. Robert, *ibid.* **1989**, *101*, 1377–1378 and **1989**, *28*, 1363–1364; S. Zhang, Y. Wei, Q. Yu, M. Shao, Y. Tang, *J. Am. Chem. Soc.* **1997**, *119*, 6440–6441, and references therein; e) W. F. Jakob, B. Jezowska, *Roczniki. Chem.* **1931**, *11*, 229–253; f) K. Wieghardt, G. Backes-Dahmann, W. Swiridoff, J. Weiss, *Inorg. Chem.* **1983**, *22*, 1221–1224; A. Müller, W. Eltzner, unpublished results.
- [12] The determination of the exact formula and especially the charge of extremely large mixed valence clusters by single-crystal X-ray

structure analysis presents a general problem, in particular if further charged lattice components of the relevant compound (small amounts of cations as well as anions located in cavities and channels) and large amounts of crystal water molecules cannot be clearly located, for instance due to disorder. In these cases, the formula including the charge can in principle only be determined if analytical data and the (formal) charges of all ingredients are taken into account. The analytical data, however, cannot be very accurate as firstly, the concentration of the mentioned charged lattice components is generally very small (but not the number of ions in the formula unit) and secondly, the large crystal water content varies to some extent. The isolated compound with cluster **1**, for instance, shows in addition to NH_4^+ ions, an "uptake" of small amounts of Na^+ and Cl^- ions which complicate the determination of the cluster charge by elemental analysis as the difference in the number of cations and anions is of relevance here. The real charge of **1** is smaller as mentioned earlier, namely 14 – which is in agreement with the average BVS (bond valence sum) values of 5.60 for the 70 (**1**) and 80 (**2**) molybdenum centers located in the peripheral incomplete double cubes, which are built up from four Mo atoms of the $\{\text{Mo}_8\}$ units as well as one $\{\text{Mo}_1\}$ -type center and six oxygen atoms. Each of the double-cube compartments contains two 4d electrons. Remarkably, the absolute divergence of the BVS values for the 56 (**1**) or 64 (**2**) outer peripheral ring positions from the $\{\text{Mo}_8\}$ units is only ± 0.05 and for the 14 (**1**) or 16 (**2**) equatorial positions ($\{\text{Mo}_1\}$ -type centers) only ± 0.10 for six different cluster structures. This corresponds (formally) to the 28 (for **1**) and 32 (for **2**) Mo^V centers and is (for the $\{\text{Mo}_8\}$ part) also in agreement with the conclusions from the EHMO calculations and the redox titrations. A related problem in charge determination was also stressed by Pope and coworkers in an important publication,^[3] though the determination of the charge of their particular cluster anion—as was also pointed out—is not so difficult. This is due to the fact that the oxidation states of the metal centers are clearly known.

- [13] The IR spectra of large clusters (of the type $\{\text{Mo}_{36}\}$,^[6] $\{\text{Mo}_{57}\}$,^[6] and partly $\{\text{Mo}_{154}\}$ ^[1a-c]) can be modeled by superposition of (weakly coupled) characteristic vibrations of different $\{\text{Mo}_m\text{O}\}$ fragments.^[14b] This simplifies of course the proof of functional groups on the one hand, but on the other complicates the differentiation of species with different numbers of these fragments, as in the case of **1** and **2**.
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- [16] The pinacoidal plates contain in the crystal lattice the smaller tetradecameric ring-type clusters corresponding to **1** with a 1:1 ratio of rings of composition $[\{\text{Mo}_{21}\}_{14}\{\text{Mo}_8\}_{14}\{\text{Mo}_1\}_{14}]$ and $[\{\text{Mo}_{21}\}_{13}\{\text{Mo}_8\}_{14}\{\text{Mo}_1\}_{14}]$; the latter have a defect. Structural data: space group $\text{P}\bar{1}$; $a = 31.007(2)$, $b = 32.818(2)$, $c = 47.325(3)$ Å; $\alpha = 90.59(1)$, $\beta = 90.11(1)$, $\gamma = 96.70(1)^\circ$; $V = 47826$ Å³; $Z = 2$; $R = 0.110$ for 57819 independent reflections ($F_o > 4\sigma(F_o)$). The rhombic plates contain in the crystal lattice the larger $\{\text{Mo}_{176}\}$ -type rings as in **2** but with different packing and with a substantially higher amount of crystal water molecules (ca. 600 H_2O). Structural data: space group $\text{P}2_1/\text{n}$; $a = 29.205(2)$, $b = 64.040(4)$, $c = 74.622(3)$ Å; $\beta = 99.81(1)$; $V = 137522$ Å³; $Z = 4$; $R = 0.192$ for 63952 independent reflections ($F_o > 4\sigma(F_o)$).
- [17] Note added in proof: The resulting product mixture obtained here is still relatively complex, but this must be put into perspective against the background that generations of chemists have attempted in vain to isolate crystals from solutions of molybdenum blue type species. The investigation of these products is also complicated due to the fact that the lattice energy is very low resulting in a series of isolated compounds with different packing of the clusters. We have succeeded in developing synthetic methods in which crystalline substances can be isolated in a few days without amorphous coprecipitation. This synthesis refers to the mentioned cluster of the type $\{\text{Mo}_{154}\}$ ($R = 0.057!$) and $\{\text{Mo}_{176}\}$, which have MeOH ligands as well as H_2O ligands. (A. Müller, M. J. Koop, H. Bögge, M. Schmidtman, *Chem. Commun.* submitted; A. Müller, E. Krickemeyer, M. J. Koop, S. Q. N. Shah, H. Bögge, M. Schmidtman, *Z. Anorg. Allg. Chem.* submitted.)

Expression of Chirality by Achiral Coadsorbed Molecules in Chiral Monolayers Observed by STM**

Steven De Feyter, Petrus C. M. Grim, Markus Rücker, Peter Vanoppen, Christian Meiners, Michel Sieffert, Suresh Valiyaveetil, Klaus Müllen, and Frans C. De Schryver*

Pasteur discovered almost 150 years ago the three-dimensional separation of the sodium ammonium salt of racemic tartaric acid in enantiomorphous crystals.^[1] Since then, chemists have been intrigued by the concept of chirality. The development of the scanning probe techniques, such as scanning tunneling microscopy (STM)^[2] and atomic force microscopy (AFM),^[3] made it possible to locally probe monolayers. Only a few reports have dealt with the direct observation of supramolecular chirality in two dimensions by use of scanning probe techniques. Spontaneous breaking of chiral symmetry by achiral molecules in a Langmuir–Blodgett (LB) film was determined by Viswanathan et al. with AFM.^[4] Enantiomorphous monolayer domains from achiral liquid crystalline molecules,^[5] achiral purine molecules,^[6] and didodecylbenzene molecules^[7] on graphite have been observed by STM. Eckardt et al. reported the separation of chiral phases in monolayer crystals of racemic amphiphiles in LB films by AFM.^[8] The direct observation of enantiomorphous monolayer crystals from liquid crystalline enantiomers and the formation of coexisting enantiomorphous domains from a racemate by STM have been described by Stevens et al.^[9] Spontaneous resolution in two dimensions was recently demonstrated by grazing-angle X-ray diffraction.^[10]

We have used small chiral organic molecules with hydrogen-bonding potential to self-assemble chiral physisorbed monolayers on a graphite surface. The *S* enantiomer of the chiral isophthalic acid derivative 5-[10-(2-methylbutoxy)-decyloxy]isophthalic acid (ISA, Figure 1A) was dissolved in 1-heptanol, and a small droplet was applied to the freshly cleaved surface of highly oriented pyrolytic graphite (HOPG). Figure 1B shows a STM image of the resulting monomolecular layer of (*S*)-ISA adsorbed to the basal plane of HOPG. The image reveals a closely packed arrangement of molecules on the graphite surface with submolecular resolution. The aromatic isophthalic acid head groups of (*S*)-ISA molecules can clearly be recognized as bright spots. Bright and dark refers to the black/white contrast in the images;

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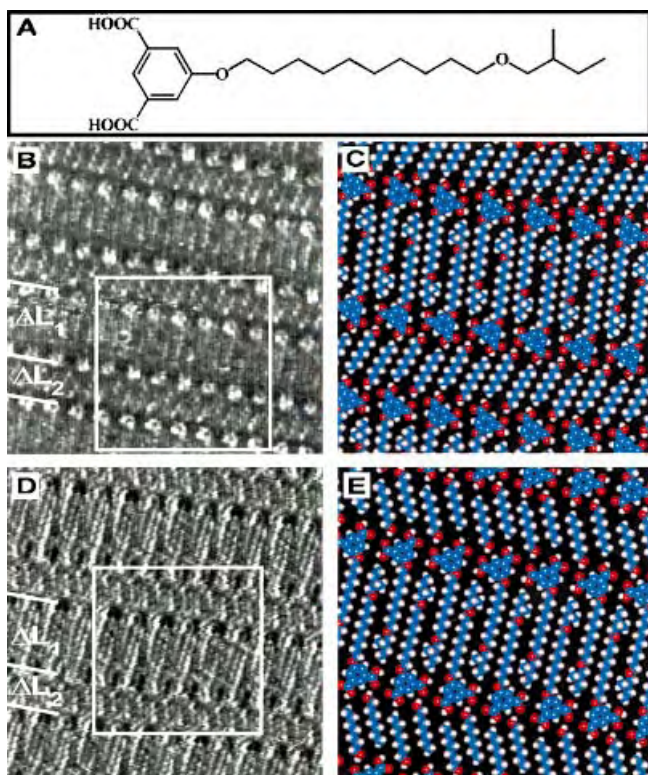


Figure 1. A) Chemical structure of ISA. B) STM image of an ordered monolayer of (*S*)-ISA molecules formed by physisorption at the 1-heptanol/graphite interface; image size: $11.7 \times 11.7 \text{ nm}^2$. ΔL_1 is the width of one lamella of interdigitated (*S*)-ISA molecules. The lamellar axis makes an angle θ of $+3.5 \pm 0.7^\circ$ with the normal to that graphite axis which is in alignment with the alkoxy chains (positive domain). ΔL_2 corresponds to the width of a lamella built up by 1-heptanol molecules. The solvent molecules form an angle φ of $+20 \pm 3^\circ$ with the normal to the lamellar axis. C) Proposed molecular model for the two-dimensional packing of (*S*)-ISA molecules in the area shown in the STM image in B. D) STM image of an ordered monolayer of (*R*)-ISA molecules formed by physisorption at the 1-heptanol/graphite interface; image size: $11.5 \times 11.5 \text{ nm}^2$. ΔL_1 is the width of one lamella of interdigitated molecules. The lamellar axis makes an angle θ of $-3.8 \pm 0.6^\circ$ with the normal to that graphite axis which is in alignment with the alkoxy chains (negative domain). ΔL_2 corresponds to the width of a lamella built up by 1-heptanol molecules. The solvent molecules form an angle φ of $-18 \pm 3^\circ$ with the normal to the lamellar axis. E) Proposed molecular model for the two-dimensional packing of (*R*)-ISA molecules in the area shown in the STM image in D.

white corresponds to the highest and black to the lowest measured tunneling current. Two different spacings are found between adjacent rows of (*S*)-ISA head groups. The largest spacing ($\Delta L_1 = 30 \pm 1 \text{ \AA}$) corresponds to the dimension of the (*S*)-ISA molecules, and 1-heptanol molecules occupy the smaller space ($\Delta L_2 = 10 \pm 1 \text{ \AA}$) between two rows of (*S*)-ISA head groups. The 1-heptanol molecules are coadsorbed and stabilized by the formation of hydrogen bonds with the (*S*)-ISA head groups. A similar observation was described by Vanoppen et al. for the imaging of achiral alkoxy-substituted isophthalic acid molecules dissolved in solvents such as 1-octanol or 1-undecanol.^[11] Grim et al. also observed this codeposition of solvent molecules for a diacetylene-containing isophthalic acid derivative,^[12] which then can be photopolymerized on the graphite surface.

To further analyze the structure of the monomolecular adlayer, a comparison with the underlying graphite surface is

made. Immediately after imaging an adlayer, the graphite surface underneath is visualized by lowering the bias voltage. This analysis indicates that the alkoxy groups are parallel to the graphite substrate and aligned with a graphite axis. The (*S*)-ISA molecules are interdigitated over the full length of the alkoxy groups. The stereogenic centers are not atomically resolved. The lamellar width indicates that the alkoxy chains tend to lie flat on the graphite surface to maximize the adsorption energy. Therefore, we suggest that the methyl group on the stereogenic carbon atom is pointing away from the graphite surface. The coadsorbed solvent molecules are not in alignment with a graphite axis. In this image, the angle φ between the solvent molecules and an imaginary line perpendicular to a row of (*S*)-ISA head groups is $20 \pm 3^\circ$. On the basis of the observed monolayer structure, a model for the molecular arrangement is proposed (Figure 1 C). The intra-lamellar distance between two head groups measures $9.60 \pm 0.05 \text{ \AA}$.

Comparison of the direction of the lamellar axes (any line parallel to a row of (*S*)-ISA head groups) with the underlying graphite substrate shows that the lamellar axis makes an angle θ of $+3.5 \pm 0.7^\circ$ with the normal to that graphite axis which is in alignment with the alkoxy chains. We call these domains positive/negative if a positive/negative^[13] angle θ is observed, irrespective of the orientation of the coadsorbed solvent molecules. In the analysis of the images of the *S* enantiomer, only a positive angle is observed. In the model shown in Figure 2 A a few (*S*)-ISA molecules are presented together with the underlying graphite substrate. The absence of negative domains indicates that, as far as the packing of the (*S*)-ISA lamellae is concerned, the *S* enantiomer has formed an enantiomorphous monolayer.

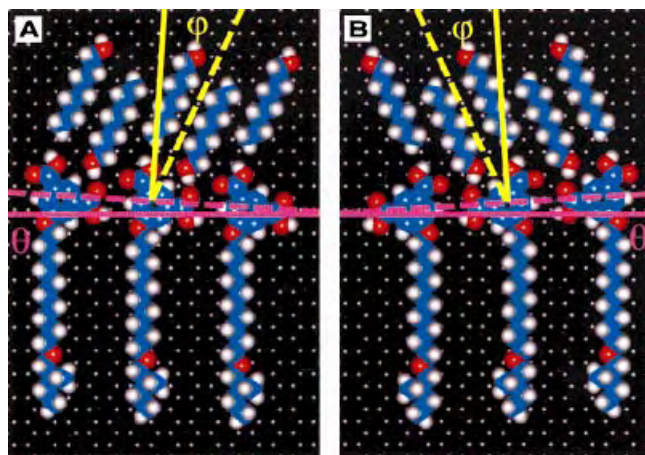


Figure 2. Proposed model for the molecular arrangement in A) a positive domain and B) a negative domain together with the underlying graphite substrate. θ is the angle between the lamellar axis (purple dashed line) and the normal to that graphite axis which is in alignment with the alkoxy chains (purple solid line). φ is the angle between the solvent molecules (yellow dashed line) and the normal to the lamellar axis (yellow solid line).

(*R*)-ISA was also dissolved in 1-heptanol and applied to the graphite surface. Comparison of the monolayer structure with the underlying graphite surface reveals that the domains are negative ($\theta = -3.8 \pm 0.6^\circ$). The STM image of (*R*)-ISA

presented in Figure 1D indicates that the alkoxy chains are interdigitated as for (*S*)-ISA. The intralamellar distance between two head groups is 9.60 ± 0.05 Å. 1-Heptanol molecules are coadsorbed between adjacent lamellae of chiral molecules. The angle φ between the solvent molecules and an imaginary line perpendicular to a row of isophthalic head groups is $-18 \pm 3^\circ$. A proposed model for the monolayer in Figure 1D is shown in Figure 1E. In Figure 2B, a model is presented of a few (*R*)-ISA molecules together with the underlying graphite surface.

Leaving aside the packing of the solvent molecules, the only difference between positive domains (only found for (*S*)-ISA) and negative domains (only found for (*R*)-ISA) is the sign of the angle θ between the lamellar axis and the normal to that graphite axis which is in alignment with the alkoxy chains. The lamellae built up by (*S*)-ISA or (*R*)-ISA molecules form positive or negative domains, respectively, which are enantiomorphous.

As already mentioned, in both positive and negative domains the coadsorbed 1-heptanol molecules are not oriented perpendicular to the lamellar axis of the isophthalic acid molecules. Moreover, the sign of the angle φ between the solvent molecules and the normal to the lamellar axis depends on the domain in which these molecules are coadsorbed. In all the STM images obtained, a positive value for φ is found in the positive domains formed by (*S*)-ISA molecules, and a negative angle is found in the negative domains formed by (*R*)-ISA molecules (presented schematically in Figure 2).^[14] The absolute value of this angle varies from 7 up to 25° . This variation could find its origin in the difference in the relative position of the ISA head groups in two adjacent lamellae between which the solvent molecules are adsorbed, resulting in subtle differences in hydrogen bonding. As the solvent molecules will tend to optimize hydrogen bonding, they will adjust their orientation (angle) to obtain maximum stabilization.

Strictly spoken, positive and negative domains are not completely enantiomorphous, owing to the nonunique value for φ . It is therefore more appropriate to use the expression “quasi-enantiomorphous” in describing this system. However, the connection between the signs of θ and φ makes it possible to unambiguously assign a domain as positive (consisting of *S* enantiomer) or negative (consisting of *R* enantiomer) without referring to the underlying graphite substrate. It is shown for the first time that the orientation of achiral coadsorbed molecules expresses the chirality of the domains.

In addition, STM images of the racemic mixture (*RS*)-ISA are obtained where a positive and a negative domain are observed in the same image (Figure 3). The inset of Figure 3 is a magnification of the domain boundary; the left domain is negative, the right domain positive. The two-dimensional packing of the isophthalic acid molecules within the positive and negative domains is identical to adlayers of (*S*)-ISA and (*R*)-ISA, respectively. This suggests that the racemic mixture forms a physisorbed monolayer composed of chiral, enriched, separated, quasi-enantiomorphous domains.

Control experiments on an achiral isophthalic acid derivative (5-octadecyloxyisophthalic acid) dissolved in 1-octanol showed that both positive and negative domains are formed.

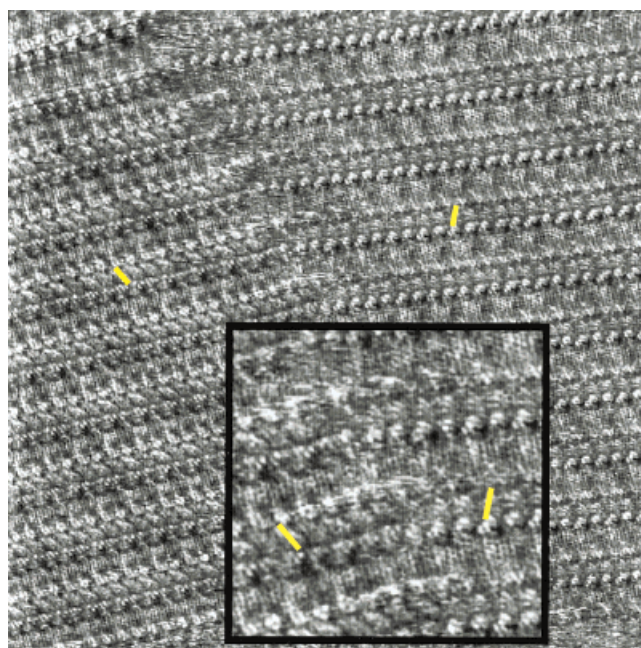


Figure 3. STM image of an ordered monolayer formed after applying a solution of the racemate (*RS*)-ISA on the graphite substrate; image size: 37×37 nm². The inset shows an enlargement of a part of the domain boundary (13.7×13.7 nm²). The left side of the image is a negative domain, and the right side a positive domain. The orientation of the coadsorbed solvent molecules, indicated by yellow lines, reflects the chirality of the respective domains.

The alcohol molecules did not reflect the chirality of the domains as both positive and negative values for φ are found, even within the same domain (image not shown). 5-[10-(Butoxy)decyloxy]isophthalic acid, the achiral analogue of the compound studied, is not an adequate reference compound as different monolayer structures were observed (image not shown).^[15]

It can not only be concluded that molecular chirality is transferred to a chiral supramolecular packing mode, but also that achiral codeposited solvent molecules express the chirality of the monolayer.

Experimental Section

(*R*)-, (*S*)-, and (*RS*)-ISA were prepared from the corresponding enantiomers or the racemate of 2-methyl-1-butanol. (*R*)-2-Methyl-1-butanol was obtained from (*R*)-2-methyl-1-butanoic acid^[16] (*R*:*S* $\approx$ 92:8, determined by GC and the optical rotation) under retention of configuration as described in reference [17]. (*S*)-2-Methyl-1-butanol was purchased from Fluka (*S*:*R* $\approx$ 99:1, determined by GC). The enantiomeric ratios of (*R*)- and (*S*)-ISA were assumed to be identical with the ones of the corresponding starting alcohols, since no racemization could be detected in the course of the synthesis. Detailed preparation procedures and spectroscopic data will be reported elsewhere.

Prior to imaging, the compound was dissolved in 1-heptanol (Aldrich, 99%) at a concentration of approximately 5 mg mL⁻¹. One drop of this solution was then applied to the basal plane of a piece of HOPG (grade ZYB, Advanced Ceramics Inc., Cleveland, OH). The tip was immersed in the solution and brought to the liquid/solid interface. The STM images were acquired in the variable-current mode (constant height) under ambient conditions. STM images obtained at low bias voltages reliably revealed the atomic structure of HOPG, providing an internal calibration standard for the monolayer studies. STM experiments were performed with a Discoverer scanning tunneling microscope (Topometrix Inc., Santa

Barbara, CA) along with an external pulse/function generator (Model HP 8111 A). Tips were electrochemically etched from Pt/Ir wire (80%/20%, diameter 0.2 mm) in an aqueous solution of 2N KOH and 6N NaCN. Typically, a tunneling current of 0.5–1 nA and a bias voltage of 0.2–1 V (sample negative) were employed. The STM images were corrected for instrumental drift.

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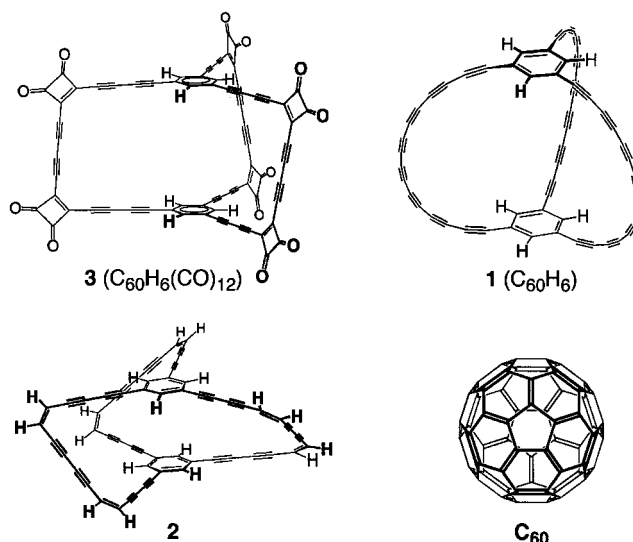
Keywords: chirality • monolayers • scanning tunneling microscopy

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- [14] Our conclusions are based upon approximately 50 STM images for each enantiomer. None of the STM images obtained are in contradiction with the results outlined in the text.
- [15] This compound forms two types of monolayer structures. Some domains are completely disordered and contain ringlike structures, individual small lamellae, etc. Other domains are composed of lamellae, but the lamellar width (20 ± 1 Å) and the intralamellar distance between two head groups (8.4 ± 0.2 Å) are much smaller than the values obtained for ISA molecules. The angle between the alkoxy chains and the lamellar axis measures approximately $43 \pm 2^\circ$. No codeposition of solvent molecules was observed. These large deviations are most likely due to the presence of an ether functionality in the alkyl chain and the absence of a stereogenic center. In ISA these stereogenic centers force, probably because of sterical hindrance, the side chains to adapt an extended conformation that is almost perpendicular to the lamellar axis.
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Acetylenic Cyclophanes as Fullerene Precursors: Formation of $C_{60}H_6$ and C_{60} by Laser Desorption Mass Spectrometry of $C_{60}H_6(CO)_{12}$ **

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In previous reports^[1] we proposed that highly unsaturated macrocyclic cyclophanes such as **1** and **2** may function as precursors of the fullerene C_{60} and its endohedral metal complexes in a process analogous to the coalescence annealing of mono- and polycycles with *sp*-hybridized carbon atoms during the gas-phase formation of fullerenes from evaporated graphite (Scheme 1).^[2, 3] Formation of endohedral transition metal complexes by this route is particularly appealing in view of the exceptional physical and chemical properties of C_{60} .^[4] Here we report for the first time that the acetylenic macrocycle **3** effectively leads to $C_{60}H_6$ and C_{60} ions in the gas phase in laser desorption mass spectroscopic experiments.^[5]



Scheme 1. Structures of the acetylenic macrocycles **1–3** and of I_h-C_{60} .

When the thermochemistry of macrocycle **2** was studied by matrix assisted laser desorption ionization Fourier transform (MALDI-FT) and atmospheric pressure chemical ionization

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(APCI) negative-ion mass spectrometry, it was found that the parent molecular ion ($C_{60}H_{18}$) showed little propensity to lose hydrogen.^[1a] This seemed somewhat surprising in view of the facile Bergman cyclization of enediyne to generate 1,4-benzene diradicals.^[1b] Since effective leaving groups should facilitate the formation and consecutive rearrangement of the more highly unsaturated precursor $C_{60}H_6$ (**1**), we decided to embark on the synthesis of the cyclobutenedione **3**. The cyclobutenedione moiety was previously found to release acetylenic bonds very efficiently in the gas phase with concomitant loss of carbon monoxide, for example in the generation of the carbocycles C_{18} , C_{24} , and C_{30} in Fourier transform ion cyclotron resonance laser desorption (FT-ICR LD) mass spectroscopic experiments or in the preparative-scale synthesis of triynes and higher polyynes by flash vacuum pyrolysis.^[2a-c, 6]

The preparation of cyclophane **3** proved to be much more challenging than expected. The protected ethylene spiroacetal **7a** was first prepared in analogy to the synthesis of the ethylene acetal precursors of the carbo[n]cycles (Scheme 2).^[7] However, the deprotected alkyne **8a** could not be cyclized to

9a under a number of oxidative coupling conditions; the attempts always resulted in rapid polymerizations. It was suggested that the homoconjugated nature of the spiroacetal moieties in **8a** (or **9a**) confers unusual reactivity upon this compound.^[8] This was indeed the case: Cyclization of the dimethoxyacetal **8b** by a modified Hay procedure gave macrocycle **9b** as a stable, waxy, yellow solid in good yields (Table 1). For the preparation of acetals **8a** and **8b**, we

Table 1. Selected spectroscopic data for **4b**, **5b**, **7b**, **9b**, and **3**.

4b: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.23 (s, 9H), 1.06 (m, 21H), 3.92 (s, 3H), 4.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.18, 11.12, 18.48, 58.40, 59.57, 79.56, 91.23, 102.37, 135.07, 165.46, 180.09; IR (neat): $\tilde{\nu}$ = 2945, 2156, 1784, 1650 cm^{-1} ; EI-HR-MS: calcd for $C_{20}H_{30}O_4Si_2$: 396.2152, found: 396.2147

5b: ^1H NMR (200 MHz, $CDCl_3$): δ = 1.08 (m, 21H), 3.52 (s, 6H), 4.38 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.07, 18.42, 53.15, 61.01, 91.86, 94.69, 99.39, 112.24, 184.07, 186.15; IR (neat): $\tilde{\nu}$ = 2945, 2148, 1790, 1614 cm^{-1} ; EI-HR-MS: calcd for $C_{18}H_{30}O_4Si$: 338.1913, found: 338.1915

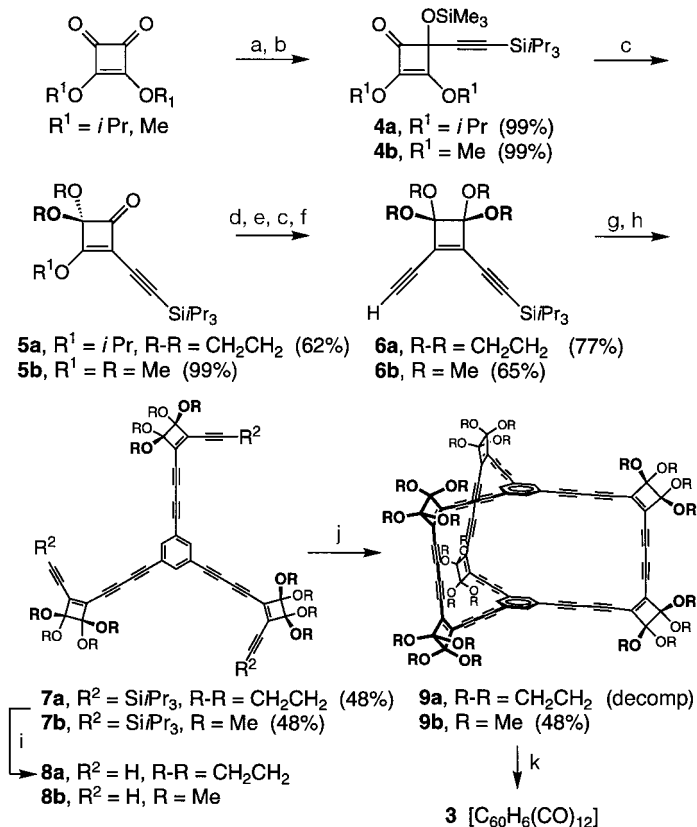
7b: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (m, 63H), 3.52 (s, 18H), 3.53 (s, 18H), 7.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.10, 18.50, 52.00, 52.05, 73.45, 75.41, 83.68, 85.52, 97.86, 108.15, 108.44, 109.96, 122.77, 133.42, 136.50, 138.88; IR (KBr): $\tilde{\nu}$ = 2943, 2207, 2130, 1600, 1576, 1463 cm^{-1} ; UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 235 (79 200), 269 (74 400), 291 (71 200), 308 (70 300), 318 sh (74 800), 326 sh (85 200), 341 (107 000), 368 nm^{-1} (96 400); FAB-HR-MS: calcd for $C_{75}H_{102}O_{12}Si_3$ (M^+): 1278.6679, found: 1278.6646; elemental analysis calcd for $C_{75}H_{102}O_{12}Si_3$: C 70.38, H 8.03; found: C 70.41, H 8.03

9b: ^1H NMR (400 MHz, $CDCl_3$): δ = 3.48 (s, 36H), 3.50 (s, 36H), 7.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.08, 52.09, 73.12, 75.08, 78.19, 85.22, 87.07, 87.97, 108.52, 108.54, 122.43, 136.26, 136.61, 138.00; IR (KBr): $\tilde{\nu}$ = 2942, 2206, 1576, 1463, 1085 cm^{-1} ; UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 280 (197 000), 300 sh (112 000), 322 (80 900), 341 (84 700), 382 (70 500), 414 nm^{-1} (48 400); FAB-HR-MS: calcd for $C_{96}H_{78}O_{24}Na$ ($M + Na^+$): 1637.4781, found: 1637.4724

3: ^1H NMR (400 MHz, CD_2Cl_2): δ = 7.70 (s); ^{13}C NMR (100 MHz, $[D_8]THF$): δ = 79.1, 79.4, 80.7, 97.1, 102.8, 108.1, 122.8, 137.8, 175.3, 178.4, 192.0, 192.5; IR (KBr): $\tilde{\nu}$ = 1784, 2136, 2198 cm^{-1} ; UV/Vis (CH_2Cl_2): λ_{max} (rel. intensity) = 245 (100), 282 (98), 316 sh (63), 347 (59), 407 sh (56), 442 nm^{-1} sh (37)

followed a disconnection similar to the synthesis of macrocycle **2**.^[1a] This required the preparation of the half-protected enediyne **6a** and **6b** in gram quantities.^[6] Liebeskind's methodology was used most effectively to form siloxy ketones **4a** and **4b**, which were converted into monoacetals **5a** and **5b** in a one-pot reaction.^[9] Addition of a second alkyne moiety to **5a** or **5b** and conversion into the stable cyclobutenedione bis(acetal)s **6a** and **6b** was achieved by in situ treatment of the initially formed lithium alkoxides with concentrated H_2SO_4 or 3 M HCl followed by a second acetalization step and selective removal of the trimethylsilyl protecting groups. Both **6a** and **6b** were converted into their yellow copper(I) acetylides and coupled with 1,3,5-tris(bromoethynyl)benzene^[1a] in pyridine or THF to give the stable cyclization precursors **7a** and **7b**. These precursors were deprotected just prior to cyclization to the unstable terminal alkynes **8a** or **8b** by treatment with tetrabutylammonium fluoride and subsequent filtration through silica gel (Et_2O).

Deprotection of the methoxyacetal moieties of macrocycle **9b** necessitated some fine-tuning. Surprisingly, we found that the cyclobutenedione macrocycle **3** was considerably less stable than the carbon oxide precursors of C_{18} , C_{24} , and



Scheme 2. Synthesis of the protected macrocycle **9b**. a) $TIPSCl$, THF, $-78^\circ C$; b) $TMSCl$, -78 to $25^\circ C$; c) $TMSOCH_2CH_2OTMS$ or $TMSOMe$, cat. $TMSOTf$, THF, 55 or $25^\circ C$; d) $TMSCl$, Et_2O , -78 to $-45^\circ C$; e) concd H_2SO_4 , $25^\circ C$, or 3 M HCl, -45 to $25^\circ C$; f) K_2CO_3 , MeOH; g) $LiHMDS$, THF, then $CuBr$; h) 1,3,5-tris(bromoethynyl)benzene, pyridine or THF, $25^\circ C$; i) TBAF, THF; j) $CuCl \cdot TMEDA$ (3 equiv), ODCB, $25^\circ C$; k) CF_3COOH , $25^\circ C$, 4–6 h. All OCH_2CH_2O -bridged acetals are spiroannulated. TMS = $SiMe_3$; TIPS = $SiPr_3$; Tf = CF_3SO_2 ; $LiHMDS$ = lithium hexamethyldisilazide; TBAF = tetra-*n*-butylammonium fluoride; TMEDA = *N,N,N',N'*-tetramethylethylenediamine; ODCB = *o*-dichlorobenzene.

C_{30} ,^[2a, 7] it could be characterized only with difficulty. Macrocycle **3** was prepared by dissolution of **9b** in trifluoroacetic acid. After three to six hours an orange-yellow precipitate had formed, which was redissolved in CH_2Cl_2 after evaporation of the acid. In CH_2Cl_2 **3** decomposed to a brown precipitate within one to two hours. In $[D_8]THF$ a ^{13}C NMR spectrum could be obtained; it shows 12 lines in the expected range (Table 1).

We were very pleased to find that macrocycle **3**, despite its instability, undergoes clean loss of its carbonyl groups in FT-ICR LD-MS experiments (Figure 1). Fragment ions are

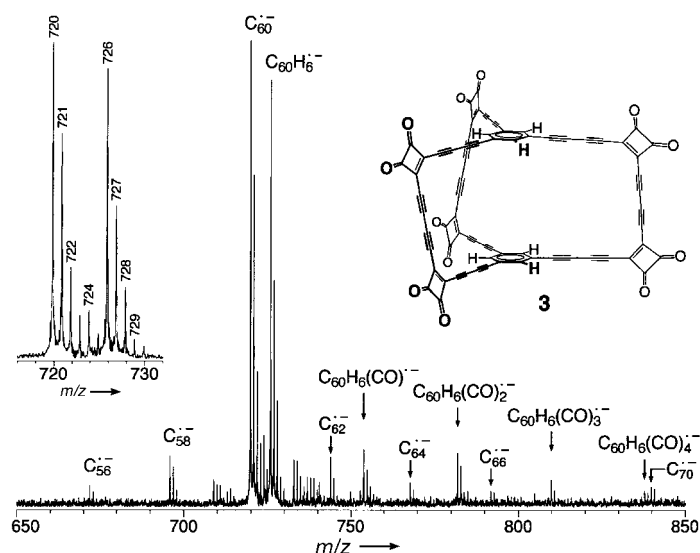


Figure 1. Negative-ion ICR-LD mass spectrum of macrocycle **3** after desorption at 10.6 μm .

observed with both CO_2 (10.6 μm) and N_2 lasers (337 nm), but much more intense ion signals are obtained with the former. In the negative-ion mode, prominent ions corresponding to $C_{60}H_6^-$ and C_{60}^- appear at $m/z = 726$ and 720 together with their isotopic clusters, whose intensities match superbly with the theoretical ratios (Figure 1, inset). The resolution of the ICR-LD mass spectrum is excellent and reaches values of up to 7500. With authentic C_{60}/C_{70} as external standards (for calibration after LD-MS measurements of **3**), the observed masses for $^{12}C_{60}$ (719.9951), $^{12}C_{60}H_6^-$ (726.0380), $^{12}C_{59}^{13}CH_6^-$ (727.0416), and $^{12}C_{58}^{13}C_2H_6^-$ (728.0599) are within 8, 13, 13, and 8 ppm of their theoretical values (720.0006, 726.0475, 727.0509, and 728.0542). In the positive-ion mode (spectrum not shown), no fragment ion corresponding to $C_{60}H_6^+$ is observed; only the peak for C_{60}^+ and less intense peaks for the higher fullerenes $C_{62}-C_{70}$ appear. In one instance C_{2n} clusters centered around multiples of C_{60} (C_{120} , C_{180}) were also observed; they are attributed to oligomerization of the unstable precursor during laser desorption or to coalescence of C_{60}^+ or radical cationic intermediates with neutral species in the gas phase.^[10] In the negative-ion spectrum, fragment ions for $C_{62}-C_{70}$ are also found, but with lower intensities (Figure 1).

The parent ion of **3** is not observed in either the positive- or negative-ion mass spectra, but its involvement is clearly

implied by its fragmentation to $C_{60}H_6(CO)_4$, $C_{60}H_6(CO)_3$, $C_{60}H_6(CO)_2$, and $C_{60}H_6(CO)$ in the negative-ion spectrum (calcd: 838.0272, 810.0322, 782.0373, 754.0424; found: m/z (deviation) = 838.0096 (21 ppm), 810.0231 (11 ppm), 782.0327 (6 ppm), 754.0460 (5 ppm)). The fullerenic nature of the C_{60} ions can be unambiguously inferred from the characteristic loss of C_2 units to give peaks at $m/z = 696$ (C_{58}) and 672 (C_{56}).^[11] At higher laser powers in both negative and positive modes, the degree of C_2 loss increases greatly. On the other hand, fragmentation with C_2 loss is not observed from $C_{60}H_6^-$, indicating that its structure is most likely non-fullerenic in nature and possibly that of **1**.

The formation of fullerene ions (e.g. C_{60} , C_{70}) from the precursors of the carbocycles C_{18} , C_{24} , and C_{30} was an important observation.^[2a,b] Interestingly, this conversion was only found in the positive-ion mode. Cations of carbon clusters are generally highly excited thermally in LD-MS experiments, which tends to induce intermolecular coalescence and fragmentation reactions.^[10, 11] In this study, we find concurrently that positive ions give rise to increased fragmentation and coalescence. In contrast, this is the first time that rearrangement of a precursor such as **1** to C_{60} is found to occur in the negative-ion mode under seemingly milder conditions. It is likely that the three-dimensional framework of cyclophane **1** lends itself ideally to fullerene isomerization. On the other hand, the negative ions of the carbocycles C_{18} , C_{24} , and C_{30} do not react with neutral species because of their excess charge.^[2a,b, 12] In addition, the three-dimensional shape of precursors such as **1** may display better suitability for metal complexation in the potential formation of endohedral metallofullerenes.

Preliminary attempts at preparative isolations showed that the precipitates obtained from the solutions of **3** in trifluoroacetic acid or from pulsed femtosecond laser irradiation at 400 nm of a dilute solution of **3** in THF did not contain buckminsterfullerene or other apolar material. Further experiments aimed at the incorporation of metals into C_{60} and preparative-scale isolations (e.g. by flash vacuum pyrolysis) are in progress.

Experimental Section

4b: To $iPr_3SiC\equiv CH$ (4.53 g, 24.8 mmol) in THF (25 mL) was added 2.5 M $nBuLi$ (9.90 mL, 24.8 mmol) dropwise at $0^\circ C$. The solution was stirred for 30 min and then added to dimethyl squarate (3.35 g, 23.6 mmol) in THF (100 mL) at $-78^\circ C$ dropwise with a syringe. After 1 h at $-78^\circ C$ TMSCl (3.26 g, 30.0 mmol) was added dropwise, and the reaction was allowed to warm to $25^\circ C$. Aqueous workup ($NaHCO_3$) and removal of the solvent in vacuo gave **4b** (9.36 g, 99%) as a pale yellow oil.

5b: To **4b** (9.36 g, 23.6 mmol) in THF (10 mL) was added MeOTMS (2.60 g, 24.8 mmol) followed by TMSOTf (0.30 mL, 1.5 mmol). The reaction was initially exothermic, and the mixture was stirred for 30 min at $25^\circ C$. Aqueous workup ($NaHCO_3$) and removal of solvent in vacuo gave a brown oil, which was purified by filtration on silica gel (Et_2O /hexanes 1/2) to give **5b** (7.99 g, 99%) as a yellow oil.

6b: 1) To $Me_3SiC\equiv CH$ (0.66 mL, 0.46 g, 4.7 mmol) in Et_2O (10 mL) at $0^\circ C$ was added dropwise 2.5 M $nBuLi$ (1.9 mL, 4.7 mmol). After the reaction mixture had been stirred for 30 min the temperature was lowered to $-78^\circ C$. Compound **5b** (1.50 g, 4.43 mmol) in Et_2O (20 mL) was added dropwise. The reaction mixture was stirred for 1 h at $-45^\circ C$. To the resulting red solution was added 3 M HCl (20 mL), and the reaction mixture was stirred at $25^\circ C$ for 1 h. Aqueous workup ($NaHCO_3$) and removal of the

solvent in vacuo gave the desired enediyne (1.67 g, 93%) as a brown oil, which was used directly in the next step. 2) To the enediyne (1.67 g, 4.13 mmol) in MeOTMS (2.0 mL, 1.5 g, 15 mmol) was added TMSOTf (0.10 mL, 0.12 g, 0.52 mmol). After the reaction mixture had been stirred for 48 h at 25 °C, aqueous workup (NaHCO₃), removal of the solvent in vacuo, and filtration through silica gel (Et₂O/hexanes 1/1) gave the desired bis(acetal) (1.38 g, 74%) as a yellow oil. 3) To the bis(acetal) (7.34 g, 16.3 mmol) in MeOH (50 mL) was added K₂CO₃ (~100 mg). After the reaction mixture had been stirred for 15 min at 25 °C, aqueous workup, removal of the solvent in vacuo, and filtration through silica gel (Et₂O/hexanes 1/1) gave **6b** (5.80 g, 94%) as a yellow oil. It was diluted with THF (100 mL) and used directly in the next step.

7b: To **6b** (6.28 g, 16.6 mmol) in THF (100 mL) at –78 °C was added LiHMDS, which was prepared from (Me₃Si)₂NH (3.50 mL, 2.68 g, 16.6 mmol) and 2.5 M *n*BuLi (6.60 mL, 16.6 mmol) in THF (15 mL). After 30 min CuBr (2.38 g, 16.6 mmol) was added, and the mixture warmed to 0 °C. To this solution was added 1,3,5-tris(bromoethynyl)benzene^[1a] (2.03 g, 5.25 mmol). After the reaction mixture had been stirred for 12 h at 25 °C, aqueous workup (NaHCO₃) and removal of the solvent in vacuo gave a brown oil, which was purified by chromatography on silica gel (hexanes to hexanes/Et₂O 3/1) to afford **7b** (3.25 g, 48%) as a colorless foam.

8b: To **7b** (500 mg, 0.391 mmol) in THF (10 mL) was added five drops of H₂O followed by 1.0 M TBAF (2.0 mL, 2.0 mmol). The reaction mixture was stirred for 2 h, diluted with hexanes (50 mL), and filtered through silica gel (Et₂O). The resulting yellow fractions were concentrated to 5 mL and diluted with ODCB (400 mL) for the immediately following cyclization.

9b: To the solution of **8b** obtained above was added CuCl (119 mg, 1.20 mmol) followed by TMEDA (1.0 mL, 0.77 g, 6.6 mmol). After the reaction mixture had been stirred for 1 h under air, the solution was poured on top of a pad of silica gel and eluted with CHCl₃ to remove most of the ODCB. Elution with Et₂O/CHCl₃ (1/2) provided a yellow fraction with the desired product. The solvent was removed, and the brown oil purified by chromatography on silica gel (Et₂O/CHCl₃ 5/95). Removal of the solvent in vacuo gave cyclophane **9b** (150 mg, 48%) as a yellow foam.

3: Aliquots of **9b** (5–30 mg) were dissolved in trifluoroacetic acid (1–3 mL). Over 3–6 h a precipitate began to form (the reaction could be monitored by ¹H NMR spectroscopy in CF₃CO₂D). After 6–12 h the trifluoroacetic acid was removed in vacuo at 25 °C in the absence of light. [D₈]THF (~0.5 mL) was immediately added to the remaining orange-red solid under argon. This solution was used for ¹³C NMR spectroscopy. For the LD-MS experiments, anhydrous CH₂Cl₂ or THF were added to dissolve the precipitate, and the solution was used immediately.

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A Dendritic Macrocyclic Organic Polyradical with a Very High Spin of S = 10**

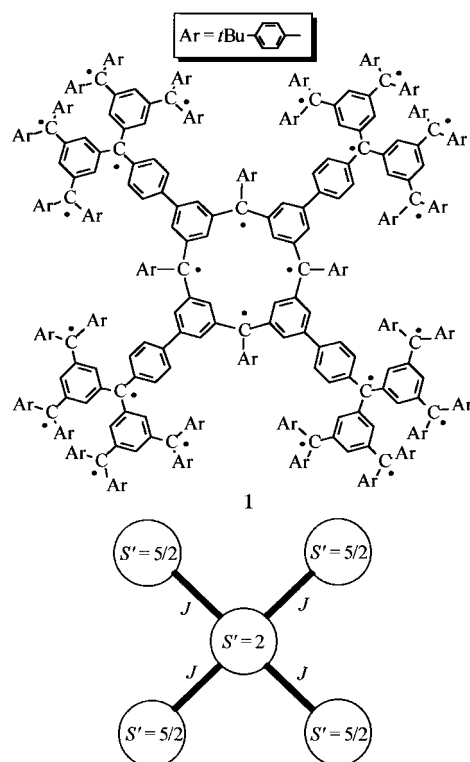
Andrzej Rajca,* Jirawat Wongsriratanakul, Suchada Rajca, and Ronald Cerny

Organic molecules with a very high spin possess a large number of ferromagnetically coupled unpaired electrons.^[1] The design and synthesis of such molecules must overcome the challenging problem of maintaining strong through-bond interactions between multiple sites within the molecule.^[1d, 2] Highly efficient generation of unpaired electrons and/or multiple pathways for ferromagnetic coupling provided organic molecules with *S* greater than 5.^[3–6] The highest spin for an organic molecule to date, a nonacarbene with *S* = 9, was reported by Iwamura and co-workers in 1993.^[3]

Polyradical **1** was designed as an “organic spin cluster”.^[6, 7] Because ferromagnetic coupling through 1,3-phenylene is significantly stronger than that through a 3,4'-biphenylene unit, unpaired electrons in the four dendritic branches and the macrocyclic core can effectively be lumped into component spins (*S'*).^[6] Such a ferromagnetically coupled spin pentamer with *S'* = 5/2, 5/2, 5/2, 5/2, 2 should have a ground state with *S* = 12 (Scheme 1). We describe here the synthesis and magnetic studies of polyradical **1**.

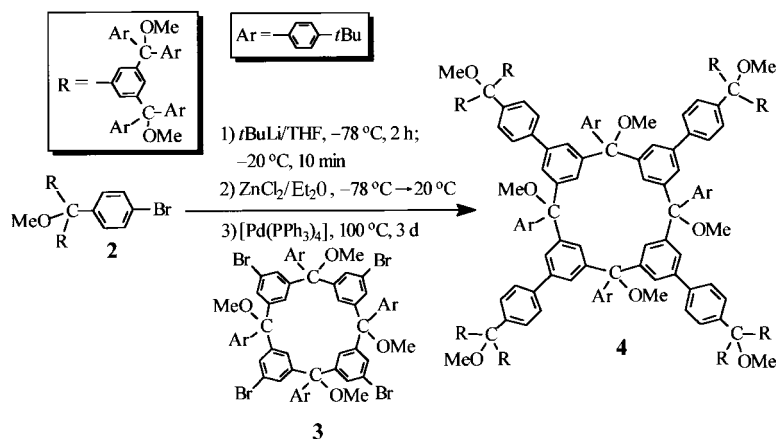
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Scheme 1. Formula of the organic polyradical **1** (top) and the schematic representation of the coupling of the component spins S' in the spin pentamer with the coupling constant J (bottom).

The synthesis of **4**, the precursor to **1**, relies on the attachment of four dendritic branches **2** to the macrocyclic core **3**.^[6, 8] Negishi coupling starting from an isomer of **3** that has fourfold symmetry gives **4** in 2% yield (Scheme 2).^[9] The low-resolution fast atom bombardment (FAB) mass spectrum for **4** shows prominent cluster ions at $m/z = 7001$ and 3485 with similar fragmentation patterns; however, the spacings between the fragmentation ions and the widths of their isotopic envelopes for the region at $m/z = 3485$ are approximately half of those at $m/z = 7001$ (Figure 1). This suggests that the peaks at $m/z = 7001$ and 3485 correspond to singly and doubly charged ions $[M - \text{OCH}_3]^+$ and $[M - 2\text{OCH}_3]^{2+}$, respectively. In the high-resolution spectra, experimental isotopic intensities for $[M - \text{OCH}_3]^+$ and $[M - 2\text{OCH}_3]^{2+}$ ions



Scheme 2. Synthesis of **4**, a precursor to polyradical **1**.

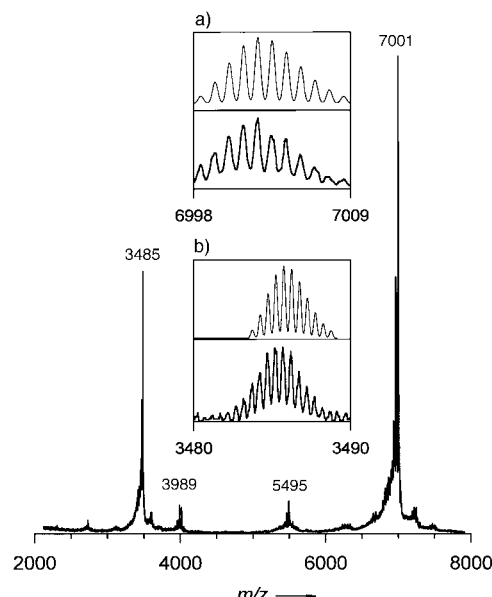
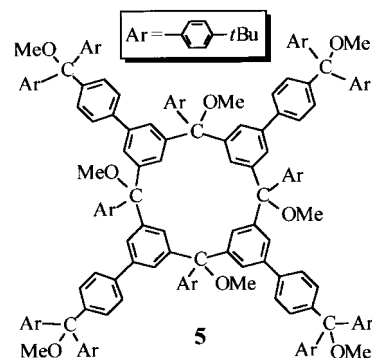


Figure 1. Section of the low-resolution FAB mass spectrum for polyether **4**. The peaks at $m/z = 7001$ and 3485 are assigned to the $[M - \text{OCH}_3]^+$ and $[M - 2\text{OCH}_3]^{2+}$ ion clusters, respectively. Their most prominent fragmentation patterns coincide with the consecutive loss of OCH_3 fragments. Weak-intensity clusters at $m/z = 5495$ and 3989 may correspond to either impurities or fragmentation ions with three and two dendritic branches, respectively. Inset: experimental high-resolution spectra (bottom in each case) for the $[M - \text{OCH}_3]^+$ (a) and $[M - 2\text{OCH}_3]^{2+}$ ion clusters (b) as well as their corresponding calculated spectra (top in each case) for the formulas $\text{C}_{503}\text{H}_{589}\text{O}_{23}$ (a) and $\text{C}_{502}\text{H}_{586}\text{O}_{22}$ (b) at natural isotopic abundance. The most intense isotopic peaks for the $[M - \text{OCH}_3]^+$ and $[M - 2\text{OCH}_3]^{2+}$ ion clusters are at $m/z = 7002.5$ and 3485.8 , respectively. The intensity of the triply charged $[M - 3\text{OCH}_3]^{3+}$ ion is negligible.

are in satisfactory agreement with the calculated values (Figure 1). In the aromatic region of the ^1H NMR spectrum at 348 K, the COSY correlation shows two “singlet” off-diagonal peaks along with four well-resolved and four overlapping “quadruplet” off-diagonal peaks (Figure 2). The “singlet” peaks are associated with coupling of doublet (16 protons) and triplet resonances (8 protons; $J = 2$ Hz), corresponding to the eight 1,3,5-trisubstituted benzene rings of the dendritic branches. The “quadruplet” peaks result from the coupling of four doublet resonances (8 protons) with four further doublet resonances (32 protons; $J = 9$ Hz), accounting for all 1,4-disubstituted benzene rings. The two broad singlets (4 and 8 protons) furthest downfield do not show off-diagonal peaks; however, in less sterically congested **5**, analogous resonances appear at



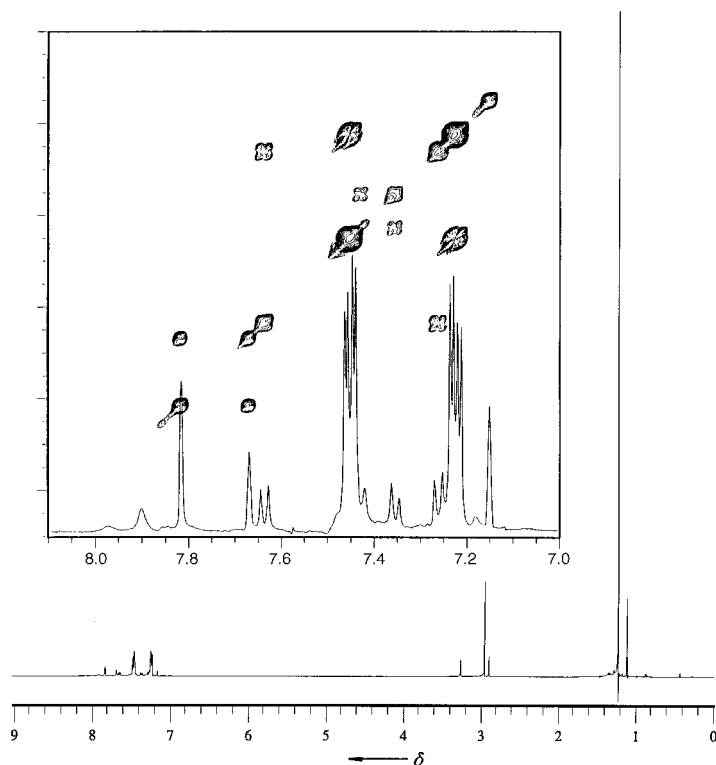


Figure 2. ^1H NMR spectrum (500 MHz, $[\text{D}_6]\text{benzene}$) for polyether **4** at 348 K with exponential (–1.2 Hz) and Gaussian multiplications (0.9 Hz). Inset: COSY ^1H – ^1H NMR spectrum in the region of the arene resonances.

similar chemical shifts and do show off-diagonal peaks in the COSY correlation at ambient temperature. Therefore, these two resonances are assigned to the four 1,3,5-trisubstituted benzene rings of the calix[4]arene core (Figure 2). In the region of the MeO and *t*Bu resonances, two sets of three resonances each (intensities 1:1:4 and 4:4:1, respectively) are resolved at 293 K. The fourfold symmetry of **4** is further corroborated by the ^{13}C NMR spectra in $[\text{D}_6]\text{benzene}$ at 348 K.

When **4** (1–2 mg) was treated with Na/K alloy in $[\text{D}_8]\text{THF}$ (80 μL), the reaction mixture briefly turned blue and subsequently deep purple-red.^[6] After five days at 283 K, the reaction mixture was filtered into a quartz tube (outer diameter 5 mm). Iodine was added in small portions at 170–167 K until the reaction mixture turned blue, green, and finally red-brown.^[6] The magnetization M of **1** was measured as a function of magnetic field H (0–5.0 T) and temperature T (1.8–160 K) in $[\text{D}_8]\text{THF}$. The values obtained at $H=0.5$ T were plotted as MT versus T and fit to a model based on a pentamer of four spin carriers with $S=5/2$ ferromagnetically coupled to one spin carrier with $S=2$. Energy eigenvalues for the Heisenberg Hamiltonian were obtained by the vector-decoupling technique, and equations for magnetization, including saturation effects, were derived with standard formulas.^[6, 10, 11] The following variable parameters were used for the numerical fits: J/k_B (spin coupling constant in Kelvin), N (number of moles of the polyradical), and, if needed, M_{dia} (correction for residual diamagnetism). The value $J/k_B=7\pm 1$ K, corresponding to a pairwise ferromagnetic coupling of spin carriers with $S=5/2$ and 2 through a 3,4'-biphenylene

moiety, was obtained for three samples of **1** (Figure 3). For an analogous triradical, in which three “colinear” spin systems with $S=1/2$ are coupled through 3,4'-biphenylene moieties, $J/k_B=90\pm 20$ K is found.^[6] Scaling of J/k_B values for **1** with the fraction of the spin sites with $S=5/2$ and 2 adjacent to the 3,4'-biphenylene moiety gives $J/k_B=70\pm 10$ K, which is in satisfactory agreement with $J/k_B=90\pm 20$ K.^[12]

The magnetic data for **1** in solution (0.003 M) at $T=1.8$, 3, 5, and 10 K were fit to a Brillouin function (M versus H/T) with two variable parameters: S and magnetization at saturation (M_{sat}).^[13] Values of S (≈ 10) slightly decreased at the lowest temperatures (e.g. S is smaller by 0.08 at 1.8 K than at 5 K). Such a change of S may be associated with very small intermolecular antiferromagnetic interactions, which may be described with a mean field parameter θ . The fit to a modified Brillouin function (M versus $H/(T-\theta)$) with $\theta=-0.03$ K^[14] gave $S=10.0$ at 1.8, 3, and 5 K and $S=9.8$ at 10 K (Figure 3). For a more dilute solution of **1** (0.002 M) $\theta=0.00$ K was found; that is, fits to Brillouin functions (M versus H/T) give identical values of $S=9.8$ in the range of 1.8–5 K.^[15] When a solution of **1** in $[\text{D}_8]\text{THF}$ (0.003 M) is measured after exposure to ambient temperature for 0.5 h, the magnetic data (M versus H) suggests sharply lowered spin of $S=2$ –3. The Brillouin function is not followed, as expected for a mixture of polyradicals with widely different values of S .^[14]

The value of $S=10$ is a new record for the spin of an organic molecule. However, $S=10$ for **1** is significantly less than the theoretical value of $S=12$ expected for 24 ferromagnetically coupled unpaired electrons. This discrepancy is ascribed to the presence of a small density of defects, which results when the generation of unpaired electrons proceeds in less than 100 % yield or when synthetic impurities are present in polyether **4**.^[14] The influence of these defects on the total spin is dependent on their positions in the molecule. One defect at the 4-biphenyl-substituted triarylmethyl spin sites and/or two defects at the macrocyclic sites would disrupt spin coupling and drastically lower the total spin of the defect polyradicals; however, defects at the outer triarylmethyl spin sites would lower the total spin in increments of 1/2 only. The sites in which a single defect would disrupt spin coupling are referred to as “defect-sensitive sites”.^[6] In **1**, such sites are substituted with stabilizing 4-biphenyl groups. Furthermore, there is a relatively small number of defect-sensitive sites in **1** (4 out of 24) compared to typical dendrimers (50 %) or linear polymers (92 % for a chain with 24 sites). A quantitative evaluation of defects in **1** can be obtained with a simple percolation model.^[6] With the assumption of identical probability p for finding an unpaired electron at each triarylmethyl site ($100p$ % yield per site), an approximate formula for average spin is $\langle S \rangle = 12p/(9-8p)$. Equating $\langle S \rangle = S$ or explicitly fitting magnetic data with a distribution of Brillouin functions gives $p=0.98$, which corresponds to 98 % yield per site for the generation of unpaired electrons. Adequate design of polyradical and very high chemical yields are prerequisites for maintaining strong through-bond interactions, such as ferromagnetic spin coupling, between multiple sites within a molecule.

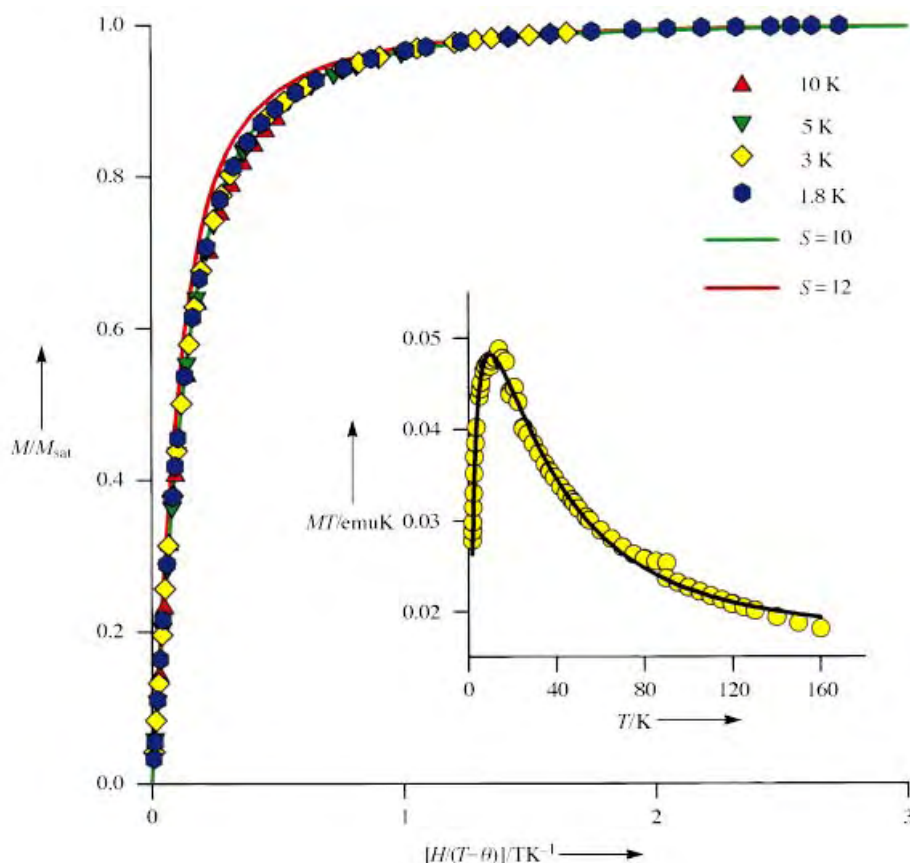


Figure 3. Superconducting quantum interference device (SQUID) magnetometry ($H=0-5.0$ T) for polyradical **1** in $[D_8]THF$, $\theta = -0.03$ K. The experimental points at different temperature are represented by symbols, and Brillouin functions by lines. The fitting parameters for $T=1.8, 3, 5$, and 10 K are $S=10.0, 10.0, 10.0$, and 9.8 and $M_{sat} \times 10^2 = 2.01, 2.01, 2.00$, and 1.96 emu; the parameter dependence is $0.26, 0.34, 0.49$, and 0.72 , respectively. Inset: Plot of MT versus T at $H=0.5$ T. The circles correspond to the experimental points, and the line is the numerical fit to the spin pentamer model. The fitting parameters (and their parameter dependencies) are $J/k_B = 6.6$ K (0.73), $N = 1.33 \times 10^{-7}$ mol (0.62), and $M_{dia} = 1.3 \times 10^{-5}$ emu (0.52). All experimental data are plotted after point-by-point and numerical corrections ($M_{dia} = 1.3 \times 10^{-5}$ emu) for diamagnetism.

In high-spin complexes containing a single transition metal or lanthanoid atom, maximum values of S are limited to $5/2$ or $7/2$ by (near) degeneracy in space of orthogonal $3d$ or $4f$ orbitals. In organic high-spin polyradicals, such a restriction is removed by the unlimited topological near degeneracy of nonbonding molecular orbitals. As long as spin coupling can be preserved in the presence of a small density of defects, "organic spin clusters" should be capable of significantly exceeding present values of S . The synthesis of higher homologues of **1**, in which dendritic branches are replaced with macrocycles, is in progress in our laboratory. This approach not only increases the number of unpaired electrons, but should improve the resistance of polyradicals to defects as well.

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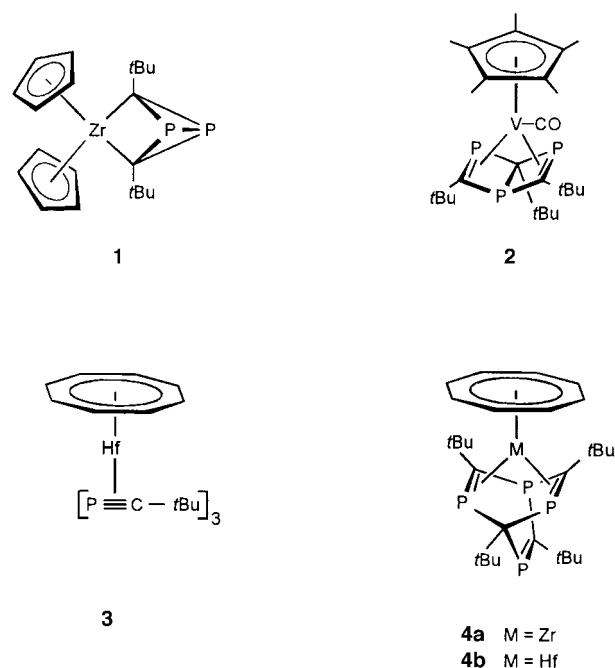
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- [15] Brillouin-function analysis of the magnetic data (M versus H) at $1.8, 3, 5$, and 10 K—which were generated with J/k_B and N values obtained from the plot of MT versus T (see Figure 3)—gives excellent fits with $S=12.0$ and $M_{sat}=0.0179$ emu in the range of $1.8-5$ K; at 10 K, $S=11.7$ and $M_{sat}=0.0177$ emu. The relatively lower values of S and M_{sat} at 10 K for both experimental and reference data for M versus H reflect a nonnegligible population of the lower spin excited states at T greater than 5 K.

Novel Reactions of Phosphaalkynes in the Coordination Sphere of *tert*-Butylimido-vanadium(v) Complexes: A Simple Synthesis of 3-Aza-1,2,4,6-tetraphosphaquadracyclanes and 1,3,5-Triphosphaabenzenes**

Frank Tabellion, Anja Nachbauer, Stefan Leininger, Christoph Peters, Fritz Preuss,* and Manfred Regitz*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Cyclooligomerization reactions of phosphaalkynes in the coordination sphere of transition metals in which the metal complex fragment is incorporated in the product have played an important role in the development of phosphaalkyne chemistry.^[1] Significant examples are the cyclodimerization of *tert*-butylphosphaacetylene (**5a**) to give the tricyclic zirconium complex **1**,^[2] cyclotrimerizations to give the vanadium and hafnium complexes **2**^[3] and **3**,^[4] and the formation of the zirconium and hafnium complexes **4**^[5] by cyclotetramerization. Treatment of **1**, **3**, and **4** with hexachloroethane leads to



detachment of the metal complex fragments and formation of *tert*-Bu-substituted 1,3,5,7-tetraphosphacubane (cyclodimerization of the residual molecule),^[6] 1,3,5-triphospha benzene

(**14a**),^[4] and 1,3,5,7-tetraphosphabarrelene.^[5] Reactions of **2** with the same reagent have not yet been investigated. We now report on the chemoselective cyclooligomerization^[7] of phosphaalkynes **5a–e** with the vanadium(v) compounds *t*BuN=VCl₃ · DME (**6**)^[8] (DME = 1,2-dimethoxyethane) and *t*BuN=VCl₃ (**13**)^[9] to produce the title compounds in good yields.

Reaction of **5a–e** with **6** in a molar ratio of 4:1 in toluene followed by column chromatography on alumina affords the previously unknown azatetraphosphaquadracyclanes **7a–e** as yellow solids in yields of 47–76 % (not optimized; Table 1).

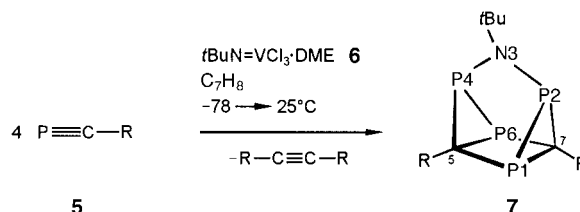


Table 1. Synthesis of the azatetraphosphaquadracyclanes **7**.

5, 7	a	b	c	d	e
R	<i>t</i> Bu	<i>t</i> Pent			
Yield [%]	76	53	55	57	47

The elemental analyses and mass spectra (Table 2) indicate that the heteropolycyclic compounds are formed from four molecules of the phosphaalkyne **5** with loss of one molecule of an alkyne RC≡CR (see Scheme 1) and incorporation of the imide ligand from the vanadium compound **6**.

As an example the NMR data of **7a** are discussed here (for further spectroscopic data of the compounds **7**, see Table 2).

Table 2. Selected spectroscopic data for the azatetraphosphaquadracyclanes **7**.^[a]

7a : ¹ H NMR: δ = 0.99, 1.00 (2 s, each 9H, CC(CH ₃) ₃), 1.53 (pseudo-t, ⁴ J(P ₄ H) = ⁴ J(P ₄ H) = 0.9 Hz, 9H, NC(CH ₃) ₃); ¹³ C NMR: δ = 28.8–31.7 (brm, CC(CH ₃) ₃ /C5/C7), 32.1 (m, C(CH ₃) ₃), 34.0 (pseudo-t, ³ J(P,C) = 10.6 Hz, NC(CH ₃) ₃), 56.8 (pseudo-t, ² J(P,C) = 14.4 Hz, NC(CH ₃) ₃); ³¹ P NMR: δ = –7.4, –123.0 (AA'XX' spin system with J(A'X) = J(A'X') = 161.1 Hz, J(A'X) = J(A'X') = 21.0 Hz, J(AA') = 22.4 Hz, J(XX') = 5.5 Hz); MS: <i>m/z</i> (%): 333 (63) [<i>M</i> ⁺], 233 (57) [<i>M</i> ⁺ – C ₃ H ₉ P], 177 (100) [<i>M</i> ⁺ – C ₄ H ₉ – C ₃ H ₉ P], 162 (38) [<i>M</i> ⁺ – C ₄ H ₉ N – C ₃ H ₉ P], 57 (21) [C ₄ H ₉]
7b : ¹³ C NMR: δ = 28.7–31.3 (brm, C5/C7), 56.9 (pseudo-t, ² J(P,C) = 13.6 Hz, NC(CH ₃) ₃); ³¹ P NMR: δ = –9.2, –123.2; MS: <i>m/z</i> (%): 361 (66) [<i>M</i> ⁺]
7c : ¹³ C NMR: δ = 30.1–32.9 (brm, C5/C7), 56.7 (pseudo-t, ² J(P,C) = 14.4 Hz, NC(CH ₃) ₃); ³¹ P NMR: δ = –14.7, –130.8; MS: <i>m/z</i> (%): 489 (19) [<i>M</i> ⁺]
7d : ¹³ C NMR: δ = 28.8–31.4 (brm, C5/C7), 56.8 (pseudo-t, ² J(P,C) = 13.6 Hz, NC(CH ₃) ₃); ³¹ P NMR: δ = –5.8, –123.8; MS: <i>m/z</i> (%): 385 (69) [<i>M</i> ⁺]
7e : ¹³ C NMR: δ = 28.6–30.6 (brm, C5/C7), 56.4 (pseudo-t, ² J(P,C) = 13.6 Hz, NC(CH ₃) ₃); ³¹ P NMR: δ = –11.9, –125.3; MS: <i>m/z</i> (%): 413 (34) [<i>M</i> ⁺]

[a] NMR: Bruker AC-200; ¹H NMR (200 MHz) and ¹³C NMR (50 MHz) in C₆D₆; ³¹P NMR (81 MHz) in C₆D₆ with 85 % H₃PO₄ as external standard; MS: Finnigan MAT90, 70 eV.

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The ^{31}P NMR spectrum of the tetracyclic product **7a** contains two signals at $\delta = -7.4$ (P2, P4) and -123.0 (P1, P6); the four P atoms form an AA'XX' spin system. While the A part of the spectrum gives rise to very broad signals on account of the vicinity of P2 and P4 to the nitrogen atom, the coupling constants (Table 2) can be derived from the X part of the spectrum.^[10] The ^1H NMR spectrum confirms this proposal by way of two different signals for the *t*Bu groups at C5 and C7; the signal of the *t*Bu group bound to N3 is split by small ^4J coupling. The skeletal carbon atoms C5 and C7 appear as a multiplet in the ^{13}C NMR spectrum and cannot be distinguished (Table 2).

The NMR data are in harmony with structure **7a** which has been confirmed by a single crystal X-ray structure analysis (Figure 1).^[11] The compound has a C_1 -symmetric quadricyclane structure, which is distorted owing to the pyramidal geometry at nitrogen.

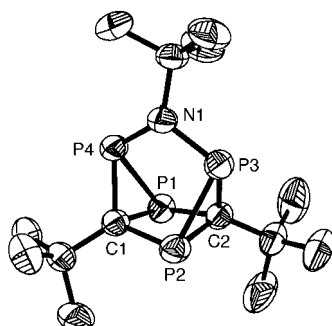
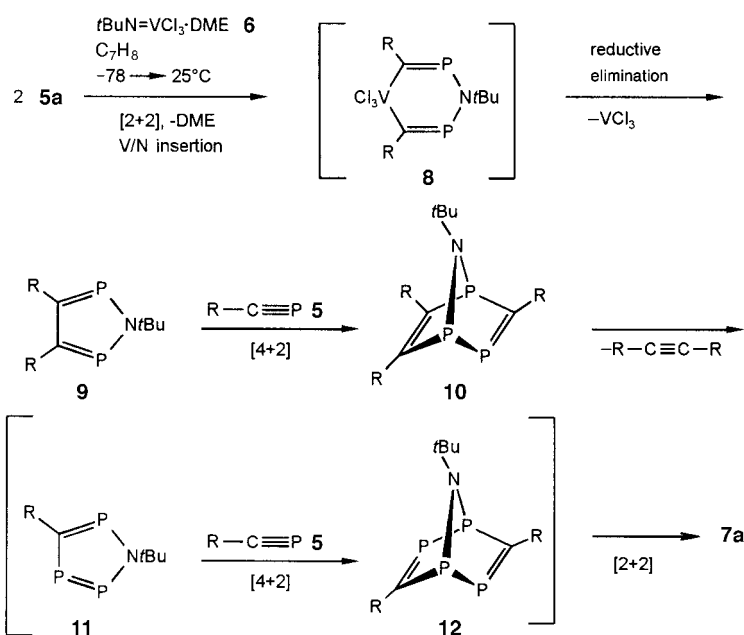


Figure 1. Structure of **7a** in the crystalline state (50% probability thermal ellipsoids). Selected bond lengths [Å] and angles [°]: P1–C2 1.880(2), P1–C1 1.894(2), P1–P4 2.2185(11), P2–C1 1.881(2), P2–C2 1.896(2), P2–P3 2.1782(10), P3–N1 1.716(2), P3–C2 1.865(2), P4–N1 1.716(2), P4–C1 1.842(2); C2–P1–C1 83.44(9), C1–P1–P4 52.50(6), C1–P2–C2 83.39(9), C2–P2–P3 53.94(6), C2–P3–P2 55.27(7), C1–P4–P1 54.67(7), P4–N1–P3 116.67(9), P4–C1–P1 72.83(8), P2–C1–P1 95.06(9), P3–C2–P2 70.79(8), P1–C2–P2 95.05(9).

In the 1,3-diphosphacyclobutane ring, the two carbon atoms protrude upwards out of the plane of the ring, as reflected in the dihedral angle at the P atoms of 19.6° . The P–C bond lengths in the 1,3-diphosphacyclobutane unit^[6] and the two diphosphirane rings^[12] of 1.842–1.896 Å are in the expected range. While one of the three-membered rings contains a relatively long P–P bond of 2.219 Å and a short P–C single bond length of 1.842 Å, the other three-membered ring has typical bond lengths.^[12] Both diphosphirane rings exhibit the typically widened internal P–C–P angles of 70.8 and 72.8° , respectively.^[12]

A firm proposal for the mechanism of formation of the azatetraphosphaquadricyclanes **7** can be made, since two intermediates were identified by NMR spectroscopic monitoring of the reaction of **5a** with **6** (Scheme 1). When the reaction is performed with a molar ratio of 2:1 under otherwise identical conditions and the solvent and unchanged **5a** are removed at 25°C and 10^{-2} mbar, a residue consisting of **7a** and the azadiphosphole **9** ($\text{R} = \text{tBu}$) is obtained. The latter is the first representative of this previously unknown class of



Scheme 1. Mechanism for the formation of **7a**.

heterocyclic compounds; its NMR data^[13] are consistent with the proposed structure. Formation of **9** presumably involves a [2+2] cycloaddition of **5a** to **6** and incorporation of a second phosphalkyne molecule into the V–N bond of the adduct to furnish **8**. Reductive elimination of VCl_3 (isolated as $\text{VCl}_3 \cdot 1.5\text{DME}$) then gives **9**. On addition of an excess of **5a** to the reaction mixture at room temperature, **9** is converted into **7a**. Firstly, an addition reaction gives the azatetraphosphanorbornadiene **10** ($\text{R} = \text{tBu}$).^[14] The retro-Diels–Alder reaction of **10** to give **11** readily explains the above-mentioned liberation of the acetylene $\text{RC}\equiv\text{CR}$. After reaction of **5c** with **6**, bis(adamant-1-yl)acetylene was isolated and identified on the basis of literature data.^[15] The conversion of **11** into **12** and the final intramolecular head-to-tail cycloaddition of the phosphalkene units^[16] to afford **7a** are equally plausible to **12** and the final intramolecular head-to-tail cycloaddition of the phosphalkene units^[16] to give **7a** are also plausible.

Cyclooligomerization reactions of the phosphalkynes **5a–e** with the strong Lewis acid **13** follow a completely different course; under comparable reaction conditions they selectively furnish the yellow 1,3,5-triphospha-benzenes **14a–e** (Table 3). The easy accessibility of the cyclotrimeriza-

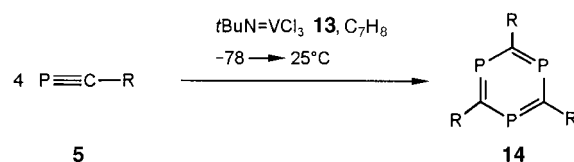


Table 3. Synthesis of the 1,3,5-triphospha-benzenes **14**.

5, 14	a	b	c	d	e
R	<i>t</i> Bu	<i>t</i> Pent			
Yield [%]	68	59	36	37	44

tion reagent **13**^[9] and the satisfactory yields (36–68%, not optimized) are major advantages compared to the previously described synthesis of **14a** via the hafnium complex **3**^[4] and thus make comprehensive studies on the reactivity of this novel heteroaromatic system possible. Cyclotrimerizations of phosphalkynes **5** with Lewis acids to give metal-free products have not been reported previously. Their spirocyclotrimerization with aluminum trichloride is noteworthy; however, in this case the metal fragment is incorporated into the product.^[17] The heteroarene **14b** is obtained as an oil, whereas **14a**, **c–e** are crystalline. The elemental analyses and comparison of the ³¹P ($\delta = 238.1–242.8$) and ¹³C NMR spectra ($\delta = 208.8–212.2$) for the skeletal atoms of **14b–e** with those of **14a**^[4] ($\delta(\text{P}) = 232.6$; $\delta(\text{C}) = 211.8$) unambiguously confirm the constitutions of the heteroarenes.

Experimental Section

7a: 5a^[18] (0.19 g, 1.90 mmol) was added to a stirred suspension of **6**^[8] (0.15 g, 0.47 mmol) in toluene (5 mL) at -78°C , and the mixture was allowed to warm to room temperature. After 12 h all volatile materials were removed at 25°C and 10^{-2} mbar. The residue was worked up by column chromatography on neutral aluminum oxide (deactivated with 4% water; column: 20×1.5 cm) with *n*-pentane as eluent. The yellow fraction was collected, the solvent evaporated, and the residue recrystallized from *n*-pentane at -78°C to give pale yellow crystals. Yield: 0.12 g (76%); m.p. 76°C .

14a: 5a^[18] (0.18 g, 1.76 mmol) was added to a stirred solution of **13**^[9] (0.10 g, 0.44 mmol) in toluene (2 mL) at -78°C , and the mixture was allowed to warm to room temperature. The solvent was evaporated at 25°C and 10^{-2} mbar and the residue purified by column chromatography on silica gel (deactivated with 4% water; column: 15×1.0 cm) with *n*-pentane as eluent. The yellow fraction was collected, and evaporation of the solvent gave pure **14a**. Yield: 0.12 g (68%); m.p. 88°C . Identification by comparison of the NMR data with those of an authentic sample.^[4]

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- [14] The typical signals of **10** are observed by NMR spectroscopic monitoring directly after thawing of the mixture; they then disappear rapidly, and the signals of **7a** appear. ³¹P NMR (81 MHz, C₆D₆): $\delta = 106.1$ (d, ³J(P,P) = 34.9 Hz), 135.7 (dd, ¹J(P,P) = 226.7 Hz, ²J(P,P) = 34.9 Hz), 314.7 (d, ¹J(P,P) = 226.7 Hz).
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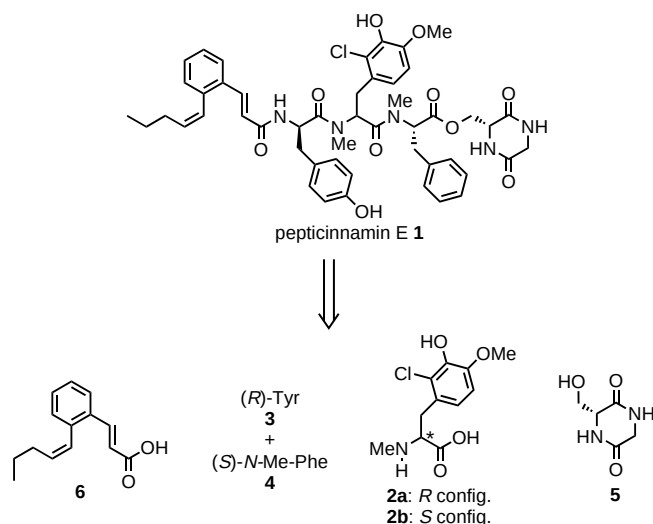
Synthesis and In Vitro Evaluation of the Ras Farnesyltransferase Inhibitor Pepticcinnamin E**

Klaus Hinterding, Patrizia Hagenbuch, Janos Rétey,* and Herbert Waldmann*

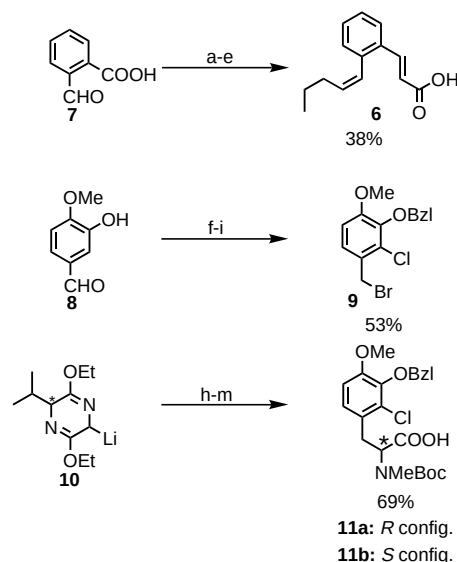
Ras proteins are S-farnesylated plasma membrane bound proteins which are decisively involved in the cellular transduction of mitogenic signals.^[1] Point mutations in the *ras* genes are found in about 40 % of all human tumors, and in more than 80 % of some of the major malignancies such as colon, breast, and pancreas cancer.^[2] To fulfill their signal-transducing function in the normal and transformed state, the Ras proteins must be farnesylated; non-lipidated Ras is cytosolic and inactive.^[2, 3] Consequently, the targeted inhibition of Ras farnesylation was identified as a promising approach to the development of new antitumor agents.^[2, 4, 5] Recent results^[5] suggest, however, that inhibitors of protein farnesyltransferase (PFT) suppress the growth of transformed cells^[6] also by blocking the farnesylation of other proteins,^[7] but their respective intracellular target sites could not yet be identified. For the study of these biological processes and the development of new drugs, alternative farnesyltransferase inhibitors are of great relevance. Inhibitors with modular structure which can be varied rapidly by combinatorial techniques are of particular interest.^[8] Furthermore, bisubstrate analogues which imitate both the farnesyl group and the peptide substrate are particularly promising; however, only a few inhibitors belonging to this class are available so far.^[9] Pepticcinnamin E (**1**, Scheme 1) is a natural PFT inhibitor from *Streptomyces* species^[10] which could meet these demands. We now report on the synthesis of both diastereomers of this unusual peptidic natural product (the absolute configuration of the central non-proteinogenic amino acid was not known) and on the evaluation of their PFT-inhibiting properties employing a recombinant protein farnesyltransferase.

Retrosynthetic analysis of pepticcinnamin E yielded, after cleavage of the amide and ester bonds, amino acids **2–4**, diketopiperazine **5**, and (pentenylphenyl)acrylic acid (**6**; Scheme 1). Acid **6**^[11] was synthesized from the commercially available aldehyde **7** (Scheme 2). The methyl ester was first prepared and subjected to a *cis*-selective Wittig reaction to give the alkene. The ester was converted into the benzaldehyde by a two-step sequence; a subsequent completely *trans*-selective Knoevenagel condensation with malonic acid provided **6**.

The non-proteinogenic amino acids **11a** and **11b** were synthesized in enantiomerically pure form by the Schöllkopf



Scheme 1. Retrosynthetic analysis of pepticcinnamin E (**1**).



Scheme 2. Synthesis of the pepticcinnamin E fragments **6**, **9**, **11a**, and **11b**. a) MeI, K₂CO₃, acetone, 76 %; b) Ph₃P=C₆H₉, THF, –100 °C, 84 %, d.r. = 92:8; c) LiAlH₄, THF, 97 %; d) PCC, CH₂Cl₂, 96 %; e) CH₂(COOH)₂, pyridine, piperidine, 70 %; f) Cl₂, CH₂Cl₂, 68 %; g) BzlBr, K₂CO₃, DMF, 93 %; h) NaBH₄, MeOH, then H₂O, 99 %; CBr₄, PPh₃, Et₂O, 85 %; j) **9**, THF, –78 °C, 85 %, d.r. = 95:5; k) 0.5 N HCl, THF, then Boc₂O, NEt₃, MeOH, 88 %; l) LiOH, THF, H₂O, 99 %; m) NaH, MeI, THF, 96. Bzl = benzyl, PCC = pyridinium chlorochromate.

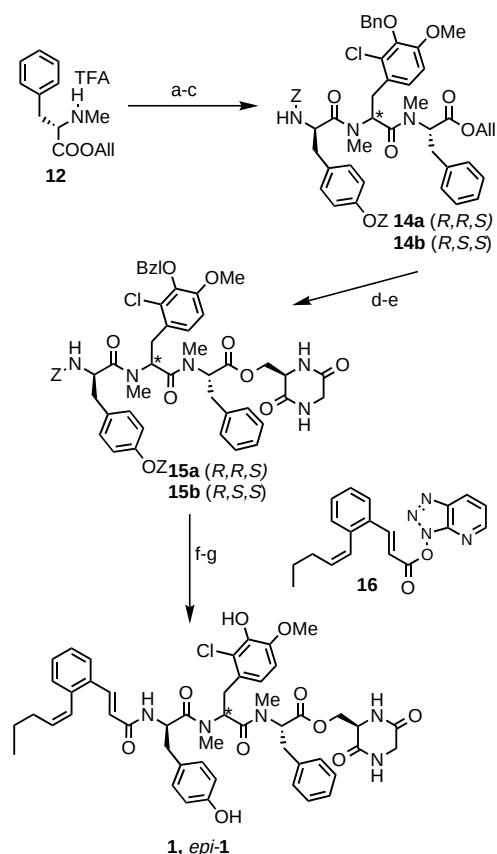
bis(lactim ether) method^[12] (Scheme 2). The benzyl bromide **9** was made from the phenol **8**. First the chlorine substituent was introduced regioselectively at the *ortho* position by treatment with liquid chlorine in dichloromethane to yield the 1,2,3,4-tetrasubstituted arene. After protection of the phenol as benzyl ether the aldehyde could be reduced to the benzyl alcohol, which was converted into the benzyl bromide **9** with the Appel reagent. The alkylation of the lithiated bis(lactim ether) **10** proceeded in 85 % yield and with a diastereomer ratio (d.r.) of 95:5. After cleavage of the bis(lactim ether)s and masking of the liberated amino termini as *tert*-butyloxycarbonyl (Boc) urethanes, the chiral auxiliary was separated by chromatography. Saponification of the ethyl ester with lithium

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hydroxide and selective N-methylation of the Boc-urethane completed the synthesis of both enantiomers of the desired amino acid (**11a** and **11b**).

For the construction of both epimers of the central tripeptide (**14a** and **14b**), the respective (*R*)- or (*S*)-amino acid **11a** or **11b** was coupled with the phenylalanine derivative **12**, and after removal of the Boc group the amino acid chain was elongated with bis(benzyloxycarbonyl)-protected tyrosine **13** to yield **14a** or **14b** (Scheme 3). After Pd⁰-mediated selective cleavage of the C-terminal allyl ester,



Scheme 3. Synthesis of pepticinnamin E (**1**). a) **11a** or **11b**, EDC, HOAt, DMF, 81% for *S,S* enantiomer, 77% for *R,S* enantiomer; b) HCl, Et₂O, quant.; c) Z-(*R*)-Tyr-(Z) (**13**), EDC, HOAt, DMF, 75% (77%); d) [Pd(PPh₃)₄], morpholine, CH₂Cl₂, 89% (88%); e) DEAD, PPh₃, **5**, DMF, 53% (55%); f) H₂, Pd/C, HOAc, EtOH; g) **16**, DMF, 31% (33%) over two steps. DEAD = diethyl azodicarboxylate, EDC = *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide.

the required diketopiperazine **5** was introduced. Whereas several established methods for the formation of esters^[13] gave unsatisfactory results, the activation of the alcohol **5** under Mitsunobu conditions^[14] was the method of choice. The three benzyl protecting groups in esters **15a** and **15b** thus obtained were removed simultaneously by Pd-catalyzed hydrogenolysis. The liberated amino group was then selectively acylated with cinnamic acid derivative **16**, which was preactivated as the 7-aza-1-hydroxy-1*H*-benzotriazole (HOAt) ester, to give the natural product **1** or its diastereomer *epi-1*. Comparison of the retention times in HPLC with four different eluents, the ¹H NMR spectra (500 MHz), and

the specific rotation of the synthetic compounds with reference values for an authentic sample of the natural product^[15] proved that the central amino acid has the *S* configuration.

The inhibition of Ras farnesyltransferase was determined with an in vitro assay in which the enzyme-catalyzed farnesyl transfer from farnesylpyrophosphate (FPP) to a dansyl-labeled (dansyl = 5-(dimethylamino)naphthalene-1-sulfonyl) substrate peptide (Gly-Cys-Val-Leu-Ser, GCVLS) is followed fluorometrically.^[16] The enzyme used was a recombinant Ras farnesyltransferase from *Saccharomyces cerevisiae*^[18] which was cloned into the plasmid pT7-7 and overexpressed in the *Escherichia coli* BL21 system.^[17] In this expression system the viral Φ 10 promoter, which stems from bacteriophage T7, guarantees a high transcriptional efficiency. An effective translation is obtained by means of a ribosomal binding site (RBS, also called a Shine–Dalgarno sequence) in front of the start codon. Furthermore, the transcription does not depend on a bacterial but on a viral T7 polymerase, whose gene is integrated into the genome of the *E. coli* BL21 cells. To express the farnesyltransferase the genes *dpr1* and *ram2*, which encode the two subunits of the heterodimeric enzyme, were isolated from the yeast plasmids YEP13 and YEP24,^[18] and an *Nde*I restriction site was introduced by site-directed mutagenesis with a polymerase chain reaction (PCR). This restriction site contains the start codon and guarantees a correct distance to the Shine–Dalgarno sequence, so that both genes inserted into the vectors are in the correct reading frame. Both genes were cloned into the pT7-7 plasmid through this restriction site. Since the vector contains only one resistance gene (the gene for ampicillin resistance, *amp*^r), only one recombinant plasmid can be used for the expression. Thus, from the pT7-7/*dpr1* plasmid the gene sequence and the RBS were cut out ($\rightarrow$ *dpr1* + RBS), the pT7-7/*ram2* plasmid was cleaved, and the fragment *dpr1* + RBS was inserted. The obtained plasmid (Figure 1) was introduced into *E. coli* BL21 cells, and the recombinant bacteria were used for the expression.

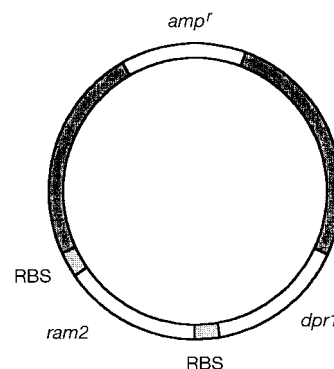


Figure 1. The pT7-7 plasmid used for the expression along with the two farnesyltransferase genes *dpr1* and *ram2*.

Analysis of the kinetic data by a Lineweaver–Burk plot (Figure 2) showed that the natural product is a competitive inhibitor with respect to both the peptide substrate and FPP. The determined *K*₁ and *K*_M values are given in Table 1. In addition, the IC₅₀ values for **1**, its diastereomer *epi-1*, and the

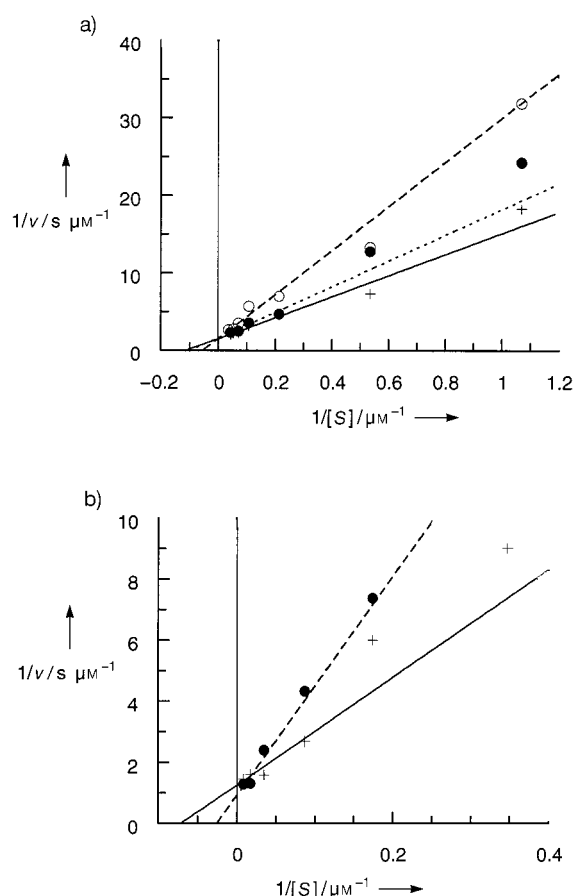


Figure 2. Lineweaver–Burk plots from which the K_i values for the inhibition of PFT by **1** were determined. For each measurement the reaction mixture (total volume 400 μL) contained 4 μg of enzyme (partially purified), 50 mM tris(hydroxymethyl)aminomethane (Tris)/HCl (pH = 7.5), 5 mM dithiothreitol, 5 mM MgCl_2 , and 10 μM ZnCl_2 . a) Inhibition with respect to the peptide substrate at a constant concentration of FPP (75 μM) and different concentrations c of the inhibitor **1**: $c=0$ (+, –), 5.5 (○, ----), and 27.5 μM (○, ----). b) Inhibition with respect to FPP at a constant concentration of the peptide substrate (84.3 μM) and $c=0$ (+, –) and 13.75 μM (○, ----). S = substrate, v = rate of reaction.

Table 1. K_M and K_i values determined from Michaelis–Menten and Lineweaver–Burk plots.

K_M [μM]		K_i [μM]	
dansyl-GCVLS	FPP	dansyl-GCVLS	FPP
9	14	30	8

tripeptide derivatives **14a** and **14b** as well as **17a** and **17b** were determined. These values, given in Table 2, demonstrate that the absolute configuration of the central amino acid is decisive for the inhibitory activity. On the one hand the natural product **1** is about six times stronger an inhibitor than its epimer *epi-1*, and, on the other hand, only acid **17b** of R,S,S configuration, but not the epimeric acid **17a** of R,R,S configuration, shows inhibitory activity under the conditions of the assay. In addition, the data prove that the C- and N-terminal modifications of the natural products are not important for inhibition of the farnesyl transfer (Table 2, entry 2).

In conclusion, we have synthesized the natural product peptidinnamin E for the first time and shown that it is a

Table 2. IC_{50} values determined for peptidinnamin E (**1**) and several synthetic derivatives.

Entry	Compound	IC_{50} [μM]
1	14a (R,R,S)	— ^[a]
	14b (R,S,S)	— ^[a]
2	17a (R,R,S)	— ^[a]
	17b (R,S,S)	67
3	peptidinnamin E 1	42
4	<i>epi</i> -peptidinnamin E <i>epi-1</i>	237

[a] No inhibition.

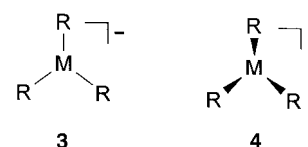
bisubstrate inhibitor for a recombinant farnesyltransferase. Furthermore, several structural parameters were identified which decisively influence the inhibition. With combinatorial synthesis further analogues of this modularly built farnesyltransferase inhibitor should be available rapidly and efficiently. These inhibitors should open up new opportunities for the study and suppression of the farnesylation of different proteins involved in cellular signal transduction cascades and the transformation of cells.

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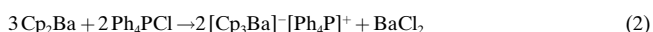
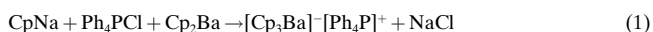
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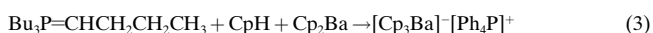


First results of our studies on $[\text{Cp}_3\text{M}]^-$ complexes of the alkaline earth metals are presented here: the synthesis and structure elucidation of $[\text{Cp}_3\text{Ba}]^-$ in the presence of a weakly coordinating cation.

$[\text{Cp}_3\text{Ba}]^-$ can be synthesized simply by treating Cp_2Ba with a free Cp anion. Accordingly, several synthetic strategies can be employed. Free Cp anions can be generated in situ from CpNa and $\text{Ph}_4\text{PCl}^{[4]}$ and then treated with Cp_2Ba [Eq. (1)]. Another possibility is the direct reaction of Cp_2Ba with a stoichiometric quantity of Ph_4PCl [Eq. (2)].



A drawback of both methods is the possible formation of side products such as $[\text{Cp}_2\text{Na}]^-$, $[\text{Cp}_2\text{BaCl}]^-$, $[\text{CpBaCl}_2]^-$, and other mixed compounds containing a variety of ions (Ba^{2+} , Na^+ , Cp^- , and Cl^-). Therefore, a new method for the generation of Cp anions was developed: a Wittig reagent is mixed with cyclopentadiene to give $[\text{Cp}^-][\text{R}_4\text{P}]^+$, which can be directly treated with Cp_2Ba [Eq. (3)].



The crystals obtained from this reaction mixture^[5] had the composition $[\text{Cp}_3\text{Ba}]^- [\text{Ph}_4\text{P}]^+ [\text{thf}]$.^[6] The $[\text{Cp}_3\text{Ba}]^-$ units form a linear coordination polymer (Figure 1) in which the

$[\text{Cp}_3\text{Ba}]^-$: The First Structurally Characterized Barate Complex**

Sjoerd Harder*

In 1994 we reported that the in situ generation of “free” cyclopentadienyl (Cp) anions in the presence of CpLi resulted in the formation of the lithocene anion (**1**).^[1] The structure of this complex is remarkably similar to that of its diagonally related neighbor magnesocene (**2**). Analogously, the treatment of Cp_2M (M = alkaline earth metal) with Cp anions could yield a $[\text{Cp}_3\text{M}]^-$ species. A thorough structural study on such compounds is justified for several reasons.

1. Although a few magnesium complexes of the type $[\text{R}_3\text{Mg}]^-$ have been structurally characterized,^[2] at present no structural data are available for heavier alkaline earth metal complexes $[\text{R}_3\text{Ca}]^-$, $[\text{R}_3\text{Sr}]^-$, or $[\text{R}_3\text{Ba}]^-$.
2. How do the structures of $[\text{Cp}_3\text{M}]^-$ species (M = alkaline earth metal) compare to those of the isovalent Group 3 and Group 13 neighbors?
3. The divalent metallocenes of the heavier alkaline earth metal complexes have an unexpected preference for bent geometries, a structural feature that has attracted and still attracts much attention.^[3] A similar trend may be found for the $[\text{Cp}_3\text{M}]^-$ complexes of the heavier alkaline earth metals. Will the metal center then prefer a planar (**3**) or a pyramidal (**4**) coordination geometry?

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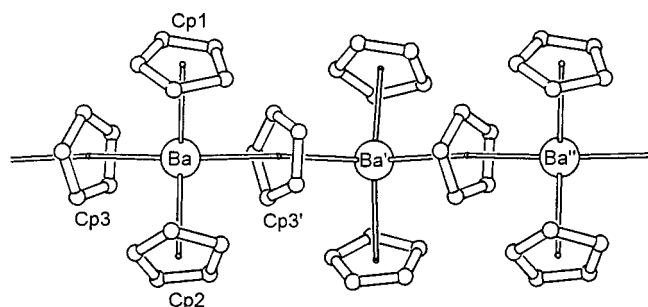


Figure 1. Structure of the linear $[\text{Cp}_3\text{Ba}]_\infty$ chain. All Cp rings are bound to Ba in an η^5 fashion. For the following Ba–C distances [Å] to the rings Cp1, Cp2, Cp3, and Cp3', the range of Ba–C distances, the mean Ba–C distances, and the Ba–Cp_C distances are given. Cp1: 3.067(5)–3.184(6), 3.123(6), 2.898(6); Cp2: 3.047(7)–3.159(6), 3.096(6), 2.876(6); Cp3: 3.091(7)–3.168(7), 3.129(6), 2.916(6); Cp3': 3.123(7)–3.220(7), 3.169(7), 2.969(6). The Cp_C–Ba–Cp_{C'} angles lie in the range 106.4(3)–114.6(3)°.

Ba^{2+} cations are tetrahedrally surrounded by four Cp anions. Both the terminal and the bridging Cp anions are bound in an η^5 fashion to the barium centers. The Ba–C distances of the terminal and bridging Cp rings are remarkably similar. The barate $[\text{Cp}_3\text{Ba}]^-$ is the first structurally characterized unsubstituted Cp–Ba complex. The average Ba–Cp_C distance (Cp_C

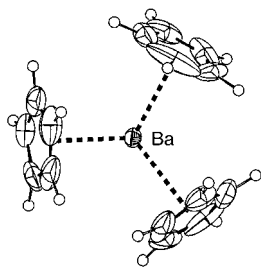


Figure 2. ORTEP plot of the $[\text{Cp}_3\text{Ba}]^-$ unit (50% probability ellipsoids). The large ellipsoids indicate the rotational disorder around the $\text{Ba}-\text{Cp}_c$ axes.

represents the geometrical center of the Cp ring) of 2.915(7) Å is considerably longer than that of the decamethyl-substituted barocene Cp_2^*Ba (av. $\text{Ba}-\text{Cp}_c$ 2.733(6) Å).^[34] Rotational disorder of the Cp rings around the Cp_c-Ba axis (Figure 2) indicates a low barrier for rotation of the Cp rings. This was also observed in the structures of the lithocene^[1] and sodocene^[4] anions.

The parallel $[\text{Cp}_3\text{Ba}]_\infty^-$ chains are bridged by intervening Bu_4P^+ cations, of which the most acidic PCH_2 protons exhibit short intermolecular $\text{CH}\cdots\text{Cp}^-$ distances to the terminal Cp anions (Figure 3). These interactions can be regarded as $\text{CH}\cdots\text{Cp}$ hydrogen bonds between

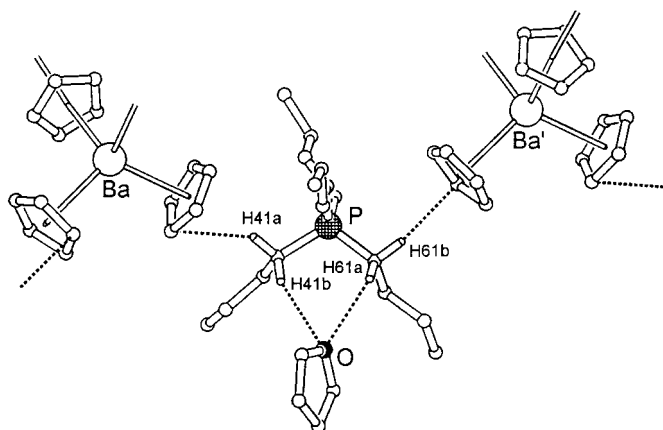
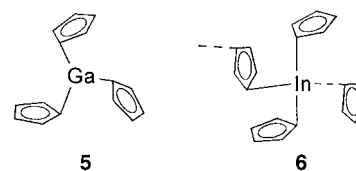


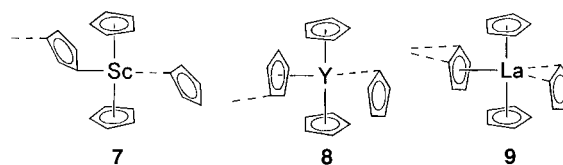
Figure 3. View of the $[\text{Bu}_4\text{P}]^+$ ion and its interaction with the barate chains. The linear $[\text{Cp}_3\text{Ba}]_\infty^-$ chains are bridged by $[\text{Bu}_4\text{P}]^+$ units. The shortest $\text{CH}\cdots\text{C}$ hydrogen bonds (distances [Å]; angles [°]) are $\text{C}-\text{H}41\text{a}\cdots\text{C}$ ($\text{C}-\text{C}$ 3.529(8), $\text{H}-\text{C}$ 2.65; $\text{C}-\text{H}-\text{C}$ 147) and $\text{C}-\text{H}61\text{b}\cdots\text{C}$ ($\text{C}-\text{C}$ 3.536(8), $\text{H}-\text{C}$ 2.68; $\text{C}-\text{H}-\text{C}$ 144). Short $\text{CH}\cdots\text{O}$ hydrogen bonds: $\text{C}-\text{H}41\text{b}\cdots\text{O}$ ($\text{C}-\text{O}$ 3.586(9), $\text{H}-\text{O}$ 2.66; $\text{C}-\text{H}-\text{O}$ 153) and $\text{C}-\text{H}61\text{a}\cdots\text{O}$ ($\text{C}-\text{O}$ 3.454(9), $\text{H}-\text{O}$ 2.65; $\text{C}-\text{H}-\text{O}$ 138). All carbon atoms of the THF molecule are disordered over two positions (the average positions are shown).

the $\text{C}^\delta--\text{H}^\delta+$ dipole and the negatively charged π -electron system of the Cp ring.^[7] The shortest $\text{CH}\cdots\text{Cp}$ distances of 2.65 and 2.68 Å are much shorter than the sum of the van der Waals radii of C and H (2.90 Å) and also shorter than the $\text{CH}\cdots\text{Cp}$ hydrogen bond of 2.72 Å in the crystal structure of $[\text{Cp}]^--[\text{Ph}_4\text{P}]^+$.^[4] This is due to the much higher acidity of a tetrabutylphosphonium group compared to a tetraphenylphosphonium group.^[8] In addition, a THF molecule interacts with two other PCH_2 protons (Figure 3). The short $\text{H}-\text{O}$ distances of 2.65 and 2.66 Å of the intermolecular $\text{CH}\cdots\text{O}_{\text{THF}}$ interactions are in the range observed for other $\text{CH}\cdots\text{O}$ hydrogen bond interactions.^[9]

How does the structure of the barate anion $[\text{Cp}_3\text{Ba}]^-$ compare to those of its isovalent Group 3 and Group 13 neighbors? The compound Cp_3Ga (**5**) is a monomer with three η^1 -Cp groups and trigonal-planar coordination geometry at the metal center.^[10] The complex Cp_3In (**6**) forms a

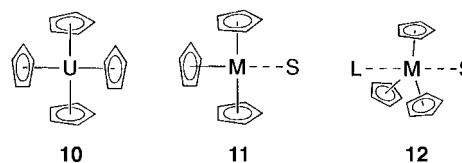


linear polymer chain with a tetrahedral arrangement of ligands. The Cp rings are bound to the metal center with a total hapticity of four.^[11] The analogous Group 3 Cp_3M complexes **7–9** form coordination polymers in which the total hapticity



at the metal center increases with increasing ionic radius of the metal cation: $\text{Cp}_3\text{Sc}^{[12]} < \text{Cp}_3\text{Y}^{[13]} < \text{Cp}_3\text{La}^{[14]}$. Therefore, the polymeric structure of $[\text{Cp}_3\text{Ba}]^-$ with fourfold η^5 -Cp–Ba coordination is not unexpected (the Ba^{2+} cation is, apart from the unstable isotopes Fr^+ and Ra^{2+} , the second largest cation in the periodic table).

The η^{20} coordination sphere of the Ba^{2+} ion is similar to that in monomeric $[\text{Cp}_4\text{U}^{\text{IV}}]$ (**10**), in which the uranium atom is tetrahedrally surrounded by four η^5 -Cp ligands.^[15] In solution the $[\text{Cp}_3\text{Ba}]_\infty^-$ polymer chain is probably broken into solvated monomers. Such solvated monomers could resemble the monosolvates **11**^[16] or disolvates **12**^[17] ($\text{S} = \text{solvent}$) of structurally characterized Cp_3M lanthanide complexes.



High-level ab initio calculations^[18] on $[\text{Ba}(\text{H}_2\text{O})_3]^{2+}$ suggest a preference for a pyramidal coordination geometry at the metal center, although the energy difference to the planar geometry is only 0.4 kcal mol⁻¹. At the same level of theory, a bent $[\text{Ba}(\text{H}_2\text{O})_2]^{2+}$ complex is 1.0 kcal mol⁻¹ more stable than its linear form. The calculations on $[\text{Ba}(\text{H}_2\text{O})_3]^{2+}$ and $[\text{Ba}(\text{H}_2\text{O})_2]^{2+}$ ^[18] indicate that the energy difference between a pyramidal and a planar barate is even smaller than that between a bent and a linear barocene. Experimental verification of the preferred coordination geometry at a three-coordinate Ba^{2+} ion will probably be difficult. The occurrence of $[\text{Cp}_3\text{Ba}]^-$ as a polymeric solid structure does not allow any discussion of the preferred ligand arrangement in a barate anion (planar or pyramidal).

The fourfold η^5 -Cp–Ba coordination in $[\text{Cp}_3\text{Ba}]_\infty^-$ suggests that a dianionic species $[\text{Cp}_4\text{Ba}]^{2-}$ possibly could be isolated as well. Although under certain conditions $[\text{Cp}_4\text{Ba}]^{2-}[\text{X}]_2^+$ complexes can be isolated, many attempts to determine their crystal structures have hitherto failed owing to twinning

problems. Even the use of the less symmetric MeCp anion as a ligand only yielded twinned crystals.^[19]

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Solid-Phase Supported Synthesis of the Branched Pentasaccharide Moiety That Occurs in Most Complex Type N-Glycan Chains**

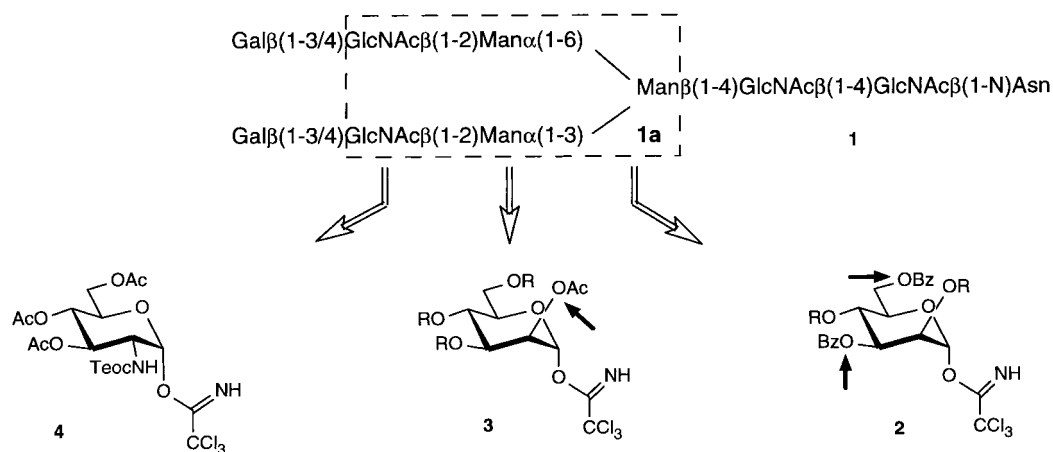
Jörg Rademann, Armin Geyer, and Richard R. Schmidt*

N-glycosylation is a well-known feature of many natural polypeptides in eukaryotic organisms that contributes to their structural as well as functional properties.^[1] It determines among others the stability, folding, and intracellular transport of proteins, and is required for cellular adhesion in events such as inflammation, immunogenicity, and metastasis. Unfortunately, naturally occurring N-glycans display a high degree of structural diversity, and an array of different carbohydrate isoforms are synthesized even on one type of protein. Varied glycan patterns are expressed in different types of tissues and at different stages of embryonic development. Consequently, for the chemical synthesis of these compounds^[2] an approach is needed that intrinsically permits a high degree of variation and the application of combinatorial^[3] as well as split-synthesis techniques to supply a broad array of natural and

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Scheme 1. Retrosynthesis of the building block **1a**. R = Bn; Teoc = trichloroethoxycarbonyl.

unnatural structures. We present here the first solid-phase synthesis of the branched pentasaccharide moiety **1a** (Scheme 1) that occurs in most complex type *N*-glycan chains **1**. The solid-phase methodology demonstrated should be applicable for the generation of molecular diversity of *N*-glycan structures with some generality.

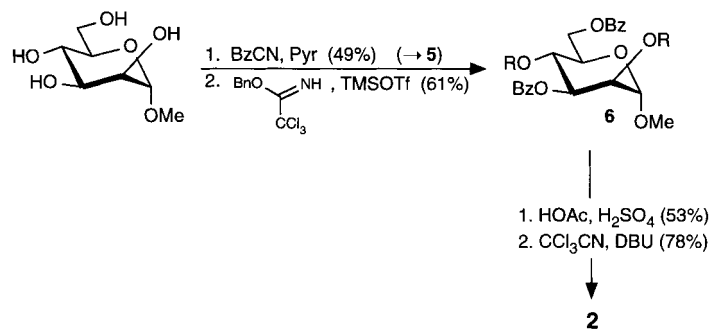
Solid-phase synthesis of oligosaccharides on polystyrene resins has recently been investigated in several research groups.^[3b, 4, 5] Preliminary studies with other polymers as the solid phase have also been performed.^[6, 7] However, the yields often drop dramatically for a repeated glycosylation protocol.^[5a]

Recently, we introduced a novel strategy for the synthesis of oligosaccharides on a solid support^[8, 9] in which an alkylthiol linker is coupled to a chloromethylated Merrifield resin; then the first sugar is attached in a standard glycosylation procedure with an *O*-glycosyl trichloroacetimidate as glycosyl donor. In this way a thioglycoside linkage is generated, which is resistant to the standard glycosylation conditions for *O*-glycosyl trichloroacetimidates as donors and to removal of various protective groups. However, this linkage is rapidly cleaved with different thiophilic reagents; thus, all the reaction steps can be monitored readily on the solid phase: the supernatant of the cleavage reaction from a small resin sample can be analyzed spectroscopically after a few minutes either by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) or by chromatographic methods. So far, this concept has essentially been employed for the synthesis of glucose (1 → 6) oligomers and of mannose α(1 → 2) oligomers.^[8, 9] The demanding pentasaccharide target chosen (**1a**)^[10] should serve to demonstrate the general validity of this concept, since regio- and stereo-selective α- and β-glycoside bond formation, respectively, is required. Additionally, the target molecule demands double glycosylation of a sugar substrate in one step, a feature that has to our knowledge not been demonstrated on solid phase so far.

Pentasaccharide **1a** consists of three differently linked sugar residues, which necessitates a corresponding protective group pattern for each of these building blocks. In solid-phase syntheses benzyl protective groups are best employed for permanent protection, and readily removable acyl groups are

generally most appropriate for temporary protection; anomeric control is achieved by anchimeric assistance, and glycosyl donor properties are generated by trichloroacetimidate formation. This protocol leads to *O*-(3,6-di-*O*-benzoyl-2,4-di-*O*-benzyl-α-D-mannopyranosyl)trichloroacetimidate (**2**) as the mannosyl residue to be attached first to the resin linker; the demands for the two mannosyl residues should be accommodated by *O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)trichloroacetimidate (**3**); finally, attachment of the two *N*-acetylglucosamine residues should be possible with *O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroethoxycarbonyl-amino-α-D-glucopyranosyl)trichloroacetimidate (**4**).

Trichloroacetimidate **2** can be readily prepared (Scheme 2): regioselective 3,6-di-*O*-benzoylation of commercially available methyl α-D-mannopyranoside (→**5**) and then benzylation



Scheme 2. Synthesis of the trichloroacetimidate **2**. R = Bn.

with *O*-benzyl trichloroacetimidate^[11] in the presence of TMSOTf as catalyst afforded fully protected methyl α-mannoside derivative **6**; the corresponding methyl β-mannoside was not detected. Acid-catalyzed cleavage of the glycosidic linkage and then treatment with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded **2** in good yield (Table 1). Trichloroacetimidates **3** and **4** were prepared as previously described.^[12, 13]

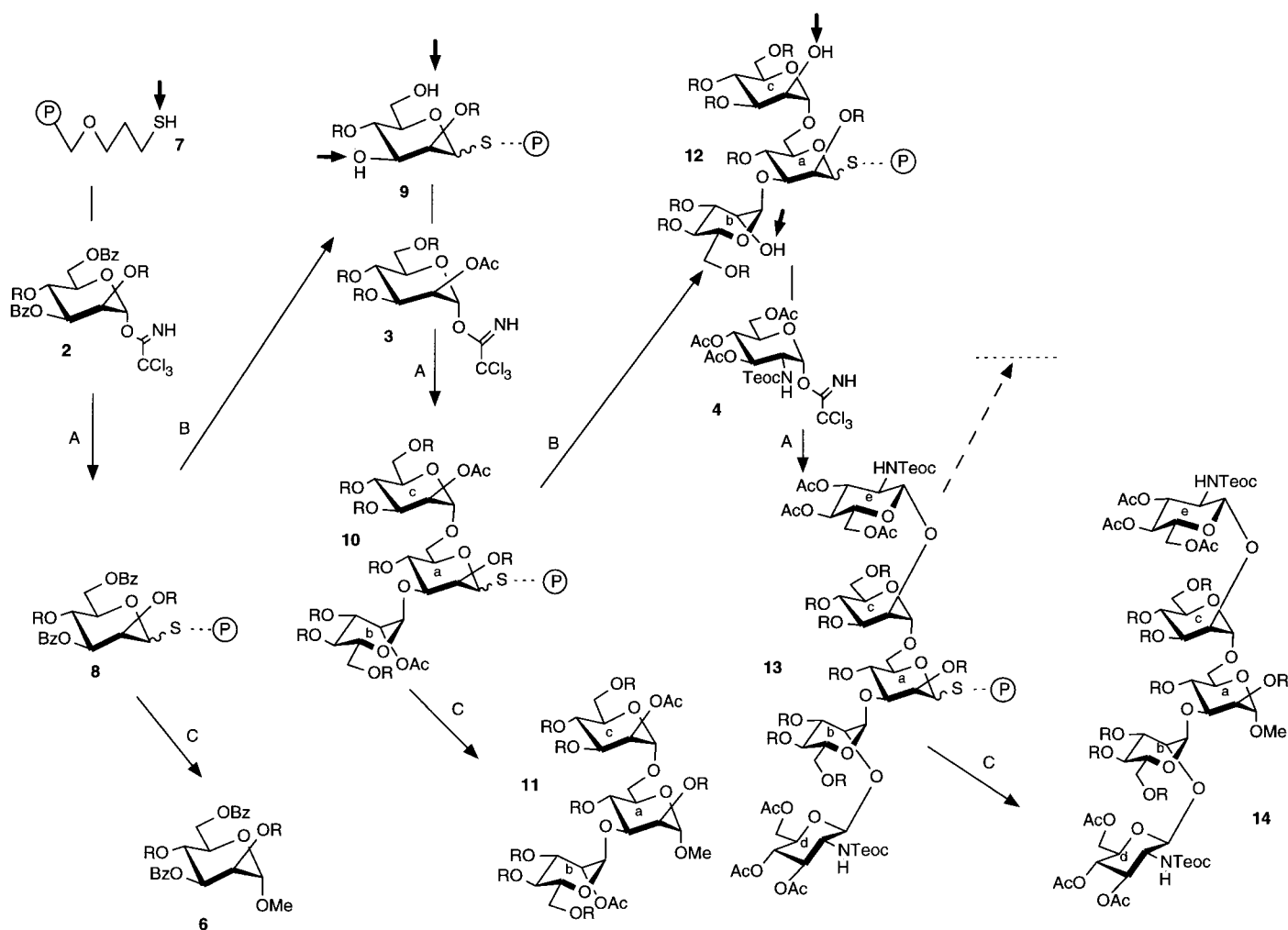
Sulfanylpropyloxymethyl-functionalized Merrifield resin (**7**) was employed for the solid-phase synthesis; this has a loading of 0.15 mmol g⁻¹ based on the dry resin.^[9] Swelling of **7** in CH₂Cl₂ (Scheme 3) and then reaction with **2** (3 equiv) in the

Table 1. Selected physical data of **2**, **6**, **11**, and **14**.

2 : ^1H NMR (250 MHz, CDCl_3): δ = 4.20–4.32 (m, 2H, 2-H, 5-H), 4.39 (dd, $J_{3,4}$ = 8.9, $J_{4,5}$ = 8.9 Hz, 1H, 4-H), 4.55–4.82 (m, 6H, 2 6-H, 2 CH_2 -Ph), 5.64 (dd, $J_{2,3}$ = 4.6, $J_{3,4}$ = 8.9 Hz, 1H, 3-H), 6.45 (d, $J_{1,2}$ = 2.3 Hz, 1H, 1-H), 7.1–8.1 (m, 20H, 4 Ph), 8.67 (s, 1H, NH). $[\alpha]_{\text{D}}^{25}$ = +34.6 (c = 1.0 in CHCl_3)
6 : ^1H NMR (250 MHz, CDCl_3): δ = 3.42 (s, 3H, OCH_3), 4.03 (dd, $J_{1,2}$ = 2.0, $J_{2,3}$ = 3.2 Hz, 1H, 2-H), 4.0–4.1 (m, 1H, 5-H), 4.27 (dd, $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.5 Hz, 1H, 4-H), 4.55–4.8 (m, 6H, 2 6-H, 2 CH_2 -Ph), 4.84 (d, $J_{1,2}$ = 1.9 Hz, 1H, 1-H), 5.59 (dd, $J_{2,3}$ = 3.2, $J_{3,4}$ = 9.5 Hz, 1H, 3-H), 7.0–8.2 (m, 20H, 4 Ph). $[\alpha]_{\text{D}}^{25}$ = +22.4 (c = 1.0 in CHCl_3)
11 : ^1H NMR (600 MHz, CDCl_3): mannosyl residue a: δ = 4.63 (d, $J_{1,2}$ < 2 Hz, 1H, 1-H), 3.78 (2-H), 4.10 (3-H), 3.84 (4-H), 3.63 (5-H), 3.63, 3.82 (2 6-H); mannosyl residue b: δ = 5.16 (d, $J_{1,2}$ = 1.7 Hz, 1H, 1-H), 5.48 (2-H), 4.00 (3-H), 3.79 (4-H), 3.76 (5-H), 3.58, 3.70 (2 6-H); mannosyl residue c: δ = 4.94 (d, $J_{1,2}$ = 1.9 Hz, 1H, 1-H), 5.44 (2-H), 3.93 (3-H), 3.87 (4-H), 3.92 (5-H), 3.66 (2 6-H)
14 : ^1H NMR (600 MHz, CDCl_3): sugar residue a: δ = 5.17 (d, $J_{1,2}$ < 2 Hz, 1H, 1-H), 3.78 (2-H), 4.15 (3-H), 4.22 (4-H), 3.80 (5-H), 3.74, 4.29 (2 6-H); sugar residue b: δ = 5.06 (d, $J_{1,2}$ = 1.9 Hz, 1H, 1-H), 3.93 (2-H), 3.79 (3-H), 3.72 (4-H), 3.62 (5-H), 3.52 (2 6-H); sugar residue c: δ = 4.89 (d, $J_{1,2}$ = 6.5 Hz, 1H, 1-H), 4.02 (2-H), 3.95 (3-H), 3.59 (4-H), 3.82 (5-H), 3.39 (2 6-H); sugar residue d: δ = 3.90 (d, $J_{1,2}$ = 8.5 Hz, 1H, 1-H), 3.47 (2-H), 4.83 (3-H), 4.87 (4-H), 2.89 (5-H), 3.93, 4.05 (2 6-H); sugar residue e: δ = 4.92 (d, $J_{1,2}$ = 8.6 Hz, 3.84 (2-H), 5.04 (3-H), 5.04 (4-H), 3.17 (5-H), 3.79, 4.01 (2 6-H)

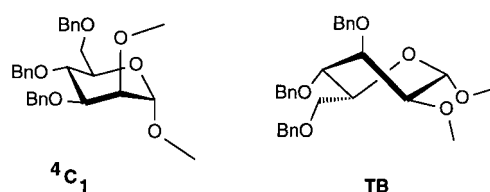
presence of TMSOTf as catalyst (0.15 equiv; Procedure A, see Experimental Section) afforded mannosylated resin **8**, as indicated after cleavage with *N*-bromosuccinimide (NBS) and di-*tert*-butylperoxide (DTBP) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (Procedure C) by MALDI-TOF analysis and NMR spectroscopy, yielding known methyl mannoside **6** (see Scheme 2). The temporary *O*-benzoyl protective groups in **8** could be readily removed by treatment with NaOMe/MeOH in MeOH/ CH_2Cl_2 (Procedure B). Washing with THF and CH_2Cl_2 led to 3,6-*O*-unprotected **9**, as indicated after cleavage from a small resin sample with AgOTf/MeOH (Procedure D).

Repetition of this sequence of reactions could be successfully carried out. Thus, reaction of **9** with **3** (Procedure A) gave trisaccharide **10**. MALDI-TOF-MS analysis of a small resin sample (Procedure D) showed a signal corresponding to the M^+ ion of **11** as the only detectable peak above m/z 380. Trisaccharide **10** was cleaved from the resin (Procedure C) to afford trisaccharide **11** in 38% overall yield; the corresponding β -derivative was not detected. Compound **11** could be fully characterized by ^1H NMR spectroscopy (Table 1). De-*O*-acetylation of **10** (Procedure B) furnished 2b,2c-*O*-unprotected trisaccharide **12** (Procedure D), which on treatment with donor **4** (Procedure A) led to resin-bound pentasaccharide **13**.



Scheme 3. Synthesis of the pentasaccharide **14**, R = Bn. A) TMSOTf (0.15 equiv), CH_2Cl_2 , room temperature; B) NaOMe, MeOH/THF or CH_2Cl_2 ; C) NBS, DTBP, $\text{CH}_2\text{Cl}_2/\text{MeOH}$; washing with CH_2Cl_2 and THF.

Cleavage from the resin (Procedure C) gave the desired methyl- α pentasaccharide **14** in 20% overall yield starting from **7**; this yield encompasses formation of five glycosidic linkages, removal of four acyl groups, and product cleavage from the resin under formation of a methyl α -glycoside (i.e. ca. 85% yield per reaction event). The pentasaccharide **14** could be fully characterized by ^1H NMR data (Table 1); the data for the mannosyl residue c exhibit an unusual twist boat (TB) conformation (Scheme 4). The structural assignments derived from NMR data indicate that the $\alpha(1\rightarrow2)$ linkage between mannosyl residues e and c is retained. Evidently, voluminous axial substituents in ring positions 1 and 2 destabilize the $^4\text{C}_1$ conformation of mannosyl residue c in **14** (but not in **11**!). The conformational equilibrium is shifted to a



Scheme 4.

twist boat. The coupling constants supporting this assignment are summarized in Table 2; they are taken from a Lorentz-to-Gauss transformed ^1H NMR spectrum and from selective TOCSY spectra (600 MHz).

Table 2. Expected and detected $^3J_{\text{H,H}}$ coupling constants [Hz] for the α -linked mannosyl residue c in **14**.

Expected ($^4\text{C}_1$ conformation)	Detected	
1-H/2-H	1.9	6.5
2-H/3-H	3.3	ca. 2 (not resolved)
3-H/4-H	9.3	2.4
4-H/5-H	9.7	7.1

In conclusion, the synthetic protocol for the solid-phase synthesis of oligosaccharides described in this paper enables repetitive stereoselective glycosylations, controlled partial deprotection, and resin cleavage in high yields, thus permitting the synthesis of oligosaccharides possessing quite complex and demanding structures. Oligosaccharide residues, for instance, found in mammalian systems, contain a limited number of different sugars, also their linkage site and stereochemistry, though manifold, is not unlimited. Therefore, the design of proper building blocks is now an important goal in order to establish a versatile methodology for fast and efficient solid-phase supported syntheses of a great variety of oligosaccharides.

Experimental Section

A) Protocol for the solid-phase glycosylation: A glass tube (8 $\times$ 80 mm) was used as reaction vessel; this vessel was tightly sealed with Teflon stoppers, fitted with a glass filter inlet to allow reactants to be added to the mixture under inert gas conditions. Dry functionalized resin (containing 0.033 mmol of **7**, **9**, or **12**) was placed under argon in the described tube. Trichloroacetimidate donor (0.1 mmol per free hydroxy group) is dissolved in CH_2Cl_2

(2 mL) and added under argon to the resin. After shaking the mixture for 15 min trimethylsilyl trifluoromethanesulfonate (TMSOTf) (30 μL of a 0.5 M solution in CH_2Cl_2) was injected and the stoppered glass tube was shaken in a horizontal position for 1 h with a mechanical shaker. Then the resin was filtered off and washed by switching between CH_2Cl_2 and THF several times and finally dried with a stream of dry argon and then in vacuo. For the glycosylation leading to the resin-bound pentasaccharide **13**, the described glycosylation procedure was repeated to ensure complete glycosylation of all hydroxy groups.

B) Protocol for the solid-phase deacylation: Glycosylated resin (ca. 0.03 mmol) was placed in the reaction vessel and suspended in CH_2Cl_2 (2.5 mL), and 0.5 M NaOMe in MeOH was added (0.25 mL). The glass tube was shaken in a horizontal position for 2 h; a prolonged reaction time of 6 h was required for the removal of benzoyl protective groups. Then the resin was filtered off and washed in a batchwise procedure first with a 0.05 M solution of [15]crown-5 in THF/acetic acid (20/1), followed by several alternating washing steps with THF and CH_2Cl_2 . The resin was dried first with a stream of dry argon and then in vacuo. Analysis was performed as described under Section D.

C) Protocol for product cleavage and isolation: Fully protected, glycosylated resin (ca. 0.015 mmol) was placed in the reaction vessel. A solution of *N*-bromosuccinimide (15 mg, 0.084 mmol), 1,6-di-*tert*-butylpyridine (20 μL) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9/1) (2 mL) was added. After 2 h of vigorous shaking, the product mixture was washed off the resin by switching between CH_2Cl_2 and THF. It was concentrated in vacuo; the crude product was analyzed by MALDI-TOF-MS (see Section D) and HPLC (Europshere 100, 5 μm C-18 material, 4 $\times$ 160 mm column, gradient: acetonitrile in water, 5% to 60% in 5 min then 60% to 100% in 15 min). It was separated over silica (toluene/acetone) and final purification was carried out with preparative RP-18 HPLC. Yields: 7.5 mg (38%) in case of compound **11**; 6.5 mg (20%) in case of compound **14**.

D) Protocol for the MALDI-TOF-MS of products: A sample of dry resin (1–2 mg) was mixed in an Eppendorf cup with a solution of dry AgOTf (4 mg) in THF/MeOH (9/1) (50 μL). After 15 min 10 μL of the supernatant was mixed with a matrix solution (10 μL of a solution of 2,4-dihydroxybenzoic acid (10 mg) in THF (1 mL)). Of this solution 1 μL was applied on the sample slide of the MALDI-TOF-MS (Kratos, Maldi Kompakt). Under the described conditions exclusively signals corresponding to the silver ions (M^+Ag^+) were observed in the mass spectrum. The same cleavage reaction was used for RP-HPLC analysis of the products as described under Section C.

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A New Carborane Cage: Hexacarba-*arachno*-dodecaborane(12)

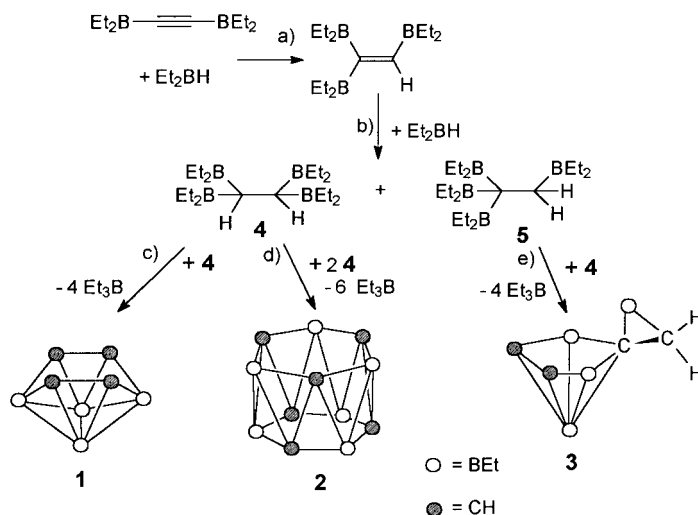
Bernd Wrackmeyer,* Hans-Jörg Schanz, Matthias Hofmann, and Paul von Ragué Schleyer

*Dedicated to Professor Heinrich Nöth
on the occasion of his 70th birthday*

The multifaceted structural and synthetic chemistry of carboranes continues to diversify after more than thirty years.^[1,2] The reactions of various polyboranes with alkynes provides an access to a variety of carboranes;^[1,3,4] however, with few exceptions, complex mixtures are obtained which may be difficult to separate. Transformations of simple organoboranes,^[5,6] mainly to B-alkylated derivatives, promise

more specific entries into carborane chemistry. Thus, the hydroboration of 1-alkynyldiethylboranes under “hydride-bath” conditions (i.e., with a large excess of diethylborane Et₂BH^[7]) gives access to new types of carboranes such as 1-carba-*arachno*-pentaborane(10),^[8,9] 2-carba-*nido*-pentaborane(8), or 2,4-dicarba-*nido*-hexaborane(8),^[10,11] and provides carboranes such as tetracarba-*nido*-octaborane(8)^[12] (**1**) which were not readily accessible or well characterized before. Carborane **1** is a member of the family of carbon-rich carboranes on the borderline between classical and nonclassical structures. The known neutral carbon-rich carborane cages are all *nido* systems with a maximum of four skeleton carbon atoms: for example C₄B₂R₆,^[13] C₄B₄R₈,^[12] C₄B₆R₁₀,^[4c,14] and C₄B₈R₁₂.^[15] There also are cationic *nido* carboranes with five carbon atoms: [C₅BR₆]⁺.^[16] We now report a carborane with six carbon and six boron atoms in the skeleton.

The reactions a–c shown in Scheme 1 provided the first straightforward route to the stable *nido*-C₄B₄ carborane **1**.^[12] While all our attempts to improve the yield of **1** over 20% failed, these experiments revealed the nature of important



Scheme 1. Synthesis of **1**–**5**.

side products. The formation of **1** is accompanied by that of isomer **3**, which normally is destroyed (e.g. by oxidation) during the purification of **1**. As shown in Scheme 1 (reactions b and e), **3** results from Et₂BH-catalyzed condensation of **4** and **5**.^[17] The spiro-carborane **3** is a new member of the still small family of 2,3,5-tricarba-*nido*-boranes(7).^[18]

Other Et₂BH-catalyzed condensations are conceivable. Thus, the condensation of three molecules of 1,1,2,2-tetraborylethane (**4**) affords carborane **2** (Scheme 1, reaction e), which was isolated as a crystalline colorless solid. The simple NMR spectra of **2** (there are no appreciable changes between –80 °C and ambient temperature) indicate either high symmetry or a highly fluxional structure. The one-dimensional ¹H–¹³C heteronuclear shift correlation detected by ¹H NMR spectroscopy proves the presence of isolated H-C-C-H units by the splitting of the ¹³C satellites (¹J(¹³C,¹H) = 152 Hz) into doublets (³J(¹H,¹H) = 8.0 Hz), and this suggests a rigid

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structure. In particular the ^{11}B NMR chemical shift at $\delta = +15.5$ supports a nonclassical structure for **2**, since trigonal-planar ^{11}B nuclei surrounded by carbon atoms should have quite different ^{11}B shifts ($\delta = +75 \pm 10$).^[19]

^{11}B and ^{13}C chemical shifts calculated by ab initio methods have been proven to be very reliable^[20] and extremely useful for determining the structures of carborane clusters.^[11, 21] We applied the ab initio/GIAO/NMR method^[20a] to confirm the proposed structure for **2**. Table 1 lists experimental ^{11}B and

Table 1. ^{11}B and ^{13}C NMR chemical shifts determined experimentally for $\text{C}_6\text{H}_6\text{B}_6\text{Et}_6$ (**2**) and calculated for the model compounds **2a**, **2b**, and **6**.

Compound	$\delta(^{11}\text{B})$	$\delta(^{13}\text{C})$
$\text{C}_6\text{H}_6\text{B}_6\text{Et}_6$ 2 ^[a]	15.5	33.7
$\text{C}_6\text{H}_6\text{B}_6\text{H}_6$ 2a ^[b]	7.6	26.0
$\text{C}_6\text{H}_6\text{B}_6\text{Me}_6$ 2b ^[b]	12.8	27.9
$\text{C}_6\text{H}_6\text{B}_6\text{H}_6$ (D_{3h}) 6 ^[b]	88.4	58.0

[a] Experimental values. [b] Calculated at the GIAO-SCF/6-31G*//MP2(fc)/6-31G* level of theory.

^{13}C NMR data of $\text{C}_6\text{H}_6\text{B}_6\text{Et}_6$ (**2**) together with computed chemical shifts (GIAO-SCF/6-31G*//MP2(fc)/6-31G*)^[22] of model compounds $\text{C}_6\text{H}_6\text{B}_6\text{H}_6$ (**2a**) and $\text{C}_6\text{H}_6\text{B}_6\text{Me}_6$ (**2b**). An alternative classical valence isomer (**6** is the parent compound) with a 2,5,7,10,11,12-hexaboro-tetracyclo-[4,4,0,1^{3,9},1^{4,8}]dodecane skeleton^[23] (see Figure 1b) might also have been formed from the condensation reactions. However, **6** is not a minimum (HF/6-31G* computations on D_{3h} symmetry) and is 68.5 kcal mol⁻¹ (MP2(fc)/6-31G* optimizations) less stable than the nonclassical isomer **2a**.

The agreement between theoretical and experimental NMR data (Table 1) is satisfactory for the D_3 -symmetric clusters (**2a** and **2b**). In contrast, **6** is computed to show the expected low-field ^{11}B chemical shift ($\delta = 88.4$, see above). We conclude from these results that the computed geometry shown in Figure 1a closely resembles that of **2**. The drumlike

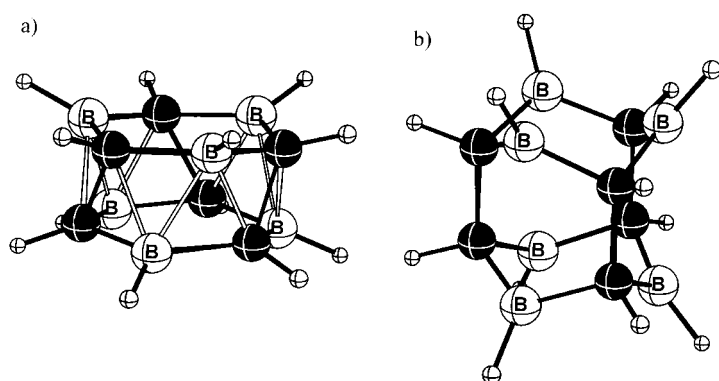


Figure 1. Geometries calculated at the MP2(fc)/6-31G* level of theory for a) **2a** (D_3 , selected distances [Å]: C–C 1.619; C–B 1.590, 1.608 (open face), 1.736; B–B 1.863; for **2b**: C–C 1.617; C–B 1.591, 1.611 (open face), 1.744; B–B 1.891) and b) **6** (D_{3h} ; C–C 1.610; C–B 1.57).

structure of **2**, a 12-vertex *arachno* cluster, is without precedent in carborane chemistry but can be derived from electron-counting^[24] and structural recognition pattern

rules.^[25] The cage is a hexagonal antiprism in which the carbon atoms are separated as far as possible. Two highly coordinated vertices above the open faces would complete a closed 14-vertex deltahedron, which was predicted for the still elusive *closo*-[$\text{B}_{14}\text{H}_{14}$]²⁻,^[26, 27] but are missing in the 12-vertex *arachno* compound.

There is great synthetic potential in the Et_2BH -catalyzed condensation of polyborylated alkanes. The new carborane **2**, with its two open hexagonal faces and doubly degenerate HOMO and LUMO, invites the addition of various fragments, in particular those which offer zero or two cage electrons.

Experimental Section

A solution of bis(diethylboryl)ethyne (3.57 g, 21.7 mmol) in Et_2BH (5.0 mL, 57.1 mmol hydride) was heated at 80 °C for 24 h. Then the solution was saturated with ethene to convert all reactive B–H bonds into B–Et bonds. Fractional distillation under reduced pressure first gave a mixture (0.97 g, 65:35) of **1** and **3** (b.p. 75–85 °C/7 × 10⁻⁵ hPa). The highly viscous residue was heated at 170–200 °C, and a colorless liquid (0.12 g, b.p. 160–165 °C/7 × 10⁻⁴ hPa) was collected containing more than 60% of **2**. On cooling the liquid to –20 °C, pure **2** crystallized as colorless prisms (0.067 g, m.p. 51–54 °C). ^1H NMR (250.1 MHz, 25 °C, CDCl_3): $\delta = 1.51$ (s, 6H, CH), 0.95 (m, 30H, BEt); ^{11}B NMR (80.3 MHz, 25 °C, CDCl_3): $\delta = 15.5$; ^{13}C NMR (62.9 MHz, –30 °C, CDCl_3): $\delta = 33.7$ (br, CH), 11.2 (br), 9.5 (BEt); EI-MS (70 eV): m/z (%) = 318 (60) [M^+], 289 (100) [$M^+ - \text{Et}$], 261 (30) [$M^+ - \text{Et} - \text{C}_2\text{H}_4$].

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Characterization of Hydrogen-Bonded Supramolecular Assemblies by MALDI-TOF Mass Spectrometry after Ag⁺ Labeling**

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Synthesis based on the formation of noncovalent bonds provides a valuable alternative to the classical chemistry of covalent bonds. It has developed into an area of enormous interest for a wide variety of scientific and technological disciplines, ranging from materials science to molecular electronics.^[1, 2] The identification of small hydrogen-bonded dimers^[3] or metal-coordinated assemblies^[4] is relatively simple. However, for large multicomponent assemblies held together by weak forces the characterization is far from straightforward and is currently one of the major challenges in this field.^[5] Most studies primarily rely on NMR data of compounds in solution, which solely provide information on the stoichiometry of the assembly, in combination with data from vapor-pressure osmometry (VPO) and/or gel-permeation chromatography (GPC).^[1, 6] The latter techniques give values for the average molecular weight with an error of up to 20%. Occasionally light- or neutron-scattering data^[7] or single X-ray crystal structures are reported.^[8] However, the characterization of weakly bound noncovalent assemblies by mass spectrometry, the only technique that provides quantitative data on the molecular composition, is still met with very limited success.^[9] For hydrogen-bonded assemblies only two cases have been reported by Lehn et al. and Whitesides et al.,^[10] but the ion-labeling methods they use either require covalent attachment of benzo[18]crown-6 moieties to one of the components or work only for extremely stable assemblies.

Here we describe a novel Ag⁺-labeling technique for the mass spectrometric characterization of multicomponent hydrogen-bonded assemblies. The method is based on the remarkably high affinity of Ag⁺ ions for a variety of aromatic π donors^[11, 12] and cyano groups,^[13] and it provides for a nondestructive way to generate positively charged hydrogen-bonded assemblies that can be easily detected by matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry.^[14] The method is applicable to assemblies of both high (type **A**) and much lower thermodynamic stability (type **B**; Figure 1). Moreover, we show that the MALDI-TOF-MS data perfectly correlate with ¹H NMR

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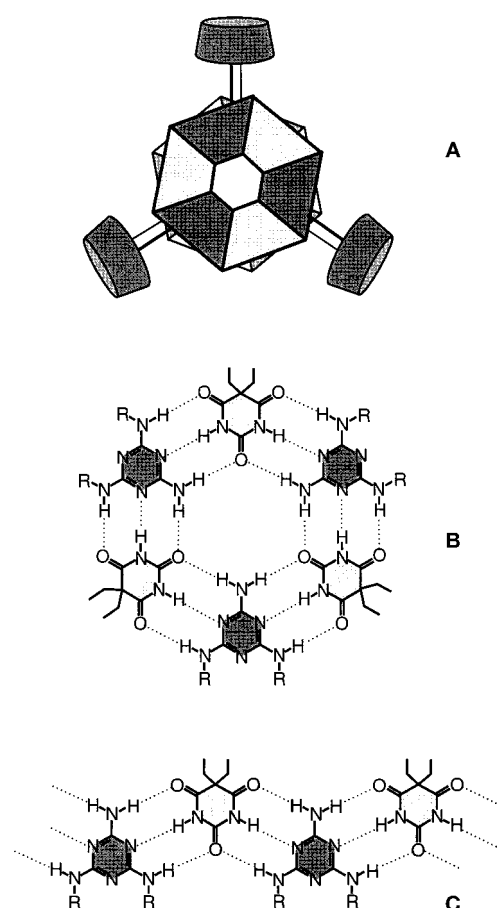


Figure 1. Hydrogen-bonded assemblies with varying thermodynamic stabilities: the cyclic nine-component (type **A**), the cyclic six-component (type **B**), and the linear nondefined assemblies (type **C**).

spectroscopic data on the stability of these assemblies in solution.^[8d, 15]

First we studied the nine-component calix[4]arene-based assemblies **A**, which are thermodynamically stable in chloro-

form even at a concentration of 10^{-4} M.^[8a, 15] All attempts to characterize assemblies of type **A** either by electrospray (ES) or MALDI-TOF mass spectrometry have so far been unsuccessful.^[10b, 16] However, samples prepared by stirring assemblies of type **A** with 1.5 equivalents of AgCF_3COO in chloroform for at least 24 hours^[17] show intense signals for the corresponding Ag^+ complexes in the MALDI-TOF mass spectrum in the case of benzyl-substituted melamine derivatives (assembly **A1**) or cyano-substituted melamine derivatives (assemblies **A4–A6**) (Table 1). For example, assembly **A1** ($\text{R}^2 = \text{benzyl}$) gives a signal at $m/z = 4278.3$ (calcd for $^{13}\text{C}_2^{12}\text{C}_{226}\text{H}_{276}\text{N}_{48}\text{O}_{30} \cdot ^{107}\text{Ag}^+$: 4276.1, Figure 2 a), while assem-

Table 1. MALDI-TOF-MS data for the hydrogen-bonded assemblies **A1–A6** and **B1–B9**.^[a]

Assembly	Molecular composition	Stability in CH_3Cl ^[b]	Calcd mass [Da] of the Ag complex ^[c]	Observed mass [Da]
A1	1 ₃ · 5 ₆	++	4276.1	4278.3
A2	2 ₃ · 5 ₆	++	4072.0	–
A3	3 ₃ · 5 ₆	++	4342.0	–
A4	2 ₃ · 6 ₆	++	4347.9	4348.1
A5	3 ₃ · 6 ₆	++	4618.8	4620.4
A6	4 ₃ · 5 ₆	++	4221.9	4220.0
B1	7 ₃ · 5 ₃	+	1831.9	1831.0
B2	7 ₃ · 8 ₃	+ ^[d]	1919.0	1919.1
B3	7 ₃ · 9 ₃	+	4947.4	4947.9
B4	7 ₃ · 10 ₃	+	3692.2	3692.0
B5	11 ₃ · 5 ₃	+	1828.4	1828.9
B6	11 ₃ · 8 ₃	+	1916.0	1915.0
B7	11 ₃ · 12 ₃	+	2475.2	2476.9
B8	13 ₃ · 5 ₃	–	1495.3	–
B9	14 ₃ · 5 ₃	–	1375.3	–

[a] After treatment with 1.5 equivalents of AgCF_3COO for 24 h at room temperature. [b] The notation “++” means that the assembly is stable above concentrations of 10^{-4} M, “+” means that the assembly is stable at concentrations above 10^{-2} M, and “–” means that the assembly is not stable in solution. [c] The calculated isotopic patterns are in good agreement with the experimentally observed molecular mass signals. [d] The ^1H NMR spectrum shows a complex pattern for the cyanurate NH protons ($\delta \approx 14$ –16), which suggests that the cyclic hexameric assemblies aggregate with themselves.

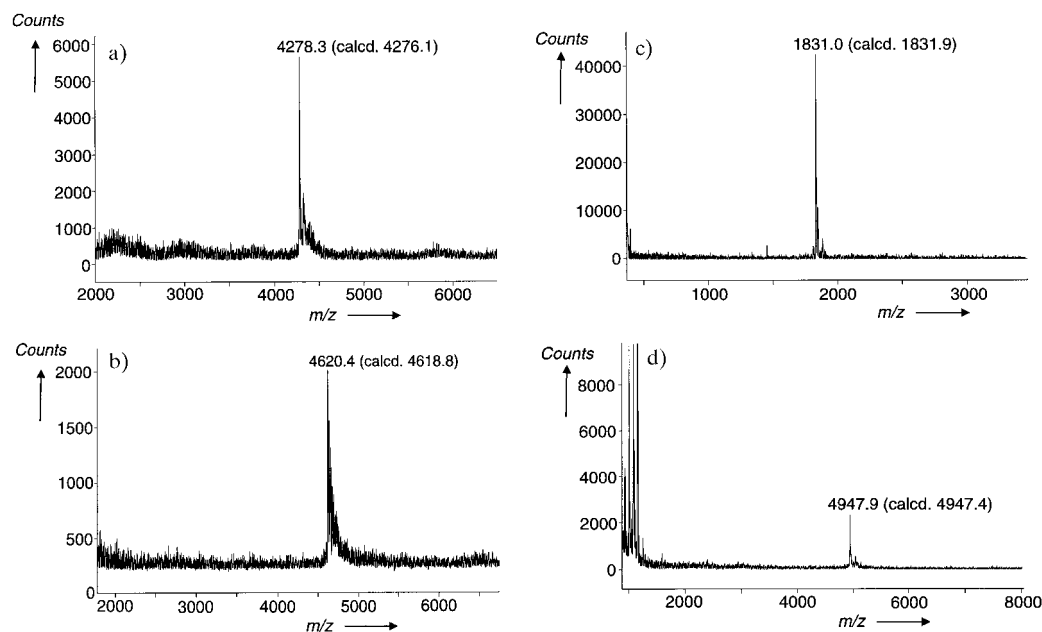


Figure 2. MALDI-TOF mass spectra of the Ag^+ complexes of a) **A1** [**1**₃·**5**₆], b) **A5** [**3**₃·**6**₆], c) **B1** [**7**₃·**5**₃], and d) **B3** [**7**₃·**9**₃].

blies **A2** and **A3** ($R^2 = \text{butyl}$) do not show any significant signals between $m/z = 1500$ and 8000 .^[18] This clearly indicates that the benzyl group is essential and contributes significantly to the stability of the **A1**· Ag^+ complex, presumably by forming a sandwich-type complex with one of the aromatic rings of the calix[4]arene (Figure 3a).

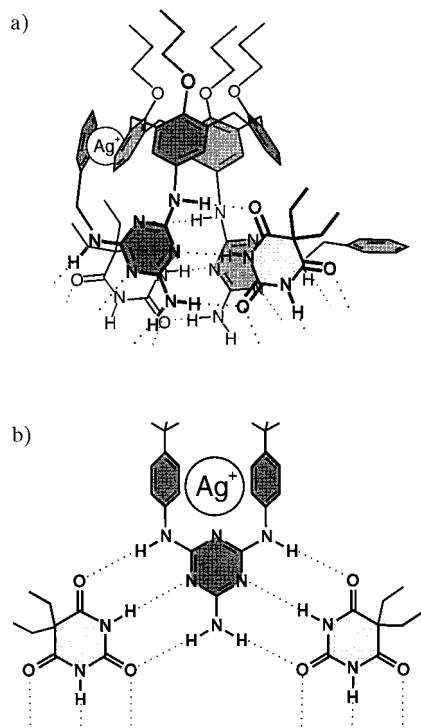
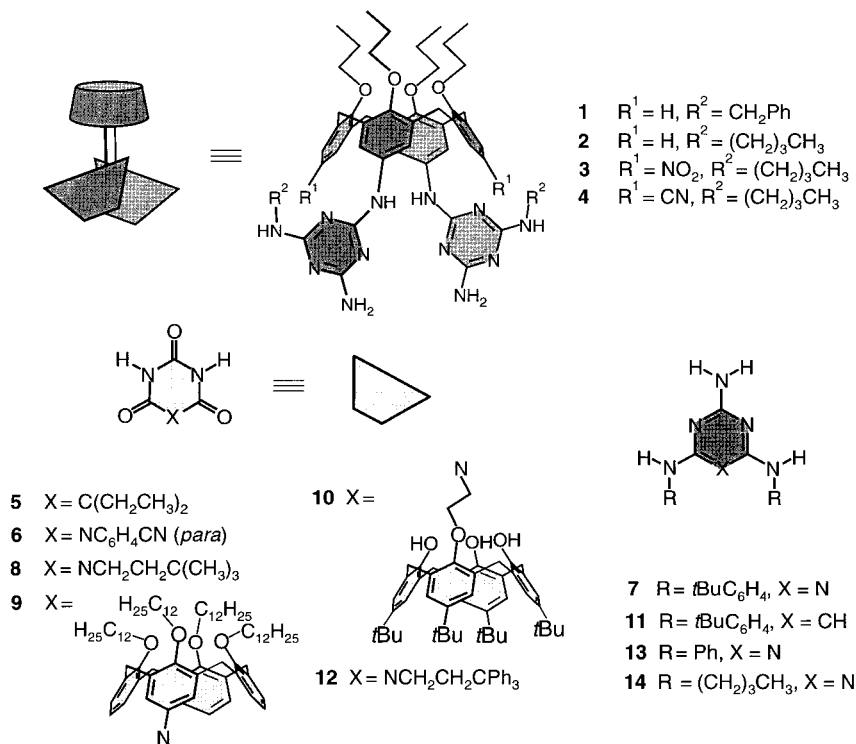


Figure 3. Proposed structure for the Ag^+ complexes of a) **A1** [**1**₃·**5**₃] and b) **B1** [**7**₃·**5**₃] (only parts of the total assemblies are shown for clarity).

For the MALDI-TOF-MS characterization of the hydrogen-bonded assemblies without benzyl groups, formation of the Ag^+ complexes can be promoted by introducing cyano substituents, which are known to have an extremely high affinity for Ag^+ ions.^[13] Samples prepared by stirring assemblies **A4** and **A5**, containing the cyano-substituted cyanurate derivative **6**, with 1.5 equivalents of AgCF_3COO in chloroform for at least 24 hours give intense signals in the MALDI-TOF spectra at $m/z = 4348.1$ (calcd for $^{13}\text{C}_2^{12}\text{C}_{220}\text{H}_{252}\text{N}_{60}\text{O}_{30} \cdot ^{107}\text{Ag}^+$: 4347.9) and 4618.8 (calcd for $^{13}\text{C}_2^{12}\text{C}_{220}\text{H}_{246}\text{N}_{66}\text{O}_{42} \cdot ^{107}\text{Ag}^+$: 4620.4; Figure 2b), respectively, for the monovalent Ag^+ complexes. Alternatively, cyano substituents can be introduced in the calix[4]arene component, as in **4**. Also in this case the monovalent Ag^+ complex of assembly **A6** was clearly observed in the MALDI-TOF spectrum at $m/z = 4220.0$ (calcd for $^{13}\text{C}_2^{12}\text{C}_{214}\text{H}_{282}\text{N}_{54}\text{O}_{30} \cdot ^{107}\text{Ag}^+$:

4221.9), confirming the formation of **A6** in solution observed with ^1H NMR spectroscopy.^[8a]

To test the applicability of the Ag^+ -labeling technique for the characterization of assemblies with much lower thermodynamic stability, we studied assemblies of type **B** made from three molecules of melamine **7** with equimolar amounts of either **5** or monosubstituted cyanurates **8–10** and **12**.^[13] These assemblies are thermodynamically stable in chloroform only at a concentration greater than 10 mM, and their characterization by MALDI-TOF-MS has so far not been successful.^[10b, c] In the literature there is only one example of a crown ether derivatized assembly of type **B** that has been characterized with ion-labeling ES-MS.^[10a] The MALDI-TOF-MS Ag^+ -labeling technique described here clearly identified the hexameric assemblies **B1–B7** as the corresponding Ag^+ complexes (see Table 1 for experimental data). For example, assembly **B1** gives a very sharp and intense signal at $m/z = 1831.0$ (calcd for $\text{C}_{93}\text{H}_{126}\text{N}_{24}\text{O}_9 \cdot ^{107}\text{Ag}^+$: 1831.9). Signals corresponding to the doubly or triply charged assemblies **B1**·(Ag^+)₂ ($m/z = 970.5$) or **B1**·(Ag^+)₃ ($m/z = 682.6$) or fragmented assemblies were not observed (Figure 2c). Also the MALDI-TOF spectra of assemblies with high molecular weight such as **B3**, consisting of three molecules of **7** and three molecules of the calix[4]arene derivative **9**, clearly show a signal for the monovalent Ag^+ complex at $m/z = 4947.9$ (calcd for $^{13}\text{C}_3^{12}\text{C}_{303}\text{H}_{453}\text{N}_{27}\text{O}_{21} \cdot ^{107}\text{Ag}^+$: 4947.4). This is the only significant signal in the spectrum between $m/z = 2000$ and 8000 (Figure 2d). Melamines without bulky substituents (e.g. **13** and **14**) only give linear type **C** assemblies of nondefined composition with equimolar amounts of the complementary barbiturate **5**. MALDI-TOF mass spectra of samples obtained by stirring these assemblies with AgCF_3COO did not show any appreciable signals for the cyclic hexameric assemblies **B8** and **B9**. This is fully in agreement with their



inherently low stability in solution according to ^1H NMR spectroscopy.^[8d]

The stable Ag^+ adducts of the assemblies clearly result from the simultaneous coordination of the Ag^+ ion to the aromatic π systems of the *tert*-butylphenyl groups (Figure 3b). Only the phenyl-substituted melamines **7** and **13** give intense signals in the MALDI-TOF mass spectrum for the corresponding Ag^+ complexes ($m/z = 497$ and 385 , respectively), while melamine **14** (carrying two butyl chains) or barbiturate **5** do not. It is most likely that the phenyl groups form a sandwich-type complex with the Ag^+ ion. Coordination of the Ag^+ ion to the triazine ring nitrogen atom does not seem to play an important role, because pyrimidine **11** (lacking this nitrogen atom) also shows a strong signal for the corresponding Ag^+ complex ($m/z = 495.7$).

We conclude that MALDI-TOF-MS after Ag^+ labeling is a convenient new tool for the mass spectrometric characterization of hydrogen-bonded assemblies. The absence of any signal corresponding to fragments of assemblies of type **A** or **B** in the mass spectrometer illustrates the unprecedented mildness of the technique. The method requires only a binding site for the soft Ag^+ ion in order to charge the noncovalent assembly in a nondestructive way. Aromatic π donors, which can sandwich a Ag^+ ion, or cyano groups are adequate for this purpose, but in principle many other functionalities such as acetylenes, ethylenes, amines, and sulfur groups may interact strongly with Ag^+ ions.^[19] These and other Ag^+ ionophores are quite common in supramolecular systems. Therefore, we feel that MALDI-TOF-MS after Ag^+ labeling might provide a method of general interest as a MS characterization technique for noncovalent assemblies or host–guest complexes.

Experimental Section

Samples were prepared by stirring solutions of assemblies **A1–A6** and **B1–B9** in CHCl_3 (5–10 mm) with solid AgCF_3COO (1.5 equiv per assembly, ACROS, 98% purity) for 24 h and mixing an aliquot of this solution (10 μL) with an aliquot (30 μL) of a solution of 2,5-dihydroxybenzoic acid (3 mg L^{-1}) in CHCl_3 . A portion (1 μL) of the resulting solution was loaded on a gold-sample plate, the solvent removed in warm air, and the sample transferred to the mass spectrometer for analysis.

The hydrogen-bonded assemblies of type **A** and **B** were identified by MALDI-TOF-MS^[14] using a PerSeptive Biosystems Voyager-DE-RP MALDI-TOF mass spectrometer (PerSeptive Biosystems, Inc., Framingham, MA, USA) equipped with delayed extraction.^[20] A 337-nm UV nitrogen laser producing 3-ns pulses was used, and the mass spectra were obtained in the linear and reflectron mode. Mass assignments were performed with unmanipulated spectra (no smoothing or centering, etc.) for an optimal correlation between observed and calculated mass.

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- [17] The use of 4.0 equivalents of AgCF_3COO leads to complete destruction of the assemblies.
- [18] It is quite remarkable that assemblies **A2** and **A3** do not form stable Ag^+ complexes by themselves, since calix[4]arenes are known to interact strongly with Ag^+ ions through the aromatic π faces at the upper rim of the cavity.^[12] This is confirmed by the presence of intense signals for the Ag^+ complexes of calix[4]arenes **2** and **3** in the MALDI-TOF mass spectra. Apparently, the calix[4]arene skeleton loses its affinity for Ag^+ ions upon formation of the hydrogen-bonded assembly. This is most probably a consequence of the extreme conformational change that the calix[4]arene skeleton undergoes when the hydrogen-bonded assembly is formed. The X-ray crystal

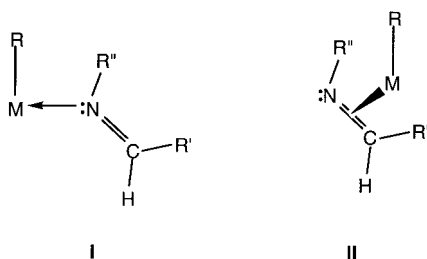
structure of assembly **A3** reveals that the melamine-substituted aromatic ring carbon atoms are 4.05 Å apart,^[8a] which is 0.75 Å less than the optimal distance measured from the crystal structure of the calix[4]arene–Ag⁺ complex.^[12a] Formation of the hydrogen-bonded assembly therefore leaves too little space for complexation of the Ag⁺ ions in between the parallel aromatic rings of the calix[4]arene fragment.

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Insertion of Imines into Palladium–Acyl Bonds: Towards Metal-Catalyzed Alternating Copolymerization of Imines with Carbon Monoxide To Form Polypeptides**

Smita Kacker, Jang Sub Kim, and Ayusman Sen*

The insertion of unsaturated molecules into metal–carbon bonds is a critically important step in many transition-metal-catalyzed organic transformations. In particular, the insertion of alkenes and alkynes into metal–carbon bonds resulting in carbon–carbon bond formation has been extensively studied.^[1] However, the analogous insertion of compounds with carbon–nitrogen multiple bonds has received far less attention: this is particularly true of imines.^[2] The difference in insertion propensity of carbon–carbon and carbon–nitrogen multiple bonds can be attributed to the coordination characteristics of the respective molecules. Alkenes and alkynes form π -complexes with metals. For imines, σ -donation of the lone pair of electrons on the nitrogen is the preferred mode of interaction with the metal center (for example, structure **I**).^[3] Since migratory insertion must be preceded by π coordination



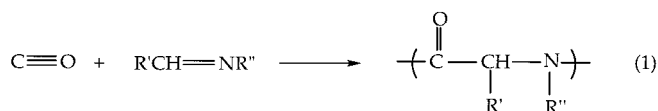
(R, R', R'' = H, alkyl, aryl)

(structure **II**), the difficulty in achieving σ to π isomerization may be the reason for the paucity of imine insertions.^[2] Herein

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we report the synthesis of amides by the insertion of imines into palladium(II)–acyl bonds. To our knowledge, this is the first direct observation of the insertion of imines into bonds between transition metals and carbon. The interest in this chemistry lies in the potentially new route to carbon–nitrogen bond formation. In particular, the alternating copolymerization of imines with carbon monoxide (in which the insertion of the imine into palladium–acyl bonds would be the key step in the chain growth sequence), if successful, should constitute a new procedure for the synthesis of polypeptides [Eq. (1)].^[4]

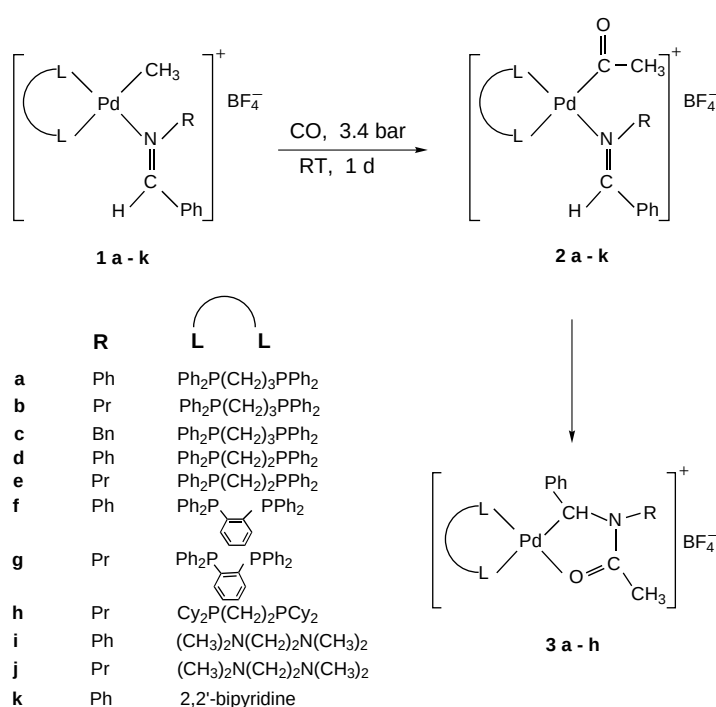


Neutral palladium(II)–methyl complexes incorporating a range of bidentate phosphane and nitrogen ligands reacted with silver tetrafluoroborate in the presence of imines to form the corresponding imine-coordinated cationic complexes **1a–k** in excellent yields. The compound **1a** (L–L = 1,3-bis-(diphenylphosphanyl)propane) was isolated as a solid consisting of 91 % **1a**·Et₂O and 9 % [(dppp)PdCl₂] (the composition was determined by a combination of ¹H and ³¹P NMR spectroscopy). A satisfactory elemental analysis (C,H) was obtained for a mixture of this composition. The complexes **1a–k** were found to be stable for over one month under nitrogen; there was no evidence of insertion of imine into the palladium–methyl bond.

The imine ligand was coordinated to the metal by σ donation of the lone pair of electrons on nitrogen (structure **I**). This was established from the ¹H and ¹³C NMR spectra of the complexes. For example, in the ¹H NMR spectrum of complex **1c** (L–L = dppp, R = PhCH=NBz), recorded in CDCl₃, the CH protons of the coordinated imine appeared at δ = 8.20 (dd, J = 2, 7.4 Hz) compared with δ = 8.29 for the CH protons of the noncoordinated imine. The corresponding carbon appeared at δ = 167.89 in the ¹³C{¹H} NMR (CDCl₃) spectrum compared with δ = 160.69 for the noncoordinated imine. On the other hand, π complexation has been shown to result in significant upfield shifts of these resonances.^[3b]

The reactivity of complexes **1a–k** towards carbon monoxide was examined by exposing them to an atmosphere of carbon monoxide at ambient temperature and a pressure of 3.4 bar. The results are summarized in Scheme 1. All the complexes reacted with carbon monoxide to form the corresponding palladium(II)–acyl species. However, the stability of these palladium–acyl species varied greatly. These complexes (**2**) could only be observed when the subsequent insertion of the imine into the palladium–acyl bond was slow or did not occur. ¹³C-labeled carbon monoxide was used to facilitate characterization of the products: complexes formed with ¹³CO are marked with an asterisk (*).

For complexes with nitrogen-donor ligands **1i–k** the corresponding palladium(II)–acyl complexes **2i–k** were formed in 16 h. The ¹³C NMR resonance due to the carbonyl of the acyl group was observed at δ $\approx$ 232 for **2i*–k*** as is typical for palladium(II)–acyl complexes.^[5] There was no



Scheme 1. Reactions of **1** with CO and insertions of the C=N group into the metal–carbon bond to form an amide group. The carbonyl oxygen atom in complexes **3** coordinates to the palladium center.

evidence for the subsequent insertion of the coordinated imine into the palladium–acyl bond at ambient temperature.

In contrast to complexes **2i–k** with nitrogen-donor ligands, subsequent insertion of the coordinated imine occurred at ambient temperature in the phosphane-coordinated complexes **2a–h** to form **3a–h** (Scheme 1). The insertion resulted in the CH unit being attached to the imine the metal and the formation of a bond between nitrogen and the carbonyl group, resulting in the formation of an amide group. In addition, the carbonyl oxygen was coordinated to the palladium to form a stable five-membered ring. Similar chelates result from the insertion of alkenes into palladium(II)–acyl bonds.^[5a, 6] The best result was obtained with compound **1a**. Exposing a solution of **1a** to carbon monoxide at a pressure of 3.4 bar for 1 d at ambient temperature yielded **3a** (or **3a***) as the only product (83 % yield). The ³¹P{¹H} NMR spectrum of complex **3a**, recorded in CDCl₃, showed two sets of doublets at δ = 0.19 and 17.14 (*J* = 70 Hz), while that of **3a*** showed a doublet of doublets at δ = 0.08 (*J* = 9.2, 70 Hz) and a doublet at 17.16 (*J* = 70 Hz). The observation of ³¹P–¹³C coupling for the upfield resonance indicates that the corresponding phosphorus atom was positioned *trans* to the weakly coordinated carbonyl group and confirms the existence of the chelate structure. The ¹³C{¹H} NMR spectrum of **3a***, recorded in CDCl₃, showed the amide carbonyl resonance at δ = 181.64 (³*J*_{P–C} = 9.4 Hz). ¹H NMR spectrum in CDCl₃ of complex **3a** showed the methyl next to the carbonyl group at δ = 1.87. The corresponding resonance in **3a*** appeared as a doublet (*J* = 6.2 Hz) at δ = 1.80. The CH group of the inserted imine in complex **3a** showed up as a doublet of doublets at δ = 4.27 (*J* = 4.8, 8.0 Hz), being coupled to the two nonequivalent phosphorus atoms. This resonance in **3a***

became a multiplet due to long range coupling to the carbonyl carbon. The IR spectrum of **3a** recorded in CDCl₃ exhibited an absorption band at 1630 cm^{−1} due to the coordinated carbonyl group of the amide. Finally, the compound **3a** was isolated as a solid consisting of 89.5 % **3a** and 10.5 % [(dppp)PdCl₂] (the composition was determined by ³¹P NMR spectroscopy). Satisfactory elemental analysis (C, H) was obtained for a mixture of this composition.

The dppp complexes **1b** (R = PhCH=NPr) and **1c** (R = PhCH=NBz) were employed to examine the relative insertion propensities of benzaldehyde propyl imine and benzaldehyde benzyl imine. Both these imines showed a greater reluctance towards insertion into the corresponding palladium(II)–acyl bond than benzaldehyde phenyl imine (cf. **1a**). The observed yields of **3b** and **3c** were 50 % and 20 %, respectively. Additionally, the reactions were accompanied by significant decomposition and precipitation of metallic palladium. The above observations indicate that the insertion of an imine into a palladium(II)–acyl bond proceeds more readily when the nitrogen bears a phenyl rather than an alkyl substituent (also, see below). This difference may be due to higher σ-bonding ability of the nitrogen bearing a relatively electron-releasing alkyl substituent, thereby disfavoring the required isomerization from the σ to π complex (structure **I** to **II**).

The effect of the chelating phosphane upon the reaction was also examined. Like complex **1a**, the PhCH=NPh complexes **1d** (L–L = 1,2-bis(diphenylphosphanyl)ethane = dppe) and **1f** (L–L = 1,2-bis(diphenylphosphanyl)benzene = dppb), formed the imine-inserted products following conversion into the corresponding acyl species, albeit at lower yields (less than 30 %). The sharply reduced ability of benzaldehyde propyl imine to undergo insertions (cf., **1b**) was not significantly altered by changing the structure of the coordinated bidentate phosphane. For example, complexes **1e** (L–L = dppe), **1g** (L–L = dppb), and **1h** (L–L = 1,2-bis(dicyclohexylphosphanyl)ethane = dcpe), could be converted into the corresponding palladium(II)–acyl species. However, the subsequent insertion of the imine into the palladium(II)–acyl bond was very slow and the imine-inserted product was formed only in low yields. In addition, the reactions were accompanied by precipitation of metallic palladium.

In conclusion, we have observed, for the first time, the insertion of the C=N bond of imines into palladium(II)–acyl bonds. The insertions resulted in the formation of palladium(II)–alkyl species with amide bonds. Moreover, the carbonyl group of the amide was coordinated to the metal to form a five-membered ring. It is interesting to note that while imine insertion into palladium(II)–acyl bonds was observed, the corresponding insertion into palladium(II)–alkyl bonds did not occur. Almost certainly, the formation of the very strong amide linkage constituted the added driving force in the former reaction. A comparison of the insertion propensity of imines with different groups on the nitrogen showed that benzaldehyde phenyl imine was far superior to benzaldehyde propyl imine and benzaldehyde benzyl imine. The effect of the nature of the auxiliary bidentate ligand on the metal was also investigated. No imine insertion was observed with bidentate nitrogen-donor ligands at ambient temperature.

Insertion was, however, observed with bidentate phosphane ligands.

For the alternating copolymerization of imine with carbon monoxide to proceed, the subsequent insertion of carbon monoxide into the palladium(II)–carbon bond of the imine-inserted product must occur. In preliminary experiments, we did not observe carbon monoxide insertion in species **3a** at ambient temperature. We ascribe our failure to the strong binding of the carbonyl group of the amide fragment to the metal, thereby preventing the coordination of an incoming carbon monoxide molecule. While a similar coordination of the carbonyl group also occurs in the intermediates involved in the alternating copolymerization of alkenes and carbon monoxide,^[5a, 6, 7] the difference lies in the greater negative charge and, therefore, stronger coordinating ability of the carbonyl oxygen of an amide fragment. Interestingly, the insertion of carbon monoxide apparently occurs readily in analogous species where the amide carbonyl is not coordinated to the metal.^[8]

Experimental Section

Synthesis of 1a–k: A solution of AgBF₄ in acetonitrile was added to a solution of L₂Pd(Me)(Cl) (1 equiv) and imine (1 equiv) in dichloromethane. After this had been stirred for 15 min, the AgCl was removed by filtration. The resulting complex was isolated by removing the solvent and drying under reduced pressure for 1 d.

Reaction of 1a–k with carbon monoxide: The complex **1a–k** (0.10 g) was dissolved in CDCl₃ and placed in a 22 mL Parr bomb, which was then charged with 3.4 bar of carbon monoxide. The mixture was allowed to stand at ambient temperature for 1 d. The excess carbon monoxide was then released, the solution filtered to remove any metallic palladium, and the product characterized by ¹H, ³¹P{¹H}, and ¹³C{¹H} NMR spectroscopy. Reactions were also run with ¹³C-labeled carbon monoxide.

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Maracin and Maracen: New Types of Ethynyl Vinyl Ether and α -Chloro Divinyl Ether Antibiotics from *Sorangium cellulosum* with Specific Activity Against Mycobacteria**

Martina Herrmann, Bettina Böhlendorf, Herbert Irschik, Hans Reichenbach, and Gerhard Höfle*

Dedicated to Professor Meinhart H. Zenk on the occasion of his 65th birthday

Even in highly developed industrial countries, tuberculosis is still one of the most common causes of death due to infection.^[1] The causative pathogen, *Mycobacterium tuberculosis*, can only be completely eliminated by a lengthy course of treatment despite the use of highly active antibiotic combination preparations (rifampicin, streptomycin, isoniazide etc.), since its growth is particularly slow and it is protected by a wax-containing cell wall.^[2] The same is true for leprosy which is also caused by mycobacteria.^[3] In AIDS, increasing occurrence of multiresistant *M. tuberculosis* strains and atypical mycobacterial infections is a particular danger.^[2, 4] New types of antibiotics are urgently needed to treat such infections, in order to aid patients in individual cases and in the long term, to prevent the spread of resistant pathogen strains.

During a screening program using the nonpathogenic *Mycobacterium phlei* as indicator organism, we discovered

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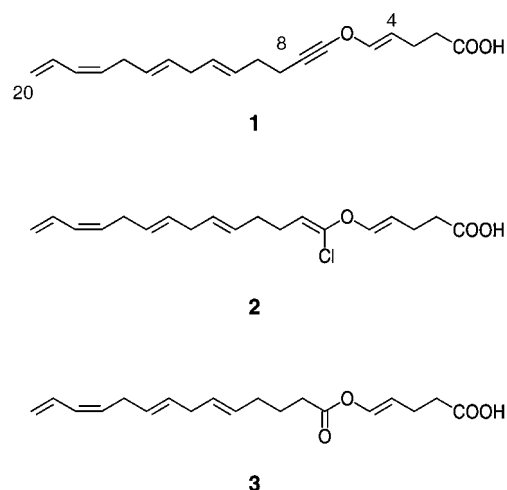
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in the *Sorangium cellulosum* strains Soce880 and Soce1128 a new group of antibiotics with specific activity against mycobacteria. TLC and HPLC analysis revealed compounds in the culture extracts of both strains that, according to polarity and UV spectra, are very similar to one another and to which the biological activity could be assigned.

To isolate the compounds, ethyl acetate extracts of 100 L cultures of the production strains Soce880 and Soce1128 were fractionated on Sephadex LH-20 (methanol) and RP-18 silica gel (methanol/0.05 M ammonium acetate buffer (80/20)). The main active components maracin A (**1**, 116 mg, Soce880) and



maracen A (**2**, 731 mg, Soce1128) thereby were obtained as colorless oils.^[5, 6] According to their migration behavior on silica gel and RP-18 silica gel, **1** and **2** are lipophilic carboxylic acids.

In the mass spectrum (direct chemical ionization, DCI) of maracin **1**, a molecular ion is observed ($m/z = 299.1644$ for $[M - H]^-$) that corresponds to the empirical formula $C_{19}H_{24}O_3$, from which eight double bond equivalents can be derived. The 2D NMR spectra indicate a terminal conjugated diene unit, two double bonds isolated by methylene groups, and a carboxy group as structural elements. The three remaining double bond equivalents can be assigned to an asymmetric substituted vinyl group and an ethynyl group, the latter documented by a conspicuous absorption band at 2280 cm^{-1} in the IR spectrum. Together, both form an ethynyl-*trans*-vinyl ether, which is a very unusual structural element for a natural substance. This assignment is supported by the chemical shifts of the C-4 and C-5 atoms (108.7 and 144.6 ppm) and the 4-H and 5-H atoms (5.57 and 6.27 ppm), the vicinal coupling constant $J_{4-H,5-H} = 12.0\text{ Hz}$,^[7] and chemical shifts of the C-7 and C-8 atoms (84.1 and 44.1 ppm, Table 1). In agreement with this, ^{13}C -labeled **1** (see below) shows a C-7,C-8 coupling of 225 Hz.^[8a]

In contrast to **1**, a molecular ion of $m/z = 337/339$ for $[M - H]^-$ occurs in the DCI mass spectrum of maracen **2**. The relative molecular mass, the isotope pattern of the molecular ion, and the absence of an acetylene band in the IR spectrum of **2** point to a chloro divinyl ether with the empirical formula $C_{19}H_{25}O_3\text{Cl}$. Its structure differs from maracin **1** in the NMR spectrum only in the replacement of the alkynyl by a α -

Table 1. Selected physical and spectroscopic data for maracin A (**1**) and maracen A (**2**).

1: $C_{19}H_{24}O_3$ ($M_r = 300.40$); colorless oil; TLC: $R_f = 0.53$ (silica gel, dichloromethane/acetone/methanol (85/15/5));^[a] IR (KBr): $\tilde{\nu} = 2280, 1712, 1673, 1662, 1222\text{ cm}^{-1}$; UV/Vis (methanol): λ_{max} (log ϵ) = 208 (4.41), 227 nm (4.47); ^1H NMR (300 MHz, CDCl_3): $\delta = 2.43$ (t, $J = 7.3\text{ Hz}$, 2H, 2-H), 2.31 (q, $J = 7.3\text{ Hz}$, 2H, 3-H), 5.57 (dt, $J = 12.0, 7.3\text{ Hz}$, 1H, 4-H), 6.27 (d, $J = 12.0\text{ Hz}$, 1H, 5-H), 2.22 (m, 4H, 9-H, 10-H), 5.43 (m, 5H, 11-, 12-, 14-, 15-, 17-H), 2.75 (m, 2H, 13-H), 2.88 (m, 2H, 16-H), 6.02 (t, $J = 11.0\text{ Hz}$, 1H, 18-H), 6.62 (dt, $J = 16.8, 11.0\text{ Hz}$, 1H, 19-H), 5.19 (d, $J = 16.8\text{ Hz}$, 1H, 20-H_a), 5.10 (d, $J = 11.0\text{ Hz}$, 1H, 20-H_b); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 178.0$ (C-1), 34.1 (C-2), 21.8 (C-3), 108.7 (C-4), 144.6 (C-5), 84.1 (C-7), 44.1 (C-8), 17.6 (C-9), 27.2 (C-10), 128.8 (C-11), 128.8 (C-12), 30.5 (C-13), 129.2 (C-14), 128.3 (C-15), 30.8 (C-16), 130.3 (C-17), 129.6 (C-18), 132.1 (C-19), 117.4 (C-20); DCI-MS (NH_3): $m/z = 299.1644$ (calcd. for $[M - H]^-$: 299.1647)

2 (only data differing from **1** are given): $C_{19}H_{25}O_3\text{Cl}$ ($M_r = 336.86$); colorless oil; TLC: $R_f = 0.55$ (silica gel, dichloromethane/acetone/methanol (85/15/5));^[a] IR (KBr): $\tilde{\nu} = 1711, 1654, 1154\text{ cm}^{-1}$; UV/Vis (methanol): λ_{max} (log ϵ) = 205 (4.25), 224 nm (4.22); ^1H NMR (300 MHz, CDCl_3): $\delta = 2.29$ (q, $J = 7.2\text{ Hz}$, 2H, 3-H), 5.22 (dt, $J = 12.1, 7.2\text{ Hz}$, 1H, 4-H), 6.26 (d, $J = 12.1\text{ Hz}$, 1H, 5-H), 5.14 (overlapping, 1H, 8-H), 2.14 (m, 4H, 9-H, 10-H), 5.41 (m, 5H, 11-, 12-, 14-, 15-, 17-H), 2.74 (m, 2H, 13-H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 178.5$ (C-1), 34.3 (C-2), 22.5 (C-3), 110.3 (C-4), 143.2 (C-5), 141.5 (C-7), 109.7 (C-8), 27.3 (C-9), 26.4 (C-10), 129.0 (C-11), 128.6 (C-12), 30.4 (C-13); DCI-MS (NH_3): $m/z = 336.1449, 338$ (calcd for $[M(^{35}\text{Cl})]^-$: 336.1492)

[a] Detection with vanillin/sulfuric acid, violet-red color on heating to 120°C .

chlorovinyl group, which shows chemical shifts of 141.5 and 109.7 ppm for the C-7 and C-8 atoms and 5.14 ppm for the H-8 atom. Determination of the configuration at the trisubstituted C-7,C-8 double bond was not possible from the NMR data. Thus attempts were made to synthesize both the (7*E*) and the (7*Z*) isomers of **2** by HCl addition at the triple bond of **1**. This was achieved by reaction of maracin **1** with lithium chloride in acetic acid; a mixture of the two isomers was obtained in a ratio of (7*E*):(7*Z*) = 1.7:1.0.^[9] Only by comparison of the NMR data of both isomers with the ^1H shifts calculated according to an incremental system^[8b] was it possible to assign the (7*Z*) configuration to the natural product maracen **2** that we had isolated. Furthermore, the result of the HCl addition at **1** demonstrated that **2** is a genuine natural compound and not an artefact. Maracin **1** was recovered from either of the stereoisomers of **2** on reversal of the HCl addition by treatment with lithium diisopropylamide.^[10] Acid-catalyzed reaction of **1** and **2** with water enabled isolation of the vinyl ester **3**, as expected, in addition to various cleavage products.^[11] However, the hydrolysis of **1** proceeded much slower than that of ethoxyacetylene, a reagent used in peptide synthesis for activation of carboxylic acids.^[12]

Until now, there have been no examples for the biosynthesis of ether groups such as in **1** and **2**. Preliminary experiments with ^{13}C -labeled acetate indicate the same assembly pattern for **1** and **2** from nine intact acetate units and a carboxy group derived from the C-2 atom of a further acetate unit (Figure 1). The ether oxygen atom may be inserted in the C-5,C-6 bond of an intermediate C_{19} fatty acid by a mechanism related to the biosynthesis of divinyl ethers,^[13] by fragmentation and Hock rearrangement^[14] of a bisallylic 6-hydroperoxide. It is noteworthy that the only natural ethynyl ether known at present, the sesquiterpene lactiflorasin from

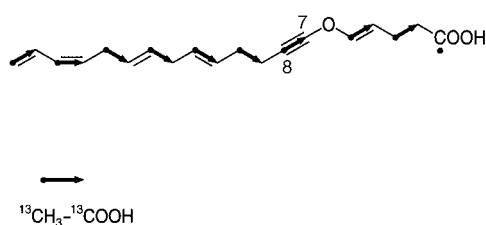


Figure 1. Biogenesis of maracin **1** from [1,2- $^{13}\text{C}_2$]acetate. The ^{13}C -labeled C_2 unit is represented by an arrow (blunt end: methyl C-atom, point: carboxy C-atom).

Artemisia lactiflora,^[15] is, like **1**, also an ethynyl *trans*-vinyl ether. α -Chloro divinyl ethers were previously unknown as natural products.

According to initial results, maracin and maracen are active in vitro against the pathogen responsible for tuberculosis ($\text{IC}_{99} < 12.5 \mu\text{g mL}^{-1}$);^[16] whether they are also active in vivo has still to be demonstrated. With an in vitro toxicity of $\geq 24 \mu\text{g mL}^{-1}$ against the mouse fibroblast line L929, they are supposedly of low toxicity for higher organisms and thus are possibly suitable for medical application.

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- [7] The coupling constant $J_{4\text{H},5\text{H}}$ is 5.7 Hz for the *cis*-vinyl ether (maracin E)^[6].
- [8] a) Compare with the value of 216.5 Hz in ethoxyacetylene: see ref. [8c], p. 151; b) (7Z)-**2**: $\delta(8\text{-H}) = 5.23$ (calc.; ref. [8c], p. 118), 5.14 (det.); (7E)-**2**: $\delta(8\text{-H}) = 4.88$ (calc.; ref. [8c], p. 118), 5.02 (det.); c) M. Hesse, H. Meier, B. Zeeh, *Spektroskopische Methoden in der organischen Chemie*, 4th ed, Thieme, Stuttgart, **1991**.
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- [10] Compare P. J. Stang, V. V. Zhdankin in *Supplement C2: The Chemistry of Triple-bonded Functional Groups* (Ed.: S. Patai), Wiley, New York, **1994**, p. 1146–1147; reaction of **2** with lithium diisopropylamide in THF for 30 min at 0°C gave **1** with 20% yield.
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π -Stacked *ortho*-Palladated Bipyridine Complexes Exhibiting Unusual Liquid Crystalline Behavior**

Abdelkrim El-ghayoury, Laurent Douce, Antoine Skoulios, and Raymond Ziessel*

Liquid crystals (LCs) have many important applications, for example in the manufacture of visual display units or temperature sensors. Despite extensive and elegant investigations of their morphological properties, it is still hazardous to predict their precise structural behavior. Several major classes of LCs have been identified, such as nematic, smectic, and columnar, and crude guidelines have been established to specify the molecular requisites for LC properties. The design of an efficacious LC requires careful consideration of the molecular architecture that might induce the formation of the desired LC and, in some cases, also the prediction of molecular interactions in the emerging mesophase. In fact, mesomorphic materials provide some of the best examples of intermolecular interaction or self-assembly at the supramolecular level.

In the search for new LCs, metal-containing mesogens (metallomesogens) have recently attracted considerable attention owing to the possibility of combining the properties of the metal (color, magnetism, polarizability, redox behavior, electronic charge, resistivity, etc.) with those of the organic framework.^[1,2] Such substances have tremendous potential as

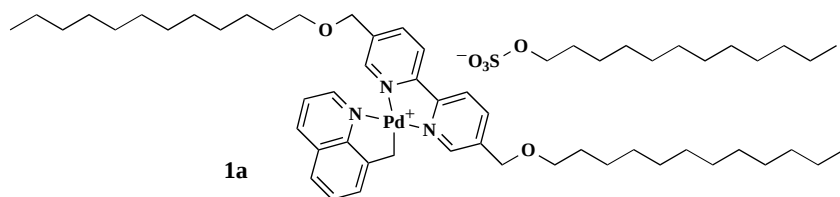
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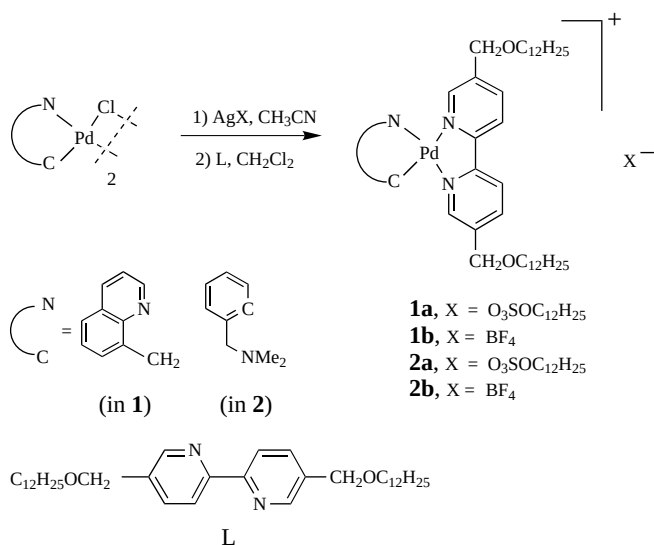
low molecular-mass systems addressable by weak magnetic or optical fields. In particular, *ortho*-palladated mono^[3] and dinuclear complexes, which yielded the first ferroelectric^[4] and cholesteric organometallic mesogens,^[5] form a major cornerstone of the subject.

Recently, considerable effort has been expended on the development of new thermotropic bipyridine-based (bipy) molecules in order to combine the powerful chelating properties of bipy with the proven self-organizational ability of the ancillary aliphatic chains.^[6, 7] Surprisingly, only one example of a bipyridine-based metallomesogen has been reported so far. The rodlike molecule contains four phenyl rings in addition to the aryl ligands that form the primary coordination shell.^[8, 9] In contrast to this calamitic (rodlike) approach we suggest the use of transition metal complexes displaying discotic (disklike) structure.

We now report that direct attachment of two dodecyl chains to the bipy chelator through an ether linkage leads to a nonmesogenic material. Subsequent coordination of a cyclopalladated fragment gives rise to a hitherto unreported family of cationic complexes, some of which display LC behavior. Interestingly, the poor thermal stability of the tetrafluoroborate salt **1b** is eradicated by the use of an alkylsulfate counteranion **1a**.



Cyclopalladated complexes **1a**, **1b**, **2a**, and **2b** were prepared by the adaptation of a literature method based on 2-phenylpyrimidine (Scheme 1).^[10] The nonmesogenic bipyridine ligand **L** was obtained by nucleophilic substitution of 5,5'-di(bromomethyl)-2,2'-bipyridine^[11] with sodium *n*-dodecyl alcoholate (yield 70%). The required palladium-containing

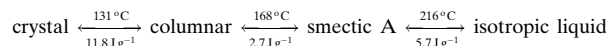


Scheme 1. Synthesis of the palladium complexes **1a**, **1b**, **2a**, and **2b**.

fragment was obtained by silver dehalogenation of the [Pd(8-mq)Cl]₂^[12] (8-mq = 8-methylquinoline) or [Pd(dmba)Cl]₂^[13] (dmba = *o*-(*N,N*-dimethylaminomethyl)phenyl) dimers. Subsequent reaction with **L** gave the desired pale yellow complexes **1a**, **1b**, **2a**, and **2b** in high yield, which have been unequivocally characterized by ¹H and ¹³C{¹H} NMR, FT-IR, and UV/Vis spectroscopy, FAB-MS, and elemental analysis.

Initial examination of the complexes with polarizing optical microscopy, differential scanning calorimetry (DSC), and X-ray diffraction showed that **2a** and **2b** melt upon heating directly into an isotropic liquid (probably because steric hindrance of the geminal methyl groups perturb the flatness of the aromatic cores). In contrast, **1a** and **1b** are perfectly able, as expected, to produce thermotropic LCs. The complex salt **1b** degrades quickly when heated at high temperature, while **1a** is fairly stable, resisting a two-hour heat treatment at 185°C without detectable damage. In the present work, attention was thus focused on the liquid crystal behavior of **1a** only.

The DSC thermograms of **1a**, in the temperature range from 25 to 220°C, displayed two sharp peaks at 131 and 168°C, indicative of reversible first-order transitions. The optical textures observed upon slow cooling from the isotropic melt showed the emergence of a smectic *A* phase at 216°C (appearance of Bâtonnet textures, turning into focal conic, then into homeotropic) and of one other liquid crystal phase at 168°C, which resembled a smectic *C* phase (appearance of fine Schlieren textures) but was, in fact, columnar in symmetry as shown by X-ray diffraction.



The X-ray diffraction pattern of the crystal contains several Bragg reflections consistent with a (pseudo)orthorhombic crystal lattice: *a* = 12.67, *b* = 3.53, *c* = 33.60 Å. The *b* period coincides with the known stacking separation of polynuclear aromatic molecules,^[14] suggesting that the aromatic cores of the molecules^[15] are stacked on top of one another to form columns aligned along the *b* axis of the crystal. The *a* period correlates with the lateral dimensions of the aromatic cores, suggesting that the columns lie side by side in close contact with one another, to form well-defined layers. The existence of several (00*l*) reflections shows that the aromatic layers are stacked along the *c* axis to form a lamellar crystal. The *c* period is larger than the size of the aromatic cores and smaller than the overall length (44.4 Å) of the molecules in a fully extended conformation; the molecules must therefore be arranged in single layers in which the flat aromatic cores lie parallel to the *b,c* crystal faces and the alkyl chains are tilted with respect to the layer normal. The dodecylsulfate counterions are inserted among the alkyl chains of the bipyridine moieties inside the aliphatic sublayers, with their ionic headgroups as close as possible to the positively charged palladium centers (vide supra).

The X-ray pattern of the columnar phase (Figure 1) contains a diffuse band (*A*, Figure 1) at 4.6 Å which shows that the alkyl chains have a liquidlike structure and are

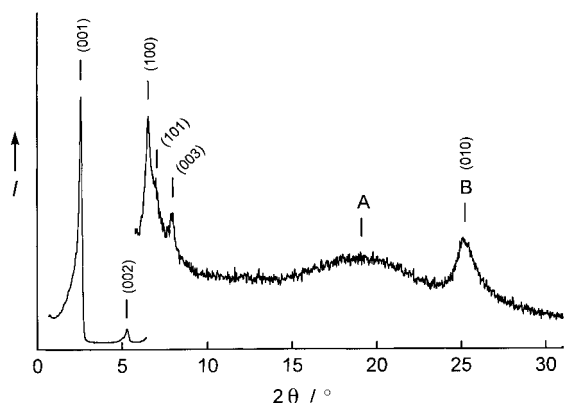


Figure 1. X-ray diffraction pattern of the columnar phase of **1a** at 152°C. For clarity, the intensities of the peaks at Bragg angles $2\theta > 5^\circ$ have been multiplied by 15. Numerals are Miller indices of the reflections (defined by the pseudo-orthorhombic lattice parameters a , b , c of the crystalline phase).

segregated from the aromatic cores. A broad band (B, Figure 1) at 3.53 Å indicates that the aromatic cores are stacked together to form columns, as in the crystal but in a looser fashion (with a correlation length of 65 Å, estimated from the width of the band). Five sharp reflections in the small-angle region are consistent with a two-dimensional rectangular lattice: $a = 13.5$, $c = 33.4$ Å, which is almost identical with the a , c lattice dimensions of the crystal (the small expansion of the a period suggests an “unlocking” of the columns inside the layers, consistent with the observed loosening of the intracolumnar stacking of the aromatic cores). It thus appears that the structure of the columnar phase is very similar to that of the crystal: the aromatic cores are stacked in columns; these lie side by side in close contact with one another to form well-defined layers, and the layers, separated by the disordered alkyl chains, stack to form a periodic lamellar structure (Figure 2). The absence of general (hkl) reflections suggests that the layers (or columns) are gliding freely along the columnar axis while maintaining position in the perpendicular direction. From the cell parameters, it is apparent that the aromatic cores cover an area of $13.5 \times 3.53 = 47.7$ Å² in the a , c plane, allowing the molten alkyl chains (including those of the alkylsulfate anions) a reasonable cross-sectional area of $2 \times 47.65/3 \approx 31.8$ Å².

The diffraction pattern of the smectic *A* phase contains, as expected, a diffuse band at 4.6 Å, characteristic of the disordered conformation of the alkyl chains, together with two sharp reflections in the small-angle region, related to a smectic single-layer arrangement of the molecules with a period of 31.3 Å. But in addition, they contain two diffuse bands at the same spacings as the sharp (100) and (010) reflections of the columnar phase, which reveal a local ordering of the molecules inside the layers reminiscent of the structure of the columnar phase. This structure is similar to that reported by Levelut et al.^[16] for the smectic *A* phase of a conducting charge-transfer assembly of tetrathiofulvalene and tetracyanoquinodimethane, in which the aromatic cores of the molecules have a tendency to stack to form juxtaposed short columns randomly oriented inside the smectic layers.

Although complying rigorously with the symmetry requirements of columnar LCs (the long-range positional ordering of

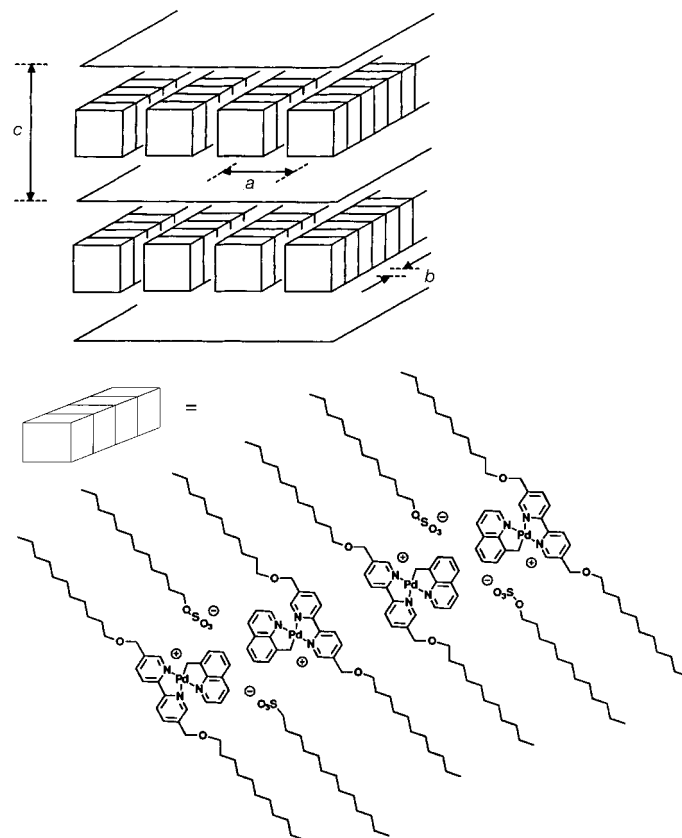


Figure 2. Idealized schematic view of the molecular packing of **1a**. The flat molecular cores of Pd atoms and coordinated aromatics rings (represented as boxes) are stacked on top of each other along the b direction to form columns (bottom half); these columns are juxtaposed along the a direction to form layers; and the layers stack along the c direction to form a lamellar structure.

the molecules is fully described by a two-dimensional crystal lattice), the columnar phase discussed in the present work is none the less quite unusual. Breaking the general rule, the columnar cores are not surrounded by the molten alkyl chains and thus entirely isolated from one another, but are joined together to form well-defined compact layers that are separated by the alkyl chains and stacked periodically. From a purely phenomenological point of view, one might wonder, therefore, whether the columnar phase could not be equally well described as a smectic mesophase, or more precisely, as an ordered smectic phase with one-dimensional ordering of the molecules within the layers. Such a phase would be a type of plastic mesophase, because the interactions between the columns are stronger than across the layers, so that the aromatic layers are able to slip on top of each other under moderate shear stresses in a direction normal to the columnar axis.

In summary, we have developed a novel synthetic strategy using the coordination of *ortho*-palladated quinolines with nonmesogenic alkyl-disubstituted 2,2'-bipyridine residues. By reducing the number of phenyl rings in the complexes to a minimum, we were able to obtain LCs at relatively low temperatures, and thus avoid thermal degradation. By studying these new complexes with X-ray diffraction, we were able to identify a smectic *A* and a columnar liquid crystalline

phase, both of which contained flat aromatic cores stacked on top of each other to form columns. The columns were arranged in compact layers separated by the alkyl chains in a disordered conformation. Obviously, these special structures are a result of stereochemical demands of the cation, the stacking ability of the ancillary *ortho*-palladated ligand, and the insertion of the counteranion among the alkyl chains. The packing mode of the aromatic cores may be optimized depending on the position of the alkyl chains on the bipy residues. The lamellar morphology of the columnar phase indicates that macroscopically oriented samples could be easily produced and could be profitably exploited for their physical properties. Because columns of closely stacked aromatic units are accessible at modest temperatures, we anticipate that these materials could be used as medium-length molecular wires or chemical sensors.

Experimental Section

L: Dodecanol (ca. 2 g) was heated with Na (0.08 g) for 2 h at 80°C to yield a white precipitate of $C_{12}H_{25}ONa$. After cooling to 20°C, a suspension of 5,5'-dibromomethyl-2,2'-bipyridine (0.30 g, 0.94 mmol) in anhydrous THF (5 mL) was added dropwise. The mixture was heated under reflux for 24 h. After distillation of the solvent, the residue was purified over a chromatography column (flash silica, *n*-hexane/ CH_2Cl_2 , gradient of 1/1 to 0/1). The analytically pure ligand **L** was then obtained (0.36 g, 70%). R_f = 0.65, SiO_2 , $CH_2Cl_2/MeOH$: 98/2; m.p. 60–62°C; UV/Vis (CH_2Cl_2): $\lambda_{max}(\epsilon)$: 290 nm (28 500); ^1H NMR (200.1 MHz, $CDCl_3$, 25°C): δ = 8.6 (s, 1H; H^6), 8.4 (d, ^3J = 8 Hz, 1H; H^3), 7.8 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H; H^4), 4.6 (s, 2H; bipy- CH_2), 3.5 (t, ^3J = 6 Hz, 2H; OCH_2), 1.6 (m, 2H; OCH_2CH_2), 1.3 (broad s, 18H; $(CH_2)_9$), 0.9 (t, ^3J = 6 Hz, 3H; CH_3); $^{13}C\{^1H\}$ NMR (50.1 MHz, $CDCl_3$, 25°C): δ = 154.7–120.1 (aromatic C), 70.2 (bipy- CH_2), 69.6 (OCH_2), 31.3 (OCH_2CH_2), 29.1 ($(CH_2)_3$), 28.9 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 25.5 ($CH_3CH_2CH_2$), 22.1 (CH_3CH_2), 13.5 (CH_3); IR (KBr): $\tilde{\nu}$ = 2925 (s), 2853 (s), 1598 (w), 1553 (w), 1467 (m), 1384 (w), 1350 (w), 1109 cm^{-1} (s). FAB⁺-MS: m/z (%): 553.4 (100) [M^+], 383.2 (32) [$M^+ - C_{12}H_{25}$]; elemental analysis calcd for $C_{36}H_{60}N_2O_2$ (552.465): C 78.21, H 10.94, N 5.07; found: C 78.09, H 10.79, N 5.02.

1a: A solution of $AgO_3SOC_{12}H_{25}$ (0.034 g, 0.090 mmol) in anhydrous CH_3CN (5 mL) was added at 20°C under argon, to a stirred suspension of $[Pd(8-mq)Cl]_2$ (0.026 g, 0.045 mmol). A white precipitate of AgCl appeared instantaneously. After 2 h, the solution was filtered over celite under argon. The filtrate was evaporated to dryness, and a solution of 5,5'-di(dodecyloxy-methyl)-2,2'-bipyridine (0.05 g, 0.09 mmol) in anhydrous CH_2Cl_2 (5 mL) was added. The yellow solution was stirred for 2 h, and the product was precipitated by addition of pentane (10 mL). **1a** was recovered by centrifugation as a yellow powder (0.08 g, 84%). UV/Vis (CH_2Cl_2): $\lambda_{max}(\epsilon)$: 229 nm (45 500), 243 (43 800), 315 (25 900); ^1H NMR (200.1 MHz, $CDCl_3$, 25°C): δ = 9.1 (d, 1H; aromatic H), 8.8 (s, 1H; aromatic H), 8.6 (dd, 2H; aromatic H), 8.4 (s, 1H; aromatic H), 8.2 (d, 1H; aromatic H), 8.1 (pseudo t, 2H; aromatic H), 7.9 (dd, 1H; aromatic H), 7.5 (m, 3H; aromatic H), 4.8 (s, 2H; bipy- CH_2), 4.5 (s, 2H; bipy- CH_2), 4.2 (t, ^3J = 7 Hz, 2H; O_3SOCH_2), 3.75 (s, 2H; CH_2Pd), 3.6 (m, 4H; OCH_2), 1.7 (m, 6H; OCH_2CH_2), 1.3 (broad s, 54H; $(CH_2)_{27}$), 0.9 (t, ^3J = 6 Hz, 9H; CH_3); $^{13}C\{^1H\}$ NMR (50.1 MHz, $CDCl_3$, 25°C): δ = 155.2–123.5 (aromatic C), 71.6 (bipy- CH_2), 69.0 (OCH_2), 67.6 (O_3SOCH_2), 34.4 (CH_2Pd), 32 (CH_2), 29.8 [$(CH_2)_n$], 29.6 (CH_2), 29.4 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 22.7 (CH_2), 14.2 (CH_3); IR (KBr): $\tilde{\nu}$ = 3055 (w), 2923 (s), 2854 (s), 1604 (w), 1509 (w), 1468 (m), 1386 (w), 1251 (s), 1223 (s), 1117 cm^{-1} (s). FAB⁺-MS: m/z (%): 800.4 (100) [$M - O_3SOC_{12}H_{25}$]⁺, expected isotopic profile, 658.3 (8) [$M - O_3SOC_{12}H_{25} - mq$], 630.2 (30) [$M - O_3SOC_{12}H_{25} - C_{12}H_{25}$], 247.9 (45) [$M - O_3SOC_{12}H_{25} - L$]; elemental analysis calcd for $C_{58}H_{93}N_3O_6SPd$ (1065.58): C 65.32, H 8.80, N 3.94; found: C 65.17, H 8.61, N 3.69.

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Anion Control in the Self-Assembly of a Cage Coordination Complex**

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Andrew J. P. White, and David J. Williams

Anion binding and recognition has attracted increasing interest because of its importance in biological and chemical processes.^[1,2] Many enzyme reactions involve the selective transformation of anions.^[1] The selective extraction of anionic pollutants also requires the development of specific coordination sites.^[2a] Classically, cations have been used to promote the assembly of ligands,^[3] but recently interest has been shown in using anions as templates for the formation of supramolecular entities.^[4]

The supramolecular interactions required for anion-assisted self-assembly involve either Lewis acid–base interactions between a metal cation and an anion^[5,6] or hydrogen-bonding

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interactions between an organic host and an anionic guest. Examples of the first type of supramolecular interaction are the 12-membered ring mercuracarborands reported by Hawthorne et al.^[5a] and the isopolyoxovanadates of Müller et al.^[6] In these rings and cages the metal ions interact due to their Lewis acidity with encapsulated anions. The second type of interaction has been illustrated recently by Stoddart, Williams, and co-workers,^[7] who reported the formation of a supermolecule based on hydrogen-bonding interactions to a PF₆⁻ anion. Here we report the novel anion-assisted self-assembly of a supermolecule in which both types of supramolecular interaction (Lewis acidity from a metal and hydrogen-bonding interactions from an organic moiety) are essential for its formation.

The coordination properties of biguanide have been known for a long time, and several of its complexes have been prepared and structurally characterized.^[8] Surprisingly, very few reports have appeared on the coordination chemistry of the analogous amidinothiourea ligand (Hatu; Figure 1), and indeed we are aware of only one such complex that has been structurally characterized.^[9]

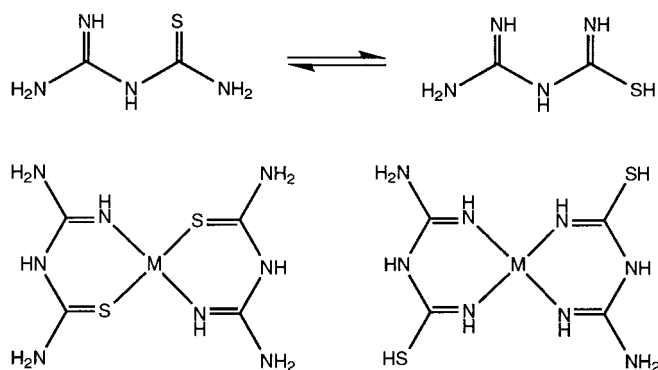


Figure 1. Two tautomeric forms of amidinothiourea and possible geometries of square-planar metal complexes with this ligand.

As part of a more general study of coordination compounds that display complementary hydrogen bonds,^[10] we have investigated the coordination chemistry of the amidinothiourea ligand with Group 10 transition metals. NiCl₂ in methanol readily reacts with amidinothiourea to give, initially, an orange intermediate that reacts further to yield a dark green compound, which was isolated and shown by single crystal X-ray analysis to be [Ni₆(atu)₈Cl]Cl₃ (**1**).^[11] The atu ligands coordinate to the nickel(II) centers by both guanidino nitrogen atoms to form square-planar units (Figure 2). This complexation resembles that observed in metal–biguanide complexes^[8] but is in contrast to the *N,S* coordination mode observed in the Pd complex formed with atu.^[9] The sulfur atoms of four {Ni(ATU)₂} units act as secondary donating sites to a further two nickel(II) ions to form the cage structure.

The Ni–N and Ni–S coordination distances in **1** are unexceptional, and comparable with those observed in related biguanide^[8] and thiourea^[12] species respectively. The most fascinating feature of this cage structure is the encapsulation of a chloride anion (Figure 3). Primary binding of the chloride

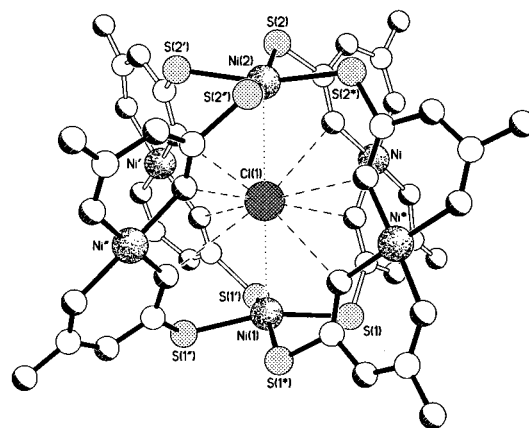


Figure 2. Structure of **1** in the crystal, showing the total encapsulation of a chloride anion through N–H...Cl hydrogen bonds. Hydrogen bonding geometries (N...Cl, H...Cl distances [Å], N–H...Cl angles [°]): 3.34, 2.45, 168; 3.29, 2.43, 149; 3.34, 2.45, 171; 3.28, 2.40, 166; 3.28, 2.39, 172; 3.30, 2.44, 161; 3.30, 2.43, 165; 3.29, 2.42, 165.

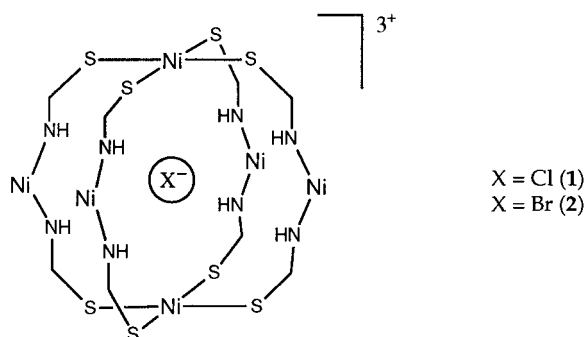


Figure 3. Schematic representation of the cage structure of **1** and the corresponding bromide species **2**.

anion is through eight N–H...Cl hydrogen bonds with N...Cl distances ranging between 3.28 and 3.34 Å. Accompanying these interactions is a marked out-of-plane distortion of each NiS₄ unit (ca. 0.33 Å) with the metal atoms approaching to 3.140(1) and 3.123(1) Å (for Ni(1) and Ni(2)) to the encapsulated chloride anion (Figure 4). This distortion suggests that there is a significant Lewis acid/base interaction between the two nickel ions and the central chloride ion. This type of interaction is similar to that previously observed in other host–guest structures such as the mercuracarborands reported by Hawthorne et al.^[5a]

The remaining three charge-compensating chloride anions in **1** are also involved in N–H...Cl hydrogen bonding interactions, but to the noncoordinated acidic N–H groups (these N...Cl distances range between 3.15 and 3.23 Å). The formation of a regular extended hydrogen-bonded network is prevented by the inclusion of ten disordered methanol molecules distributed over seventeen full and partial occupancy sites throughout the asymmetric unit.

The generality of the above anion-controlled self-assembly is supported by the ability to synthesize the analogous bromine species [Ni₆(atu)₈Br]Br₃ (**2**). This has been structurally characterized by single crystal X-ray analysis and has been shown to have a structure that is essentially isomorphous to **1**. The encapsulated bromide is bound by eight N–H...Br

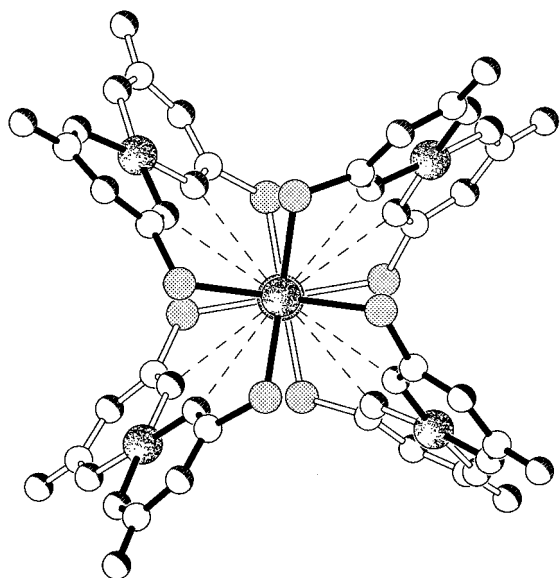
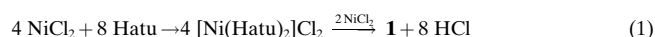


Figure 4. View, in parallel projection, down the Ni(1)···Cl(1)···Ni(2) direction of **1** showing the twisted, four-bladed propellerlike conformation of the five component complex: the two NiS₄ units have a slightly skewed (ca. 18°) square-prismatic orientation, an arrangement that is also adopted by the eight hydrogen-bonded ligand nitrogen atoms with respect to the entrapped chloride anion [twist angle ca. 15°].

hydrogen bonds with N···Br distances between 3.33 and 3.40 Å and axial Ni···Br distances of 3.128(4) and 3.134(4) Å for Ni(1) and Ni(2) respectively (the nickel atoms are again “bowed” inwards towards the encapsulated anion, here by about 0.35 Å).

The formation of the above complexes can be rationalized on the basis of the sequence of reactions shown in Equation (1). The first step may be the formation of the square-



planar complex [Ni(Hatu)₂]Cl₂. Deprotonation of the coordinated amidinothiourea ligands enables four of the molecules to act as ligands towards two additional Ni²⁺ ions to form a cage containing six nickel ions. The second step takes place in the presence of a templating anion (chloride or bromide) to form the final cage compound **1**.

Confirmation of the role of the chloride or bromide in the self-assembly process is demonstrated by the inability to form analogous cage structures with either nitrate, acetate, or perchlorate. In these cases, orange compounds characterized as salts of the simple monomer [Ni(Hatu)₂]²⁺ were obtained. When, however, these salts are treated with stoichiometric amounts of either nickel or potassium chloride, the cage compound **1** is formed immediately. The ability of chloride and bromide anions to template the formation of the novel cage complexes **1** and **2** provides another elegant demonstration of the little appreciated potential role of anions in self-assembly processes. We are currently exploring how this concept can be utilized in the anion-assisted self-assembly synthesis of mixed-metal species as potential precursors for new materials with controllable physical properties.

Experimental Section

A solution of NiCl₂·6H₂O (1.03 mmol, 243 mg) in methanol (10 mL) was added to a solution of amidinothiourea (2.00 mmol, 236 mg) in methanol (30 mL) and stirred. Initially the reaction mixture had a dark orange color, which disappeared after 10 min to give a dark green solution. The reaction mixture was stirred for a further 2 h and left to stand for 12 h. After this time dark green crystals of **1** had formed, and were separated by filtration. Some of the crystals were suitable for X-ray structural analysis. An analogous procedure was followed to prepare **2** from NiBr₂·3H₂O and amidinothiourea. Crystals of **2** were obtained by slow diffusion of diethyl ether into a methanol/acetone mixture.

1: Yield: 52%; ¹H NMR ([D₆]methanol): δ = 6.2–6.4 (br; NH); IR (KBr): $\tilde{\nu}$ = 3434 (m), 3330 (m) (N–H), 1660 (vs) (C–N), 1590 (s) (C–S), 1176cm^{−1} (s). UV/Vis: λ_{max} = 642 nm; FAB-MS: *m/z* (%): 1395 (**1** – Cl[−]; 20), 645 (**1** – 4Cl – 3Ni – 4L, 90); elemental analysis calcd for C₁₆H₄₀Cl₄N₃₂Ni₆S₈: C 13.4, H 2.8, N 31.3; obtained: C 13.0, H 2.8, N 28.2.

2: Yield: 56%; IR (KBr): $\tilde{\nu}$ = 3436 (m), 3330 (m) (N–H), 1660 (vs) (C–N), 1585 (s) (C–S), 1176cm^{−1} (s); UV/Vis: λ_{max} = 645 nm; FAB-MS: *m/z* (%): 645 (**2** – 4Br – 3Ni – 4L, 50); elemental analysis calcd for C₁₆H₄₀Br₄N₃₂Ni₆S₈·3MeOH·3H₂O: C 12.9, H 3.3, N 25.4; obtained: C 12.6, H 3.1, N 25.0.

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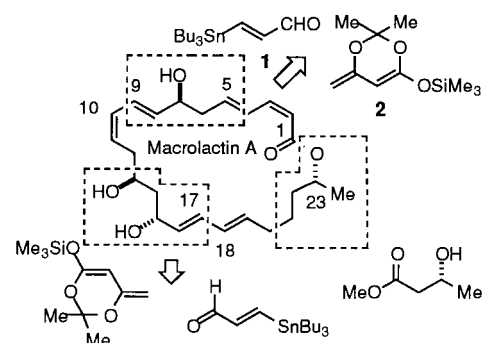
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Total Synthesis of Macrolactin A with Versatile Catalytic, Enantioselective Dienolate Aldol Addition Reactions**

Yuntae Kim, Robert A. Singer, and Erick M. Carreira*

Polyene macrolide antibiotics form a diverse group of natural products that display a wide range of biological activities.^[1] Impressive and elegant synthetic strategies have been used in their syntheses.^[2–6] Recently, macrolactin A was isolated from a bacterium of unclassified taxonomy, and in preliminary studies it was shown to inhibit HIV replication in T-lymphoblast cells (Scheme 1).^[7] As the organism was isolated from deep-sea coring and is no longer readily available, further biological research must rely on de novo synthesis of macrolactin A that utilizes modern asymmetric catalytic

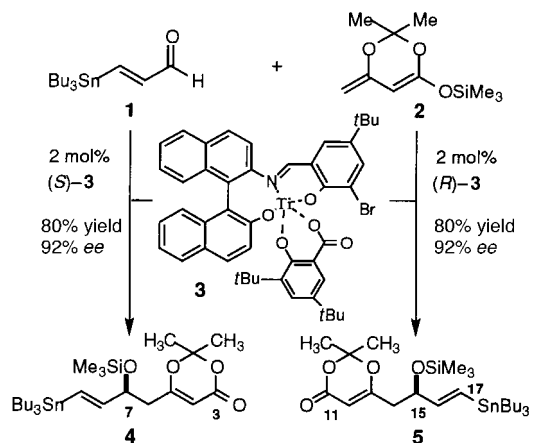


Scheme 1. Retrosynthetic analysis of macrolactin A.

C–C coupling methods in a highly convergent fashion.^[8] A common enantioselective, catalytic dienolate addition reaction was used to synthesize two key fragments that contain most of the molecule's stereochemical complexity, and Pd⁰ Stille coupling chemistry was used to assemble the principal fragments.

Central to our retrosynthesis (Scheme 1) was the recognition of structural homology between the three different regions that contain the stereogenic centers found in macrolactin A. In this analysis the latent 1,3-oxygenation pattern of the acetogenic macrocycle guides the disconnection of the macrocycle into three key subunits of approximately equal complexity: C(2)–C(9), C(11)–C(17), and C(18)–C(24). We speculated that the first two of these could be constructed with their attendant hydroxy-substituted stereocenters by an acetoacetate aldol addition reaction; each subunit could then be joined pairwise by Pd⁰-catalyzed sp²–sp² coupling reactions. Importantly, implementation of this strategy was facilitated by our recently developed catalytic, enantioselective dienolate aldol addition.^[9]

Fragments **4** and **5** were synthesized by a known strategy that started with aldehyde **1**, dienolate **2**, and the enantiomeric Ti^{IV} catalysts (*S*)- and (*R*)-**3** (Scheme 2). Treatment of



Scheme 2.

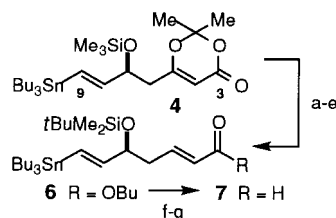
propynal diethyl acetal with Bu₃SnH/BuLi/CuCN followed by mildly acidic workup conveniently provided 3-tributylstannyl-2-propenal.^[10] In separate experiments with 2 mol % of (*S*)- and (*R*)-**3**, protected acetoacetate aldol adducts **4** and

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5 were each isolated in 80 % yield and 92 % *ee*, determined by derivatization as the (*S*)-(-)- and (*R*)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (MTPA) esters and analysis of the ^1H NMR spectra.^[11]

Acetoacetate adduct **4** was elaborated into the C(3)–C(9) subunit by a short, high-yielding reaction sequence (Scheme 3): hydrolysis of the acetonide protecting group



Scheme 3. a) *n*BuOH, 80°C, 99%; b) NaBH₄, MeOH, 0°C; c) MsCl, Et₃N, 23°C, 71 % over two steps; d) HF·py, THF, 23°C; e) *t*BuMe₂SiCl, DMAP, CH₂Cl₂, Et₃N, 90 % over two steps; f) DIBAL-H, THF, –78°C; g) Swern oxidation, 80 % over two steps. Ms = methane sulfonyl; py = pyridine; DMAP = 4-dimethylaminopyridine; DIBAL-H = diisobutylaluminum hydride.

afforded the corresponding β -keto ester (*n*BuOH, 80°C, 99 %), which was reduced with NaBH₄ to provide a diastereomeric (1:1) mixture of β -hydroxy esters. The unpurified reaction mixture was treated with MsCl and Et₃N to form the corresponding α,β -unsaturated ester (71 %, two steps), and after hydrolysis of the Me₃Si-ether the resulting 2° alcohol was protected as its *t*BuMe₂Si-ether to give **6**. Reduction of **6** to the primary alcohol and Swern oxidation yielded aldehyde **7** (80 %, two steps), a structural subunit that later forms the C(3)–C(9) fragment of macrolactin A.^[12]

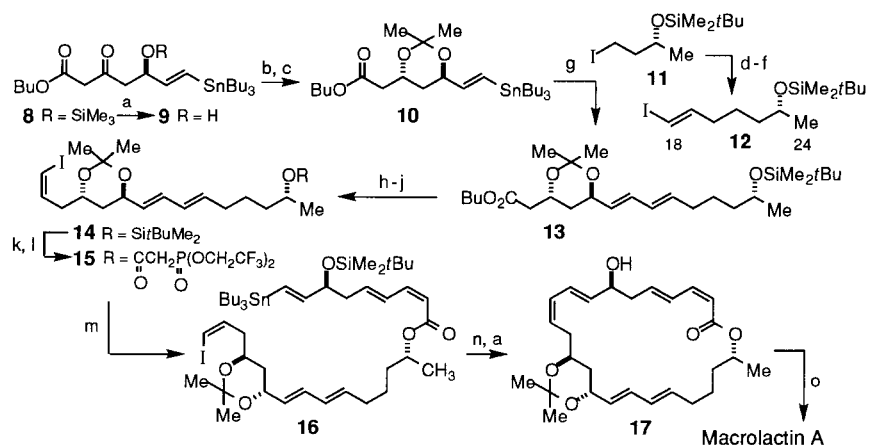
With the synthesis of the C(3)–C(9) fragment complete, we proceeded to elaborate dienolate adduct **5**. Treatment of **5** with *n*BuOH (80°C) afforded keto ester **8**, which yielded δ -hydroxy- β -keto ester **9** with HF·py (96 %, two steps, Scheme 4). Selective reduction of **9** with Me₄NBH(OAc)₃ converted **9** into the corresponding 1,3-*anti*-diol in 87 % yield and 14:1 diastereoselectivity, determined by ^1H NMR spectroscopy of the unpurified diol product.^[13] This 1,3-*anti*-diol was protected (Me₂C(OMe)₂, PPTS, 23°C) as acetonide **10** (89 %). Synthesis of the C(18)–C(24) fragment **12** was achieved with iodide **11**, prepared from commercially available ethyl 3-(*R*)-hydroxybutyrate.^[14] Enolization of acetaldehyde *N,N*-dimethylhydrazone (LiNiPr₂, THF) and alkylation with **11** provided the corresponding alkylated hydrazone (75 %). Ozonolytic cleavage of this hydrazone afforded 5-(*R*)-*tert*-butyldimethylsilyloxyhexanal, which was subjected to the Takai olefination (CHI₃, CrCl₂, THF) without purification to yield (*E*)-iodoalkene **12** (68 %, two steps).^[15, 16]

The first of the Pd⁰-coupling reactions, which links stannane **10** with vinyl iodide

12, was effected with [Pd₂(dba)₃], *i*Pr₂NEt, and CdCl₂ to provide diene **13** (69 %).^[17] Homologation of **13** to (*Z*)-vinyl iodide **14** as a single diastereomer (determined by ^1H NMR spectroscopy) was effected in 78 % yield by treatment of the aldehyde derived from **13** with Ph₃PCH₂I₂ under conditions developed by Stork.^[18] Deprotection of the silyl ether in **14** provided a secondary alcohol, which was acylated with *O,O*-bis-(2,2,2-trifluoroethyl)phosphonoacetyl chloride to give **15** (90 %).^[19, 20] Condensation of **15** with fragment **7** yielded hexaene **16**, an intermediate that incorporates the complete carbon skeleton and all the concomitant stereocenters found in the target macrolactin A. An intramolecular Pd⁰-mediated coupling reaction afforded the macrocyclic lactone, which, without purification, was treated with HF·py to give macrolactin A acetone **17**. Hydrolysis of this acetonide with Dowex resin yielded macrolactin A, which proved to be identical in all respects with the data reported for the material isolated from natural sources.^[21]

We have described an enantioselective total synthesis of macrolactin A, a rare polyene macrolide antibiotic that inhibits HIV replication in T-lymphoblast cells. Our synthetic strategy utilizes our recently developed catalytic, enantioselective dienolate addition methodology to introduce key stereocenters. The availability of both enantiomeric forms of the Ti^{IV} catalyst allows ready access to two of the three fragments in macrolactin A, and constitutes the first application of enantioselective dienolate addition reactions to natural product synthesis. This highly convergent route, in which the longest linear sequence is 16 steps with an average yield of 86 % per step, can provide 1.1 g of bioactive, but otherwise inaccessible, macrolactin A from as little as 15 g of the commercially available 3-(*R*)-hydroxybutyrate.

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Scheme 4. a) HF·py, THF, 23°C, 96 % (from **5**); b) Me₄NBH(OAc)₃, MeCN, –10°C, 87 %; c) Me₂C(OMe)₂, PPTS, 23°C, 89 %; d) MeC(H)NNMe₂, LDA, THF, 0°C, 75 %; e) O₃, CH₂Cl₂, –78°C; f) CHI₃, CrCl₂, THF, 68 % over two steps; g) Pd₂(dba)₃, CdCl₂, *i*Pr₂NEt, 69 %; h) DIBAL-H, –78°C, THF, 80 %; i) Swern oxidation; j) Ph₃PCH₂I₂, KHMDs, THF, –78°C, 78 % over two steps; k) HF·py, THF, 23°C, 80 %; l) (CF₃CH₂O)₂POCH₂COCl, DMAP, CH₂Cl₂, 90 %; m) **7**, KHMDs, 18-C-6, THF, 60 %; n) [Pd₂(dba)₃], *N*-Me-pyrrolidinone, 58 %; o) Dowex-H⁺, 23°C, MeOH, 60 %. PPTS = pyridinium-*p*-toluene sulfonate; LDA = lithium diisopropylamide; dba = dibenzylidene acetone; KHMDs = potassium bis(trimethylsilyl)amide.

Keywords: aldol reactions • asymmetric catalysis • macrolactin A • natural products • palladium • total synthesis

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Redox-Active Nanotubes of Vanadium Oxide

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Martin Müller, F. Krumeich, and Hans U. Nissen

Dedicated to Professor Roald Hoffmann on the occasion of his 60th birthday

Nanoporous materials (nanostructures), which are considered as intermediates between classical molecular scale and micro-sized entities, constitute a rapidly growing field of scientific interest and industrial applications. Well-defined structures of this length scale are difficult to obtain because neither typical physical tailoring techniques nor planned chemical syntheses are very applicable in this size domain. Since chemical reactivity and physical properties in the nano-region are strongly dependent on the size of the structures, such materials are very interesting in many respects, particularly for the production of highly functional, finely dispersible, and resource-saving base materials for “nanodevices”. Nanoparticles may be of quite different shapes such as spheroids, mushrooms,^[1] platelets, rods, or tubes; the form adopted plays a large role in determining the basic properties, for example, isotropic or anisotropic behavior and region-dependent surface reactivity.

The tubular form is particularly attractive since it provides access to three different contact regions: inner and outer surface as well as the tube ends. Carbon nanotubes^[2, 3] establish such singly or multiwalled entities that consist of graphite-like sheets depending on the synthesis conditions.^[4, 5] They have already attracted a great deal of interest because they might turn out to become very useful in future nanodevice technology. Another very interesting family are the nanoporous MCM-aluminosilicates^[6, 7] with continuous framework structures that have tunnel dimensions between 3 and 10 nm, extending the range of zeolite-like materials. The synthesis of these mesostructured molecular sieves relies on surfactant micelles or liquid-crystal arrays of micelles as structure-directing agents for the assembly and subsequent polymerization of inorganic aluminosilicate precursors at the surfactant-solution interface. The application of complementary electrostatic interactions between surfactant molecules and charged or polarized metal oxy precursors as the inorganic component has opened a way to new metastable modifications of metal oxides.^[8] Quite recently it has been shown that hydrogen bonding^[9] or real coordinative interactions^[10–12] between the ligand liquid crystal template and the metal center offer new perspectives for the controlled synthesis of surfactant-based periodic inorganic structures.

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One of our aims in this area is to produce specialized nanostructures from transition metal oxides for potential applications in electrochemical devices and for catalytic applications, and in appropriate template syntheses we have used neutral surfactant molecules such as primary aliphatic amines, together with vanadium alkoxide precursors to generate a novel nanotubular redox-active form of vanadium oxide. The hydrolysis of a solution of vanadium (V) triisopropoxide in hexadecylamine gave, after aging, a yellow, lamellar-structured composite of surfactant and hydrolyzed vanadium(v) oxide (Figure 1). The layer distance of this homogeneously periodic vanadium oxide surfactant assembly is about 3 nm. Treatment of this hydrolysis product under hydrothermal conditions yielded a product of isolated and starlike grown-together nanotubes with the nominal composition $\text{VO}_{2.40}(\text{C}_{16}\text{H}_{33}\text{NH}_2)_{0.34}$.^[14, 15]

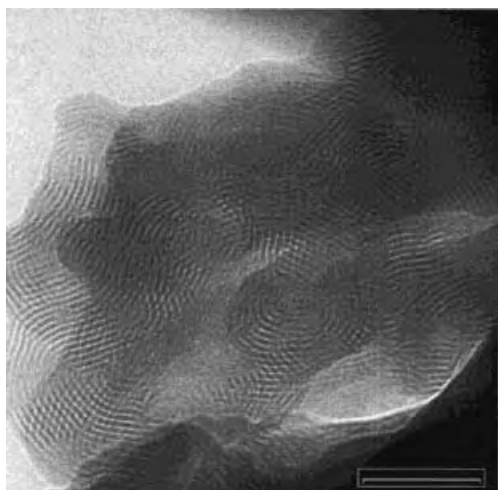


Figure 1. TEM image of the lamellar-structured, periodic assembly of surfactant and vanadium(v) oxide obtained after hydrolysis of the vanadium alkoxide in the presence of the surfactant templates. Layer thicknesses in the range of about 2.8 to 3.0 nm are observed. The bar shown in the box (bottom right) denotes 50 nm.

The black powdered material is paramagnetic, and shows a semimetallic conductivity presumably due to mixed-valent vanadium centers. Electron microscopic investigations show nearly exclusively isolated starlike or grown-together nanotubes up to 2000 nm long (Figure 2a). The scanning electron microscope image in Figure 2b illustrates the cylindrical open-ended shape of the tubules. The high-resolution transmission electron microscopy (TEM) photographs (Figures 2c and 2d) show that the walls are formed of several concentric shells each of about 3 nm. In fact, this corresponds to the most pronounced 2θ value found in the very broad X-ray powder patterns shown in Figure 2e. The tube diameters range from 15 to 100 nm and have tunnel openings between 5 and 50 nm (cf. Figure 2a). In accordance with the general practice for zeolite-like and mesoporous materials we call this product ETH1. Under slightly different conditions tubes with closed ends can also be obtained (Figure 2f).^[14]

Attempts to release the template from the material by calcination were unsuccessful because of the thermal lability of the nanotubes above 250 °C; however, the surfactant

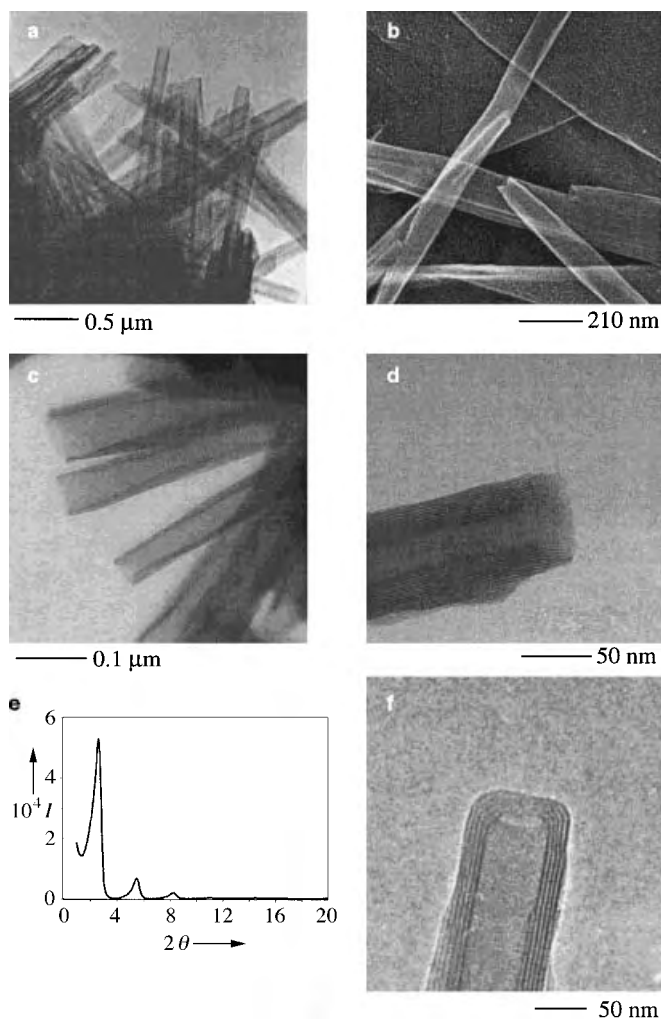


Figure 2. ETH1: a) Scanning electron micrograph of the open-ended vanadium oxide nanotubes that are up to 2000 nm long. b) Low-resolution TEM images of the hydrothermal reaction product, indicating isolated or grown-together vanadium oxide nanotubes as the main product. c and d) High-resolution TEM images of the vanadium oxide nanotubes, indicating the multishell structure of the tube walls with an average layer thickness of about 3 nm. The free inner diameter of the tubes range between 25 and 35 nm and the total tube diameters are between 50 and 70 nm. e) Powder X-ray diffraction pattern of the vanadium oxide nanotube material. The peak with the highest intensity at $2\theta = 2.66^\circ$ corresponds to a d -value of 3.3 nm, and reflects the layer distance of two concentric single shells of the multi-shell structure of the tube wall. f) Closed multiwalled vanadium oxide nanotube generated at alkoxide to template ratio of 1:1.

could be partially extracted under mild acidic conditions without structural damage. According to a recent publication by Antonelli and Ying,^[13] protonation of the alkylamine by alcoholic NH_4Cl solutions and subsequent replacement by OH groups should lead to a template exchange. Although we were able to exchange the template molecules by using NH_4Cl in ethanol we believe that this mechanism is not applicable in our case because reactions with nonhydrolyzing salts, such as NaCl , CsCl , CoCl_2 and even $[\text{Co}(\text{NH}_3)_6]\text{Cl}_3$, also gave rise to a complete exchange of the templates, while solutions of LiCl and CuCl_2 did not show a significant removal of the templates. Thus, we believe that the alkylamine is already protonated

during the synthesis and that the resulting ammonium ion is then replaced by a cation exchange for a sufficiently large M^{n+} . This is supported by EDX analyses which, for example, for the Co-exchanged samples clearly reveal considerable cobalt but no chlorine content in the tubes.

Interestingly, the layer distances change from about 2.8 to 3.0 nm for the templated (ETH1) to 0.86 nm for the template-exchanged material (formation of ETH2; Figure 3 top left). As the majority of the tubes are preserved, this exchange is presumably based on a cooperative mechanism. Notably, the crystallinity of the template-exchanged product is considerably better than that of the primary tubes ETH1; for some tubes even contrasts of about 0.65 nm are observed, which are indicative of an ordered structure within and between the individual shells of the tube walls (see arrows in center of Figure 3). This is supported by the fact that the vanadium oxide tubes exhibit a much better stability in the electron beam after the template exchange. We call this template-exchanged material ETH2.

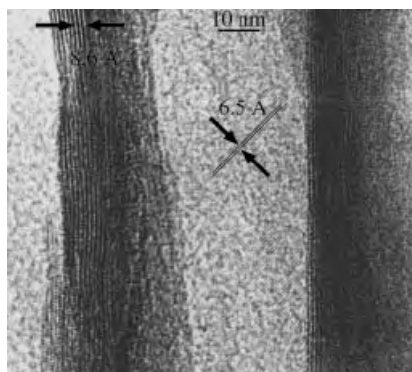


Figure 3. ETH2: High-resolution TEM image of a cation template-exchanged multiwalled vanadium oxide nanotube. The contrasts along the walls exhibit a distance of about 0.86 nm (see arrow top left). Several regions show a fine structure with contrast distances of about 0.65 nm (see arrow in the center), which are indicative of an ordered structure within and between the individual shells of the tube wall.

To our knowledge, the vanadium oxide materials reported herein are the first redox-active transition metal oxide nanotubes prepared and characterized.^[15] In contrast to the much smaller carbon nanotubes, the vanadium oxide tubes are obtained as the main product by a direct chemical synthesis at relatively low temperatures. Here, unlike other nanoporous oxidic materials such as MCM41 and MCM48 isolated tubes are present. The MCM-type nonredox-active aluminosilicates have only been synthesized with somewhat smaller tunnel diameters (roughly by a factor of ten) in the form of condensed extended structures but not as isolated tubes. Furthermore, no multishelled walls are present in the MCM materials. This might be the reason that isolated tubular aluminosilicate intermediates have not yet been observed.

The novel vanadium oxide nanotubes open fascinating possibilities for further chemical and physical explorations of nanostructures and hold promise for possible applications. The cooperative cation exchange behavior between the layers may allow incorporation of numerous functional cations or cation complexes. Although the tubes are interesting in terms

of the high surface area, we believe that even more interest lies in their potential for hosting functional molecules and for combining inorganic material and polymer organic compounds or even biological entities.

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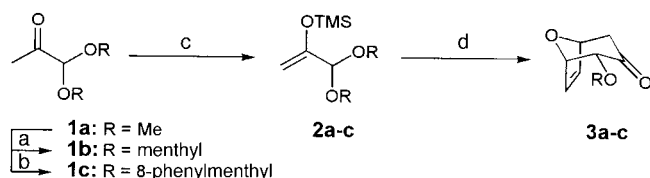
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Chiral Allyl Cations in Cycloadditions to Furan: Synthesis of 2-(1'-Phenylethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one in High Enantiomeric Purity**

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Asymmetric synthesis continues to be a major challenge of organic chemistry. In studies directed towards the total synthesis of marine natural products we required a simple route to enantiomerically pure 8-oxabicyclo[3.2.1]oct-6-en-3-ones, functionalized in the C₃ bridge. In the past a number of approaches to enantioenriched oxabridged seven-membered rings have been reported.^[1, 2] However, fundamental problems remain, such as lack of generality. The direct introduction of a chiral center α to the carbonyl group of the C₃ bridge requires generation of a planar allyl cation in chiral space. The chiral carbocation^[3] must be sufficiently reactive for π -facially selective, external capture by furan.

Lewis acid promoted ionization of silyl enol ether **2a** of pyruvic aldehyde dimethyl acetal (**1a**) in the presence of furan affords racemic 2-methoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (**3a**, Scheme 1).^[4] We decided to introduce a chiral auxiliary

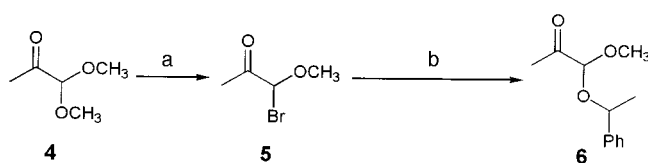


Scheme 1. Exploratory work on asymmetric [4+3] cycloadditions. a) (–)-menthol, *p*TsOH (cat.), heptane, water separator, reflux, 60%; b) (–)-8-phenylmenthol, *p*TsOH (cat.), heptane, water separator, reflux, 6% (and 65% mixed acetal); c) LDA, TMSOTf, THF, –78°C, quantitative; d) furan, TMSOTf, DCM, –78°C, 60–72%. *p*TsOH = *p*-toluene sulfonic acid, TMS = trimethylsilyl, OTf = trifluoromethane sulfonate, DCM = dichloromethane.

into the acetal function. Initial attempts with (–)-menthol and (–)-8-phenylmenthol were unsatisfactory, and suffered from the drawback that the chiral alcohols could not easily be detached from the cycloadducts. Moreover, in the case of allylic acetal **2c**, (–)-8-phenylmenthol served as an expensive leaving group. We therefore prepared mixed chiral acetals from 1-phenylethanol, which is readily available in either enantiomeric form^[5] (Scheme 2). Since 1-phenylethanol tends to form ethers and to racemize under S_N1 conditions such as prolonged contact with acids or on warming, the acetal was generated under basic conditions by deprotonation of the alcohol with *n*-butyllithium and S_N2 displacement of bromide ion from α -bromo ether **5**.^[6]

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Scheme 2. Synthesis of mixed acetals **6** under basic conditions. a) AcBr, neat, room temperature, 89%; b) 1-phenylethanol, Et₂O, *n*BuLi, –20°C, then addition of **5** at –78°C, 92% (based on recovered 1-phenylethanol).

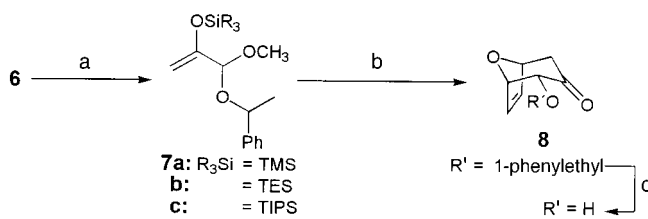
The resulting α -ketoacetal **6**^[7] was transformed into the trialkylsilyl enol ethers **7a–c** (Table 1). The simple tri-

Table 1. Effect of the silyl capping substituent in enol ether **7a–c**.

Entry	7	Yield of 8 [%]	α : β ^[a]	<i>de</i> [%]
1	a	28–48	2.0:1 to 4.3:1	33–62
2	b	58	5.3:1	68
3	c	35	5.5:1	69

[a] For the definition of α and β see Figure 1.

thylsilyl enol ether **7a** could not be purified, and cycloaddition to furan proceeded with variable diastereoselectivity and in irreproducible yield (Table 1, entry 1; Scheme 3). Triethylsilyl enol ether **7b** was more promising and therefore investigated in detail (Tables 2 and 3).



Scheme 3. Lewis acid promoted diastereoselective [4+3] cycloaddition. a) LDA, R₃SiCl, THF, –78°C, 70–85%; b) furan, TMSOTf. For conditions see Tables 2 and 3; c) silica gel, DCM, 9% HCl, reflux, 5 h, 60%. TES = triethylsilyl, TIPS = triisopropylsilyl.

Table 2. Effect of temperature on the cycloaddition of **7b** to furan.^[a]

Entry	<i>T</i> [°C]	Yield [%] of 8	α : β ^[b]	<i>de</i> [%]
1	–20	55	2.9:1	49
2	–78	58	5.3:1	68
3	–95	67	7.5:1	76

[a] Reaction time *t* = 10 min. [b] See Figure 1.

Table 3. Influence of solvent on the cycloaddition of **7b** to furan.

Entry	Solvent	<i>t</i> [min]	Yield [%] of 8 ^[a]	α : β ^[b]	<i>de</i> [%]
1	diethyl ether	90	10	1.2:1	10
2	THF	90	14	1.3:1	13
3	pentane	60	21	2.1:1	36
4	furan (neat) ^[c]	30	54	2.9:1	49
5	nitromethane	10	36	4.1:1	61
6	DCM	10	67	7.5:1	76
7	DCM/pentane ^[d]	10	37	8.2:1	78

[a] α -Methoxyketone **8** (R' = Me) was formed as a by-product. [b] See Figure 1. [c] At –78°C. [d] At –110°C. All other experiments were carried out at –95°C.

It is well known that the stereochemical outcome of an asymmetric transformation is temperature-dependent. Lowering the temperature often improves *de*'s. However, reaction rate and yield may decrease. In our case, a reduction in temperature from -20°C to -95°C increased the *de* of cycloadduct **8** from 2.9:1 to 7.5:1, while the chemical yield of cycloadduct **8** actually increased from 55 to a respectable 67% (Table 2, entry 2).^[8] Solvent effects were also observed (Table 3). Oxygen-containing solvents, such as diethyl ether and THF, were unsatisfactory. In contrast dichloromethane (DCM) worked well, and a further decrease in solvent polarity (change from DCM to DCM/pentane) allowed a further reduction in temperature to -110°C , when a *de* of 78% was achieved. However, the chemical yield fell (Table 3, entry 7).

Subsequent to this exploratory work with racemic 1-phenylethanol (Tables 1–3), cycloadditions with enantiopure (*S*)-(-)-1-phenylethanol were equally successful. Thus, conversion of the α -bromo ether **5** into mixed acetal **6** and subsequent cycloaddition to form **8** do not affect the potentially sensitive asymmetric center of the chiral auxiliary. The adducts are readily separable on workup, and enantiopure α stereoisomer is obtained after chromatography.^[9] Notably, carbon center C2 is conformationally constrained and proximate to carbon C1' of the chiral auxiliary. Thus, diastereomeric differences are maximized.

Presumably, the observed stereoselectivity results from preferential shielding of one allyl cation π -face by the phenyl ring of the chiral auxiliary. In the transition state the reactive allyl cation is sandwiched between a 4π and a 6π system. An important intramolecular interaction is thought to exist between the silicon and the ether oxygen of the chiral auxiliary (Figure 1, broken line). The carbocation involved in

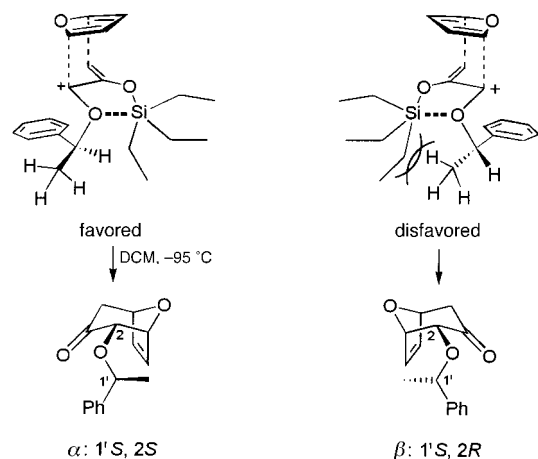


Figure 1. Possible routes to diastereoisomeric products in the cycloaddition of **7a** to furan.

the favored and disfavored path is structurally identical, but conformationally different. In the favored path the cation is thought to adopt the conformation which places the C1'-methyl group into the sterically least hindered position, remote from the TES group (Figure 1). The absolute config-

uration at carbon C2 of the major cycloadduct is in accord with this model.^[9]

We have developed a simple route with high chemical yields and *de*'s to 2-(1'-phenylethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one. Simple chromatography affords enantiopure materials. 1-Phenylethanol is both a convenient chiral auxiliary and a protecting group. Currently, applications of this new diastereo- and enantioselective [4+3] cycloaddition in natural product synthesis^[10] and extensions to related systems are being examined.

Experimental Section

General procedure for the asymmetric [4+3] cycloaddition of silyl enol ethers **7b** to furan: (-)-**7b** (12.9 g, 40.0 mmol; obtained from (*S*)-(-)-phenylethanol) and furan (2.80 mL, 2.72 g, 40.0 mmol) were dissolved in dry DCM (400 mL, 0.1 M). The solution was cooled to -95°C and TMSOTf (0.72 mL, 4.0 mmol, 0.1 equiv) was added dropwise. The reaction mixture was stirred for 10 min, poured into saturated NaHCO_3 solution, and extracted with DCM. The combined organic phases were dried (MgSO_4) and concentrated in vacuo. Column chromatography (ether/petroleum ether 1/3) afforded (-)- α (5.78 g, 23.7 mmol, 59.1% yield) and (-)- β (0.77 g, 3.15 mmol, 7.9% yield) as colorless solids (for a definition of α and β see Figure 1). (-)- α : m.p. $87-89^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} = -166.7^{\circ}$ ($c = 1.0$ in CHCl_3); ^1H NMR (200 MHz, CDCl_3 , TMS): $\delta = 7.27-7.41$ (m, 5H, Ph), 6.38 (dd, $J = 5.8$ Hz, 1.6 Hz, 1H; H-7), 6.28 (dd, $J = 5.8$ Hz, 1.6 Hz, 1H; H-6), 4.94 (dd, $J = 4.8$ Hz, 1.6 Hz, 1H; H-5), 4.83 (q, $J = 6.4$ Hz, 1H, PhCH), 4.70 (dd, $J = 4.8$ Hz, 1.6 Hz, 1H; H-1), 3.94 (d, $J = 4.8$ Hz, 1H; H-2ax), 2.69 (dd, $J = 15.6$ Hz, 4.8 Hz, 1H; H-4ax), 2.33 (d, $J = 15.6$ Hz, 1H; H-4eq), 1.45 (d, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , TMS): $\delta = 205.8, 143.3, 134.5, 132.0, 128.6, 127.9, 126.4, 82.8, 80.2, 79.2, 78.3, 45.9, 24.2$; IR (CHCl_3): $\tilde{\nu} = 3022, 2980, 1724, 1452, 1328, 1264, 1176, 1144, 1100, 1076, 1044, 1008, 968$; MS (70°C): m/z (%): 244 (2) [M^+], 216 (12), 215 (28), 161 (12), 148 (25), 140 (94), 105 (100), 97 (50), 77 (94); HRMS: calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3$ 244.1100, found: 244.1100. (-)- β : m.p. $90-92^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} = -93.9^{\circ}$ ($c = 0.95$ in CHCl_3); ^1H NMR (200 MHz, CDCl_3 , TMS): $\delta = 7.25-7.36$ (m, 5H, Ph), 6.39 (dd, $J = 6.4$ Hz, 1.7 Hz, 1H; H-7), 6.31 (dd, $J = 6.4$ Hz, 1.7 Hz, 1H; H-6), 5.06 (dd, $J = 4.8$ Hz, 1.7 Hz, 1H; H-1), 4.98 (d, $J = 4.8$ Hz, 1H; H-5), 4.76 (q, $J = 6.4$ Hz, 1H, PhCH), 4.08 (d, $J = 4.8$ Hz, 1H; H-2ax), 2.66 (dd, $J = 15.2$ Hz, 4.8 Hz, 1H; H-4ax), 2.35 (d, $J = 15.2$ Hz, 1H; H-4eq), 1.50 (d, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , TMS): $\delta = 202.9, 143.5, 134.7, 131.8, 128.5, 127.8, 126.4, 82.7, 78.9, 78.3, 77.1, 45.7, 24.0$.

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 [8] Less than 0.1 equivalent of TMSOTf sufficed for this transformation; cf also ref. [4].
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Neutron Diffraction Study of $[\text{Nd}(\text{AlMe}_4)_3] \cdot 0.5 \text{Al}_2\text{Me}_6$ at 100 K: The First Detailed Look at a Bridging Methyl Group with a Trigonal-Bipyramidal Carbon Atom**

Wim T. Klooster, Roy S. Lu, Reiner Anwander, William J. Evans,* Thomas F. Koetzle,* and Robert Bau*

Pentacoordinate carbon is an unusual entity. When it is observed, it exists in the form of a bridging alkyl group^[1] or, in a few rare cases, as an interstitial atom in a metal cluster complex.^[2] Although several examples of bridging alkyl groups have been structurally characterized,^[3–15] the hydrogen atoms associated with such bridges have not always been located in the X-ray diffraction studies. We describe here the first example of a bridging methyl group structurally characterized with neutron diffraction^[4] and show that it can adopt a trigonal-bipyramidal-like geometry.

The title compound **1** is the mixed-metal complex $[\text{Nd}(\text{AlMe}_4)_3]$ (isolated as a cocrystalite with Al_2Me_6),^[8] which contains asymmetrical methyl bridges between neodymium

and aluminum atoms. Pale purple-blue crystals of **1** were produced by the reaction of excess Al_2Me_6 with $[\text{Nd}(\text{NMe}_2)_3 \cdot (\text{LiCl})_3]$ ^[8] and recrystallized from hexane. The transportation and mounting of the crystals for neutron diffraction was challenging because of the moisture and temperature sensitivity of the sample (it decomposes above -40°C).^[16] The crystal was mounted in a specially designed anaerobic cold-box. A crystal with approximate volume 1.0 mm^3 was sealed in an aluminum container under a helium atmosphere and cooled to 100 K for neutron data collection. A total of 4535 reflections were scanned and refinement of the structure with 4013 independent F_o^2 values yielded final agreement factors of $R = 0.142$ and $R_w = 0.139$ based on 3σ data.^[17] Despite the fact that these values are relatively high (due to the small size of the crystal and also possibly due to partial decomposition during the difficult crystal-mounting procedure), the final geometrical results (distances, angles, and their esd's) are quite respectable.

A molecular plot of the structure (Figure 1) shows the sixfold coordination of carbon atoms around neodymium. Each AlMe_4 unit is coordinated to the central Nd atom

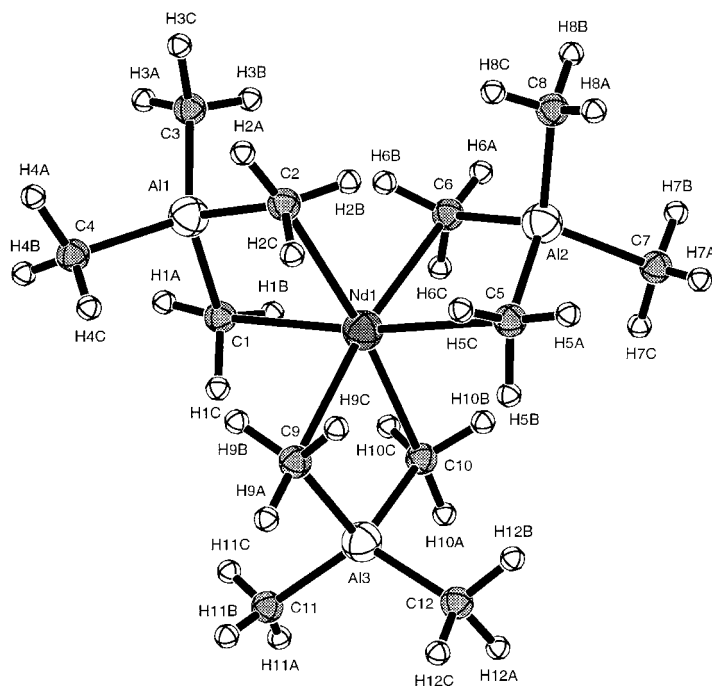


Figure 1. Structure of $[\text{Nd}(\text{AlMe}_4)_3]$ as determined by single-crystal neutron diffraction. Each methyl group is oriented such that one hydrogen atom (labeled H_{1A} , H_{2A} , etc.) is essentially *trans* to the Nd atom. Average distances [$\text{\AA}$] and angles [$^\circ$]: Nd–C 2.598(11), Nd–H 2.649(13), Nd–Al 3.138(10), Al–C(bridge) 2.087(11), Al–C(terminal) 2.006(11), C– H_A 1.09(1), C– $\text{H}_{B,C}$ 1.08(1); Nd–C– H_A 173.8(8), H_B –C– H_C 107.4(9), Al–C– $\text{H}_{B,C}$ 123.2(9), Nd–C–Al 83.4(4), Nd–C– $\text{H}_{B,C}$ 80.3(4), Al–C– H_A 91.2(10), H_A –C– $\text{H}_{B,C}$ 102.2(14).

through two bridging methyl groups, which in turn are oriented such that two of their three H atoms are directed at the Nd atom. The coordination number around Nd is either six (if only Nd–C bonds are counted) or eighteen (if Nd...H interactions are included). Apparently, it is the steric unsaturation of the larger Nd^{III} atom rather than the enhanced Lewis

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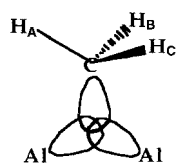
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acidity of the Al^{III} center, which directs the methyl hydrogen atoms towards neodymium rather than aluminum.

The most significant feature about the structure of **1** is the fact that the carbon atoms of the bridging methyl groups adopt approximately trigonal-bipyramidal (tbp) configurations. In each of the six methyl bridges, one of the three hydrogens (labeled H1_A, H2_A, etc.) is essentially trans to the Nd atom (average Nd–C–H_A angle 173.8(8)°). Thus, Nd and H_A take up the axial positions of the tbp, while Al, H_B, and H_C occupy the equatorial positions (Figure 1). All other molecular parameters are as expected.^[18]

The present structure determination is the first neutron diffraction study of a compound with bona fide *intramolecular* methyl bridges. As mentioned in reference [4], a weak intermolecular methyl interaction of the type Si–CH₃⋯Mg was observed in polymeric [Mg{CH(SiMe₃)₂}₂] by single-crystal neutron diffraction.^[6] In that case, the carbon atoms were also found to be distorted trigonal-bipyramidal, but of a different type with equatorial H atoms and axial positions occupied by Si and a relatively long C⋯Mg interaction (2.535(4) Å). Another example is illustrated by the neutron analysis of tetrameric [Li(BMe₄)] in which intermolecular B–CH₃⋯Li interactions were found.^[7]

Low-temperature X-ray analysis of the heteroleptic complex [Nd(NiPr₂){(μ-NiPr₂)(μ-Me)AlMe₂}{(μ-Me)₂AlMe₂}]^[10] revealed an analogous orientation of the hydrogen atoms of the bridging methyl groups as in **1**. In contrast, the methyl bridge found in the low-temperature X-ray analysis of Al₂Me₆ adopts a symmetric (and hence different) geometry, whereby the pseudo-C₃ rotation axis of the bridging CH₃ group bisects the Al–C–Al angle (I).^[9]



I

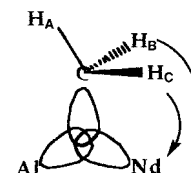
The bonding in Al₂Me₆ is generally accepted to be of the usual three-center two-electron type, involving a three-center overlap of two Al orbitals and an sp³ hybrid orbital from carbon. In [(C₅H₅)₂Y(CH₃)₂] the H atoms in the symmetrical Y–CH₃–Y bridge are arranged in a manner similar to I,^[11] while in other complexes of the type [(C₅R₅)₂Ln(AlMe₄)] (with Ln–CH₃–Al bridges) the H atoms were not located.^[3, 12] Related structures include compounds with linear symmetric Zr–CH₃–Zr^[13] and Lu–CH₃–Lu^[14] bridges, and one compound with a linear asymmetrical Yb–CH₃⋯Be^[15] bridge, all involving C atoms in tbp configurations with equatorial hydrogen atoms.

It is interesting to note that the tbp geometry of the carbon atom in [Nd(AlMe₄)₃] bears a superficial resemblance to a carbon atom in an S_N2 transition state. Although there is a fundamental difference (the S_N2 transition state being a ten-electron system while the bridging methyl group in **1** represents an eight-electron system), the validity of the atomic geometry for this type of five-coordinate carbon is established.

The main Nd–C bonding in [Nd(AlMe₄)₃] is almost certainly augmented by Nd⋯H interactions involving the H_B and H_C atoms. These interactions are presumably weak: a normal bridging Nd–H bond length can be estimated from the Nd^{III} ionic radius^[19] to range from 2.23–2.36 Å, based on the value

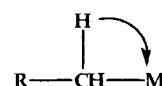
for Th–H of 2.29(3) Å measured from the neutron analysis of [(ThH₂Cp₂^{*})₂].^[21] In contrast, the Nd–H distances in **1**, ranging from 2.58(2) to 2.75(2) Å, are quite long and correspond to weaker-than-covalent bonding forces, probably of the agostic variety (vide infra).^[23]

The apparent tbp coordination of the carbon atom is intriguing. Trigonal-bipyramidal coordination normally corresponds to sp³d hybridization, but this is obviously not an option for carbon. In **1** the “axial” C–H_A distances (average 1.09(1) Å) are not perceptibly different from the “equatorial” C–H_{B,C} distances (average 1.08(1) Å), which would have been expected for a normal tbp geometry. Perhaps one way of rationalizing the bonding in **1** is to start with the “normal” symmetric bridge (as found in **I**) and then to imagine the CH₃ group being “tipped” towards Nd to accommodate additional C–H⋯Nd agostic interactions (**II**), Nd–C–H_{B,C} 80.3(4)°.

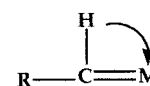


II

This “tipping” (or tilting) towards the large Lewis acidic Nd center results in a nearly linear Nd–C–H_A angle of 173.8°, as opposed to an angle of 147.5° expected for a symmetrical bridge of type **I**. Such a “tipped” geometry has been found in several structures suspected to have C–H⋯M agostic interactions, mostly metal–alkyl (**III**) or



III



IV

metal–alkylidene (**IV**) complexes involving the early transition metals Ti and Ta.^[24] In those molecules, the existence of agostic interactions between C–H bonds and electron-deficient metal atoms is manifested by highly distorted and unusually small M–C–H angles.

Finally, we should include a few words about the Al₂Me₆ “solvate” molecule present in the crystal. The terminal Al4–C14 and Al4–C15 distances are similar to those found in [Nd(AlMe₄)₃], but the bridging Al4–C13 distance is longer (2.17(3) Å). The Al4–C13–Al4' angle is 72.8(13)°, close to the value of 75.7° observed in the low-temperature X-ray study of Al₂Me₆.^[9c] However, only two out of the three H atoms could be located at the bridging position C13. Given their location, this strongly suggests that the Al₂Me₆ solvate molecule is disordered—a feature of the structure that unfortunately could not be conclusively resolved in this study. Our attempts to model this disorder are described in the details of the structure analysis.^[17]

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Two-Dimensional Nitroxide-Based Molecular Magnetic Materials**

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The temperature at which molecular solids exhibit macroscopic magnetic properties is strongly dependent on the dimensionality of the structure and on the magnitude of the exchange interactions between the spin carriers.^[1] Only a few species meet the criteria at room temperature, namely, hexacyanometalates^[2, 3] and an adduct of vanadium and tetracyanoethylene;^[4] they exhibit ferro- or ferrimagnetic ordering. In these compounds a three-dimensional structure and a fairly strong exchange coupling are probably the cause of high-temperature magnetic ordering.

Most strategies for designing molecular magnetic materials involve antiferromagnetically coupled alternating metal ions with different spins that do not compensate one another. These ferrimagnetic structures are assembled with polydentate bridging ligands such as oxalato, oxamato, oxamido, oximato, and dithiooxalato groups.^[5] The use of these ligands has been fruitful, and several structures of high dimensionality have been reported. These include a few three-dimensional structures in which control over the chirality of the coordination sphere of the metal was achieved.^[6–8] However, the Curie temperatures of these materials are low because the compounds contain either diamagnetic bridging ligands, which are poor mediators of the magnetic interactions, or diamagnetic metal ions.

In contrast, the metal-radical approach^[9, 10] exploits the direct coordination of a ligand atom of high spin density to the

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metal center, which ensures large exchange interactions. In addition, the ease of modification of the radical ligand allows versatility in the design of multidimensional structures. However, most of the reported metal-radical complexes with an extended structure are one-dimensional,^[11–13] because the nitroxyl groups are so weakly basic that they bind only to sterically congested metal centers that bear electron-withdrawing groups. This limitation was overcome by using trinitroxide ligands with a quartet ground spin state. Their complexes with manganese(II) hexafluoroacetate are two- or three-dimensional and exhibit ferrimagnetic behavior.^[14, 15] In all other known high-dimensionality compounds involving nitroxides, the role of the organic spin carrier was not optimized, and the magnetic behavior was still dependent on diamagnetic bridging groups.^[16, 17]

Here we report another successful strategy based on bis-chelating nitronyl-nitroxide ligands (Figure 1). Their manganese(II) complexes are two-dimensional species in which the

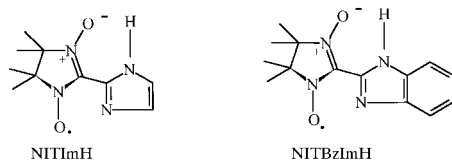


Figure 1. Formulas of the nitroxide ligands.

metal coordination sphere is free of electron-withdrawing groups and is occupied exclusively by paramagnetic bridging ligands. The complexes were obtained by mixing two equivalents of manganese(II) acetate, three equivalents of 2-(2-imidazolyl)-4,4,5,5-tetramethyl-4,5-dihydro-1H-imidazolyl-3-oxide-1-oxyl (NITImH) or 2-(2-benzimidazolyl)-4,4,5,5-tetramethyl-4,5-dihydro-1H-imidazolyl-3-oxide-1-oxyl (NITBzImH), and one equivalent of a sodium salt in methanol. The complex $[\text{Mn}_2(\text{NITIm})_3]\text{ClO}_4$ (**1**) was characterized by X-ray structure analysis.

Despite the small size of the crystals ($0.12 \times 0.14 \times 0.005$ mm), the quality of the reflections collected at 313 and 193 K was sufficiently high to allow a precise structure determination and an unambiguous description of the chemical features of the compound. These results were used as a guide to interpreting the magnetic properties of other compounds in this series. The molecular structure of the complex is shown in Figure 2. The asymmetric unit comprises two metal ions, three radical ligands, and one perchlorate anion. In the space group $P2_1$, this unit develops along the bc plane into a honeycomb structure in which the shortest and longest distances between metal centers are 6.3(2) and 13.2(2) Å. Therefore, the solid may be viewed as a lamellar material composed of $[\text{Mn}_2(\text{NITIm})_3]_\infty$ layers that are roughly perpendicular to the a axis and separated by 10.32(1) Å. The interlayer space is occupied by the perchlorate anions. Both metal coordination spheres are highly distorted octahedra with angles far from the ideal values of 180 and 90° (N3B–Mn1–N3C 159(1), N3B–Mn1–N3A 102(2)°), but the Mn–O and Mn–N bond lengths are within the range observed in most manganese(II) complexes. A detailed description of the

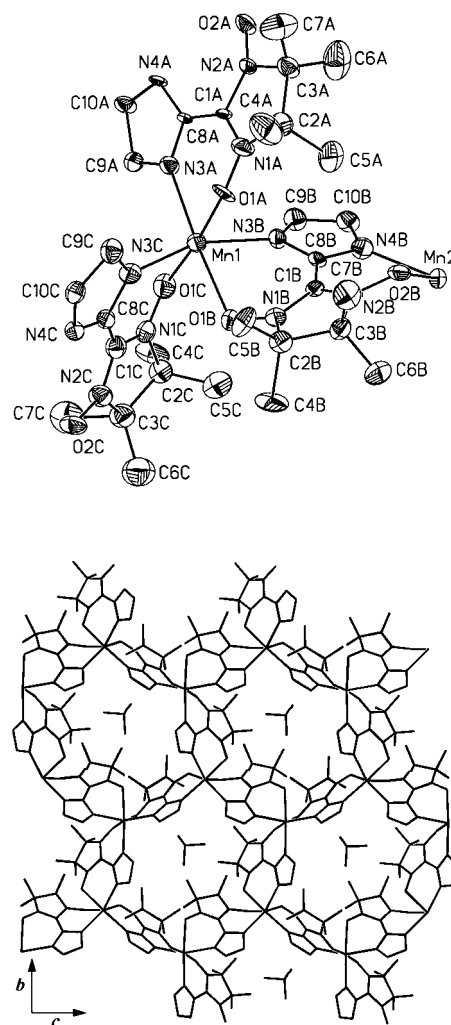


Figure 2. View of the asymmetric unit (top) and section of the honeycomb-like structure (bottom) of **1**. Selected bond lengths [Å] and angles [°]: Mn1–O1A 2.18(2), Mn1–O1B 2.29(2), Mn1–O1C 2.16(2), Mn1–N3A 2.22(2), Mn1–N3B 2.26(2), Mn1–N3C 2.11(3), Mn2–O2A 2.19(2), Mn2–O2B 2.20(2), Mn2–O2C 2.23(2), Mn2–N4A 2.17(2), Mn2–N4B 2.17(3), Mn2–N4C 2.20(2); O1C–Mn1–O1A 174.7(8), N3B–Mn1–N3C 159.9(9), O1B–Mn1–N3A 176.0(8), O2B–Mn2–O2C 170.9(8), N4B–Mn2–N4A 161.6(9), O2A–Mn2–N4C 171.5(9).

coordination sphere of both manganese ions must take into account the possible isomers resulting from an octahedral arrangement of the MX_3Y_3 type. In this planar complex, only an $OC\text{-}6\text{-}21$ (*mer*) arrangement is present. Further isomers could result from the chelating nature of the ligand, which can lead to Δ or Λ enantiomerism. Indeed, within a sheet, Δ and Λ configurations alternate regularly, and each crystallographically independent metal center has a specific chirality. Therefore, since the layers are related by a translation along the a axis, the crystal as a whole has a definite chirality that corresponds to one of the four diastereoisomers that can be formed from alternating Δ and Λ building blocks. It is also noteworthy that, as is commonly accepted, only the $\Delta\Lambda$ and $\Lambda\Delta$ configurations result in a planar structure;^[6, 7] the two other possibilities involve metal centers of the same chirality and would lead to a three-dimensional network.^[8]

At room temperature the magnetic susceptibility χ of **1** of $1.92 \times 10^{-2} \text{ cm}^3 \text{ mol}^{-1}$ is lower than that expected for inde-

pendent spins ($2.46 \times 10^{-2} \text{ cm}^3 \text{ mole}^{-1}$), and this indicates fairly large antiferromagnetic interactions between the manganese ions and the nitroxide radicals. With decreasing temperature, χ increases slightly to $2.87 \times 10^{-2} \text{ cm}^3 \text{ mol}^{-1}$ at 300.2 K and then decreases to reach a broad minimum ($2.53 \times 10^{-2} \text{ cm}^3 \text{ mol}^{-1}$) at 260 K. On further lowering the temperature, a sharp increase is observed, which gradually reaches a limiting value at low temperature. This limiting value is dependent on the applied field strength. The magnetic behavior is better described by the $1/\chi$ versus T curve, which shows two Curie–Weiss regimes with θ values of 101 and 23 K at high- and low temperature, respectively. In the series, only **1** exhibits such behavior. The closely related compounds $[\text{Mn}_2(\text{NITBzIm})_3]\text{ClO}_4$ (**2**) and $[\text{Mn}_2(\text{NITIm})_3]\text{BPh}_4$ (**3**) both exhibit only simple Curie–Weiss behavior with θ values of 105 and 71 K, respectively, which correspond fairly well to that of the high-temperature region of **1**. Compounds **1**, **2**, and **3** have Curie constants C of 6.8(2), 7.3(2), and 6.9(2) $\text{cm}^3 \text{ K mol}^{-1}$, respectively. These values are lower than that of $7.8 \text{ cm}^3 \text{ K mol}^{-1}$ expected for two Mn^{II} ions that are antiferromagnetically coupled to three nitroxide radicals. However, the presence of ferrimagnetic coupling within the layers is confirmed by the magnetization values M , which for all compounds exhibit saturation values close to the theoretical value of $7 \mu_{\text{B}}$ (6.7(1), 7.1(1), and 6.9(1) μ_{B} for **1**, **2**, and **3**, respectively).

Since the interlayer distance is large, one can assume that the Curie–Weiss behavior approximately reflects the properties of magnetically isolated layers. To understand the presence of two different Curie–Weiss regions in **1** the crystal structure was also determined at 193 K. No clear evidence for a phase transition was obtained, since the space group did not change, and the variation in the cell volume was smaller than 3%. However, on comparing the structures at both temperatures, one observes slight structural differences, which may result in a variation of the magnitude of the intralayer exchange interactions. Unfortunately, numerous possibilities exist for coupling in a layer: 1) Direct coupling between manganese(II) ions and organic radicals is expected to be large and antiferromagnetic.^[18, 19] 2) A competing interaction between manganese ions by a superexchange pathway through the imidazole fragment is expected to be weaker.^[20] 3) Finally, direct through-space intramolecular interactions between the nitroxide ligands within the metal coordination spheres (O1A–O1B 3.29(4) Å) are difficult to quantify but can be rather large.^[21, 22] Therefore, no unambiguous correlation can be found between exchange interactions and structural parameters, but comparison of the high- and low-temperature structures suggests that at lower temperature slight structural changes lessen the average coupling constant within the layers. Nevertheless, the low magnetic susceptibility at 400 K and the low magnetization at 5 K indicate that ferrimagnetic coupling occurs in both Curie–Weiss regions of **1** and that such a coupling scheme holds for the other compounds in the series.

Preliminary measurements of the magnetization of **1** and **2** at low temperature are shown in Figure 3. On examining the zero-field magnetization and field-magnetization curves one observes the onset of remanence below 1.4 K in **1**. The

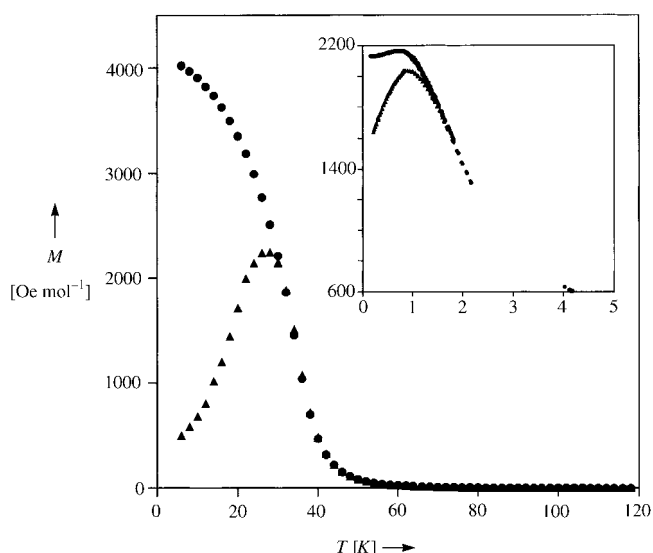


Figure 3. Magnetization–temperature curves of **1** (inset) and **2** in the low-temperature region in a field of 0.5 G. The zero-field magnetization is represented by triangles, and the field magnetization by solid circles.

presence of magnetic ordering below 1.4 K is confirmed by the field dependence of the magnetization at 85 mK. The curve exhibits a weak hysteresis loop with a coercive field of 270 Oe and a remnant magnetization of $0.22 \mu_{\text{B}}$. Similar behavior is observed for **2** and **3** for which remanence appears below 40 and 3.6 K, respectively. No hysteresis loop could be detected for **2** at 4.5 K. These results clearly indicate the presence of a weak ferromagnetic ground state, the full characterization of which is in progress.

Three-dimensional ordering in these compounds clearly depends not only on intralayer exchange coupling, but also on the interlayer interaction. For **1**, examination of the low- and high-temperature structures reveals a change in the three-dimensional arrangement. On lowering the temperature the lattice constants b and c become smaller, but surprisingly the lattice constant a increases by 0.363 Å. Since the layers are related by a translation along the a axis, the interlayer interaction is probably weakened. Therefore, the low-temperature properties of **1** are not only the consequence of a weaker intralayer interaction, but also of a modification of the coupling pathway between the layers. For **3**, the large θ value suggests a stronger intralayer interaction, but the bulkiness of the BPh_4 group is probably responsible for a weaker interlayer interaction. Finally, **2** deserves special mention. Its high-temperature magnetic behavior also follows a Curie–Weiss law, and the θ value of 105 K is almost equal to that of **1** in the high-temperature region; this suggests that a strong intralayer interaction associated with the small perchlorate anion is responsible for the high ordering temperature of 40 K. In this respect, the behavior of these compounds closely resembles that of recently described heteropolymetallic layered compounds, in which slight changes in the chemical nature of the counterion has strong effect on the low-temperature magnetic properties.^[23, 24]

The results obtained with the planar compounds **1–3** provide support for the metal-radical strategy towards molecular magnetic materials and represent important prog-

ress in the design of multidimensional structures. Although two-dimensional systems with a honeycombl-like layered structure have been described,^[23–26] the derivatives of tetradentate bis-chelating nitroxides are unique because exchange coupling within the layers is large. This work can probably be extended to the field of intercalation compounds. The synthesis of similar compounds with other transition metal ions, counteranions, and/or chiral nitroxides is in progress.

Experimental Section

NITImH:^[27] 2-imidazolecarboxaldehyde (1.3 g) and 2,3-bis(hydroxylamino)-2,3-dimethylbutane (2 g) were dissolved in methanol (40 mL). The solution was stirred for 36 h at room temperature. The solvent was then removed under vacuum, the crude product dissolved in CH₂Cl₂ (200 mL), and the resulting solution oxidized at 0°C for 30 min with NaIO₄ (5 g) in water (60 mL). After work up, the nitroxide was purified by chromatography on neutral alumina (type III, ethyl acetate eluent) to give pure NITImH (1.92 g, 64%); m.p. 152°C.

NITBzImH: 2-hydroxymethylbenzimidazole was prepared as previously described.^[28] This compound (5 g) was oxidized with MnO₂ (6 equiv) in dioxane for 60 h at room temperature. The mixture was filtered, the filtrate discarded, and the precipitate extracted continuously for 5 h with methanol to give 3.8 g of 2-benzimidazolecarbaldehyde (76%, m.p. 166°C). A suspension of 2 g of this aldehyde and 2,3-bis(hydroxylamino)-2,3-dimethylbutane (2 g) in methanol (60 mL) was heated to reflux for 30 min and then stirred for 48 h at room temperature. The methanol was then evaporated off, and the residue dissolved in dichloromethane (200 mL). The solution was cooled in an ice bath, and NaIO₄ (4.5 g) in water (50 mL) was added slowly over a period of 15 min. Evaporation of the organic solvent and chromatography on alumina (type III, ethyl acetate eluent) afforded 2.3 g (61%, m.p. 260°C decomp) of NITBzImH.

Preparation of the complexes: To a solution of the nitronyl nitroxide (3 mmol) in methanol (50 mL) was added manganese(II) acetate tetrahydrate (2 mmol). To the resulting green solution was added a solution of a sodium salt (1 mmol; counterions: ClO₄⁻, B(C₆H₅)₄⁻). In most cases precipitation occurred immediately, except for the perchlorate salt of the imidazolyl derivative **1**, which was obtained as tiny crystals. Satisfactory elemental analyses. X-Ray powder diffraction spectra did not show the presence of Mn₃O₄. All complexes decompose before melting.

Crystal structure determination of **1:** *M_r* = 879.09, Siemens SMART system, MoK_α radiation, λ = 0.71073 Å, graphite monochromator. Data collection, solution and refinement: monoclinic, space group *P*2₁; *T* = 313 K, *a* = 10.325(1), *b* = 17.870(6), *c* = 11.063(1) Å, β = 93.43(4)°, *V* = 2037(1) Å³, ρ_{calc} = 1.428 g cm⁻³; 2958 unique reflections, 1020 with *I* > 2σ(*I*), 496 parameters refined, *R*(*F*) = 0.090, *R*_w(*F*²) = 0.153; *T* = 193 K, *a* = 10.688(3), *b* = 17.165(5), *c* = 10.761(4) Å, β = 90.648(6)°, *V* = 1974(1) Å³, 2678 unique reflections, 962 with *I* > 2σ(*I*), *R*(*F*) = 0.102, *R*_w(*F*²) = 0.189. The data were processed with the SAINT^[29] program package, and the structure was solved with the SHELXTL^[30] program package. The absolute structure was determined by the method described by Flack.^[31] 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-100351. 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).

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Simultaneous Dual Living Polymerizations: A Novel One-Step Approach to Block and Graft Copolymers**

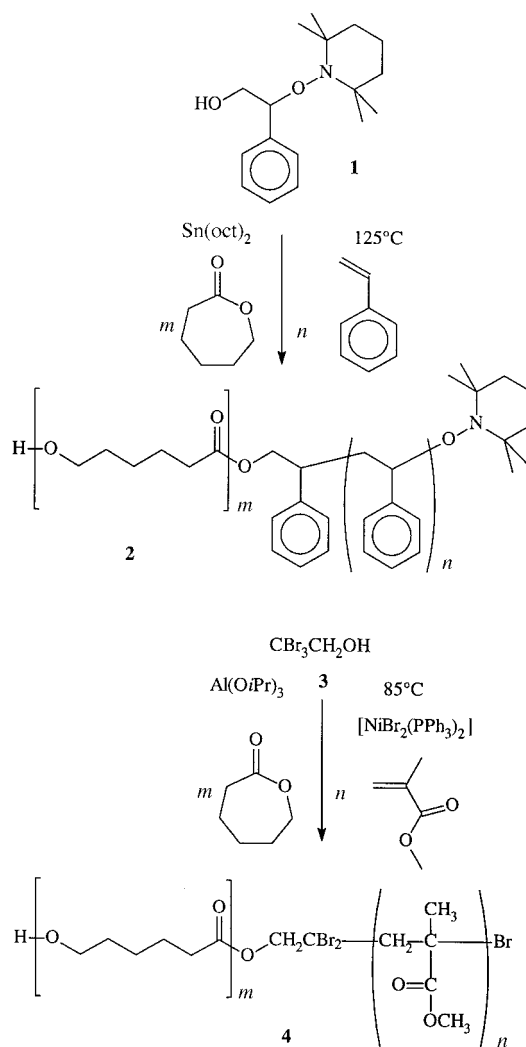
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The need to control the polymer properties in an increasingly precise manner explains why the synthesis of block copolymers of well-defined macromolecular architecture is a continuing theme of research in polymer chemistry. Since its discovery by Szwarc et al.^[1] in 1956, living polymerization remains the main tool for polymer chemists to efficiently control length, composition, and architecture of polymer chains.^[2] The last two decades have witnessed the emergence of new “living” (controlled) polymerization reactions based on radical chemistry.^[3] While not strictly living polymerizations, these new procedures have many of the attributes of traditional living polymerizations such as living anionic or cationic procedures. Among them, stable free radical polymerization (SFRP) and atom transfer radical polymerization (ATRP) are the most successful methods which allow molecular weight, polydispersity, and chain-end functionality to be controlled accurately. The renewed interest in the ring-opening polymerization (ROP) of lactones and lactides is justified by the capability of organometallic compounds to synthesize aliphatic polyesters of high molecular weight. For instance, ROP mediated by aluminum alkoxide has proved to be a living polymerization^[4] and leads to the controlled synthesis of oligomers and block copolymers with functional groups at the chain ends.^[5]

The traditional synthesis of block copolymers relies upon the sequential polymerization of corresponding comonomers by the same chemistry (e.g. anionic polymerization). Although this strategy may be successful, its extension to comonomers which do not polymerize by the same chemistry is usually a challenge. In this case, two strategies have been proposed: the coupling of preformed polymers with func-

tional groups at the chain ends and the use of a macro-molecular initiator for the polymerization of the second monomer. The second strategy usually requires a sequence of transformation reactions to convert the propagation center of the first block into an initiating site for the polymerization of the second monomer. Whichever method is used, two polymerization steps cannot be avoided.

Here we propose a new strategy for the one-step synthesis of block copolymers. It involves the use of an asymmetric difunctional initiator that is able to start the simultaneous polymerization of two comonomers by different polymerization chemistries in such a way that this initiator remains attached to each type of growing chain. We previously reported the successful synthesis of diblock copolymers by a sequential two-step method without any transformation or activation of intermediates.^[6] The implementation of this one-step synthesis is not straightforward: The two catalysts must be compatible and tolerate each other as well as the monomers, the reaction temperature must remain constant, and the kinetics must be closely controlled. “Living” radical polymerization and ROP by coordination and insertion can, at least in principle, meet these requirements (Scheme 1).



Scheme 1. Synthesis of block copolymers **2** and **4**.

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Initiator **1** contains a single primary alcohol functionality, which is the initiation center for the living ROP of cyclic lactones, as well as a secondary benzyl group linked to an alkoxyamine; the benzyl group is an efficient initiator for the nitroxide-mediated “living” free radical polymerization of styrene. Polymerization of a mixture of styrene (S) and ϵ -caprolactone (CL) initiated by **1** in the presence of Sn(oct)₂ as ROP catalyst produces the block copolymer PS-*b*-PCL (**2**; “P” = poly). Analysis of the molecular weight M_n of **2** at various levels of conversion reveals a linear relationship, which agrees with the “living” or controlled nature of both polymerization processes. In the same way, 2,2,2-tribromoethanol (**3**) contains a single primary alcohol functionality and an activated bromoalkyl group, which is an efficient initiator for the ATRP. Thus, polymerization of a mixture of methyl methacrylate (MMA) and ϵ -caprolactone initiated by **3** in the presence of Al(O*i*Pr)₃ as ROP catalyst and [NiBr₂(PPh₃)₂] as ATRP catalyst^[7] leads to the formation of the block copolymer PMMA-*b*-PCL (**4**). The characteristics of the copolymers are shown in Table 1. Particularly noteworthy are the unusually high conversions (70–90%) for these polymer-

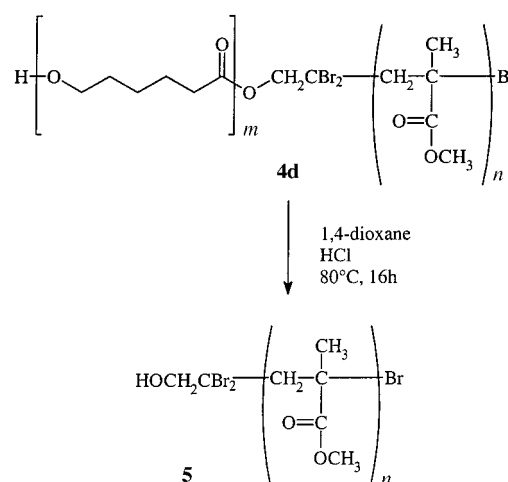
between the molecular weights calculated from the monomer-to-initiator molar ratio and the experimental values. Even though the molecular weights are not absolute values (calibration of size-exclusion chromatography (SEC) with PMMA or PS standards), they are in the range of the expected values. ¹H and ¹³C NMR and IR spectra of the block copolymers show signals typical for the different blocks, and SEC analysis shows unimodal molecular-weight distributions. The dynamic mechanical thermal analysis (DMTA) of block copolymer **2** also shows two glass-transition temperatures, one each for the caprolactone block and the polystyrene block. To conclusively confirm the formation of the block copolymer, **4d** was hydrolyzed with HCl to poly(methyl methacrylate) (**5**, Scheme 2). The ¹H NMR and IR spectra clearly show the total

Table 1. Synthesis of block copolymers PS-*b*-PCL (**2**) and PMMA-*b*-PCL (**4**).

Polymer	<i>T</i> [°C]	<i>t</i> [h]	<i>f</i> _{CL} ^[a]	<i>F</i> _{CL} ^[b]	Yield [%]	<i>M</i> _{n(theor)} ^[c]	<i>M</i> _{n(SEC)} ^[d]	<i>M</i> _w / <i>M</i> _n
2a	125	12	0.5	0.67	70	6000	6300	1.6
2b	125	24	0.5	0.60	75	12000	14000	1.7
2c	125	24	0.33	0.38	85	18000	17000	1.4
2d	125	24	0.25	0.26	85	24000	21000	1.5
4a	75	20	0.47	0.48	95	20000	20000	2.3
4b	75	1	0.47	0.85	55	10000	25000	1.3
4c	75	4	0.47	0.61	80	16000	24000	1.9
4d ^[e]	75	4	0.47	0.63	85	17700	26000	1.4
4e ^[e]	75	4	0.47	0.67	87	8700	11000	1.4
4f	60	13	0.47	0.70	75	7500	13000	1.7
4g	60	13	0.47	0.70	75	15000	26000	1.7

[a] Molar ratio of ϵ -caprolactone in the feed: $f_{CL} = [CL]_0 / ([CL]_0 + [MMA \text{ or } S])_0^{-1}$. [b] Molar ratio of ϵ -caprolactone in the copolymer as measured by ¹H NMR spectroscopy. [c] Theoretical molecular weight = $\{[CL]([initiator] \times 114)^{-1}\} + \{[MMA \text{ or } S]([initiator] \times 100)^{-1}\} + MW_{INT}$. [d] $M_{n(SEC)}$ with use of PS (**2a–2d**) or PMMA (**4a–4g**) as standards. [e] Addition of three equivalents of pyridine (with respect to Al(O*i*Pr)₃).

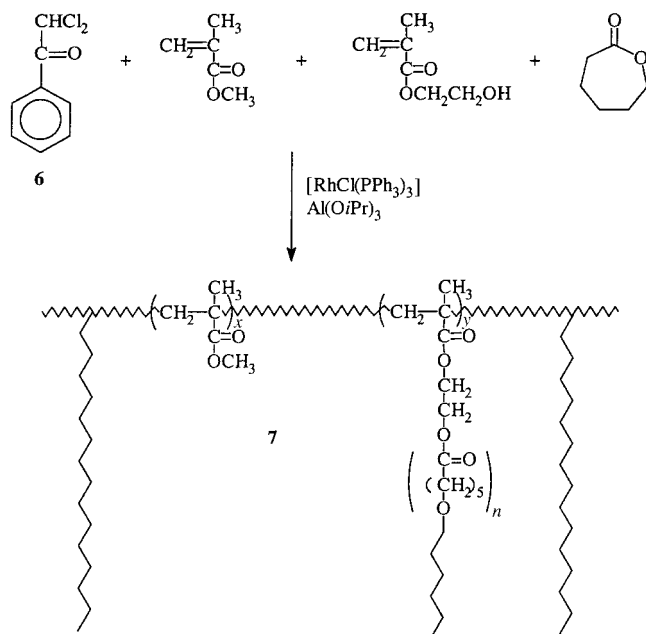
izations, even though they are performed without any added solvent in an unusual dual-monomer bulk procedure. Interestingly, under both sets of reaction conditions, the ROP occurs at a much faster rate than the “living” free radical polymerization, which results in a reduced molar fraction of caprolactone in the product upon increasing the reaction time or the number of conversions. For example, the mole fraction of caprolactone in **4** decreases from 85 to 61 to 48% on increasing the reaction time from 1 to 4 to 20 hours, while a concomitant increase in the conversion from 55 to 80 to 95% is observed. The molecular-weight distributions are somewhat broader (1.5–2.3) than for most living polymerizations, possibly owing to inadequate kinetic control and occurrence of side reactions, particularly polyester transesterifications. The extent of the transesterifications is decreased by the addition of pyridine when the ROP catalyst is an aluminum alkoxide.^[8] This is confirmed by a narrower molecular-weight distribution in the case of polymers **4d** and **4e** (Table 1). The most important observation is the relatively good agreement



Scheme 2. Hydrolysis of **4d**.

disappearance of the poly(caprolactone) block and, as expected, a complete shift of the SEC trace to lower molecular weights. The experimental molecular weight of **5** ($M_n = 7000 \text{ g mol}^{-1}$) is in good agreement with the theoretical molecular weight ($M_n = 6000 \text{ g mol}^{-1}$), and the polydispersity is low (PDI = 1.2). This observation confirms the reliability of the synthetic strategy and the production of only negligible amounts of homopolymers.

Interestingly, the “one-step” approach can be extended to the synthesis of graft copolymers. This strategy is illustrated in Scheme 3 for the particular case of the simultaneous “living” radical copolymerization of MMA and 2-hydroxyethyl methacrylate (HEMA), initiated by 2,2-dichloroacetophenone (**6**) and catalyzed by [RhCl(PPh₃)₃], and the ROP of ϵ -caprolactone promoted by the hydroxyl groups from the HEMA units and Al(O*i*Pr)₃ as ROP catalyst. As an example of this one-step production of graft copolymers, polymerization of a 1:0.1:1 mixture of MMA, HEMA, and ϵ -caprolactone initiated by **6** gave the expected poly(MMA-*g*-CL) copolymer (**7**) after 18 hours at 50 °C. The polymer was isolated in 73% yield after purification by precipitation in heptane, and the presence of PMMA and PCL was confirmed by ¹H NMR spectroscopy. As with the block copolymers, the poly(caprolactone) grafts were hydrolyzed to analyze the molecular parameters of the backbone. ¹H NMR spectroscopy clearly



Scheme 3. Synthesis of graft polymer 7.

shows the disappearance of the resonances for ϵ -caprolactone. Size-exclusion chromatography of the isolated backbone polymer reveals a molecular weight M_n of 30000, which is in agreement with that expected from the monomer-to-initiator molar ratio, while the polydispersity was quite low ($M_w/M_n = 1.25$).

A one-step approach based on dual simultaneous living polymerizations has been demonstrated to be a viable technique for the synthesis of a wide range of block and graft copolymers. The main advantages of this methodology are the bulk conditions used for the polymerization and the fact that only one step is required, making it very attractive from an industrial and academic point of view. Future work will concentrate on developing procedures for reducing the polydispersity of the block copolymers, which are broader than those obtained by traditional anionic procedures, as well as extending the method to other monomer and monomer combinations.

Experimental Section

Starting materials: 2,2,2-Tribromoethanol (97%), $[\text{NiBr}_2(\text{PPh}_3)_2]$ (99%), $[\text{RhCl}(\text{PPh}_3)_3]$ (99%), pyridine (99%), and 2,2-dichloroacetophenone (99%) were purchased from Aldrich and used as received. Triphenylphosphane (Aldrich) was purified by recrystallisation in methanol. Methyl methacrylate (MMA, 99% Aldrich), styrene (S, 99% Aldrich), and ϵ -caprolactone (CL, 99% Janssen) were dried over CaH_2 for 24 h and distilled under high vacuum before use. 2-Hydroxyethyl methacrylate (HEMA, Aldrich) was dried over molecular sieves and distilled just before the reaction. THF and toluene were dried by heating under reflux over sodium benzophenone and degassed by bubbling nitrogen for 15 min just before use. $\text{Al}(\text{O}i\text{Pr})_3$ (Aldrich, sublimed twice) was dissolved in dry toluene and titrated by complexometry with a standard solution of EDTA. Pyridine was dried over KOH and distilled just before use.

PS-b-PCL (2): In a typical experiment a 100-mL round-bottom flask that had been previously dried with a flame was charged with styrene (6.2 g, 62 mmol), CL (6.2 g, 54.3 mmol), and 1-phenyl-1-O-(2,2',6,6'-tetramethylpyperidin-1-yl)ethane-1,2-diol (0.2 g, 0.72 mmol) and heated to 120 °C under nitrogen. $\text{Sn}(\text{oct})_2$ (0.004 g, 0.1 mmol) was added, and the reaction

allowed to proceed for 12–24 h. Finally, the reaction mixture was dissolved in THF, and the block copolymer precipitated into cold methanol, filtered, and dried to provide a white powder.

PMMA-b-PCL (4): In a typical experiment $[\text{NiBr}_2(\text{PPh}_3)_2]$ (0.074 g, 0.1 mmol) was introduced into a Schlenk tube that had been previously dried with a flame and purged with nitrogen. The tube was then closed with a three-way stopcock, and a cycle of evacuation and filling with nitrogen was repeated three times. Then MMA (1 g, 1 mmol) and CL (1 g, 0.88 mmol) were added with a syringe. Finally, a previously prepared solution of $\text{CBr}_3\text{CH}_2\text{OH}$ (0.1 mmol) and $\text{Al}(\text{O}i\text{Pr})_3$ (0.017 mmol) was added. The isopropyl alcohol contaminant of aluminum alkoxide was previously removed by azeotropic distillation with toluene. The reaction mixture was heated at 75 °C under N_2 . After the appropriate reaction time, the reaction mixture was dissolved in THF, and the reaction ended with a small excess of HCl (0.1M). The copolymer was precipitated by dropwise addition to cold heptane, filtered, and dried at 50 °C until a constant weight was obtained.

PMMA-g-PCL (7): In a typical experiment $[\text{RhCl}(\text{PPh}_3)_3]$ (0.109 g, 0.12 mmol) and PPh_3 (0.217 g, 0.83 mmol) were introduced under nitrogen into a 100-mL round-bottom flask that had been previously dried with a flame and purged with nitrogen. Then MMA (3.56 g, 35.5 mmol), HEMA (0.41 g, 3.18 mmol), and CL (4.12 g, 36.1 mmol) were successively added with a syringe. Finally, 2,2-chloroacetophenone (0.23 mmol) and $\text{Al}(\text{O}i\text{Pr})_3$ (0.15 mmol) were added, and the reaction mixture was heated at 50 °C. After 18 h the mixture was diluted with THF, and the graft copolymer precipitated into cold heptane (yield: 5.50 g, 73%).

General procedure for hydrolysis: the block copolymer (1 g) was dissolved in 1,4-dioxane/37% HCl (95/5, 30 mL). Hydrolysis was carried out at 85 °C for 16 h. The product was isolated by precipitation in cold methanol (yield: 0.30 g, 75%).

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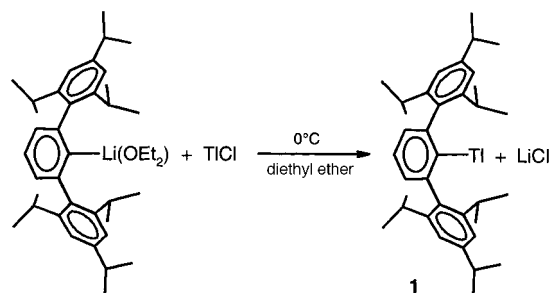
Synthesis and Solid-State Structure of 2,6-Trip₂C₆H₃Tl (Trip = 2,4,6-*i*Pr₃C₆H₂): A Monomeric Arylthallium(I) Compound with a Singly Coordinated Thallium Atom**

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For thallium, the heaviest element of Group 13, the univalent state is the most stable oxidation state, at least in aqueous solution. This, however, no longer applies to organothallium(I) compounds with σ -bonded substituents, which have attracted much less attention.^[1] Structurally characterized moieties with a Tl^I–C bond were limited for a long time to compounds with cyclopentadienyl ligands.^[2] Only very recently Uhl et al. described the synthesis of Tl[C(SiMe₃)₃].^[3] This alkylthallium(I) compound is tetrameric in the solid state. Thallium(I) derivatives with thallium bonded to higher homologues of Group 14 have not been obtained so far. Efforts to synthesize corresponding compounds with a Tl–Si bond surprisingly resulted in the formation of the thallium(II) derivatives Tl₂[Si(SiMe₃)₃]₄^[4a] and Tl₂(Si^{*t*}Bu)₃.^[4b]

Fully characterized thallium(I) aryl compounds were not previously known. We are interested in their properties, because they could serve as mild reagents for the synthesis of otherwise inaccessible aryl derivatives of main group and rare earth elements. Suitable substituents for this purpose are the terphenyl ligands 2,6-Mes₂C₆H₃ and 2,6-Trip₂C₆H₃ (Mes = 2,4,6-Me₃C₆H₂, Trip = 2,4,6-*i*Pr₃C₆H₂). These sterically congested ligands have been used successfully in the last few years for the stabilization of low coordination numbers,^[5] compounds free of Lewis donors,^[6] and new multiple-bond systems.^[7]

Thallium(I) chloride was allowed to react at 0 °C with 2,6-Trip₂C₆H₃Li · Et₂O^[5c] in diethyl ether (Scheme 1). After several minutes the suspension becomes red-orange. The workup procedure affords the thallium(I) aryl product (**1**) as



Scheme 1. Synthesis of **1**.

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bright orange, extremely air-sensitive crystals in 58 % yield. A second compound, 2,6-Mes₂C₆H₃Tl (**2**) can be prepared in a similar manner as shown in Scheme 1. The isolated deep-red solid is thermally very labile and could not be fully characterized. Freshly synthesized **1** is stable in the mother liquid at –40 °C for long periods whereas the isolated solid cannot be stored indefinitely, but slowly decomposes even at low temperatures. This decay is accelerated autocatalytically once thallium metal is formed. In solution **1** is thermally fairly stable, but very light sensitive. A solution of **1** in benzene in an NMR tube exposed to bright sunlight forms a thallium mirror after only a few seconds. The characteristic absorption in the UV/Vis spectrum of **1** at 487 nm is the band with the strongest shift to longer wavelengths. No ²⁰³Tl or ²⁰⁵Tl couplings are observed in the ¹H and ¹³C NMR spectra even at low temperatures (203 K), which could point to a dynamic exchange in solution.

The X-ray structure analysis^[8] reveals the solid-state structure of **1** to consist of monomeric 2,6-Trip₂C₆H₃Tl units with a singly coordinated thallium atom (Figure 1). The

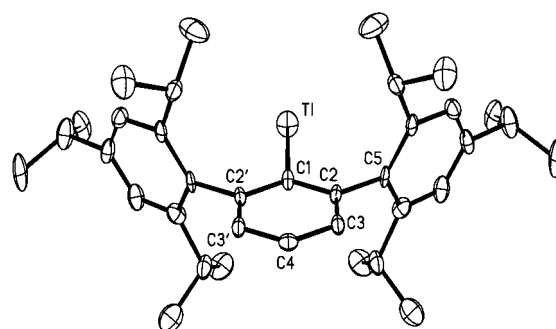


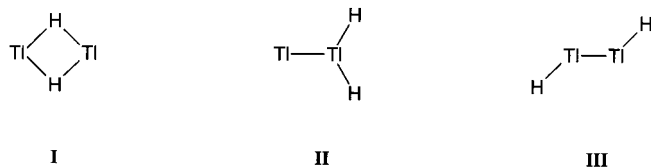
Figure 1. Molecular structure of **1** in the crystal; hydrogen atoms have been omitted for clarity. Selected bond distances [pm] and angles [°]: Tl–C1 234(1), C1–C2 139(1), C2–C3 138(1), C3–C4 138(1), Tl–C1–C2 120.2(6), C2–C1–C2' 119(1).

shortest intermolecular Tl–Tl and Tl–C distances are 681 and 419 pm. The Tl–C1 bond (234(1) pm) is marginally shorter than the corresponding value for Tl₄[C(SiMe₃)₃]₄ (average 237 pm)^[3]. As expected, shorter distances of 209 to 221 pm^[11] are observed in arylthallium(III) derivatives. The dihedral angle between the phenyl substituents of the Trip groups and the central phenyl ring is 81°. This deviation from orthogonality leads to a displacement of the Tl atom from the C(1)–C(6) plane by 28 pm. Additional contacts of the thallium to C2 (327(1) pm) and C5 (335(1) pm) are observed, but these are geometrically determined. The long-known neutral arenethallium(I) complexes^[12] with η^6 -coordination show Tl–C contacts between 313 and 352 pm and distances between the Tl atom and the center of the arene ring of 294–311 pm. The corresponding value of 392 pm in **1** indicates no significant interaction with the Trip substituents.

Monomeric Tl^I compounds are relatively rare in the solid state. The known examples are mainly limited to thallium(I) trispyrazolylborates, which have a three-coordinate metal center.^[1] The recently published gas phase structure of Ga[C(SiMe₃)₃]^[13] is a rare example of a monomeric singly coordinated metallorganic compound of a Group 13 element.

To the best of our knowledge, there are only two published examples of a metal with a coordination number of 1 in the solid state.^[14] The composition of the species 2,4,6-Ph₃C₆H₂M (M = Cu, Ag), however, is doubtful as subsequent investigations have revealed.^[15] Therefore, the arylthallium(I) compound **1** may be the first example, or at least a good approximation, of a singly coordinated metal atom in the solid state.

Why does **1** show no tendency to oligomerize? According to semiempirical^[16a] and ab initio^[16b, c] calculations on the model system H₂Tl₂ the potential energy surface contains at least three minima. The most stable valence isomer (Scheme 2) is the dibridged isomer **I**, followed by the



Scheme 2. Possible valence isomers for the system Tl₂H₂.

structural type **II** and the *trans*-bent form **III**. Substitution of the hydrogen atoms by 2,6-Trip₂C₆H₃ groups leads to severe overcrowding. Therefore valence isomer **II** should not be stable for steric reasons. This is also likely for the bridged form **I**, which has been observed in the less crowded dimers 2,4,6-(CF₃)₃C₆H₂OTl^[17a] and TlN(SiMe₃)₂^[17b]. Corresponding dimeric metal(I) compounds ([2,6-Mes₂C₆H₃M]₂, M = Li,^[6a] Na^[6c]) have been synthesized before with the smaller 2,6-Mes₂C₆H₃ ligand. It is possible that this structural type is realized in the complex 2,6-Mes₂C₆H₃Tl (**2**, deep-red color!).

For the *trans*-bent form **III** with a H-Tl-Tl angle of 115°, the dissociation energy was calculated to be 14 kJ mol⁻¹ taking relativistic pseudopotentials into account.^[16b] This structural type was observed for pentabenzylcyclopentadienylthallium(I).^[2c] The same compound also crystallizes in a polymorphic form^[16c] with a Cp-Tl...Cp arrangement, indicating relatively weak Tl^I-Tl^I interactions. A comparison with the recently published dianion [2,6-Trip₂C₆H₃Ga₂]²⁻^[7c] shows that **1** could assume a *trans*-bent form similar to **III** for steric reasons. However, relatively small energies, which can be attributed to packing effects and Pauli repulsion forces, seem to be sufficient to stabilize the unusual monomeric structure of **1**.

Experimental Section

Thallium chloride (1.02 g, 4.25 mmol) was added to a solution of 2,6-Trip₂C₆H₃Li·Et₂O^[5c] (2.39 g, 4.25 mmol) in 25 mL diethyl ether, and the suspension was stirred with exclusion of light for 5 h at 0°C. The precipitated lithium chloride and thallium were rapidly separated over a glass filter frit. Cooling of the filtrate to -40°C afforded orange needles of **1**. Yield 1.69 g (58%). M.p. (under argon) 242°C, crystals change color from orange through red to black from 90°C upwards. A cryoscopic molecular mass determination could not be obtained due to the poor solubility of **1** in benzene. ¹H NMR (C₆D₆): δ = 1.19 (d, ³J(H,H) = 6.9 Hz, 12H; *o*-p-CH(CH₃)₂), 1.26 (d, ³J(H,H) = 6.9 Hz, 12H; *o*-p-CH(CH₃)₂), 1.27 (d, ³J(H,H) = 6.9 Hz, 12H; *o*-p-CH(CH₃)₂), 2.86 (sept., ³J(H,H) = 6.9 Hz, 2H; *p*-CH(CH₃)₂), 3.24 (sept., ³J(H,H) = 6.9 Hz, 4H; *o*-CH(CH₃)₂), 7.27 (s, 4H; *m*-Trip), 7.31 (t, ³J(H,H) = 7.4 Hz, 1H; *p*-C₆H₃), 7.98 (d, ³J(H,H) =

7.4 Hz, 2H; *m*-C₆H₃); ¹³C NMR ([D₈]THF): δ = 24.6 (*o*-p-CH(CH₃)₂), 25.3 (*o*-p-CH(CH₃)₂), 30.8 (*o*-CH(CH₃)₂), 35.4 (*p*-CH(CH₃)₂), 121.1 (*m*-Trip), 125.0 (*p*-C₆H₃), 136.5 (br., *m*-C₆H₃), 138.7 (*i*-Trip), 146.0 (br., *o*-C₆H₃), 148.0 (*o*-Trip), 148.3 (*p*-Trip), signal for *i*-C₆H₃ not observed; UV/Vis (toluene): λ_{max} (ε) = 400 (520), 487 nm (250); MS (70 eV): *m/z* (%): 686.4 (36) [*M*⁺ with ²⁰⁵Tl], 685.4 (45) [*M*⁺ - H with ²⁰⁵Tl], 482.4 (100) [C₃₆H₃₀]⁺, 205.0 (60) [²⁰⁵Tl]; C,H analysis (C₃₆H₄₉Tl): calcd C 63.02, H 7.20; found C 61.35, H 7.34.

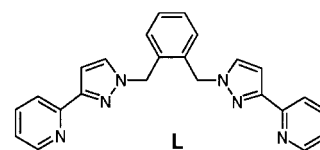
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Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-100750. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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fied by numerous “molecular grids”,^[2] and by some tetrahedral complexes prepared by Saalfrank et al.^[3] and Raymond et al.^[4] In other cases two or more different structures can arise from a single metal/ligand combination in which all components have the same stoichiometry (a “virtual combinatorial library” according to Lehn).^[5–7] The nature of the product in such cases is thus often impossible to predict and can depend on subtle factors such as interligand stacking interactions^[8] and the participation of noncovalently bonded anions^[7, 9, 11] or cations^[3, 10] in the resultant assembly.

We describe here complexes of the new ligand L, which contains two bidentate pyrazolyl–pyridine binding sites separated by an *o*-xylyl spacer. The complexes are $[\text{Co}_4\text{L}_6][\text{BF}_4]_8$ (**1**) and $[\text{Ni}_2\text{L}_3][\text{BF}_4]_4$ (**2**), which have the same

metal-to-ligand stoichiometry but surprisingly different structures given the very similar properties of the metal ions (size, charge, and preference for octahedral coordination).

The ligand L was simply prepared from reaction of 3-(2-pyridyl)pyrazole with 1,2-bis(bromomethyl)benzene.^[12] Given that it has four donor atoms an M_2L_3 stoichiometry seemed likely to occur with Co^{II} and Ni^{II} . A material analyzing as $[\text{Co}_2\text{L}_3][\text{BF}_4]_4$ was easily prepared,^[13] but the FAB mass spectrum (Figure 1) clearly indicated formation of a Co_4L_6 species, associated with varying numbers of $[\text{BF}_4]^-$ anions. The

Anion-Templated Assembly of a Supramolecular Cage Complex**

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A current goal in supramolecular coordination chemistry is to understand how the self-assembly process between labile metal ions and flexible multidentate ligands is controlled.^[1–11] In some cases the course of self-assembly may be controlled by using relatively rigid ligands, in which the symmetry of the arrangement of binding sites dictates only one possible outcome for the self-assembly process with a metal ion of a given stereoelectronic preference; this approach is exempli-

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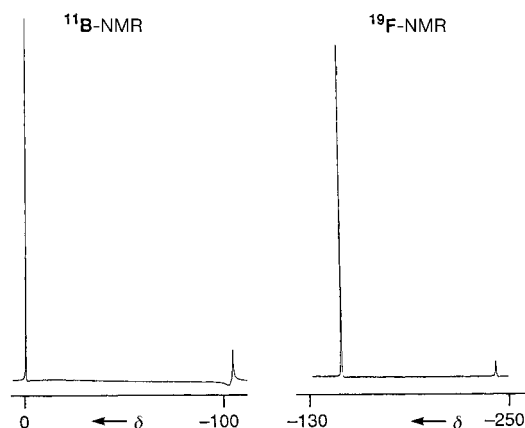
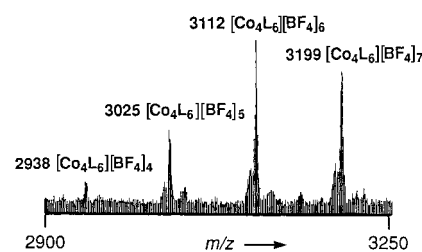
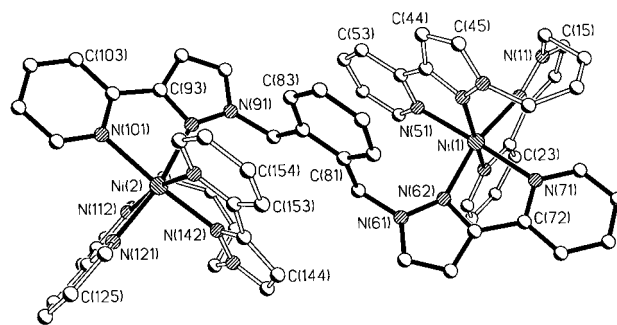


Figure 1. Top: part of the FAB mass spectrum (3-nitrobenzyl alcohol matrix) of **1**. Bottom: ^{11}B and ^{19}F NMR spectra of **1** (MeCN, room temperature): ^{11}B shifts vs. $\text{BF}_3(\text{Et}_2\text{O})$, ^{19}F shifts vs. CFCl_3 .

between two metal ions, spans one edge of the tetrahedron.^[14] Multiple π -stacking interaction between ligands is evident (Figure 2). Each Co^{II} ion is therefore pseudo-octahedrally coordinated by one bidentate arm from each of three separate ligands. The Co–N bond distances lie in the range 2.11–2.21 Å (average 2.151 Å), typical for high-spin Co^{II} . There is no imposed symmetry within each complex unit, and the $\text{Co}\cdots\text{Co}$ separations (all different) are between 8.98 and 10.07 Å. This adamantoid topology is identical to that observed in other complexes where six bridging ligands containing two bidentate compartments span the edges of a tetrahedron of metal ions.^[3, 4] Complex **1** has a charge of +8 and has eight $[\text{BF}_4]^-$ anions associated with the complex cation, of which one is contained in the tetrahedral cavity. Although the $[\text{BF}_4]^-$ anion can act as a weak ligand,^[15] the encapsulation cannot be ascribed to weak $\text{Co}\cdots\text{F}$ interactions in this case, because each fluorine atom of the trapped anion is directed towards the center of a triangular face of the Co_4

The Ni^{II} complex also analyzed as $[\text{Ni}_2\text{L}_3][\text{BF}_4]$.^[13] However, its FAB mass spectrum showed no evidence for formation of a tetranuclear Ni_4L_6 complex: the peak with highest mass corresponded only to a dinuclear $\{\text{Ni}_2\text{L}_3\}$ species. The crystal structure (Figure 4) confirmed the formulation



[Ni₂L₃][BF₄]₄, in which one ligand linked the two metal ions as a bis-bidentate bridge and the remaining two terminal ligands each coordinate as tetradentate chelates to one (pseudo-octahedral) metal ion.^[14] The Ni–N distances lie in the range 2.05–2.13 Å (average 2.096 Å). This structure is an unusual alternative to the triple helical architecture well-known in M₂L₃ complexes and is similar to the structure of the Fe^{III} complex of the tetradentate siderophore alcaligin, which was reported recently.^[17]

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ical shifts of the minor peaks do not correspond to any conceivable decomposition product of a $[\text{BF}_4]^-$ anion and, significantly, are absent in the spectra of both the batch of NaBF_4 used to prepare the complexes and of **2**. Also, they are present reproducibly in the NMR spectra of several different batches of **1**. These peaks therefore correspond to the $[\text{BF}_4]^-$ anion encapsulated in the cavity of the paramagnetic tetrahedral complex and exchanging with the free anions slowly on the NMR timescale, if at all (the two distinct signals were retained up to 70°C). The electrospray mass spectra of MeCN solutions of both **1** and **2** show the same general behavior as the FAB spectra. For **1** peaks corresponding to the series $[\text{Co}_4\text{L}_6(\text{BF}_4)_x]^{(8-x)+}$ ($x=6, 5, 4$) at m/z 1555, 1008, and 734, respectively, are observed: of these the peak at m/z 1008 for $[\text{Co}_4\text{L}_6(\text{BF}_4)_5]^{3+}$ in particular is significant, because no simpler combination of metal, ligand, anion and charge can give the same m/z value. In contrast, for **2** the only significant peak was at m/z 1294, corresponding to $[\text{Ni}_2\text{L}_3]^+$. The NMR and ES mass spectroscopic data both clearly suggest that the core of **1** is retained to a significant extent in solution (although some dissociation cannot be ruled out), but that no such tetrahedral complex forms in solution when Co^{II} is replaced by Ni^{II} .

There is no simple explanation for the fact that the assemblies of complexes of L with Co^{II} and Ni^{II} proceed along such different lines. However, the observations that a) we could not isolate or detect a $[\text{M}_4\text{L}_6]^{8+}$ core without an encapsulated $[\text{BF}_4]^-$ anion and b) any exchange between free and encapsulated $[\text{BF}_4]^-$ in **1** is slower than the NMR timescale both suggest that the encapsulated anion is an essential part of the structure. This implies that in **1** the anion may act as a template around which the four metals and six ligands assemble, and that in the absence of this templating effect, simpler dinuclear species such as **2** form.

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- [12] A mixture of α, α' -dibromoxylene (5.5 g, 20.9 mmol), 3-(2-pyridyl)-pyrazole^[15] (6.4 g, 44.1 mmol), toluene (200 cm³), $n\text{Bu}_4\text{NOH}$ (1 cm³ of a 40% aqueous solution), and aqueous NaOH (14.9 g dissolved in 35 cm³ water) was heated to 85°C for 24 h whilst stirring vigorously. After cooling the organic phase was separated, washed with H₂O, and dried (MgSO₄). Removal of the solvent gave an oil, which afforded a white powder (L) on recrystallization from CH₂Cl₂/Et₂O (Yield: 6.7 g, 82%). EIMS: m/z = 392. Satisfactory analytical and NMR spectral data were obtained.
- [13] **1** and **2**: Reaction of L (0.24 mmol) with the appropriate metal(II) acetate hydrate (0.16 mmol) in MeOH (5 cm³) for 1 h resulted in clear orange (Co) or blue (Ni) solutions. Addition of aqueous NaBF₄ resulted in precipitation of the complexes, which were filtered off, washed with MeOH, and dried in vacuo to give the complexes in 80–90% yield. Satisfactory analytical data (C, H, N) were obtained for both.
- [14] a) Crystal data for **1**·17.5H₂O: orange block, size 0.25 × 0.15 × 0.15 mm; C₁₄₄H₁₅₅B₈Co₄F₃₂N₃₆O_{17.5}, triclinic, space group $P\bar{1}$; a = 16.827(3), b = 18.909(4), c = 25.381(3) Å, α = 87.22(2), β = 84.723(14), γ = 86.74(2)°; V = 8021(3) Å³, Z = 2; ρ_{calcd} = 1.491 g cm⁻³; μ = 0.518 mm⁻¹. A sphere of data collected to $2\theta_{\text{max}}$ = 45° gave 20911 unique reflections (R_{int} = 0.078). Refinement of 2197 parameters with 12 restraints (applied to the thermal parameters of some of the tetrafluoroborate anions) gave $R1$ = 0.0745, $wR2$ = 0.2300; residual electron density between +1.06 and -0.69 e Å⁻³. Apart from the complex cation and the counterions, each asymmetric unit contains 17.5 molecules of water which form a hydrogen-bonded network also incorporating the $[\text{BF}_4]^-$ anions. b) Crystal data for **2**·3 MeCN·Et₂O·1.5H₂O: blue block, size 0.2 × 0.1 × 0.1 mm; C₈₂H₈₃B₄F₁₆N₂₁Ni₂O_{2.5}, triclinic, space group $P\bar{1}$; a = 10.839(2), b = 19.030(5), c = 21.800(8) Å, α = 92.61(2), β = 91.61(3), γ = 101.83(2)°; V = 4393(2) Å³, Z = 2; ρ_{calcd} = 1.411 g cm⁻³; μ = 0.522 mm⁻¹. A sphere of data collected to $2\theta_{\text{max}}$ = 40° gave 8192 unique reflections (R_{int} = 0.139). Refinement of 1185 parameters with 1764 restraints gave $R1$ = 0.0840, $wR2$ = 0.2445; residual electron density between +0.55 and -0.39 e Å⁻³. This crystal diffracted very weakly. To assist in the refinement, several restraints were applied: 1) all aromatic rings were restrained to be flat; 2) in the tetrafluoroborate anions all B–F bonded and all F...F nonbonded distances were restrained to be similar; 3) thermal parameters on adjacent atoms were restrained to be similar. c) 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-100861. 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@chemcrs.cam.ac.uk).
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High-Resolution ^{14}N Solid-State NMR Spectroscopy**

Gunnar Jeschke and Martin Jansen*

The element nitrogen plays an important role in chemistry, particularly in the chemistry of materials and of life. With few exceptions, NMR spectroscopic structure determinations on solid nitrogen compounds have been restricted to the rare spin 1/2 isotope ^{15}N (natural abundance 0.33 %), which usually requires an expensive isotope enrichment. On the other hand it has been assumed since the introduction of high-resolution magic angle spinning (MAS) NMR spectroscopy that the quadrupole interaction precludes the application of this method to ^{14}N , as typical quadrupole couplings are at least two orders of magnitude larger than the sample rotation speeds that were initially achieved. Meanwhile commercial MAS systems have become available that can stabilize spinning speeds between 10 and 20 kHz to about 0.2 %. This precision led us to expect that the MAS method would now also be applicable to ^{14}N . In addition to the characterization of the chemical environment of the nitrogen nucleus by the chemical shift and its anisotropy, such experiments would also allow access to the quadrupole interaction and thus to the electric field gradient at the nucleus. Our own interest in this method is focused on its potential for characterizing the nitrogen environment in cubic and hexagonal boron nitride. These compounds in turn are reference compounds for the structure determination of amorphous Si-B-N and Si-B-N-C ceramics.^[1]

The application of MAS NMR spectroscopy to ^{14}N measurements on nitrogen nuclei in highly symmetric environments was not expected to pose any problems, as the quadrupole interaction vanishes in tetrahedral or higher symmetry. Indeed, the ^{14}N MAS NMR spectrum of cubic boron nitride was obtained readily with excellent signal-to-noise ratio and high resolution (Figure 1 a). We find a line width of 90 Hz and a chemical shift of $\delta = -17.6$ with respect to NH_4Cl that is also used as a reference in ^{15}N solid-state NMR spectroscopy.^[2] The rotational side bands in this spectrum are caused by heteronuclear dipole-dipole couplings with ^{11}B . We were able to exclude a small residual quadrupole interaction arising from slight symmetry deviations by a comparison of ^{10}B and ^{11}B wideline spectra.^[3]

To study the influence of a moderate quadrupole interaction on the spectra, we decided to use NH_4SCN as a model sample since it has been well characterized by wideline NMR and by NQR methods.^[4] The experimental spectrum assigned to the NH_4^+ ion (quadrupole coupling $\chi = e^2qQ/h = 93$ kHz, $\eta = 1$) is displayed together with a simulation in Figure 2. For the given measurement conditions, no signals are observed that can be attributed to the SCN^- ion ($\chi = 2.28$ MHz). Except

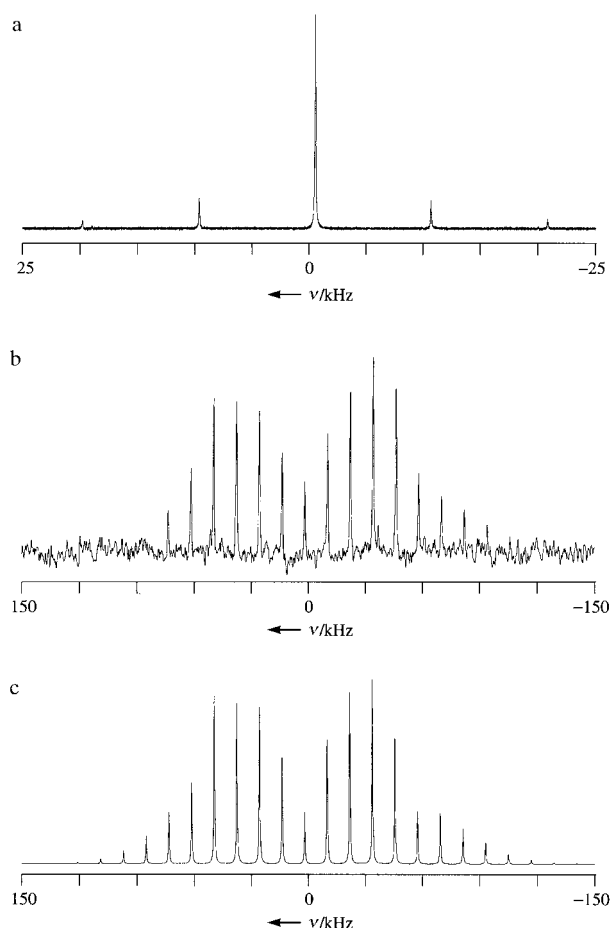


Figure 1. ^{14}N MAS NMR spectra of boron nitrides at 28.809 MHz. a) Cubic boron nitride, $\delta_{\text{iso}} = -17.6$ ppm; b) hexagonal boron nitride; c) simulation of the spectrum of hexagonal boron nitride with the parameters $\delta_{\text{iso}} = 63$ ppm, $\Delta\sigma = 160$ ppm, $e^2qQ/h = 140$ kHz, $\eta = 0$.

for a notable asymmetry in the experimental spectrum, the agreement between experiment and simulation is good; we attribute this asymmetry to a small anisotropy of the chemical shift. The line width in the MAS spectrum (80 Hz) is reduced by a factor of about 1000 with respect to that in the wideline NMR spectrum. Note that NH_4SCN represents a regime of moderate quadrupole coupling that is also met in some nitrogen-containing phospholipids.^[5]

Encouraged by the relatively high sensitivity of ^{14}N MAS NMR spectroscopy for moderate quadrupole couplings, we applied the method to hexagonal boron nitride. In this case we were not able to obtain a ^{14}N wideline NMR spectrum under static conditions. As a result of the rigid lattice and of the absence of protons, spin-lattice relaxation of ^{14}N is quite slow, so that the optimum recovery time between the measurement of two transients is as long as 30 minutes. Nevertheless, a spectrum with satisfactory signal-to-noise ratio can still be obtained (Figure 1 b). For the simulation of this spectrum, we have extended the method by Herzfeld and Berger to the case of a spin 1 with quadrupole coupling and anisotropic chemical shift.^[6] By fitting the parameters and subsequently correcting the isotropic shift by the second-order quadrupole contribution, we obtain the values $\chi = 140 \pm 10$ kHz, $\delta_{\text{iso}} = 63 \pm 3$ ppm, and an anisotropy of the chemical shielding of $\Delta\sigma = 160 \pm$

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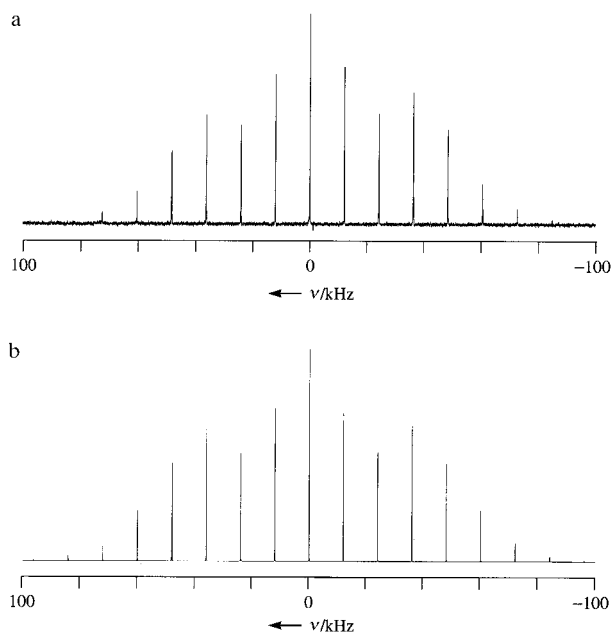


Figure 2. ^{14}N MAS NMR spectrum of ammonium thiocyanate at 28.809 MHz. a) Experimental spectrum; b) simulation with quadrupole coupling parameters taken from literature.^[4]

20 ppm. Hereby, on the basis of the known crystal structure we have assumed axial symmetry of both tensors ($\eta = 0$). Evidently, three-coordinate nitrogen in hexagonal boron nitride can be safely distinguished from four-coordinate nitrogen in cubic boron nitride solely based on the isotropic chemical shift. The chemical shift found for the hexagonal modification is in relatively good agreement with a calculated value ($\delta = 56 \pm 5$ ppm with respect to NH_4Cl),^[7] while χ is unexpectedly low. Note, however, that the strong dependence of the theoretical results for χ (0.75–1.33 MHz)^[8] on the basis set already reveals some difficulties in these calculations. Furthermore, it is remarkable that the anisotropy of the chemical shift can be estimated from the side band pattern, although it is smaller than the sample rotation speed.

From the spectra in Figures 1 and 2 one may conclude that ^{14}N MAS NMR spectroscopy with contemporary spectrometers should also be feasible for larger χ values of about 1 MHz. Indeed we have also succeeded in detecting MAS side band patterns for glycine ($\chi = 1.25$ MHz^[9]). However, to be able to analyze spectra in this regime of medium quadrupole couplings quantitatively, further developments are needed mainly in broad band spectral excitation. In this respect it is also significant that state-of-the-art commercial spectrometers now achieve 50 % larger resonance frequencies and three times faster sample spinning than are used in this work. These developments should drastically improve the performance of ^{14}N MAS NMR spectroscopy for larger quadrupole couplings. With such experiments, an important gap in the applicability of high-resolution NMR spectroscopy is finally closed.

Experimental Section

All NMR spectra were measured with a Unity 400 NMR spectrometer (Varian) and a 5-mm MAS probe head (Doty) at a resonance frequency of $\nu_0 = 28.809$ MHz and a sample rotation speed of 12 kHz. The length of a 90°

pulse was 6 μs , to obtain more uniform excitation over a broader band and to improve sensitivity we have measured all spectra with excitation pulses of 2 μs duration. Cubic boron nitride (MICRONABN300, DeBeers), hexagonal boron nitride (99%, Aldrich), NH_4SCN , NH_4Cl , and glycine (Merck) were used without further purification. Spectra were simulated with the program WIN-MAS (Bruker). The anisotropy tensors for the two NMR transitions of a spin-1 nucleus are calculated from the shielding tensor σ and the quadrupole tensor χ as $\sigma \pm 3\chi/(4\nu_0)$. The spectra of the two transitions were calculated separately and added. For NH_4SCN we have neglected σ . Second-order contributions of the quadrupole coupling were neglected in the simulation of the side band patterns in both cases.

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Methyl Transfer from Methanol to Co-cobyrinate: A model for the Coenzyme B₁₂ Dependent Methyltransferase?*

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Methanol can be used by certain methanogenic and acetogenic microorganisms as a source of methyl in the synthesis of methane and acetyl-CoA.^[1–4] In the cases reported, Co-corrinoids function as prosthetic groups and form Co-CH₃ complexes, which transfer the methyl group to coenzyme M ($\text{HSCH}_2\text{CH}_2\text{SO}_3^-$) or possibly to tetrahydro-

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folate in the production of acetyl-CoA. Experiments with chiral CHDT groups have provided convincing evidence that methyl transfer to Co^I in enzymatic reactions involves a nucleophilic substitution.^[5, 6] Since general experience shows that the OH groups have to be activated by an energy-consuming process to become a leaving group in substitution reactions, the activation in the enzymatic reactions has to be addressed.^[7] Whereas protonation of N⁵-methyltetrahydrofolate has been suggested to be the most effective mode of activation for the transfer of the N⁵-methyl group to cob(II)alamin in the methionine synthase catalyzed methyl transfer, ubiquitous ATP might be the activator for methanol.^[10]

However, it was recently reported that Zn²⁺ is essential for the transfer of the methyl group from methanol to Co^I in methanogenic bacteria. A Gibbs energy ΔG° of approximately -7 kJ mol^{-1} was found for the formation of methylcobalamin from cob(II)alamin and methanol.^[11] The powerful Lewis acid Zn²⁺ is known to activate substrates for nucleophilic attack, for example, by water in hydrolytic enzymes.^[12] Other examples of substrates activated by Zn²⁺ have recently been described.^[13, 14]

After considering model systems for this reaction without transformation of methanol into methylphosphate or another ester, we concluded that a direct transfer of methyl from methanol might be possible if Co^I is used as a supernucleophile^[15] and the leaving group is activated by reversible complexation of the OH group by a Lewis acid.^[16] To assess the reactivity of methanol and to investigate the potential role of Zn²⁺ as activator in the S_N2 reaction involving Co^I, we studied the reaction shown in Scheme 1.

When the Co^{II} complex **1a** was treated in CH₃OH with an excess of NaBH₄ in the presence of ZnCl₂ at room temperature or at 37 °C, the color changed immediately from orange to dark green, indicating a reduction of Co^{II} to Co^I. No Co-CH₃ complex **2a** could be detected after 3 h under these conditions. However, when the mixture was heated under reflux for 3 h, **2a** and **3a** were formed in 15–20% yield and a ratio of 10:1. No methylation takes place in the absence of this Lewis acid. This result might be interpreted in terms of a methylation by CH₃OH activated by Zn²⁺ or an intra- or intermolecular methyl transfer from one of the methoxycarbonyl groups. An intramolecular S_N2 reaction is rather unlikely, because the short alkyl chains do not allow the stereoelectronically required linear alignment between the Co^I and the methoxycarbonyl group.^[17, 18]

To exclude an intermolecular substitution at one of the methoxycarbonyl groups, the methylation reaction was carried out in CD₃OH as solvent. After 3 h only the CD₃-Co complex, but no **2a**, was detected. However, some of the CH₃O groups from the heptamethylcobyrinate **1a** were replaced by CD₃O. Similarly, in the reaction of the hepta-ethylester **1b** the Co-CH₃ complexes **2b** and **3b** rather than Co-C₂H₅ compounds were formed.^[19] Partial transesterification was also observed in this case. To exclude an intermolecular methyl transfer from one of the ester groups completely, the methylation reaction was carried out with the heptaalkyl Co^{II} complex **1c**. This reacts in CH₃OH under reflux for 3 h to give a Co-CH₃ complex in 3% yield.^[20]

Although these reactions have not yet been optimized, it is apparent that methanol can be used as a methylating agent for Co^I-corrinoids under conditions where no ATP is needed. The supernucleophilic Co^I complex reacts with methanol when the leaving group is activated by the Lewis acid ZnCl₂.^[21] Methyl transfer from cobalt to thiols and the combination of the two reactions in a catalytic cycle will be investigated.

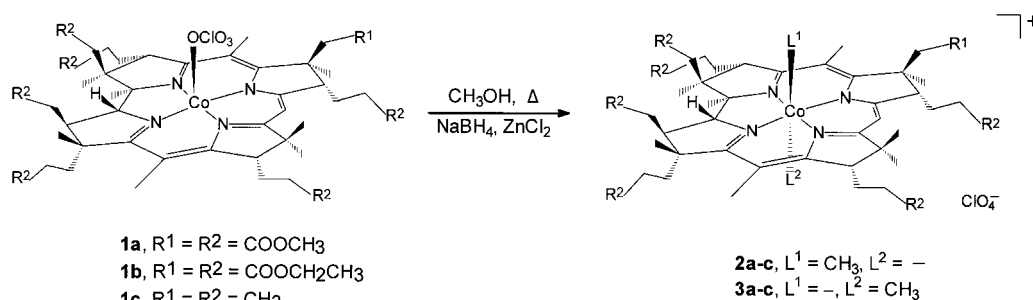
Experimental Section

Methylation with methanol: To a solution of **1a**^[22] (25 mg, 0.022 mmol) in absolute CH₃OH (10 mL, deoxygenated by sonification under N₂ for 30 min) was added NaBH₄ (8.4 mg, 10 equiv) and ZnCl₂ (200 mg). The reaction mixture was stirred in the dark for 3 h at 100 °C. The Co-CH₃ complex **2a** was detected by thin layer chromatography (TLC) by comparison with a sample of **2a** prepared from MeI (**2a**: R_f = 0.54, **3a**: R_f = 0.27; CH₂Cl₂/Et₂O/THF 2/2/1^[23]). For further identification of **2a**, the reaction mixture was worked up by adding HClO₄ (1 mL, 60%) and H₂O (2 mL) and extracted with CH₂Cl₂. After the solution was dried over MgSO₄ and solvent evaporated, the ¹H NMR spectrum of the crude product was measured in CDCl₃ with TMS as internal standard (**2a**: $\delta(\text{Co}-\text{CH}_3) = -0.13$, **3a**: $\delta(\text{Co}-\text{CH}_3) = -0.22$). The yield was determined from the ratio of the ¹H NMR signals for the protons on C(10) of all corrinoids to the Co-CH₃ peaks for the isomers **2a/3a**. The reactions with **1b**^[19] and **1c**^[24–26] were performed as with **1a**.

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Supporting information available 



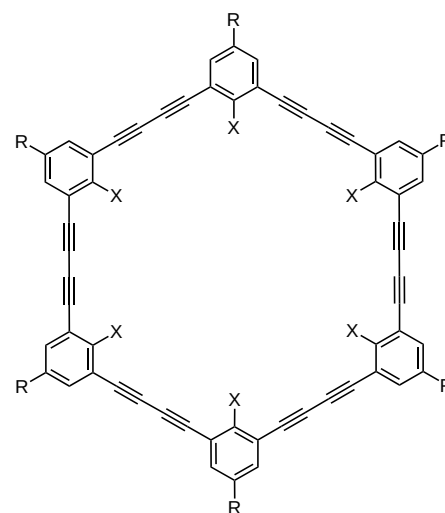
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Synthesis and Association Behavior of [4.4.4.4.4.4]Metacyclophanedodecayne Derivatives with Interior Binding Groups

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Recently Moore et al. disclosed the intriguing properties of phenylacetylene macrocycles (PAMs), which are based on self-organization properties owing to π – π stacking interactions.^[1] Moreover, Höger et al. reported the guest binding ability of a large macrocyclic metaparacyclophane to a large amine guest.^[2] These properties based on weak intermolecular interactions can be fine-tuned by modifying the ring size, shape of the macrocycles, and the substituents on the periphery or interior of the macrocyclic framework. As an extension of our work on diethynylbenzene macrocycles (DBMs),^[3] we disclose here the synthesis and novel association behavior of the hexameric DBM **1**, which has cyano groups in the interior of the macrocyclic framework. DBM **1** can be regarded as an extended derivative of the cyanospherand, which was shown to bind metal cations.^[4] In contrast to the cyanospherand, we anticipated that **1** would be capable of binding relatively large molecules by ion-dipole or hydrogen-bonding interaction, because **1** possesses a well-defined cavity of about 7 Å diameter into which the geometrically ordered cyano groups are pointing. In addition, it is interesting to study the effect of cyano groups on the self-association behavior, since it has been well demonstrated that the π – π interaction is sensitive to the substituent on aromatic rings.^[5] It turned out that **1** exhibited novel association behavior; it

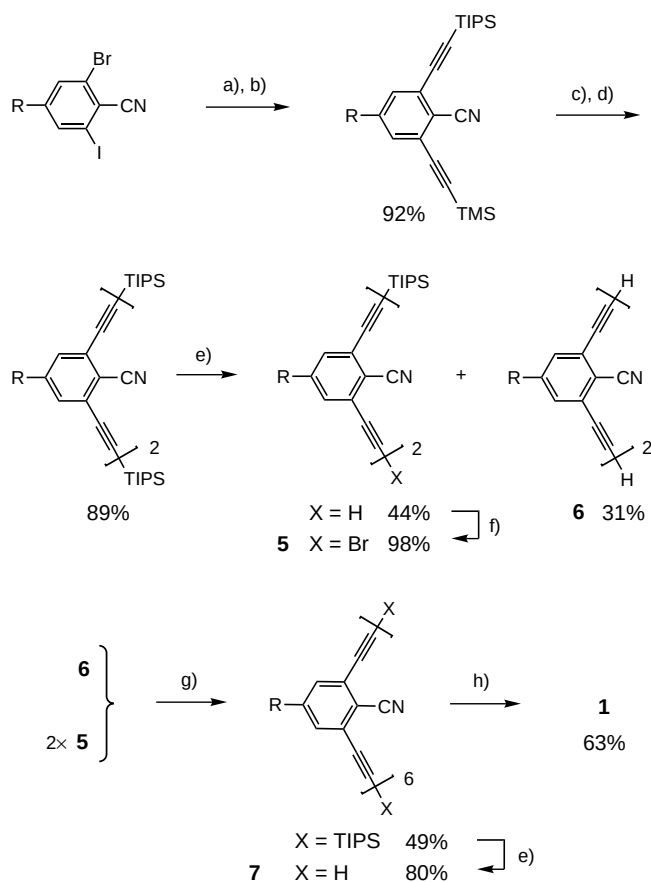


1	R=CO ₂ C ₈ H ₁₇	X=CN
2	R=CO ₂ C ₈ H ₁₇	X=H
3	R=H	X=CN
4	R=H	X=H

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formed heteroaggregates with its analogue **2** and 2:1 (host: guest) complexes with organic cations.

Compound **1** was synthesized by intramolecular coupling of open-chain precursor **7**, which was prepared by heterocoupling of dimer units **5** and **6** (Scheme 1).^[6] The hexamer **2**, which has no cyano groups, was synthesized in a similar fashion.^[7]



Scheme 1. Synthesis of **1** ($R = \text{CO}_2\text{C}_8\text{H}_{17}$). a) triisopropylsilylacetylene, $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$, CuI, PPh_3 , NEt_3 , 70°C ; b) trimethylsilylacetylene, $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$, CuI, PPh_3 , NEt_3 , 70°C ; c) LiOH, THF/ H_2O , room temperature, 5 min; d) CuCl, N,N,N',N' -tetramethylethane-1,2-diamine (TMEDA), O_2 , acetone, room temperature; e) Bu_4NF , THF/ H_2O , room temperature; f) N -bromosuccinimide (NBS), AgNO_3 , acetone, room temperature; g) $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$, CuI, $i\text{Pr}_2\text{NH}$, benzene, room temperature; h) $\text{Cu}(\text{OAc})_2$, pyridine/benzene ($3:2$), $[\text{7}] = 5.0 \times 10^{-4} \text{ mol L}^{-1}$, room temperature. dba = dibenzylideneacetone, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

We found that **2** self-associated to form a dimer in solution (CDCl_3) with $\Delta G = -3.4 \text{ kcal mol}^{-1}$ at 293 K .^[7] In contrast, the chemical shift of the aromatic protons of **1** did not show any concentration dependence in CDCl_3 even in the wide concentration range of 8.9×10^{-5} to $9.9 \times 10^{-3} \text{ mol L}^{-1}$, indicating that **1** did not self-associate. We attribute this to the electrostatic repulsion between the nitrogen atoms, and the nonplanarity of the macrocyclic framework of **1**.^[8] On the other hand, when **1** and **2** were mixed in CDCl_3 , the chemical shift of the aromatic protons of **1** moved upfield depending on the concentrations of the both components (Figure 1). Since the plots of the chemical shift change did not fit the theoretical curve obtained by assuming the competitive formation of heterodimer **1·2** and homodimer (**2**)₂, we

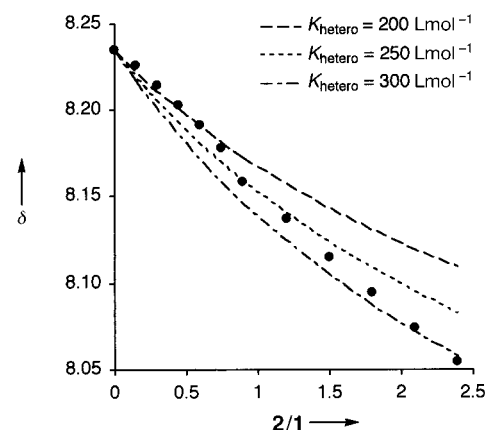


Figure 1. Chemical shift of the signal of the aromatic proton of **1** (CDCl_3 ; 303 K). The plot shows the observed values ($\bullet$) from the titration of **1** with **2**, and the calculated values (dashed lines) based on the assumption of the formation of a heterodimer **1·2** and a homodimer (**2**)₂ with the given association constants K_{hetero} and the association constant $K_{\text{homo}} = 174 \text{ L mol}^{-1}$, respectively. The ideal chemical shift of heterodimer **1·2** was assumed to be constant ($\delta_{\text{hetero}} = 7.0$).

deduce that **1** associates with **2** to form not only dimer **1·2** but also higher aggregates, that is, oligomers. Thus, the cyano groups of **1**, which hinder this self-association, serve to enhance an attractive π - π stacking interaction toward **2** owing to their electron-withdrawing effect.

While hexamer **1** did not bind neutral molecules in CDCl_3 ,^[9] distinct changes in the ^1H NMR chemical shifts were observed with cationic species such as tropylium tetrafluoroborate (Tr^+BF_4^-) and guanidinium tetraphenylborate ($\text{Gu}^+\text{BPh}_4^-$) in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (8/2) (Figure 2). Although we expected the formation of 1:1 complexes,^[10] the Job plots showed maxima at $x = 0.6$ – 0.65 of the mole fraction of **1**, indicating the competitive formation of 1:1 and 2:1 (host: guest) complexes. Moreover, from the nonlinear least-squares regression analysis of the titration curve (Figure 2), we estimated the association constants K_{11} and K_{21} for 1:1 and 2:1 complexations, respectively, with Tr^+BF_4^- to be 4.0×10^4 and $6.3 \times 10^4 \text{ L mol}^{-1}$, respectively, and with $\text{Gu}^+\text{BPh}_4^-$ to be

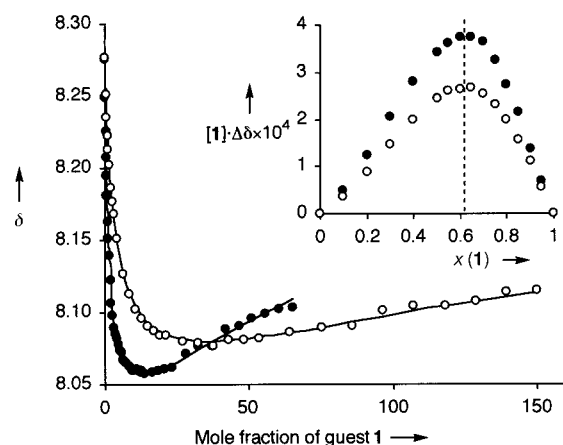


Figure 2. Chemical shift of the signal of the aromatic proton of **1** ($\text{CDCl}_3/\text{CD}_3\text{CN}$: 8/2; 303 K) in the titration with Tr^+BF_4^- ($\bullet$) and $\text{Gu}^+\text{BPh}_4^-$ ($\circ$). The lines were generated by computer-assisted curve fitting. Insert: Job plots for titration of **1** with Tr^+BF_4^- ($\bullet$) and $\text{Gu}^+\text{BPh}_4^-$ ($\circ$). Total concentration of host plus guest was maintained at $2.3 \times 10^{-3} \text{ mol L}^{-1}$.

4.0×10^1 and $2.5 \times 10^4 \text{ L mol}^{-1}$, respectively. In contrast, the linear hexamer **11** did not show any binding ability to Tr^+BF_4^- .

The driving force for the formation of the 1:1 complex between **1** and the organic cations is the electrostatic ion–dipole interaction between the cation and the cyano groups preorganized to point inside the cavity of **1**. Regarding the driving force for the extremely facile formation of 2:1 complexes, we assume that the electrostatic interaction between the guest molecule in the 1:1 complex and the cyano groups of free **1** is most important.^[11] Figure 3 shows that the electrostatic potential surface derived based on the AM1 calculations for a planar conformer of the model compound **3** changes dramatically when it binds a guest cation (Tr^+) to form a complex $\mathbf{3} \cdot \text{Tr}^+$.^[12] As a result of the development of positive charge, the 1:1 complex $\mathbf{3} \cdot \text{Tr}^+$ could bind another molecule of **1** by electrostatic interaction. In addition, a π – π stacking interaction between the aromatic rings of **1** may also be operative, because the calculated electron densities on the aromatic rings of $\mathbf{3} \cdot \text{Tr}^+$ are substantially reduced compared to that of **3**. In this respect, it should be pointed out that in the optimized geometry of complex $\mathbf{3} \cdot \text{Tr}^+$ the host molecule **3**

adopts a planar conformation, which is favorable for π – π stacking. Accordingly, it is deduced that complexation of **1** with a guest cation induces aggregation to another molecule of **1** to form 2:1 complexes.

In summary, we have synthesized the diethynylbenzene macrocycle **1**, which has intraannular cyano groups, and demonstrated its novel association behavior by which it forms heteroaggregates with **2** and 2:1 (host:guest) complexes with tropylium and guanidinium cations.

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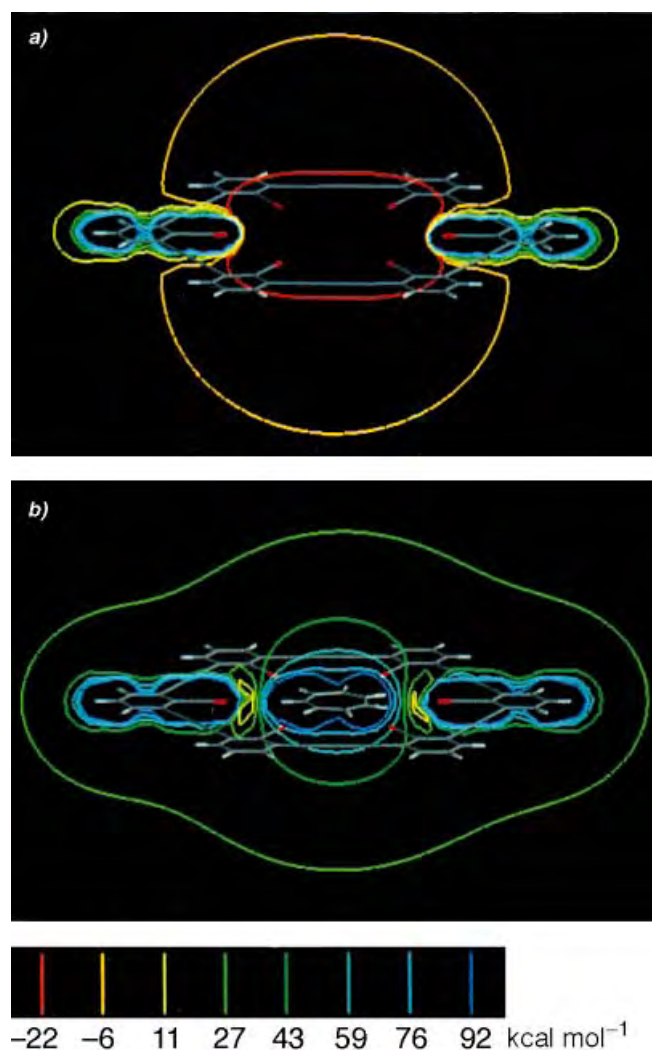


Figure 3. Contour plots for the calculated electrostatic potential surface (scales in kcal mol^{-1}) of **3** (a) and $\mathbf{3} \cdot \text{Tr}^+$ complex (b), sliced through the mirror plane that bisects the benzene rings. Calculations were done using the AM1 Hamiltonian implemented in SPARTAN 5.0.

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- [6] **1**: pale orange solid; m.p. $> 220^\circ\text{C}$ (decomp); ^1H NMR (270 MHz, CDCl_3 , 30°C): $\delta = 8.24$ (s, 12H; CH), 4.38 (t, $J = 6.8$ Hz, 12H; CH_2), 1.80 (quintet, $J = 6.8$ Hz, 12H; CH_2), 1.30 (m, 60H; CH_2), 0.9 (t, $J = 6.8$ Hz, 18H; CH_3); ^{13}C NMR (67.5 MHz, CDCl_3 , 30°C): $\delta = 163.4$, 134.1, 133.9, 126.4, 123.9, 114.2, 80.3, 79.1, 66.7, 31.8, 29.2, 29.1, 28.5, 25.9, 22.6, 14.1; UV (CHCl_3): λ_{max} ($\log \epsilon$) = 375 (4.93), 328 (4.98), 304 (4.97), 296 (4.98), 280 (5.18), 253 nm (5.23); MALDI-TOF MS: m/z 1854 [$M - \text{H} + \text{Na}^+$].
- [7] The details for the synthesis and self-association properties of **2** will be reported elsewhere. **2**: pale yellow solid; m.p. $> 225^\circ\text{C}$ (decomp); ^1H NMR (400 MHz, CDCl_3 , 30°C , 14.9 mmol L^{-1}): $\delta = 7.23$ (s, 12H; CH), 7.07 (s, 6H; CH), 4.02 (s, 12H; CH_2), 1.69 (m, 12H; CH_2), 1.40 (m, 60H; CH_2), 0.97 (t, $J = 6.7$ Hz, 18H; CH_3); ^{13}C NMR (100.5 MHz, CDCl_3 , 30°C , 14.9 mmol L^{-1}): $\delta = 163.2$, 138.3, 132.4, 130.29, 130.3, 122.0, 79.8, 75.7, 65.5, 32.0, 29.5, 29.3, 28.5, 26.1, 22.8, 14.3; UV (CHCl_3): λ_{max} ($\log \epsilon$) = 338 (5.21), 315 (5.30), 296 (5.08), 278 nm (4.93); MALDI-TOF MS: m/z 1683 [$M^+ + \text{H}$].
- [8] The most stable geometry of the model compound **3** estimated by AM1 calculations is a chair conformation with a bent angle of about 35° . The planar conformation of **3** is less favored by 0.7 kcal mol^{-1} . Because the model compound **4** adopts a planar conformation, the dipole–dipole repulsion between the neighboring cyano groups must be responsible for the preference of nonplanar geometry of **3**.
- [9] The neutral molecules examined include benzene, halobenzene derivatives, phenol, and aniline.
- [10] AM1 calculations indicate large enthalpy gains for the complexation in the gas phase between the model compound **3** and Tr^+ (37 kcal mol^{-1}) and Gu^+ (38 kcal mol^{-1}), though the former cation has the wrong symmetry and the latter cation is too small to fit the cavity of **3**.
- [11] Because of the instability of the complexes, we were not able to obtain crystals suitable for X-ray structure determination. We do not have, therefore, any structural information on the 2:1 complexes.
- [12] A similar electrostatic potential surface was obtained for the 1:1 complex $\mathbf{3} \cdot \text{Gu}^+$.

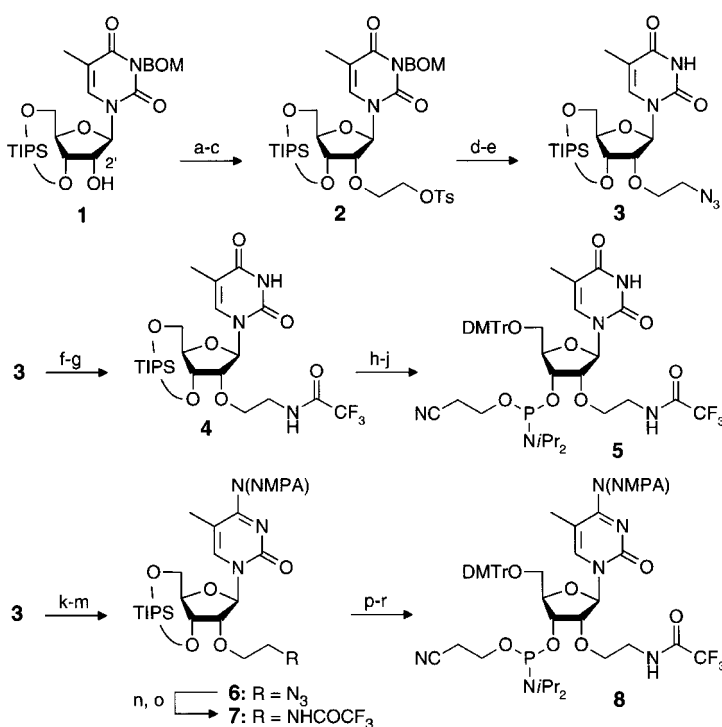
Dual Recognition of Double-Stranded DNA by 2'-Aminoethoxy-Modified Oligonucleotides**

Bernard Cuenoud,* Florence Casset, Dieter Hüsken, François Natt, Romain M. Wolf, Karl-Heinz Altmann, Pierre Martin, and Heinz E. Moser

Molecular recognition of duplex DNA by proteins plays a central role in biology. Although there are no clear and simple rules or codes to describe sequence-specific recognition, hydrogen bonds with the nucleic bases as well as with the phosphodiester backbone are of critical importance.^[1] Efforts to mimic such recognition with smaller synthetic biopolymers have been described.^[2] However, in all these cases, specific contacts with the DNA duplex are only provided by hydrogen bonds with the bases, and potential interactions with the DNA backbone are left unexploited. Here we report that 2'-aminoethoxy-modified oligonucleotides can interact simultaneously with the bases and the phosphodiester backbone at each base-pair step of the DNA target, which provides for a dramatic increase in the binding affinity as well as in the association rate constant.

The sequence-specific recognition of duplex DNA by pyrimidine oligonucleotides involves the formation of triple-helical structures, which are stabilized by Hoogsteen hydrogen bonds between the bases on the DNA target and the pyrimidine third strand.^[3] Examination of a molecular model of a triple helix with a RNA third strand indicates that the 2'-hydroxyl groups of the RNA and the phosphate groups of the DNA second strand are in close proximity.^[4] Thus, it appeared conceivable that the attachment of a short amino alkyl group at the 2' position of the ribose of the third strand would allow the protonated amino group to form a specific intermolecular contact with a proximal phosphate group of the DNA duplex. Such charge–charge interactions should strongly enhance the affinity of the modified oligonucleotide for double-strand DNA.

To test this hypothesis, we first examined the properties of a 2'-aminoethoxy-modified oligonucleotide with regard to tripleplex formation. The synthesis of the 2'-aminoethyl-modified monomeric thymidine and C5-methylcytidine building blocks is summarized in Scheme 1. Alkylation of protected ribothymidine **1**^[5] with methyl bromoacetate followed by reduction of the ester group and tosylation gave the tosylate **2**. Hydrogenolytic removal of the BOM group and subsequent replacement of the tosyloxy group by an azide substituent yielded the azidoethyl derivative **3**, which was further transformed into the desired protected 2'-aminoethoxy-thymidine



Scheme 1. Synthesis of protected 2'-aminoethoxy phosphoramidites thymidine (**5**) and C5-methylcytidine (**8**): a) BrCH₂CO₂Me (5 equiv), NaH (2.2 equiv), DMF, 1.5 h, –5 °C, 98 %; b) LiBH₄ (4 equiv), MeOH/THF (2/8), 1.5 h, 5 °C, 84 %; c) TsCl (1.5 equiv), NEt₃ (1.6 equiv), DMAP (10 wt %), CH₂Cl₂, 8 h, 22 °C, 89 %; d) H₂, Pd/C (20 wt %), HCl (0.02 equiv), THF/MeOH (1/1), 7 h, 22 °C, 88 %; e) NaN₃ (3 equiv), DMF, 3 h, 65 °C, 92 %; f) SnCl₂ (3.5 equiv), MeOH, 1 d, 22 °C, 70 %; g) (CF₃CO)₂O (1.2 equiv), pyridine, 2 h, 22 °C, 57 %; h) TBAF (2.1 equiv), THF, 15 min, 22 °C, 100 %; i) DMTTrCl (1.2 equiv), pyridine, 16 h, 22 °C, 85 %; j) (iPr₂N)₂-POCH₂CH₂CN (2.2 equiv), diisopropylammonium tetrazolide (2.4 equiv), CH₂Cl₂, 1 h, 22 °C, 85 %; k) triazole (22.5 equiv), POCl₃ (2.5 equiv), NEt₃ (23 equiv), CH₃CN/CH₂Cl₂ (1/1), 3 h, 22 °C; l) concd NH₃ (aq)/dioxane (1/1), 1 h, 22 °C, 84 % over two steps; m) *N*-methyl-2,2-dimethoxypyrrolidine (1.8 equiv), pyridine, 3 h, 22 °C, 95 %; n) H₂, Pd/C (10 wt %), MeOH/THF (1/1), 3 h, 22 °C; o) CF₃COOEt (10 equiv), NEt₃ (7 equiv), MeOH, 1 h, 22 °C, 96 % over two steps; p) TBAF (1.0 equiv), THF, 1 h, 22 °C, 100 %; q) DMTTrCl (1.2 equiv), pyridine, 1 h, 22 °C, 85 %; r) (iPr)₂N₂-POCH₂CH₂CN (2.2 equiv), diisopropylammonium tetrazolide (2.4 equiv), CH₂Cl₂, 2 h, 40 °C, 87 %. TIPS = 1,1,3,3-tetraisopropylidisiloxane, BOM = benzyloxymethyl, N(NMPA) = *N*-methylpyrrolidinamidine, DMF = *N,N*-dimethylformamide, THF = tetrahydrofuran, DMAP = 4-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride, DMTTr = 4,4'-dimethoxytriphenylmethyl, Ts = toluene-4-sulfonyl.

and C5-methylcytidine phosphoramidites **5** and **8** by standard procedures. A pentadecameric oligonucleotide containing five 2'-aminoethoxy-modified thymidines was synthesized, and its affinity for a double-stranded DNA target measured by UV-melting experiments (Figure 1A). A large increase in melting temperature *T*_m of 17.5 °C was observed compared to the unmodified DNA oligonucleotide control of identical length and sequence, corresponding to an increase of +3.5 °C per modification (Figure 1B). The magnitude of the difference in *T*_m (ΔT_m) was not significantly affected by changes in KCl concentration, replacement of KCl by NaCl, use of other buffers, or addition of MgCl₂ or spermine. Moreover, the modified oligonucleotide remains sensitive to a single base-pair mismatch.^[6]

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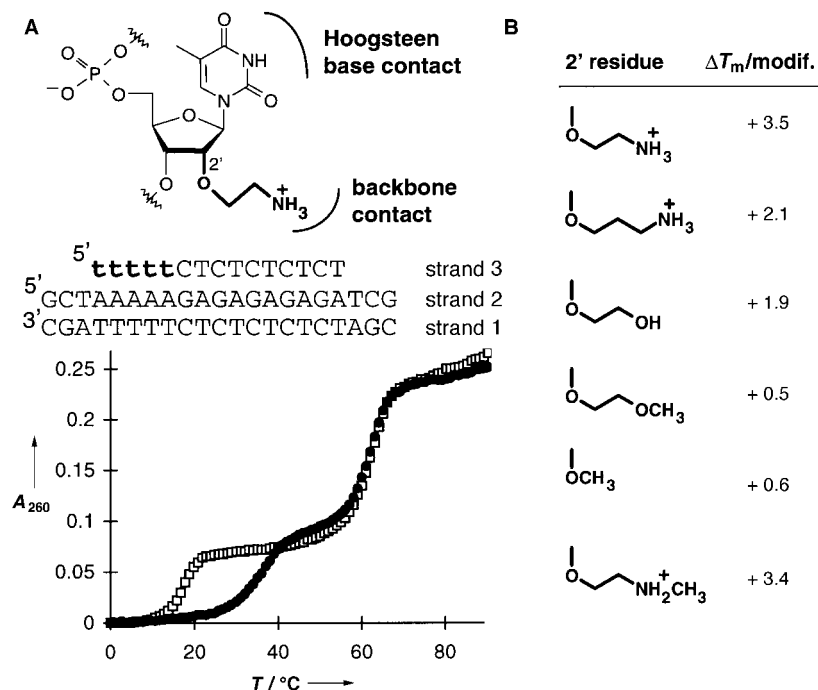


Figure 1. Affinity of modified oligonucleotides for duplex DNA. A) A pentadecameric oligonucleotide containing five 2'-aminoethoxy-modified thymidines (boldface, lower-case letters, strand 3) was hybridized to its duplex DNA target (strands 1 and 2) in a solution with 180 mM KCl, 20 mM Na⁺, 10 mM phosphate (pH 7.0), and 0.1 mM ethylenediamine tetraacetate (EDTA). Thermal denaturation resulted in two UV transitions. The first transition corresponds to the melting of the triple helix (dissociation of strand 3), and the second to melting of the DNA duplex (dissociation of strands 1 and 2). The T_m values for the triplex helices with modified oligonucleotides (●) were compared to that obtained for an unmodified DNA oligonucleotide control (□). A_{260} = absorption at 260 nm. B) Structure–affinity relationships for different 2'-substituted oligonucleotides. The T_m values were obtained by mathematical curve fitting assuming a two-state model for each UV transition; calculated $\Delta T_m/\text{modifications}$ are within 0.1 °C uncertainty. The purity and identity of each oligonucleotide were determined by capillary electrophoresis and matrix assisted laser desorption time of flight (MALDI-TOF) mass spectroscopy.^[13] A pK_a of 8.7 was determined for the 2'-aminoethoxy modified thymidine, indicating that the 2' side chain is protonated under physiological conditions.

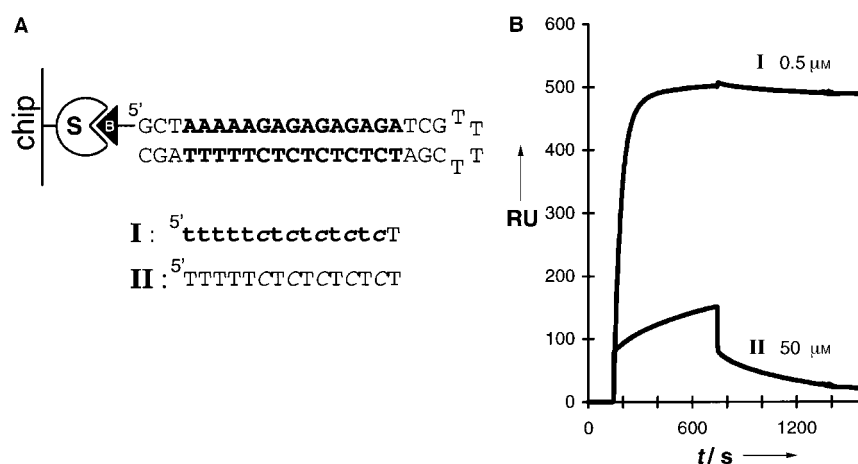


Figure 2. Real-time detection of triplex association and dissociation with the surface plasmon resonance sensor BIAcore 2000 system (Pharmacia Biosensor). A) A 5'-biotinylated DNA hairpin containing the duplex target sequence (boldface) was immobilized on a chip coated with streptavidine (S). Binding of the fully modified 2'-aminoethoxy oligonucleotide **I** to the hairpin was compared to the DNA oligonucleotide control **II**. Binding buffer: 150 mM NaCl, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES, pH 7.4), 3.4 mM EDTA, 0.05 % Tween 20. Both oligonucleotides contained C5-methylcytidines (italics) instead of natural cytosine bases owing to their more favorable DNA-binding properties under physiological conditions.^[14] B) Sensograms showing changes (in resonance units, RU) upon association and dissociation of the third oligonucleotide strand to the double-stranded DNA hairpin.

To explore the molecular basis of this pronounced enhancement in binding affinity, we investigated the affinity of a series of other related 2'-O-modified oligonucleotides for double-stranded DNA (Figure 1B). Extension of the spacer between the protonated amine group and the 2'-oxygen atom by one additional methylene group (2'-aminopropoxy substituent)^[7] resulted in a significant decrease in triplex stability. This indicates that the protonated aminoethoxy side chain is ideally positioned to interact specifically with the nearby phosphate group, and that the enhanced triplex stability is not the result of a mere nonspecific electrostatic effect. Replacement of the amino group by an uncharged hydrogen-bond donor (2'-hydroxyethoxy substituent) also led to a considerable increase in binding affinity as compared to an unmodified DNA third strand, but the magnitude of the effect was significantly smaller than that observed for the 2'-aminoethoxy-modified oligonucleotide. This finding is consistent with the proposed intermolecular contact, as the positively charged amino moiety should interact with the negatively charged phosphate backbone more strongly than the uncharged hydroxyl group. Moreover, complete removal of the hydrogen bond donor capacity of the side chain (2'-methoxy-ethoxy substituent)^[8] reduced the affinity of the modified oligonucleotide for the DNA duplex to a level similar to that of the 2'-methoxy analogue. This effect is unlikely to be the result of an unfavorable steric interaction between the added methyl group and the major groove of the DNA, as 2'-aminoethoxy and 2'-monomethylaminoethoxy derivatives display the same binding enhancement with respect to the oligonucleotide control.

To gain further insight into the origins of this large improvement in binding affinity, we determined the kinetic and thermodynamic parameters for the binding of a fully modified 2'-aminoethoxy oligonucleotide to a double-stranded DNA target. Measurement of hybridization kinetics by real-time surface plasmon resonance^[9] revealed that the association rate constant of the fully modified 2'-aminoethoxy oligonucleotide **I** was more than a 1000 times greater than that of the unmodified oligonucleotide control **II** (Figure 2 and Table 1). The magnitude of the increase in association rate suggests

Table 1. Association (k_a) and dissociation rate constants (k_d), calculated dissociation binding constants K_D , and dissociation free energies ΔG (25 °C) for the 2'-aminoethoxy-modified oligonucleotide **I** and DNA control **II**.^[a]

Oligo-nucleotide	k_a [M ⁻¹ s ⁻¹]	k_d [s ⁻¹]	K_D [M]	ΔG [kcal mol ⁻¹]
I	$3.6 \pm 1.6 \times 10^4$	$3.3 \pm 1.3 \times 10^{-5}$	0.91×10^{-9}	-12.2
II	33 ± 19	$1.4 \pm 0.2 \times 10^{-3}$	4.2×10^{-5}	-5.9

[a] By a quantitative DNase I footprint experiment,^[16] K_D was determined to be 4.8×10^{-9} M for oligonucleotide **I** (buffer: 140 mM KCl, 10 mM NaCl, 1 mM MgCl₂, 1 mM spermine, 20 mM 3-(*N*-morpholine)propanesulfonic acid (MOPS), pH 7.2), which is similar to that obtained by the surface plasmon experiment.

that the formation of specific contacts between the 2'-aminoethoxy side chains and the phosphate backbone of the DNA duplex contributes actively to the nucleation-zipping association process.^[10] Consistent with the stabilizing effect of additional specific interstrand contacts, the rate constant for dissociation of the third strand indicated that the modified oligonucleotide **I** dissociates 40 times more slowly from its target duplex than the oligonucleotide control **II**. Remarkably, the equilibrium dissociation constant calculated from the rate constants for modified oligonucleotide **I** (10^{-9} M) is 46 000-fold smaller than that obtained with **II**, which represents a gain of 6.3 kcal mol⁻¹ in binding energy.

A model of a triple helix containing a fully modified 2'-aminoethoxy third strand was derived from molecular-dynamics (MD) simulations, and revealed that the protonated 2'-aminoethoxy residue is indeed capable of interacting with an adjacent phosphate group of the second strand without compromising the overall triplex architecture (Figure 3).^[11] Throughout the MD trajectory, several observations pointed toward a specific interaction. The protonated aminoethoxy side chain (in a low-energy (+)-*gauche* conformation) always interacts with the *pro-R*-oxygen atom of residue $i - 1$, but not of residue i , regardless of whether the orientation is originally *trans* or *gauche*. Similar MD experiments performed with a 2'-aminopropoxy-modified third strand indicated that in this case the amino group did not exhibit any preference for an interaction with either the i or $i - 1$ *pro-R* oxygen atom and, in addition, could make contacts with its own 2'-oxygen atom.

Overall, these results are consistent with the specific effects displayed by the 2'-aminoethoxy-modified oligonucleotides for DNA binding, and support the existence of a novel interstrand contact with stringent geometrical requirements between the protonated aminoethoxy side chain and one phosphodiester oxygen atom of the DNA backbone. Moreover, they confirm the energetically important role of backbone contacts often seen in protein–DNA complexes.

Modulation of gene expression by oligonucleotide-directed formation of triple helices has been limited in part by weak affinity, slow association rate, and lack of nuclease resistance of the unmodified oligonucleotides. 2'-Aminoethoxy-modified oligonucleotides, for the first time, offer an efficient solution to these problems by combining high affinity, fast rate of association, and high nuclease resistance (data not shown

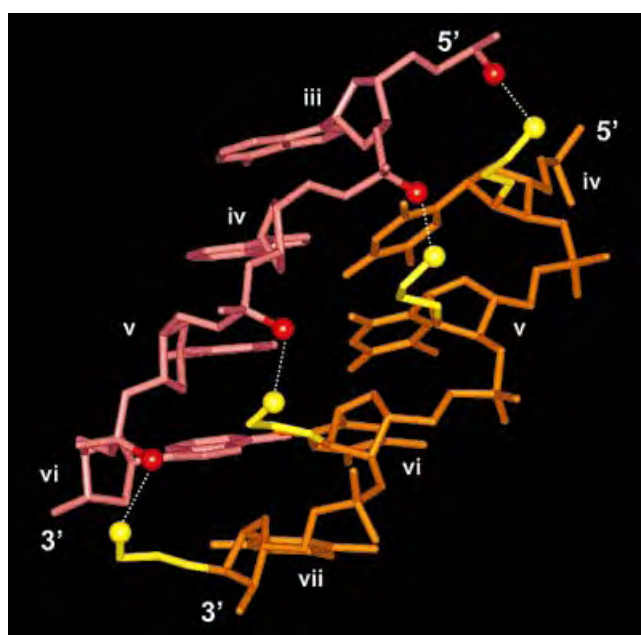


Figure 3. Molecular model showing the interaction of the 2'-aminoethoxy side chains (yellow) with the *pro-R*-phosphate oxygen atoms (red); with a N–O distance of 2.8 Å. For clarity, only four residues of the second (pink) and third strand (orange) are shown. This model was obtained from the average MD structure after 1-ns simulation performed on a T₁₀:A₁₀:T₁₀ triple-helical complex with a fully modified 2'-aminoethoxy third strand (boldface, lower-case letters). A distance-dependent dielectric function was used to simulate an aqueous environment, and counterions were not included; an approximation was judged sufficient for the geometrical factors analyzed here.^[15]

and reference [12]). Therefore, they should compete effectively for DNA binding with proteins such as transcription factors, and eventually provide powerful compounds for the regulation of gene expression.

Experimental Section

Kinetic measurements: A biotinylated DNA hairpin (2 μM) in binding buffer was applied to a chip coated with streptavidine (SA-5, Pharmacia Biosensor) and extensively washed. The association curve was obtained by injection of the oligonucleotide in binding buffer at a rate of 5 μL min⁻¹ for 10 min at 25 °C. The oligonucleotide solution was then substituted by binding buffer alone, and the dissociation curve was recorded for 10 min. The jump (in resonance units, RU) between the association and the dissociation curve corresponds to a change in refractive index between the two solutions. To completely remove the third strand oligonucleotide from the chip, a denaturing step (10 mM NaOH, 1 min) followed by a washing step with binding buffer was performed after each measurement. Rate constants were evaluated with a nonlinear curve fitting program (BIA Evaluation, Pharmacia Biosensor) assuming first-order kinetics.

A range of oligonucleotide concentrations was tested (oligonucleotide **I**: 0.1–1.0 μM, oligonucleotide **II**: 10–100 μM) as well as different amounts of immobilized biotinylated hairpin. The rate constants reported correspond to the average of at least twelve measurements at these various concentrations. Control experiments indicated that oligonucleotide **I** or **II** did not bind to the streptavidine chip alone.

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New Iron–Mercury Clusters:

[Hg₇{Fe(CO)₄}₅(S*t*Bu)₃Cl],
[Hg₁₄Fe₁₂{Fe(CO)₄}₆S₆(S*t*Bu)₈Br₁₈], and
[Hg₃₉Fe₈{Fe(CO)₄}₁₈S₈(S*t*Bu)₁₄Br₂₈]**

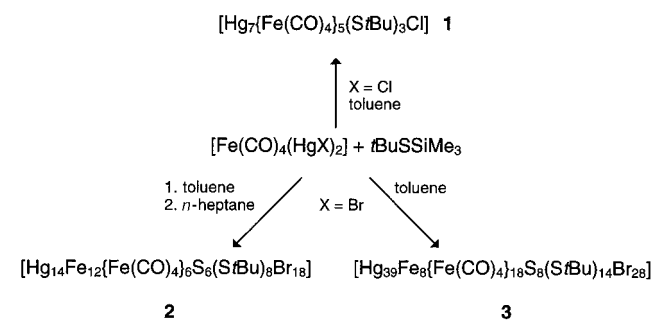
Dieter Fenske* and Marco Bettenhausen

The reaction of coinage-metal salts with phosphanes and silylated chalcogen derivatives has already led to a great number of new compounds.^[1] For example, the reaction of PR₃ complexes (R = organic group) of copper and silver

halides with silylated derivatives of selenium and tellurium led to the isolation and characterization of many Cu–Se clusters such as [Cu₁₄₆Se₇₂(PPh₃)₃₀],^[2] and a large number of Ag–Te clusters such as [Ag₄₈(*n*BuTe)₂₄Te₁₂(PEt₃)₁₄].^[3] This method was applied recently for the synthesis and subsequent structure determination of [Cd₃₂Se₁₄(SePh)₃₆(PPh₃)₄] and [Hg₃₂Se₁₄(SePh)₃₆].^[4] These compounds have similar structures to the previously described [Cd₃₂Se₁₄(SR)₃₆(L)₄] clusters (R = organic group; L = H₂O, DMF).^[5] The compound [Hg₃₂Se₁₄(SePh)₃₆] can be formed by the treatment of [Fe(CO)₄(HgCl)₂] with PhSeSiMe₃. The synthesis of [Fe(CO)₄(HgCl)₂] was described in 1928 by Hock and Stuhlmann.^[6] Recently the phosphane-bridged mercury cluster [(HgPtBu)₄]₃ was synthesized by the treatment of [Fe(CO)₄(HgOAc)₂] with *t*BuP(SiMe₃)₂.^[7] This cluster is not accessible from the reaction of HgCl₂ with silylated phosphanes.

In this work we present the reactions of [Fe(CO)₄(HgX)₂] (X = Cl, Br) with the silylated sulfur derivative *t*BuSSiMe₃. Only a few examples of metal-rich chalcogen-bridged mercury complexes, such as the adamantane-like compounds [Hg₄(SPh)₆(PPh₃)₄](ClO₄)₂, [Hg₄(SPh)₅(μ₂-Br)Br₄](PPh₄)₂,^[8] and the complex [Hg₄(*t*BuS)₄(μ₂-Cl)₂(Cl)₂(py)₂]^[9] have been reported. Clegg and Sola et al.^[10] have isolated the compound [Hg₇(SC₆H₁₁)₁₂Br₂], and characterized it by X-ray crystallography.

Treatment of a suspension of [Fe(CO)₄(HgX)₂] (X = Cl, Br) in toluene with *t*BuSSiMe₃ affords a yellow-red solution within a few days. Crystals of the iron–mercury clusters **1–3**, which were characterized by X-ray crystallography, were grown directly from this solution or by layering with *n*-heptane (Scheme 1).^[11]



Scheme 1. Synthesis of the iron–mercury clusters **1–3**.

The reaction of [Fe(CO)₄(HgCl)₂] with *t*BuSSiMe₃ leads to a yellow solution from which orange needles of **1** (Figure 1) crystallize. Compound **1** consists of an Hg₃Fe₂ (Hg5-Fe4-Hg6-Fe5-Hg7) and an Hg₄Fe₃ fragment (Hg1-Fe1-Hg2-Fe2-Hg3-Fe3-Hg4). These Hg–Fe chains are linked together by three sulfur atoms from the *t*BuS groups and a chlorine atom. The chlorine atom is in the center of the molecule with Hg–Cl bond lengths of 298.2(7)–359.6(7) pm. These values lie significantly above the sum of the ionic radii of Hg²⁺ and Cl[–] (Cl–Hg1 302.5(7), Cl–Hg5 303.5(7), Cl–Hg7 298.2(7) pm) or in the range of the van der Waals radii (Cl–Hg2 359.6(7), Cl–Hg3 330.4(7), Cl–Hg4 337.0(7), Cl–Hg6: 348.7(7) pm). Thus, the Hg–Cl bonds are very weak. In

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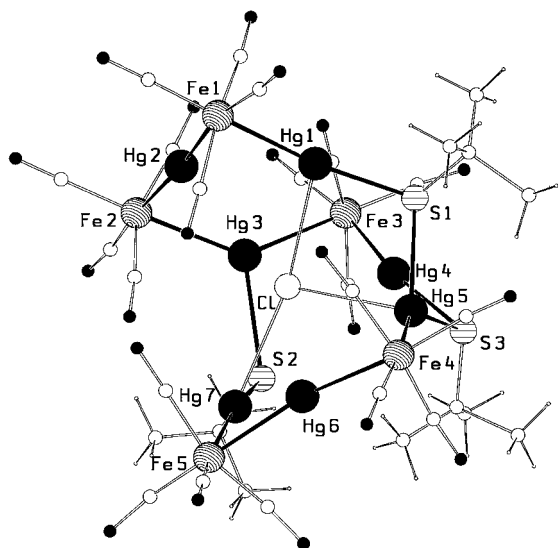


Figure 1. The molecular structure of **1** in the crystal. Hg–Cl bonds are shown up to 330 pm. Selected bond lengths [pm] and angles [°]: Hg⋯Hg 329.4(2)–373.1(2); Hg–Fe–Hg 80.21(10)–88.65(11); Cl–Hg1 302.5(7), Cl–Hg5 303.5(7), Cl–Hg7 298.2(7); Hg with coordination number 3 (Hg3, Hg5): Hg–Fe 254.1(4)–267.2(4), Hg–S 254.9(8)–281.9(7), sum of the angles 355.3–359.6; Hg with coordination number 2 (Hg1, Hg2, Hg4, Hg6, Hg7): Hg–Fe 250.5(4)–257.6(4), Hg–S 241.3(8)–245.0(8); Fe–Hg–Fe and Fe–Hg–S 167.5(2)–175.3(2).

agreement with this the estimated values for ν_{ij} , calculated from the equation developed by Brese and O’Keeffe, are in the range 0.3–0.14.^[12] If the chlorine atom is not considered because of the long Hg–Cl bond lengths, the mercury atoms have either a distorted trigonal planar (Hg3 and Hg5) or almost linear coordination environment (Hg1, Hg2, Hg4, Hg6, and Hg7). All the iron atoms (as in the reactant) are in distorted octahedral environments, coordinated by four CO ligands and two *cis*-positioned Hg atoms (Hg–Fe–Hg angle: 80.21(10)–88.65(11)°). In [Fe(CO)₄(HgCl)₂] the average Hg–Fe–Hg angle is 80.9°.^[13] Because of the large Hg–Hg distances (329.4(2)–373.1(2) pm) one can assume that only very weak interactions between the Hg atoms exist, which are clearly weaker than in [(η^5 -CH₃C₅H₄)Mn(CO)₂Hg]₄ in which the Hg–Hg bond lengths were found to be 289 pm.^[14] Similar bonding relationships are found in [(HgPrBu)₄]₃ (Hg–Hg: 333.0(1)–356.4(1) pm).^[7]

Reaction of [Fe(CO)₄(HgBr)₂] with *t*BuSSiMe₃ in toluene leads to **2** and **3**. Compound **2** is formed by layering the reaction mixture with *n*-heptane, and crystallizes in the form of small orange crystals after two weeks. Figure 2 shows the molecular structure of the Hg₁₄Fe₁₂ cluster **2**; the CO ligands attached to the Fe atoms and the *t*Bu groups attached to the S atoms have been omitted for the sake of clarity. An inversion center is located in the center of the cluster. As in **1** the periphery contains six FeHg₂ units (Hg1–Fe–Hg2, Hg3–Fe2–Hg4, Hg5–Fe3–Hg6, and their symmetry equivalents), which are also present in the reactant. The iron atoms Fe1, Fe2, Fe3, Fe1’, Fe2’, and Fe3’ are coordinated in a distorted octahedral fashion by four CO ligands and two *cis*-positioned Hg atoms (Hg–Fe–Hg angle: 77.96–79.62(9)°). The shortest Hg–Hg bond length is 318.2 pm and is thus about 12 pm shorter than those in **1**.

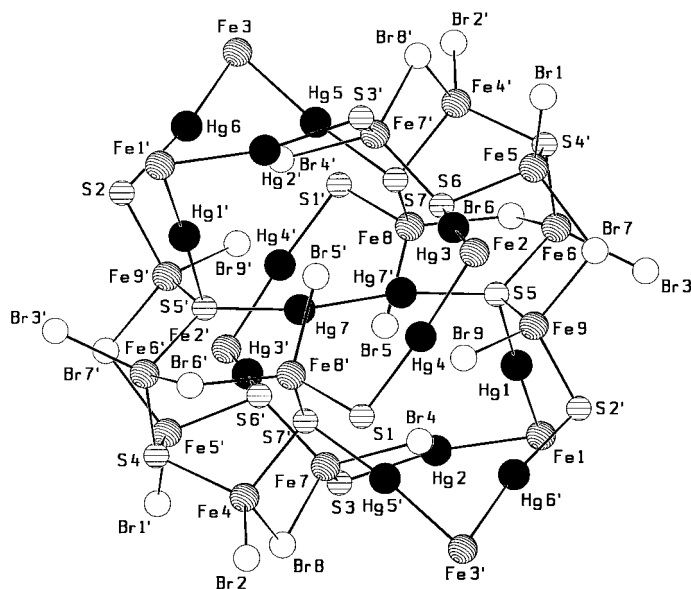


Figure 2. The molecular structure of **2** in the crystal (without C, H, and O atoms). There are four CO groups coordinated to each of the iron atoms Fe1–Fe3 and Fe1’–Fe3’ and a *t*Bu group to the sulfur atoms S1–S4 and S1’–S4’. Selected bond lengths [pm] and angles [°]: Hg^I–Hg^I 245.6(10)–254.6(8), Hg^I–S 237.1(6)–250.2(8), Hg^{II}⋯Hg^{II} 318.2(2)–322.5(1); Hg–Fe–Hg 77.96(9)–79.62(9); Hg^{II}–S 240.2(5)–242.4(5), Hg–Fe 251.0(3)–253.6(3), Fe–S 233.4(5)–240.3(6), Fe–(μ_2 -Br) 246.0(3)–251.3(4), Fe–Br_{terminal} 234.3(4)–236.4(4).

The iron atoms Fe4–Fe9 (and their symmetry equivalents) have distorted tetrahedral environments, coordinated by Br[–], *t*BuS[–], and S^{2–} ligands. The core of the cluster contains six μ_3 -bridging S^{2–} ligands (S5, S6, S7, S5’, S6’, and S7’) that form a trigonal antiprism. Within this antiprism there is a threefold disordered mercury “dumbbell” (Hg7 and Hg7’); each possible position is found between opposite pairs of sulfur atoms with Hg–Hg bond lengths of 245.6(10)–254.6(8) pm and Hg–S bond lengths of 237.1(6)–250.2(8) pm.

There are several facts that support the existence of an Hg₂²⁺ dumbbell. On the one hand a short Hg–Hg distance is also observed in the compounds [Hg₂(*p*-SC₆H₄NO₂)]NO₃ (254.8 pm)^[15] and [Hg₂S₂C₄H₄](NO₃)₂ (252.7 pm).^[16] The Hg–S bond lengths in **2** are, however, 10 pm shorter than those reported in the literature. On the other hand the estimation of the valence sum according to Brese and O’Keeffe^[12] for Hg7 is 1.2 and for the rest of the mercury atoms in the Hg₂Fe fragments 2.0.^[17] Furthermore the overall charge of the cluster with the Hg₂²⁺ dumbbell is balanced.

If we assume that *t*BuS[–], S^{2–}, Br[–], and (Fe(CO)₄)^{2–} ligands are present, then we arrive at a formal charge of +50 for the Hg₁₄Fe₁₂ cluster. Following the above assumption that the central Hg₂ dumbbell has a charge of +2 and the rest of the mercury atoms (Hg1–Hg6 and their symmetry equivalents) have a formal oxidation state of +2, then the tetrahedrally coordinated Fe atoms (Fe4–Fe9 and symmetry equivalents) must have a formal oxidation state of +2. This is supported by the fact that the valence sum of the Fe atoms Fe4–Fe9 lies between 2.3 and 2.4.

Orange needles of **3** crystallize within a few weeks directly from the mother liquor. The crystal structure of **3** (Figure 3)

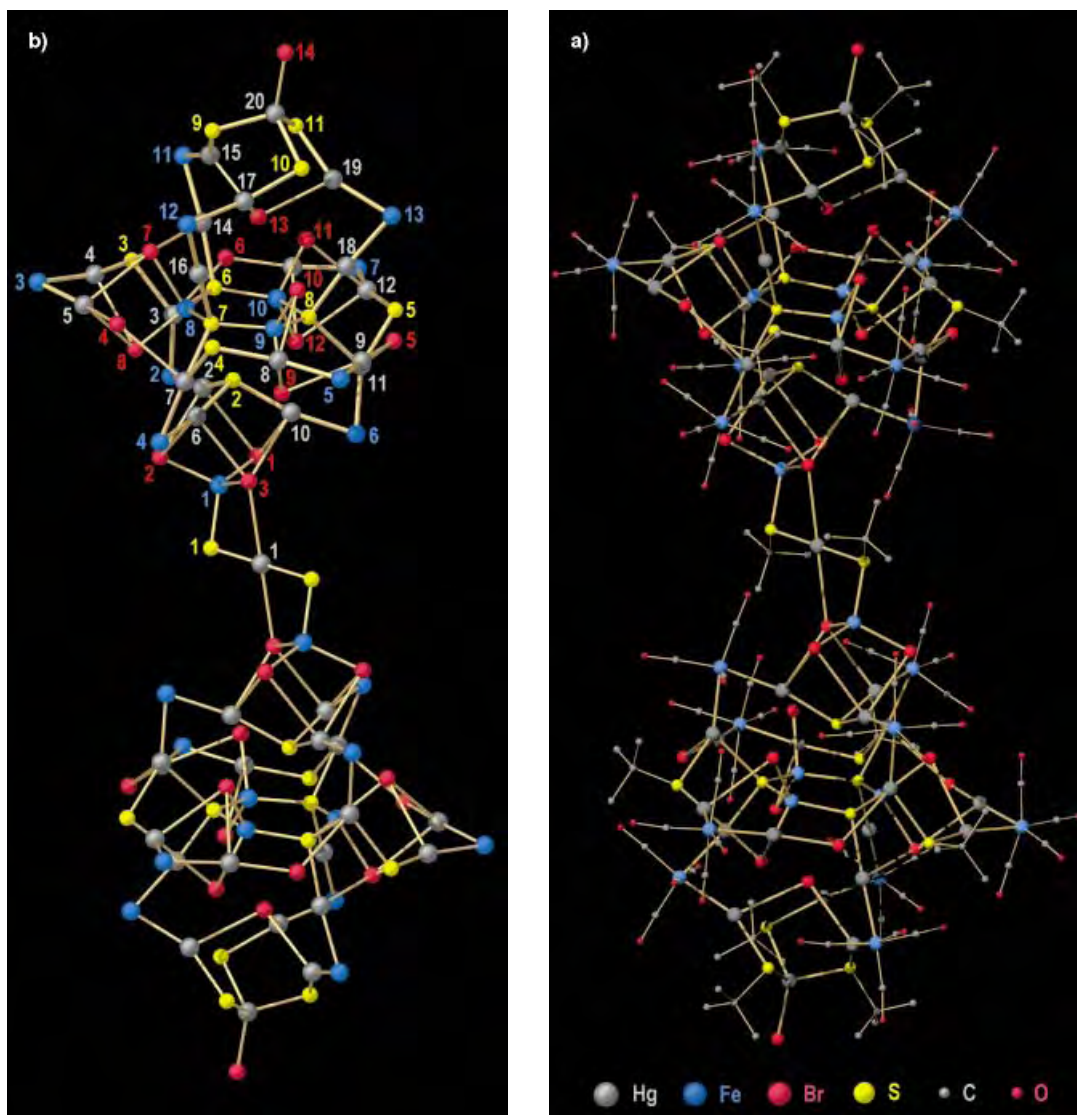


Figure 3. Two views of the molecular structure of **3**. a) With all heavy atoms. b) Without the C, H, and O atoms. The Hg–Br bonds are shown up to 334 pm. Selected bond lengths [pm] and angles [°]: Hg⋯Hg 306.4(2)–336.5(2); Hg–Fe–Hg 74.04(11)–83.71(11); Hg–Fe 251(2)–256.3(4), Hg1–S1 235.7(9), Hg–(μ_2 -S) 237.8(13)–259.2(8), Hg–(μ_3 -S2) 244.5(6)–245.0(6), Hg–(μ_4 -S) 239.7(7)–280.3(7), Fe–S 230.3(9)–236.8(9), Hg–Br14 246.0(5), Hg–Br 250.3(3)–252.7(13), and 292.3(4)–333.4(7).

shows that it is built up from two $\text{Hg}_{19}\text{Fe}_{13}$ clusters that are linked together by a bridging central Hg atom (Hg1), which is situated on an inversion center. The CO and *t*Bu groups are omitted from Figure 3b for the sake of clarity. Hg1 is linearly coordinated by two S atoms from *t*BuS groups if one ignores the Br3 center that lies within the coordination sphere of Hg1 at a distance of 315.3 pm. The FeHg_2 units, which are present in the reactant, are also found again in this cluster (Fe2–Fe7, Fe11–Fe13, and their symmetry equivalents). However, there are also Hg (Hg1, Hg20) and Fe atoms (Fe1, and Fe8–Fe10) that have no Hg–Fe bonds. A characteristic of this cluster is an almost planar Fe_3S_3 six-membered ring (S7, Fe8, S6, Fe10, S8, Fe9) in the center of the $\text{Hg}_{19}\text{Fe}_{13}$ fragment. The largest deviation of any atom out of the plane of this six-membered ring is about 13 pm. Holm et al.^[18] have reported an iron

thiolate compound $[\text{Fe}_3(\text{SR})_3\text{X}_6]^{3-}$ (R = organic group, X = Cl, Br) in which the $\text{Fe}_3(\text{SR})_3$ structure corresponds to that found in the center of the $\text{Hg}_{19}\text{Fe}_{13}$ fragment.

If the $\text{Hg}_{19}\text{Fe}_{13}$ cluster is described starting from the six-membered ring, then three S–Hg–Fe–Hg–S–Hg chains (e.g., S6–Hg14–Fe11–Hg15–S9–Hg20) connect one sulfur atom from the six-membered ring to a terminal Hg atom (Hg20) and likewise three S–Hg–Fe–Hg–Br–Fe–S–Hg chains (e.g., S6–Hg3–Fe2–Hg2–Br2–Fe1–S1–Hg1) link the Fe_3S_3 ring to the bridging Hg atom (Hg1). The first mercury atom (Hg3) is linked through a bridging sulfur atom (S3) to a further H_2Fe unit (Hg4–Fe3–Hg5) that lies in the plane of the six-membered ring. As in **1**, the Hg atoms in **3** have the formal charge of +2 (d^{10} configuration). Correspondingly one observes only very long Hg–Hg contacts of the order of 306.4(2) pm.

Experimental Section

1: $t\text{BuSSiMe}_3$ (0.53 mL, 2.7 mmol) was added to a suspension of $[\text{Fe}(\text{CO})_4(\text{HgCl})_2]$ (0.43 g, 0.67 mmol) in toluene (20 mL) at room temperature. A yellow powder precipitated immediately, and the solution turned yellow within two days. After three days orange needles of **1** were formed in the solution (yield 45%).

2: $t\text{BuSSiMe}_3$ (0.18 mL, 0.9 mmol) was added to a suspension of $[\text{Fe}(\text{CO})_4(\text{HgBr})_2]$ (0.34 g, 0.47 mmol) in toluene (20 mL) at room temperature. The brown solution was layered with *n*-heptane and after two weeks small orange crystals of **2** were formed together with a black-brown precipitate (yield 15%).

3: $t\text{BuSSiMe}_3$ (0.27 mL, 1.4 mmol) was added to a suspension of $[\text{Fe}(\text{CO})_4(\text{HgBr})_2]$ (0.50 g, 0.7 mmol) in toluene (20 mL) at room temperature. Within a few weeks, a light brown precipitate and orange crystals of **3** were formed from the yellow-brown solution (yield 30%). Satisfactory elemental analyses (Hg, Fe, C, and H) were obtained for **1–3**.

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1: monoclinic, space group $P2_1/n$ (no. 14), $Z = 4$, $T = 200 \text{ K}$, $a = 1106.4(2)$, $b = 4379.6(9)$, $c = 1208.7(2) \text{ pm}$, $\beta = 107.69(3)^\circ$, $V = 5580(2) \times 10^6 \text{ pm}^3$, $\mu(\text{MoK}_\alpha) = 206.57 \text{ cm}^{-1}$, $2\theta_{\text{max}} = 48^\circ$, 17550 reflections (empirical absorption correction), 7529 independent reflections ($R_{\text{int}} = 0.1259$) and 6014 observed with $I > 2\sigma(I)$, 622 parameters (Hg, Fe, Cl, S, O, and C anisotropic; the positions of the H atoms were calculated for ideal positions), max. residual electron density: $3.868 \text{ e } \text{\AA}^{-3}$, $R1 = 0.0758$, $wR2 = 0.2407$. **2:** $2 \cdot 2 \text{ C}_7\text{H}_8$; monoclinic, space group $C2/c$ (no. 15), $Z = 4$, $T = 200 \text{ K}$, $a = 3061.7(8)$, $b = 1651.2(6)$, $c = 3244.9(10) \text{ pm}$, $\beta = 110.97(2)^\circ$, $V = 15318(8) \times 10^6 \text{ pm}^3$, $\mu(\text{MoK}_\alpha) = 205.43 \text{ cm}^{-1}$, $2\theta_{\text{max}} = 45^\circ$, 36397 reflections (empirical absorption correction), 9740 independent reflections ($R_{\text{int}} = 0.0874$) and 6748 observed with $I > 2\sigma(I)$, 695 parameters (Hg, Fe, Br, S, O, and C anisotropic; the positions of the H atoms were calculated for ideal positions), max. residual electron density: $2.394 \text{ e } \text{\AA}^{-3}$, $R1 = 0.0501$, $wR2 = 0.1333$. With the disordered Hg7 atom an occupation of 1/3 was assumed for the threefold disordered position. **3:** $5 \text{ C}_7\text{H}_8$; monoclinic, space group $I2/a$ (no. 15), $Z = 4$, $T = 190 \text{ K}$, $a = 3145.9(6)$, $b = 3205.8(6)$, $c = 3380.2(7) \text{ pm}$, $\beta = 101.62(3)^\circ$, $V = 33391(12) \times 10^6 \text{ pm}^3$, $\mu(\text{MoK}_\alpha) = 224.80 \text{ cm}^{-1}$, $2\theta_{\text{max}} = 45^\circ$, 59953 reflections (empirical absorption correction), 21145 independent reflections ($R_{\text{int}} = 0.1009$) and 14405 observed with $I > 2\sigma(I)$, 1099 parameters (Hg, Br, Fe, and S

anisotropic; O and C isotropic; the positions of the H atoms were calculated for ideal positions), max. residual electron density: $2.775 \text{ e } \text{\AA}^{-3}$, $R1 = 0.0628$, $wR2 = 0.1718$. The heavy-metal skeleton of **3** is partly disordered (Hg12–Hg15, Fe7, Fe11, Br6, Br7, Br11, and S9). An indication of a possible superstructure could not be found. Further details of the crystal structure investigations 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 numbers CSD-408008, CSD-408009, and CSD-408010.

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Supramolecular Daisy Chains**

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The appeal that interlocked molecular assemblies and intertwined superarchitectures holds for chemists is reflected in the extensive literature^[1] devoted to the construction and characterization of such systems. A natural development is the fabrication of interwoven^[2] supermolecules and supramolecular arrays by the noncovalent oligomerization/polymerization^[3] of self-complementary (plerotopic^[4]) monomeric species. An approach that offers much potential involves^[5] a plerotopic macrocyclic monomer that can oligomerize or polymerize through noncovalent bonds. However, this monomer must be designed in such a way that its two complementary sites are compelled to recognize each other in an intermolecular,^[6] rather than an intramolecular,^[7] sense; that is, the plerotopic monomer must be prevented from “biting its own tail” and encouraged to form a “daisy chain”^[8] instead (Figure 1).

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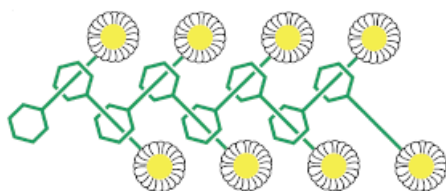


Figure 1. Cartoon representation of a supramolecular daisy chain.

When this hurdle has been surmounted, another issue has to be addressed: Will the self-complementary monomer oligomerize noncovalently to form a discrete daisy-chain-like supramolecular macrocycle, or will it polymerize noncovalently^[2b] to generate a macromolecular daisy chain?

An inspection of molecular models convinced us that **1-H**⁺, a dibenzo[24]crown-8 (DB24C8) derivative bearing a secondary dialkylammonium^[9] sidearm, would be a suitable plerotropic monomer for an initial investigation. The question then posed was: would **1-H**⁺ self-assemble^[10] to generate macrocyclic supramolecular oligomers or acyclic supramolecular polymers (Scheme 1); that is, would the self-complementary cation **1-H**⁺ congregate into supermolecules or supramolec-

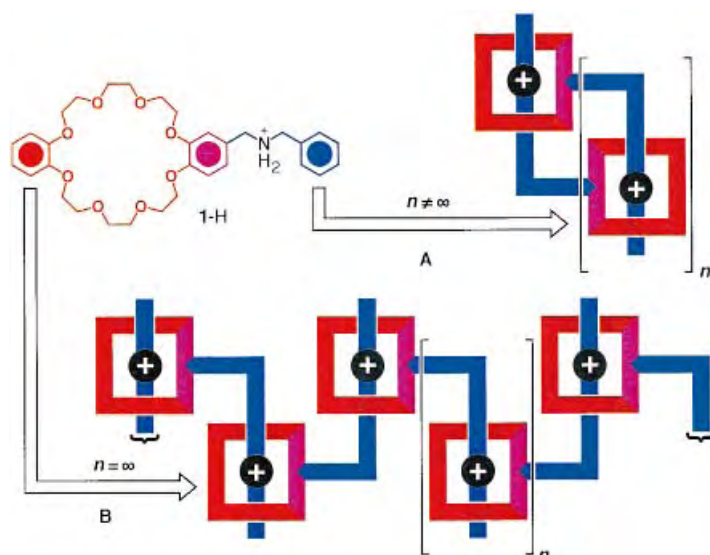
ular arrays?^[11] Here we describe the synthesis of cation **1-H**⁺ and its characterization as a dimeric supramolecular macrocycle—the smallest daisy chain imaginable—in both the gas phase and the solid state by mass spectrometry and X-ray crystallography, respectively.

Scheme 2 outlines the synthesis of **1-H**⁺ as its hexafluorophosphate salt. The requisite aldehydic precursor of **1-H**·PF₆, (2-formyl)dibenzo[24]crown-8 (**2**), was prepared in 17% overall yield from 3,4-dihydroxybenzaldehyde, catechol, and triethylene glycol monotosylate.^[12] Reductive amination of **2** with benzylamine furnished **1**, which was transformed into **1-H**·PF₆ by protonation with hydrochloric acid followed by counterion exchange from chloride to hexafluorophosphate.

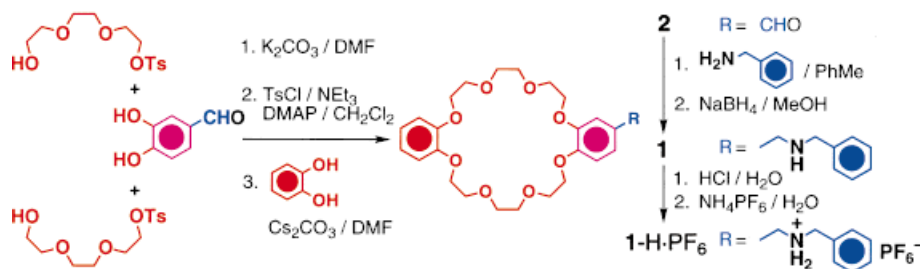
The liquid secondary ion (LSI) mass spectrum^[13] of **1-H**·PF₆ revealed intense peaks at *m/z* = 1281 and 1135, corresponding to the creation of dimeric supermolecules in the gas phase. These peaks can be identified as the supramolecular ions [(**1-H**)₂(PF₆)]⁺ and [(**1-H**)(**1**)]⁺, respectively, and indicate the aggregation of two monomer units. Interestingly, the peak at *m/z* = 1135 is the base; it is approximately twice as intense as the peak at *m/z* = 568, which corresponds to [**1-H**]⁺. However, the isotope peaks were separated by 0.5 mass units around this lower mass peak, thus providing evidence for the existence of the doubly charged dimer [(**1-H**)₂]²⁺ in the gas phase. Moreover, the fact that no higher order oligomers could be detected in the mass spectrum confirmed the integrity of the dimer in the gas phase.^[14]

In accord with the LSI-MS studies, the X-ray crystallographic analysis^[15] of **1-H**·O₂CCF₃ (Figure 2) reveals the formation of a two-component daisy-chain-like supermacrocycle, possessing C₂ symmetry,^[16] in which the NH₂⁺-containing sidearms of each component are threaded simultaneously through the complementary DB24C8 recognition sites of their counterparts. This supermolecule is stabilized by a combination of π–π stacking between the NH₂⁺-bearing catechol rings (interplanar separation 3.36, centroid–centroid separation 3.55 Å) and hydrogen bonds involving one of the hydrogen atoms on each NH₂⁺ group and a polyether oxygen atom from each DB24C8 component (N⁺⋯O 2.91, H⋯O 2.02 Å; N⁺–H⋯O 170°).

An investigation of the packing of the supermolecules (Figure 3) reveals the formation of a mosaiclike^[17] sheet composed of enantiomeric dimer pairs [(**1-H**)₂]²⁺. This supramolecular sheet self-assembles in one direction by face-to-face π stacking of the terminal phenyl groups of each monomer (interplanar separation 3.62, centroid–centroid separation 3.73 Å), supplemented by edge-to-face interactions between these pairs of interacting terminal rings and the



Scheme 1. Cartoon representations of the viable types of self-assembled superarchitectures that can be created from the plerotropic **1-H**⁺ cation. A) The supramolecular association of a finite number of **1-H**⁺ monomer units in a cyclic fashion generates oligomeric daisy-chain-like macrocycles. B) The noncovalent polymerization of an infinite number of **1-H**⁺ monomer units furnishes a supramolecular array that is commensurate with a macromolecular daisy chain.



Scheme 2. Synthesis of the plerotropic salt **1-H**⁺·PF₆[−]. Ts = *p*-toluenesulfonyl, DMAP = 4-dimethylaminopyridine.

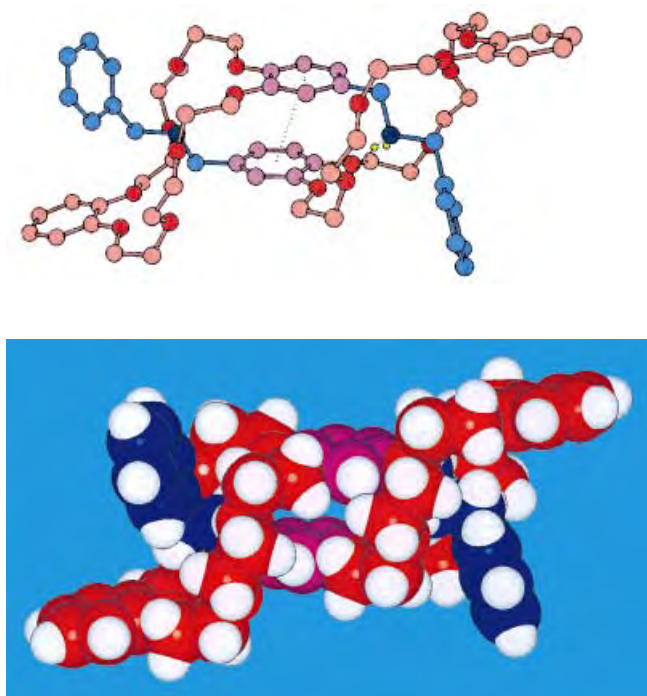


Figure 2. The crystal structure of the supermolecule $[(1-H)_2]^{2+}$, which may be classed as a $[c2]$ daisy chain (c designates^[8] that the daisy chain is cyclic, while the 2 symbolizes the number of components of which it is composed). Top: Ball-and-stick representation. Bottom: Space-filling representation. Blue: Secondary dialkylammonium sidearms; magenta: sidearm-bearing catechol rings; red: polyether loops and unsubstituted catechol rings.

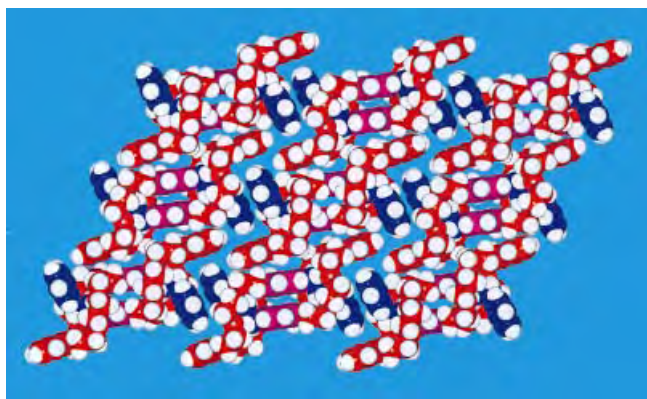


Figure 3. Space-filling representation of the mosaiclike sheet comprised of enantiomeric $[(1-H)_2]^{2+}$ supermolecules.

immediately adjacent unsubstituted catechol rings of contiguous dimer pairs (centroid–centroid separation 5.06 Å, rings being inclined by 83° to each other). Neighboring rows of supermolecules are then aligned such that pairs of the OCH_2 hydrogen atoms within the polyether linkages in one π -stacked row are directed from above and below into the π faces of the already π - π stacked substituted catechol rings within each dimer ($H \cdots \pi$ 2.69 Å, $C-H \cdots \pi$ 161°). Channels which are populated by $CF_3CO_2^-$ counterions and CF_3CO_2H molecules are created between each sheet.

The self-assembly of the finite $[c2]$ daisy chain $[(1-H)_2]^{2+}$ demonstrates^[18] that it is extremely difficult to overcome the enthalpic and entropic costs of generating infinite supramolecular arrays in noncovalent syntheses which operate

under thermodynamic control. Nevertheless, the research presented here is an initial step along the road to a novel range of molecular and supramolecular polymers. By way of illustration, one can envisage functionalized $[c2]$ daisy chain superarchitectures undergoing condensation polymerization reactions with difunctional spacer units to generate novel mechanically interlocked molecular polymers.^[19] Moreover, it can be imagined that replacement of the $1-H^+$ cation's substituted catechol unit—which is involved in stabilizing π - π stacking interactions in the supermolecule $[(1-H)_2]^{2+}$ (see above)—with a bulky, sterically cumbersome unit, that cannot enter into π - π stacking interactions, could lead to the supramolecular syntheses of acyclic $[a\infty]$ daisy chain supramolecular polymers that are composed of an infinite number of monomer units. Indeed, it may be that the “stoppering”^[20] of such species could lead, ultimately, to unique mechanically interlocked polymers,^[19] namely, macromolecular daisy chains.

Experimental Section

2: Reaction of 3,4-bis[2-(2-(2-(*p*-toluenesulfonyloxy)ethoxy)ethoxy)benzaldehyde^[21] (8.43 g, 11.9 mmol) with catechol (1.31 g, 11.9 mmol) in the presence of CS_2CO_3 (19.30 g, 59.3 mmol) in DMF (700 mL) at 100 °C furnished, after standard extractive workup with PhMe and 1N HCl, a crude product, which was subjected to column chromatography (SiO_2 ; gradient elution with EtOAc/MeOH, 100/0–95/5). The ensuing material was recrystallized from EtOAc/ nC_4H_{14} to provide **2** (2.31 g, 41%) as a white solid. M.p. 105–107 °C; ^1H NMR (300.1 MHz, $CDCl_3$, 20 °C): δ = 3.82–3.85 (m, 8H), 3.89–3.97 (m, 8H), 4.12–4.24 (m, 8H), 6.83–6.90 (m, 4H), 6.93 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 1.8 Hz, 1H), 7.42 (dd, J = 8.1, 1.8 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 20 °C): δ = 69.4, 69.5, 69.7, 70.0, 71.3, 71.4, 71.5, 111.1, 111.9, 114.0, 121.4, 126.8, 130.2, 148.9, 149.2, 154.3, 190.9; MS (LSI): m/z = 477 $[M+H]^+$; calcd for $C_{25}H_{32}O_9$ (476.5): C 63.01, H 6.77; found: C 63.12, H 6.54.

1-H · PF₆: Reductive amination of **2** (1.50 g, 3.2 mmol) with $PhCH_2NH_2$ (0.34 g, 3.2 mmol) by standard procedures^[2b,9] afforded the amine **1** (1.42 g, 79%) as a pale yellow oil [^1H NMR (300.1 MHz, $CDCl_3$, 20 °C): δ = 3.71 (s, 2H), 3.77 (s, 2H), 3.82 (s, 8H), 3.88–3.93 (m, 8H), 4.11–4.17 (m, 8H), 6.78–6.91 (m, 5H), 7.20–7.34 (m, 7H)]. According to a typical protocol,^[9] a portion of **1** (0.47 g, 0.8 mmol) was then allowed to react with 5N HCl (50 mL) to furnish, after counterion exchange with NH_4PF_6 , **1-H · PF₆** (0.55 g, 93%) as a white powder. M.p. > 210 °C (decomp); ^1H NMR (300.1 MHz, $(CD_3)_2SO$, 20 °C): δ = 3.68 (s, 8H), 3.74–3.83 (m, 8H), 4.04–4.16 (m, 12H), 6.86–6.99 (m, 4H), 7.02 (s, 2H), 7.13 (s, 1H), 7.47 (brs, 5H), 9.09 (brs, 2H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 20 °C): δ = 49.9, 50.0, 68.7, 69.0, 69.1, 70.4, 113.5, 114.0, 115.4, 121.1, 123.0, 124.2, 128.7, 129.0, 129.9, 132.0, 148.2, 148.4, 148.9; MS (LSI): m/z = 1135 $[2M - HPF_6 - PF_6]^+$; calcd for $C_{32}H_{42}NO_8PF_6$ (713.6): C 53.86, H 5.93, N 1.96; found: C 53.60, H 5.84, N 2.05.

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- [14] However, the solution-phase behavior of $1\text{-H}^+\text{-PF}_6^-$ was not as straightforward as that in the gas phase. The ^1H NMR spectrum (400.1 MHz, CD_3CN with a drop of D_2O , 0°C) of $1\text{-H}^+\text{-PF}_6^-$ was extremely complicated as a result of various aggregation–deaggregation phenomena occurring simultaneously. This spectrum gradually simplified, indicating the presence of completely disassociated 1-H^+ , when the temperature was increased stepwise to 80°C . A simple ^1H NMR spectrum was also obtained in $(\text{CD}_3)_2\text{SO}$, a solvent that has a strong preference^[9] for entering into hydrogen bonds with secondary dialkylammonium ions and which consequently disfavors intermolecular interactions between distinct units of 1-H^+ .
- [15] The salt $1\text{-H}^+\text{-O}_2\text{CCF}_3$ was prepared by allowing **1** to react with an excess of $\text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2 and then removing the solvent under reduced pressure. Single crystals suitable for X-ray crystallographic analysis were obtained when a solution of the salt in $\text{EtOAc}/n\text{C}_6\text{H}_{14}/\text{MeCN}$ was allowed to stand at 20°C for about 1 d. Crystal data for $[\text{C}_{32}\text{H}_{42}\text{NO}_8][\text{O}_2\text{CCF}_3] \cdot \text{CF}_3\text{CO}_2\text{H}$: $M_r = 795.7$, monoclinic, space group $C2/c$, $a = 22.936(4)$, $b = 23.249(3)$, $c = 15.393(3)$ Å, $\beta = 112.14(1)^\circ$, $V = 7603(2)$ Å³, $Z = 8$, $\rho_{\text{calc}} = 1.39$ g cm^{−3}, $\mu(\text{MoK}\alpha) = 1.22$ cm^{−1}, $F(000) = 3328$. Crystal dimensions $0.33 \times 0.33 \times 0.80$ mm (needles), Siemens P4 diffractometer, graphite-monochromated $\text{MoK}\alpha$ radiation, ω -scans, $T = 203$ K. Of 6449 independent reflections measured ($2\theta \leq 50^\circ$), 2715 had $I_0 > 2\sigma(I_0)$ and were considered to be observed. The structure was solved by direct methods, and the major occupancy non-hydrogen atoms refined anisotropically. The positions of the NH_2^+ hydrogen atoms were located from a ΔF map and refined isotropically subject to an N–H distance constraint. The remaining hydrogen atoms were placed in calculated positions, assigned isotropic thermal parameters $U(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$, and allowed to ride on their parent atoms. Refinement was by full-matrix least squares based on F^2 to give $R_1 = 0.092$ and $wR_2 = 0.222$. Computations were carried out with the SHELXTL 5.03 package. 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-100961. 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).
- [16] Interestingly, in this instance, the interaction between the two achiral 1-H^+ cations is dissymmetrizing, rendering a chiral association and resulting in the formation of a pair of enantiomeric C_2 -symmetric supramolecular stereoisomers. This kind of interaction occurs because the enantiotopic faces of the interacting 1-H^+ cations possess the same prochirality. However, an alternative situation can also be envisaged: A diastereoisomeric “*meso*” supramolecular stereoisomer—endowed with C_i symmetry—would have been created if the interacting faces of individual 1-H^+ cations had maintained different prochiralities upon crystallization. In other words, the noncovalent dimerization of the 1-H^+ cation proceeds diastereoselectively, at least in the solid state, to furnish a racemic mixture of the C_2 -symmetric supramolecular stereoisomers.
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Chemical safety



Chemical Safety—An International Challenge**

Bernd-Ulrich Hildebrandt and Ulrich Schlottmann*

Today, when we talk of chemistry, we usually mean more than just the science in its purest sense. The term chemistry is often associated with products, industry, jobs, trade, progress, and risks. In the last 15 years in particular, improved levels of knowledge, and the experience of certain incidents, have raised awareness of possible risks in the chemicals sector, both amongst scientists and the public at large. Germany's response has been to create an appropriate statutory framework. However, particularly in an industry which relies on global trade, guarding against these risks is an international task. The export and import of chemicals has created flour-

ishing global trade flows; the natural transportation of chemicals through the atmosphere, water, or the food chain, resulting in their presence in environmental compartments or geographical regions where they are undesirable or even potentially harmful, is also a significant factor as chemicals become more widespread. There is also the economic aspect to consider, whereby one-sided restrictions may lead to distortions of competition in this fiercely contested market. Above and beyond this, it is a question of combining the economic interests of the industrialized nations with their moral obligations towards developing countries. Faced with these conflicts of

interests, numerous bodies and organizations, at both the national and international level, have taken up the issue with the aim of harmonizing the approach to chemical safety as far as possible. This review aims to provide an overview of the principal bodies and organizations involved in this field, and give an insight into the closely interwoven structures of cooperation taking place at both a political and a technical level.

Keywords: chemical safety • ecology • environmental protection • toxicology

1. Introduction

The chemical industry employs a large number of people and, hence, represents a key social and economic factor. The Organization for Economic Cooperation and Development (OECD) has estimated that some 12 million jobs around the world are dependent on the chemical industry. However, the production and use of certain chemicals also entails potential hazards for humans and the environment. Environmental awareness and particularly an awareness of the risks to human health have risen sharply in recent years. What is more, international commitments have been formed to create global conditions for sustainable development. These commitments were undertaken partly out of a sense of moral responsibility towards developing countries, who are themselves rarely producers but often customers or consumers of goods from

industrialized nations. This role distribution means that developing countries are often less knowledgeable about the risks associated with these products than the industrialized countries which produce them. There have been policy responses to address this issue. One key aspect is improving the level of knowledge vis-à-vis individual chemicals and expanding the exchange and dissemination of such knowledge.

2. National Regulations and the European Community

The formulation and introduction of statutory regulations and technical measures to reduce the adverse effects of chemicals is an on-going process in the Federal Republic of Germany. At the heart of these statutory regulations is the *Act on Protection against Dangerous Substances* (Chemicals Act).^[1] The essential character of the Chemicals Act is the manner in which it transcends individual products, media, and protection objectives.

- The substances themselves, as well as their presence in various products or usage forms, are evaluated with regard to their potential risks.

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[**] A list of the abbreviations used is presented in the Appendix. Further information concerning the flags and symbols in the frontispiece on the left are available from the authors.

- The effects on all compartments of the environment are significant.
- Equal weighting is given to the three protection objectives: environmental protection, occupational safety, and health protection.

The Chemicals Act has been concretized in numerous subsidiary regulations such as the Ordinance on Dangerous Substances, the Chemicals Prohibitions Ordinance, the Ordinance on Test Certifications and Other Documents under the Chemicals Act, the Ordinance on Costs of Official Acts under the Chemicals Act, the Poisons Information Ordinance, and the Ordinance on the Execution of Regulations of the European Communities on Substances and Preparations, as well as administrative regulations governing existing and new substances and good laboratory practice.

A large number of employees in industry, science, and government agencies are involved in implementing the Chemicals Act. At government level, there is a central chemicals registration office at the Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, BAuA) and three evaluation offices: BAuA, the Federal Environmental Agency (Umweltbundesamt, UBA), and the Federal Institute for Health Protection of Consumers and Veterinary Medicine (Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin, BgVV). The aim is to ascertain the potential hazards of a substance in its *entirety*. This approach serves as a basis in all EC states within the context of complete harmonization of chemical legislation within the EC through directives and regulations. The principal statutory instruments are the following directives: The directive on dangerous substances, the directive on the application of the principles of good laboratory practice, directives on risk evaluation for new and existing substances, directives relating to restrictions on

marketing and use, and preparation directives. These are supplemented by regulations on existing substances, the import/export of dangerous substances (prior informed consent procedure, PIC), and on substances which deplete the ozone layer. Substance legislation is characterized by the following three aspects:

- Obtaining scientifically validated data on the substance in question.
- Identifying the hazardous properties of substances through classification and labeling.
- Creating the necessary legal measures under administrative law to minimize the risks for humans and the environment.

Figure 1 contains an overview of the principle EC regulations. Regulations relating to the protection of the ozone layer are not included here.

Before a new chemical is launched on the market, all such “new substances” must be subjected to testing within the context of registration; the extent of testing is based on the planned substance volume. On the basis of the results, scientifically valid statements can be made concerning the dangers of a substance with regard to the protection objectives cited, and appropriate measures can be introduced to minimize the potential risks.

To achieve equally high protection objectives for existing substances (i.e., substances which were brought into circulation prior to September 18, 1981) the *Council Regulation (EEC) No. 793/93 of March 23, 1993 on the Evaluation and Control of the Risks of Existing Substances* was passed at the EC level. This introduced a procedure for uniform control and risk evaluation which also covered existing substances. Initially, existing data is accumulated on the most significant substances in terms of volume; these substances will then be subjected to comprehensive analysis within the context of risk

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U. Schlottmann

Ulrich Schlottmann, born in 1941, studied chemistry and pharmacy in Berlin and Marburg. He obtained his certificate as a pharmacist in 1966 and finished his Ph.D. in 1971 at the Universität Marburg. From 1967 to 1973 he taught pharmaceutical chemistry at the Institut für Pharmazeutische Chemie und Lebensmittelchemie der Universität Marburg. In 1974 he moved to the Federal Ministry for Youth, Family, and Health in Bonn, where he became leader of the chemicals department in 1982. In 1986 he overtook the same work in the newly founded Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety. Since 1979 he has been lecturing on “Special Areas of Law for Pharmacists” and since 1984 on “Health” at the Universität Bonn.

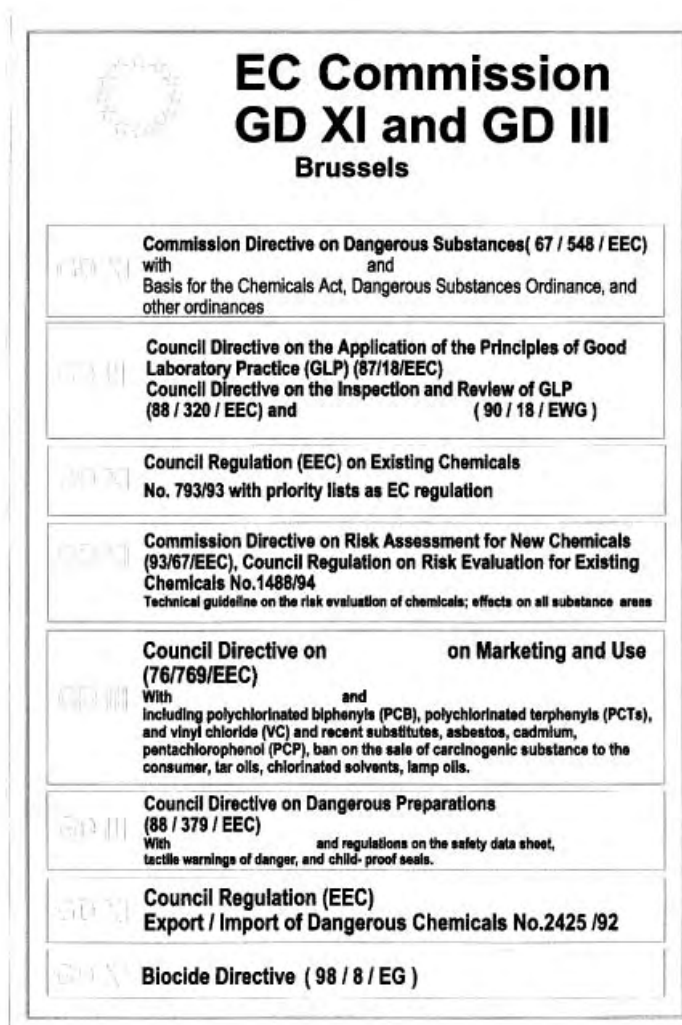


Figure 1. EC rulings on chemical safety.

evaluation. The criteria of risk evaluation, and the methodology to be employed, have been drawn up by experts from the member states at the EC level and summarized in a comprehensive document (*Technical Guidance Document (TGD) on Risk Evaluation of Chemicals*). The current state of the art regarding the evaluation of existing and new substances is reflected in this document. Essentially, evaluation involves comparing the concentration levels at which a substance occurs in the environment under given conditions (predicted environmental concentration, PEC), or to which humans may be exposed, with the concentration level not deemed likely to have an adverse impact on humans (*no observed adverse effect level*, NOAEL) and ecosystem (predicted *no-effect* concentration, PNEC). This creates the basis for a uniform EC approach to substance evaluation. Having been hampered by various problems, the first EC reports on existing substances were not completed until the end of 1997. These reports, which are prepared by the member states, also contain recommendations on whether or not measures should be taken to minimize the risks posed by a given substance. The EC Commission then distributes a proposal on possible measures amongst the member states.

The results are published in the official journal of the EC in the form of a "short report".

At the EC Commission, overall control of chemical safety is the responsibility of Directorate General (DG) XI (environment, nuclear safety, and civil protection), Directorate E (industry and environment), and in particular Directorate E2 (chemical substances and biotechnology). Directorate General XI is assisted by the European Chemicals Bureau (ECB), affiliated to the EC Commission's Joint Research Center (JRC, Ispra, Italy), which provides support on technical issues and overall handling of the labor-intensive risk evaluations. The ECB's work includes evaluation of existing substances, classification and labeling, the area of new substances, biocides, test methods, and issues relating to the export/import of chemicals. In its work, the ECB is dependent on intensive support from the member states, and therefore collaborates closely with them at a technical level.

In addition to the legal measures described, certain sectors of the German industry (e.g. wood preservatives, detergents) have also undertaken *voluntary commitments* as supporting measures. In these, for example, an industry may undertake to supply data on its products to a central authority, or to remedy existing data and knowledge deficiencies regarding the potential hazards of its products through appropriate studies. Voluntary commitments are always useful if they can respond to the need for action just as quickly, or indeed more quickly, than would be possible through the creation of a legal framework. In this way, unnecessary legislation procedures can be avoided. Admittedly, the observation, transparency, and efficiency of such voluntary commitments always needs to be accompanied by a government review in each individual case.

2.1. Advisory Committees for Existing Substances

In 1982 the Chemicals Act empowered the Federal Government to have existing substances tested in the same way as new substances, provided there are grounds for suspicion that the substance poses a hazard. In 1982 the Advisory Committee on Existing Chemicals of Environmental Relevance (Beratergremium für umweltrelevante Altstoffe, BUA) of the German Chemical Society (Gesellschaft deutscher Chemiker, GDCh) was created at the request of the Federal Government, with the aim of systematically ascertaining the risk potential of existing substances. In accordance with the principle of cooperation, the BUA is composed of equal numbers of representatives from the authorities, industry, and science. It creates a forum for continuous, scientifically based dialogue between these three groups on the subject of existing substances. The *BUA Substance Reports* were devised as a foundation for decision makers in government and industry. The BUA has since published over 200 reports on some 250 substances, the benefits of which have been manifold (e.g., as a decision-making aid for risk management of chemicals). The substance reports are available in book shops.^[2] Whenever topical issues arise requiring special discussion, ad hoc working groups are

deployed by the BUA; the following working groups exist at present:

- Endocrine disruptors
- Selection criteria for persistent organic pollutants (POP)
- Structure–effect relationships
- Ecotoxicological significance of the algae test
- Evaluation criteria for the maritime sector
- Safety factors within the context of risk evaluation
- Assessing exposure in soils and sediments
- Hydrocarbons as solvents

To implement the Federal Government's existing substance programme of December 1988, the BUA assumed responsibility for selecting those existing substances most worthy of reports; this work continues today. The reports were translated into English to make them accessible to a wider international public. In addition, the BUA assists the Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit, BMU) in implementing the EC Existing Substances Regulation. The BUA was reorganized in the course of adaptation to EC Regulation 793/93 (Existing Substances Regulation). In the future, the aspect of occupational safety is also to be taken into account by the BUA. As a result, it is being renamed as the Advisory Committee for Existing Substances, but will retain the acronym BUA. In addition, membership of the BUA has been limited to a total of 13 in order to increase its effectiveness. The new BUA was founded in December 1997.

Since 1986 the Employment Accident Insurance Fund of the Chemical Industry (Berufsgenossenschaft der chemischen Industrie, BG Chemie) has published *toxicological evaluations*,^[3] aimed primarily at protecting employees from health impairments associated with the handling of materials. The evaluations are coordinated with the work of other national and international bodies (e.g. BUA, European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), EC), to avoid duplication. To date, some 190 evaluations have been produced, representing an important contribution to the toxicological evaluation of existing substances. In view of the keen international interest in these publications, they are also available in English (*Toxicological Evaluations*^[3]).

Thanks to the Chemicals Act and other statutory instruments such as the *Federal Immission Control Act* and the *Federal Water Act*, Germany enjoys extensive protection against the risks from chemicals to humans and the environment.

3. International Activities

Joint international action is of great importance given the pronounced levels of imports and exports in the chemicals and products trade, and also in view of the ubiquitous spread of certain chemicals through air, water, and the food chain. Its importance is underlined by the concrete example of chloro-fluorocarbons (CFC) and other ozone-depleting substances. To begin with, CFCs were distinguished by their excellent refrigeration properties and cost-effective production; only later were the grave effects of these substances on the ozone

layer realized. This emphasizes the need for a comprehensive, cross-media approach when evaluating the environmental relevance of a substance, and illustrates the drastic effects of failure to adopt such an approach.

Within the context of a legislative framework, and also thanks to a voluntary initiative by industry, the production of CFCs in Germany has been discontinued altogether, and their use reduced substantially. It is a well-known fact that depletion of the ozone layer is a global problem which cannot be solved by a single state acting in isolation. A joint approach, such as that agreed in the Montreal Protocol and its amendments, is the only way forward if we are to counteract the destruction of the ozone layer. At the 9th Conference of the Parties to the Montreal Protocol in September 1997, the parties intensified and concretized their commitments. Classified according to their production and use in industrialized and developing nations as well as according to the respective substances or substance groups CFCs have already been phased out completely in some cases, or are due to be phased out in the foreseeable future. However, the phasing out of partially halogenated CFCs (H-CFC) will take effect more slowly since, according to current agreements, complete curtailment by the industrialized countries is not due until 2030 (2040 in developing countries).

3.1. Intergovernmental Forum on Chemical Safety (IFCS)

Agenda 21 is the work programme for the 21st century signed by more than 170 states in Rio de Janeiro in 1992 at the United Nations Conference on Environment and Development. In chapter 19 (Table 1) there are detailed mandates on the “environmentally sound handling of toxic chemicals” (“toxic” is used here in the sense of “hazardous”). Key cornerstones include the intensification of international cooperation and the coordination of on-going international and regional activities. In the course of implementing this programme, in April 1994 the International Conference on Chemical Safety in Stockholm—staged by the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO)—was attended by 110 states. The Intergovernmental Forum on Chemical Safety (IFCS) was founded at this conference; its main tasks are to control and harmonize the procedure for implementing Chapter 19. It is to draw up

Table 1. Key issues of Chapter 19 of Agenda 21 of the UNCED.

UNCED - Rio 1992 	
Resolutions included in Chapter 19 of Agenda 21 with six key issues which were drafted by the IPCS:	
1. Risk assessment 2. Harmonization of classification 3. Exchange of information 4. Risk minimization 5. Management 6. Illegal traffic	

recommendations for governments as well as international and intergovernmental organizations. Six key issues were identified at the conference, and a plan of action with concrete activities along with timetable was drawn up for each. This plan of action was welcomed and accepted by the Commission on Sustainable Development (CSD), a UN body which monitors the implementation of Agenda 21.

Figure 2 illustrates the development of the IFCS over time.

Following the first meeting in Stockholm in 1994, the second forum (IFCS II) was held in Ottawa in February 1997 under the motto "In Partnership For Global Chemical Safety". It was attended by some 350 delegates from 116 states, 25 nongovernmental organizations (NGO), and 10 intergovernmental organizations (IGO). Topics of the meeting included the continued international approach to POPs, future work on substance evaluation, endocrine disruptors, and the development of national structures for chemical safety (capacity building), particularly in developing countries. The third forum (IFCS III) is due to be held in Brazil in the latter half of the year 2000.

In between these meetings, the Intersessional Group (ISG) is active. It consists of 26 government representatives as well as the President and four Vice-Presidents of the IFCS. Ad hoc

working groups may be deployed both by the forum itself and by the ISG to address certain issues (e.g., for POPs, see Section 3.1.3). Above and beyond this, the Forum Standing Committee (FSC) was formed from 14 states and 4 NGOs as a steering organization.

The foundation of the IFCS created a mechanism which allows all governments, as well as all interest groups, to become involved in the international approach to chemical safety, including NGOs. NGOs include industry, trade unions, environmental and consumer associations, and representatives from the world of science such as the International Council of Chemical Association (ICCA), the International Federation of Chemical, Energy, Mine and Federal Workers Union (ICEM), Greenpeace International, the World Wildlife Fund (WWF), GDCh, the International Union for Pure and Applied Chemistry (IUPAC), and the International Union for Toxicology (IUTOX). All groups have been involved since the inception of the IFCS.

In 1995 the UN organizations UNEP, WHO, ILO, Food and Agriculture Organization (FAO), United Nations Industrial Development Programme (UNIDO), and OECD established the Inter-Organization Programme for the Sound Management of Chemicals (IOMC) as a mechanism for coordinating the activities in Chapter 19 of Agenda 21. The foundations for this were created at the first meeting of the IFCS in Stockholm. It was joined by the United Nations Institute for Training and Research (UNITAR) in 1997. To help cut costs, the IOMC is integrated into the WHO infrastructure and is therefore based in Geneva. The Inter-Organization Coordinating Committee (IOCC) assumes a steering function within the IOMC. Summaries of the individual programmes and dates of the various meetings on key issues are available from the IOMC.

3.1.1. Capacity Building

To protect against potential dangers and minimize the risks from chemicals, an infrastructure is required to ensure appropriate chemical management. Elements of such a management system include relevant legislation, the option and capability of performing risk evaluations, information to avoid the incorrect handling of chemicals, and the ability to respond in the best possible way in the event of an accident or poisoning incident. Most industrialized countries have such structures, but developing countries and many countries whose economic systems are currently in the throes of transformation often have substantial deficits in this respect. Developing such infrastructures (capacity building) is also addressed by Chapter 19 of Agenda 21, and UNITAR plays a key role in this field. In 1996 UNITAR and the member organizations of the IOMC launched a pilot programme to assist governments with the development of infrastructures. In four countries (Argentina, Ghana, Slovenia, and Indonesia), the aim is to initiate development towards a chemical safety structure, with procedures being tailored to the specific requirements of each individual country. The first step involves the drafting of a national profile (NP), in which existing management structures are subjected to comprehen-

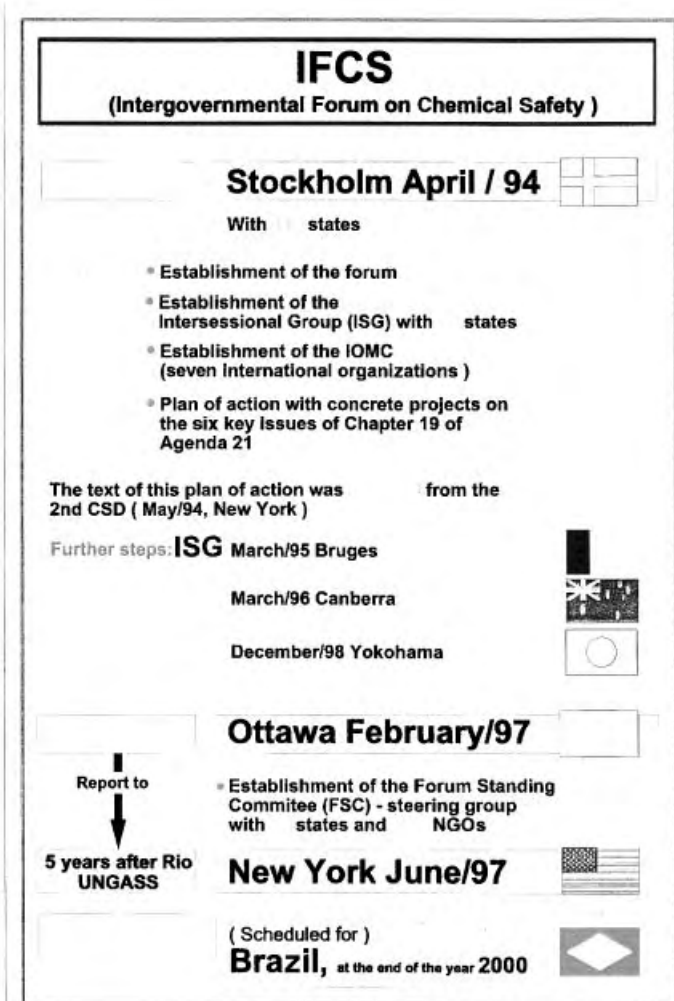


Figure 2. Development of the IFCS.

sive analysis. UNITAR has devised a guide to simplify and standardize the procedure for preparing an NP. Although NPs are primarily designed for developing countries, some industrialized nations (e.g. the USA, Australia) have also drawn up their own NPs. The NPs may serve as examples to other states, or aid in the critical review of the structures in the own country. Germany, too, is currently in the process of preparing an NP. The UNITAR project also involves assistance with the preparation of appropriate training documents, and, finally, the promotion and coordination of all on-going bilateral and multilateral initiatives in this field. The Federal Government has also commissioned the Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) to implement a capacity building project which includes the following aspects:

- There is a provision of technical background information to serve as a decision-making basis for developing countries.
- The concepts will be tested in selected developing countries (a maximum of six).
- The opportunities afforded by alternative products will be taken into account.
- A contribution will be made to national and international coordination and cooperation.

At the planning stage, care was taken to ensure sufficient scope, so that the needs of the partner countries could be accommodated in a targeted manner. The project is being implemented in collaboration with other bilateral and international programmes

3.1.2. Prior Informed Consent (PIC)

Within the context of the UNEP and the FAO, the *PIC Convention* was drawn up to protect developing countries from hazardous chemical imports. It aims to obligate exporting countries to notify the importing country in advance of their intention to transfer hazardous chemicals, and not to import them without the consent of the latter. In the past, this occurred internationally on a voluntary basis; Agenda 21 calls for the creation of a legally binding convention. Negotiations on the PIC were completed in March of this year, with ratification expected in September 1998 in Rotterdam. Table 2 lists the substances included in the PIC Convention.

3.1.3. Persistent Organic Pollutants (POP)

Persistent organic pollutants represent a particular problem for humans and the environment around the world, as their physical-chemical properties, persistency, and propensity for bioaccumulation mean that they can be transported across national borders and may accumulate in certain organisms. They are highly soluble in fat, which encourages bioaccumulation in the fatty tissues of organisms. They are deposited as a result of, for example, "global distillation" or condensation in the colder regions of the planet. This explains why northern states such as Canada are particularly interested in a global limitation of such substances. POPs are manufactured primarily in industrialized countries, but used predominantly in

Table 2. Lists of chemicals of the PIC Convention.

2,4,5-T ("agent orange")
aldrin
captafol
chlordane
chlordimeform
chlorbenzilate
DDT
dieldrin
dinoseb and dinoseb salts
1,2-dibromoethane
fluoroacetamide
HCH (mixed isomers)
heptachlor
hexachlorobenzene
lindane
mercury compounds
PCP
monocrotophos
methamidophos
phosphamidon
methylparathion
parathion
crocidolite
polybrominated biphenyls (PBBs)
polychlorinated biphenyls (PCBs)
polychlorinated terphenyls (PCTs)
tris(2,3-dibromopropyl) phosphate

newly industrializing and developing countries, since they are relatively cheap and simple to produce and have a low *acute* toxicity.

In accordance with decision 18/32 of the UNEP Governing Council in May 1995, the ad hoc working group on POPs was set up by the IFCS. Its task is to compile data on the sources, chemical and toxicological properties of POPs, and their modes of transfer as well as possible substitutes. From June 17–22, 1996 this working group held a conference in Manila. The conference was divided into a session of international experts and the working-group session; it was attended by 32 states, 7 NGOs and 7 IGOs. Assisted by the experts, the working group drafted a report on possible approaches for reducing or eliminating POPs. The key point of this report is the IFCS's concluding recommendation to the UNEP Governing Council and the World Health Assembly (WHA), the decision-making body of the WHO: It calls for the creation of a globally valid, internationally binding instrument to minimize the risks emanating from POPs. An Intergovernmental Negotiating Committee (INC) will be deployed to prepare such an agreement. Initially, it will focus on 12 POPs (aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, mirex, toxaphene, hexachlorobenzene, PCBs, dioxine, furans), which also form part of negotiations by the UN and the Economic Commission for Europe (ECE) on the *Geneva Convention on Long-Range Transboundary Air Pollution* (LRTAP). These substances are pesticides, industrial chemicals, and unwanted by-products of production processes. In compiling the substances, no uniform criteria were applied. Consequently, in the future, a UNEP/IFCS group of experts, using the work of the IFCS working group as a basis, is to draw up scientifically validated criteria for considering additional POPs with regard to international activities.

3.1.4. Endocrine Disruptors

There is unanimous international agreement that the effects of certain chemicals on the hormone system will constitute a key aspect of chemical safety in future, and hence for evaluating substance-inherent properties. There is growing suspicion that certain substances in this group may adversely affect fertility. However, there is a major need for research in this field. To ensure that the necessary resources are utilized in a targeted manner (and avoid duplication), and to obtain substantiated results as quickly as possible, international cooperation is needed. As agreed at IFCS II, the IOMC is to adopt a coordinating role in this respect. Germany has also earmarked substantial resources for research into these substances and their effects. The IPCS is endeavouring to draw up an international inventory of on-going research projects. In addition, the OECD will work on developing appropriate test methods.

3.2. International Programme on Chemical Safety (IPCS)

The IPCS was founded in 1980 as a cooperation between the UNEP, the WHO, and the ILO. The objective of the IPCS is to determine scientific foundations for assessing the risk to human health and the environment from chemicals, with the aim of strengthening national and international endeavours in the field of chemical safety. A total of 36 states are involved in the IPCS's work. It is not only the states involved who benefit from this work, but also, and in particular, those countries with little experience in the creation of chemical safety structures.

3.2.1. Results

One key focus of the IPCS's work is undoubtedly the compilation and dissemination of findings concerning the risks to humans and the environment from chemicals which may be of industrial or natural origin. To this end, numerous monographs have been prepared on substances (generally existing substances) and evaluation methods (Figure 3), and there have been collaboration between the nations involved in IPCS and internationally recognized experts from around the globe. The following results have been published:^[4]

- *Substance reports* (Environmental Health Criteria, EHC)

These reports are designed for scientific experts and contain the latest findings on health hazards and risks for a given substance or group of substances. More recent EHCs also contain details of impact on the environment. There are currently some 190 EHCs.

- *Safety guidance documents* (Health and Safety Guides, HSG)

HSGs contain details of toxicity in a language which is also accessible to nonexperts as well as information on usage, handling, storage, and first-aid treatment. They are aimed at decision makers in industry and administration. Some 100 HSGs have been published to date.

- *Safety data sheets* (International Chemical Safety Cards, ICSC)

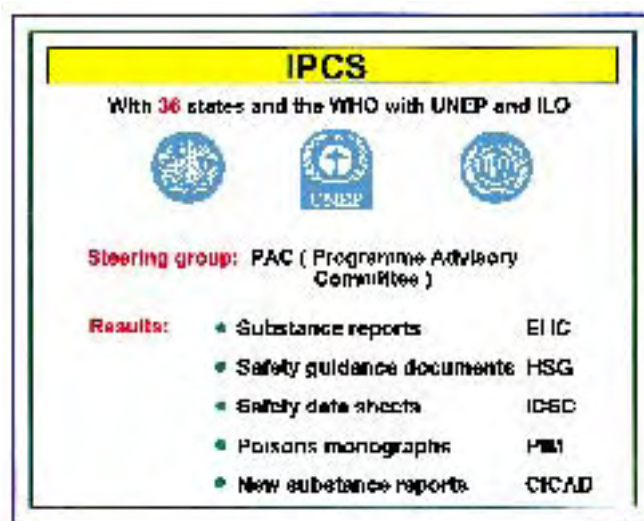


Figure 3. IPCS publications.

These contain essential data on individual products and information about health protection and safe handling, tailored to the use of the product (e.g. in factories or agriculture). There are currently some 1000 chemical safety cards at the UN level, which have also been translated into German by the BgVV.

- *Poisons monographs* (Poisons Information Monographs, PIM)

These contain a brief description of the principal chemical, physical and toxicological properties of each substance, and advice on the diagnosis and treatment of poisoning victims. PIMs are designed for poisons information centers and other advice agencies.

The IPCS will continue to produce these publications, which are to be made available to as many interested individuals as possible. With this in mind, the expectations of the users of these reports are taken very seriously. Interested parties in developing countries and in countries in the throes of economic transformation can obtain the publications at a reduced price. Germany is actively involved in the preparation of EHCs and HSGs and bears the printing costs for these documents.

3.2.2. Pilot Phase for New Substance Reports

In addition to the monographs cited above, a pilot phase is currently underway to produce "Concise International Chemical Assessment Documents" (CICAD) containing data on the hazard potential of a given substance, dosage/effect ratios, and risk characterizations based on sample exposure data. CICADs are generally based on preexisting substance reports. These national or regional substance reports are to be updated within the context of the IPCS; in other words, any studies published since the report was drawn up are to be included. Where available and meaningful, exposure data will also be logged. This is implemented under the aegis of scientific authorities or institutes, who will then hand over the revised report to international experts for their opinion. Institutions who do not produce any substance reports

themselves can also get involved in the preparation of CICADs, by collaborating with the country or institution which produced the original report. Experts hope that the CICAD procedure will enable existing national substance reports to be converted into internationally applicable, recognized substance reports at a comparatively low cost and reasonable manpower input and within a relatively short amount of time. The BUA substance reports described above are particularly well-suited to inclusion in the CICAD procedure. Some states have also expressed an interest in preparing CICAD reports on substances not previously covered by other documents. Following conclusion of the pilot phase, which comprises 15 substance reports, a critical review will be needed to determine whether expectations have been met. The BMU has donated financial and manpower resources to the CICADs. The first six CICADs (over 1,2-dichloroethane, 3,3-dichlorobenzidine, 1,1,2,2-tetrachloroethane, methyl methacrylate, limonene, and *o*-toluidine) are scheduled for publication in early 1998.

3.2.3. Preserving Transparency and Acceptance

To gain general international acceptance, the IPCS has always placed great value on the scientific integrity and independence of the experts involved in its work and the transparency of its procedures. Consensus can generally be reached on the overall message of reports such as EHCs or HSGs. Should this prove impossible in individual cases, dissent may be documented in the report at the insistence of one or more experts. To promote transparency, working-group meetings at which evaluations, summaries, or recommendations are drafted are also open to observers not directly involved in the preparation process.

Beginning with an inventory of all existing methods, the IPCS is currently involved in an extensive project to compare the various procedures for evaluating chemicals. The aim of this project is to promote mutual understanding and acceptance.

3.3. OECD Activities

Another key international player in the field of chemical safety is the OECD.^[5] Together, the 29 OECD member states cover some 78 % of global chemical production. Over the past 20 years the OECD has demonstrated great commitment to chemical safety, from the point of view of securing economic growth whilst embracing environmental protection considerations (Table 3). In 1971 the OECD set up a chemicals programme specifically for this purpose, which underwent a major expansion in 1978 (Environmental Health and Safety Programme, EHS). The objectives are to protect humans and the environment from chemicals, to render chemical policy transparent, and to avoid trade barriers. Its activities encompass new chemicals, pesticides, pharmaceutical products, and existing substances. The OECD has emerged as a central coordinator in the preparation of substance reports.

Governments and industry have derived significant benefits from the EHS programme. The mutual recognition of data on

Table 3. Activities of the OECD, Paris, in chemical safety (with 29 states).



Principal focuses of work: international harmonization of measures to identify and prevent risks from chemicals.
– Mutual acceptance of data
• Test methods for chemicals and pesticides
• GLP for pharmaceuticals, chemicals, and pesticides
– Processing of existing chemicals
• Evaluation of substances, with the work to be shared between member states
• Proposed measures for selected substances
– Risk identification and minimization
– Chemical accidents
– Biotechnology
Working groups:
– Chemical test methods
– GLP
– Existing substances
– Risk evaluation
– Plant-protection agents
– Harmonization of classification
Organization of the work:
– Plenum (joint meeting) every nine months
– Combined session with the pesticides group
– Steering committee

new products, the avoidance of work duplications, the exchange of expertise and information, and the harmonization of regulations have led to substantial savings. The OECD estimates that savings to date for industry and the member states, after deducting the expenses for the secretariat and the contributions of the member states, amount to some 100 million DM. Added to this are other benefits, such as the reduction in the number of animal experiments and the advantages for health and the environment.

3.3.1. Screening Information Data Sets (SIDS)

With the intensive collaboration of the member states and industry since 1990, Screening Information Data Sets (SIDS) on existing substances have been drawn up, containing details of substances, risks, and in some cases, exposure.^[6] SIDS target substances produced in volumes of more than 10 000 tonnes in one member state, or more than 1 000 tonnes in at least two member states. The work is coordinated with the activities of the EC and the IPCS. Between 1992 and 1996 some 100 chemicals were considered; a further 200 or so are currently in progress. The SIAR (SIDS Initial Assessment Reports) prepared on the basis of SIDS are not as extensive as EHCs or the EC substance reports currently under preparation. They are intended primarily to indicate whether the existing data on a given substance is in need of supplementation, and whether the substance is worthy of further investigation on the basis of the data available (e.g. within the context of a risk evaluation).

3.3.2. Mutual Acceptance of Data (MAD)

The OECD also plays a key role in the mutual recognition of test data. In collaboration with the member states, industry, and science, it has drawn up guidelines for test methods which

are recognized and applied by all member states. There are currently some 90 test methods in existence, which are continually updated. These test methods are supplemented by the principles of good laboratory practice (GLP), which lays down international standards governing the manner in which experiments are performed on substances (particularly for chemicals, pharmaceuticals, and pesticides). These GLP principles were revised and updated in 1997. Texts and comments on the test methods and GLP are available in book shops.^[7, 8]

3.3.3. Harmonization of Classification and Labeling

Chapter 19 of Agenda 21 also calls for a harmonized international system for the classification and labeling of chemicals by the year 2000. This means specifying a common basis for all chemicals and preparations, including the various forms of use. The systems currently in place make a distinction between dangerous goods and dangerous substances. It is hoped that the new system will be based as far as possible on existing systems, such as those of the USA, the EC, and the United Nations Committee of Experts on the Transport of Dangerous Goods (UNCETDG). There are numerous factors favoring the introduction of a harmonized international system, such as the elimination of trade barriers, reduced costs, avoidance of duplication of tests (which in turn means fewer experiments with animal), and a higher degree of acceptance through transparency.

The harmonization of criteria for the classification of health and environmental risks is being spearheaded by the OECD. In addition, a working group set up by the ILO and UNCETDG is currently reviewing the criteria for the classification of physical-chemical risks, whilst the ILO is reviewing the harmonization of hazard disclosure (labeling/safety data sheets). The organizations have agreed that the criteria for classification and labeling should be completed during the course of 1998.

3.4. Improved Coordination of Cooperation

Programme area A of Chapter 19 of Agenda 21 includes the obligation to evaluate chemicals on an international basis. At the first IFCS meeting, delegates formulated the ambitious target of conducting international evaluations of some 200 substances by 1997, and a further 300 substances by the turn of the millennium. In view of the limited financial and staff resources available, it is all the more important to coordinate on-going work as effectively as possible, particularly if duplication is to be avoided. Consequently, the OECD and IPCS are endeavoring to harmonize their sub-

stance evaluation involvement even more closely. The formation of a joint IPCS/OECD steering group could aid progress. Possible members of such a group would include the secretariats of the IPCS and OECD as well as representatives of involved member states and international organizations. Such a steering group could define the framework within which evaluation of a substance or group of substances is to take place (e.g. EHC, CICAD, SIAR). Consequently, EC studies on existing substances are likewise included, since the EC submits drafts of the EC reports on existing substances to the OECD, and these are discussed at the SIDS Initial Assessment Meetings (SIAM) before being subjected to final discussion amongst EC experts. Figure 4 summarizes the activities involved in the preparation of substance reports.

4. Outlook

The implementation of Chapter 19 of Agenda 21 has made good progress compared with other topics in the Agenda, and tangible achievements have already been made. Nevertheless, international negotiations are by their very nature highly complex and generally hard-going. Linking official tasks, scientific findings, and economic concerns at the international level makes it even more difficult to achieve concrete improvements in chemical safety.

In the future, continuing the work on substance reports will remain an essential task at the national and international level, since the vast diversity of existing substances means that a knowledge of their potential risks is very limited or only accessible to certain groups. Without a doubt, future international cooperation in the field of chemical safety will continue to focus on the central themes of POPs and the development of national structures for chemical safety (capacity building) in developing countries and countries in the throes of economic transformation.

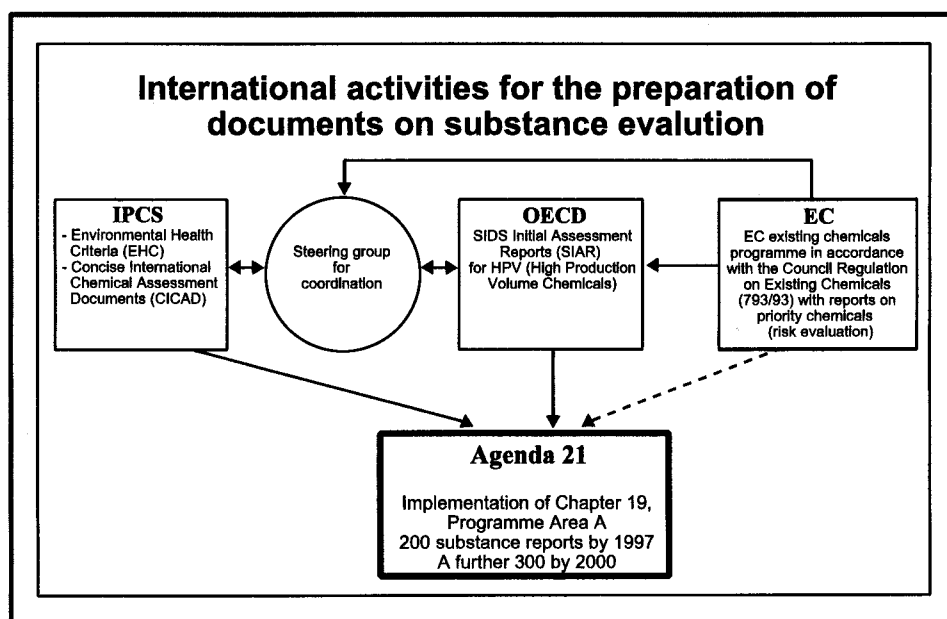


Figure 4. International preparation of substance reports.

With financial and staff resources becoming increasingly limited, in the future it will become all the more important to prioritize. Only those problems requiring an *international* solution, or which can only be solved *internationally*, should be addressed.

In addition to all these activities, we also need to consider whether developments in the chemical sector are consistent with the principle of sustainable development. Without a doubt, risk evaluations and substance regulations are only part of such a development, since they do not take effect until a product becomes tradable and not at the design stage. A farther reaching approach to sustainability lies in excluding the potential hazard features and associated risks at the development stage of a chemical compound. In addition, we also need to consider whether it is actually expedient for risk reduction to focus on individual substances, or whether we need to find ways of reducing the volume of chemicals used. Added to this are the aspects of resource conservation and energy saving, which have been neglected to date.

Appendix: List of Abbreviations

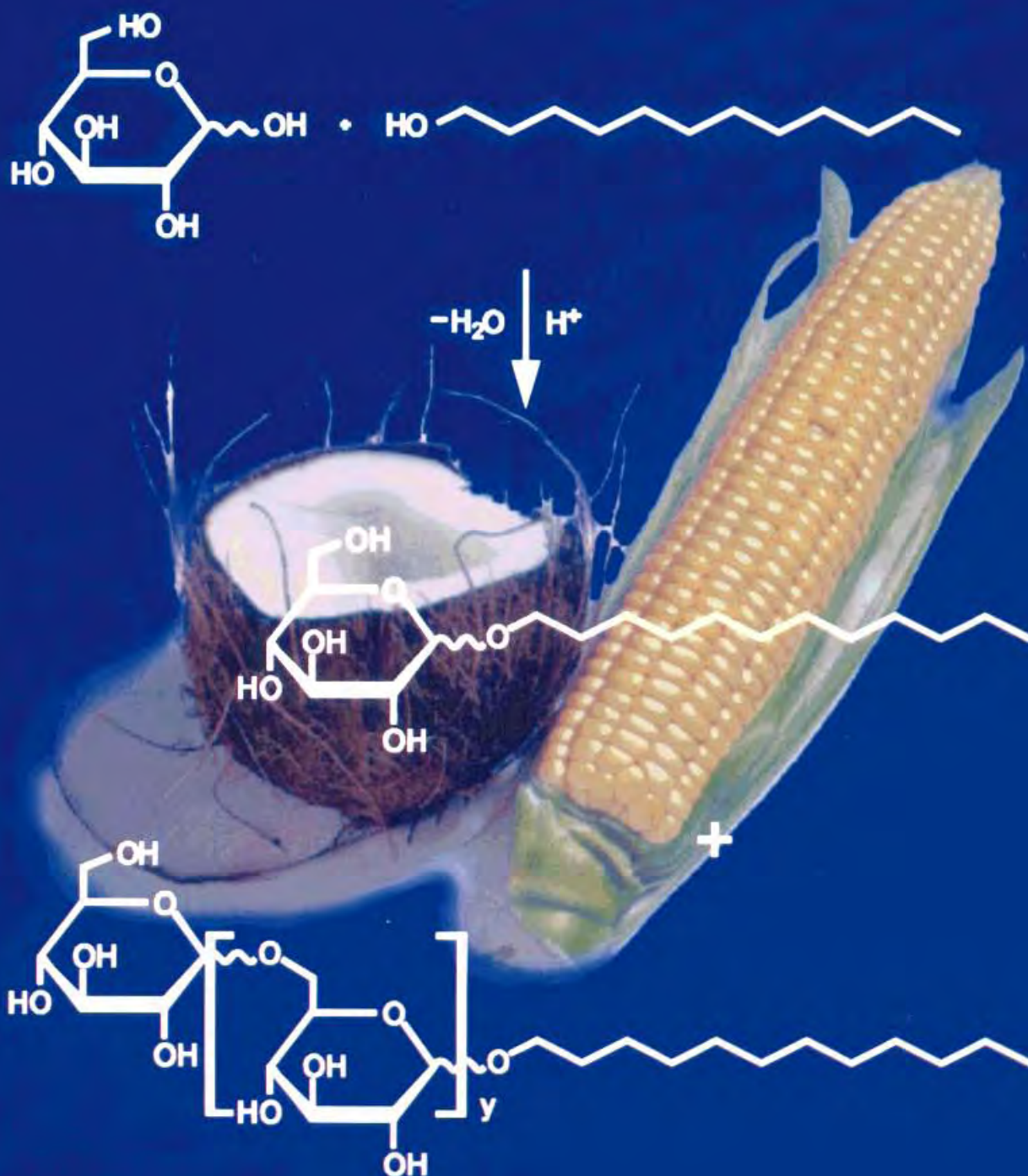
BAuA	Federal Institute for Occupational Safety and Health
BG Chemie	Employment Accident Insurance Fund of the Chemical Industry
BgVV	Federal Institute for Health Protection of Consumers and Veterinary Medicine
BMU	Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety
BUA	Advisory Committee on Existing Substances
CFC	Chlorofluorocarbon
ChemG	Chemicals Act
CICAD	Concise International Chemical Assessment Document
CSD	Commission on Sustainable Development
DG	Directorate General of the EC Commission
EC	European Community
ECB	European Chemicals Bureau
ECE	Economic Commission for Europe
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EHC	Environmental Health Criteria
FAO	Food and Agriculture Organization of the United Nations
FSC	Forum Standing Committee of the IFCS
GDCh	German Chemical Society
GefStoffV	Dangerous Substances Ordinance
GLP	Good Laboratory Practice
GTZ	Deutsche Gesellschaft für Technische Zusammenarbeit
H-CFC	Partially halogenated chlorofluorocarbon
HSG	Health and Safety Guide
ICCA	International Council of Chemical Association
ICEM	International Federation of Chemical, Energy, Mine and General Workers Union
ICSC	International Chemical Safety Cards
IFCS	Intergovernmental Forum on Chemical Safety

IGO	Intergovernmental Organization
ILO	International Labour Organization
INC	Intergovernmental Negotiating Committee
IOCC	Interorganization Coordinating Committee
IOMC	Interorganization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
ISG	Intersessional Group of the IFCS
IUPAC	International Union for Pure and Applied Chemistry
IUTOX	International Union of Toxicology
JRC	Joint Research Center
LRTAP	Long-Range Transboundary Air Pollution
MAD	Mutual Acceptance of Data
NGO	Nongovernmental Organization
NOAEL	No Observed Adverse Effect Level
OECD	Organization for Economic Cooperation and Development
PAC	Programme Advisory Committee of the IPCS
PEC	Predicted Environmental Concentration
PIC	Prior Informed Consent Procedure
PIM	Poisons Information Monograph
PNEC	Predicted No-Effect Concentration
POP	Persistent Organic Pollutant
SIAM	SIDS Initial Assessment Meeting
SIAR	SIDS Initial Assessment Report
SIDS	Screening Information Data Set
UBA	Federal Environmental Agency
UNCED	United Nations Conference on Environment and Development
UNCETDG	United Nations Committee of Experts on the Transport of Dangerous Goods
UNEP	United Nations Environment Programme
UNGASS	United Nations General Assembly Special Session, June 1997, New York
UNIDO	United Nations Industrial Development Organization
UNITAR	United Nations Institute for Training Research
WHA	World Health Assembly
WHO	World Health Organization
WWF	World Wildlife Fund

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Coconut oil and corn starch are the raw materials in the technical synthesis of alkyl polyglycosides.

Alkyl Polyglycosides—Properties and Applications of a new Class of Surfactants

Wolfgang von Rybinski* and Karlheinz Hill*

The development of surfactants based on carbohydrates and vegetable oils is the result of a product concept based on the exclusive use of renewable resources. While oils and fats have been known for a long time as suitable raw materials for the production of surfactants such as soap, alkyl sulfate, and alkyl ether sulfate, their derivatization with a carbohydrate molecule as the hydrophilic moiety has just recently become possible on a large industrial scale. The resulting sugar-surfactants sucrose esters, sorbitane esters, *N*-methyl glucamides, and alkyl polyglycosides are based on carbohydrate raw materials, which are available on the world market in large quantities and at competitive prices: sucrose, glucose, and sorbitol.^[1] The selective functionalization of sucrose or sorbitol to con-

struct an ideal amphiphilic structure cannot be achieved by simple chemical processes due to the polyfunctionality of the molecules and the relatively small differences in the reactivity of the hydroxyl groups. As a result the products on the market are predominantly composed of a mixture of mono-, di-, and triesters and are used in special applications only, for example as emulsifiers in foods and cosmetics and, in case of the sorbitan esters, in technical fields like explosives and emulsion polymerization. Glucose is the carbohydrate raw material of choice for selective derivatization. The reaction with alcohols leads to alkyl glucosides. *N*-methyl glucamides are formed by reductive amination and subsequent acylation. Both products have proved to be high-

performance surfactants for detergents, and one company at present exclusively uses *N*-methyl glucamides. Alkyl glucosides have a broader application spectrum and are used as well in cosmetic products, as surfactants for industrial cleaners, and in agricultural applications. Based on the annual production figures they can be considered as the most important sugar-surfactant today. The following survey on alkyl glucosides covers various aspects on synthesis, industrial production, physico-chemical properties, ecotoxicological evaluation, and selected fields of application.

Keywords: glucosides • interfaces • surface chemistry • surfactants

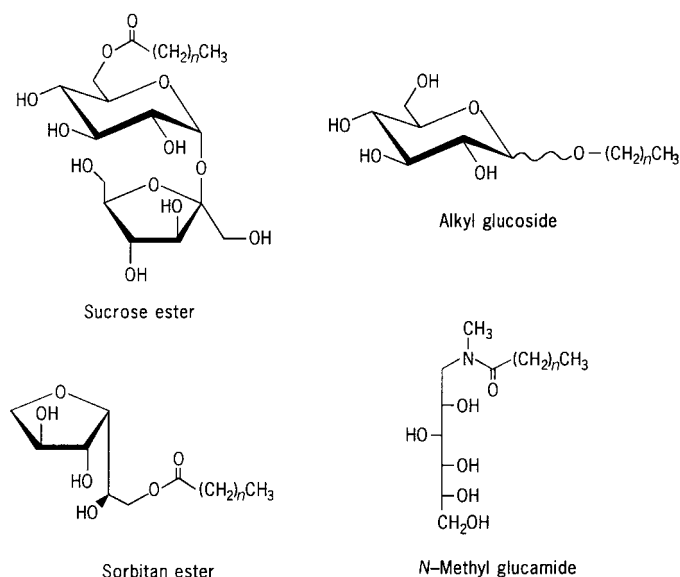
1. Developments in Industry

Alkyl glucosides—or alkyl polyglycosides as the industrially manufactured products are widely known—are a classic example of products which, for a long time, were of academic interest only. The first alkyl glucoside was synthesized and identified by Emil Fischer more than 100 years ago. The first patent application describing the use of alkyl glucosides in detergents was filed in Germany some 40 years later.^[2] Another 40 to 50 years went by before research groups in various companies redirected their attention to alkyl glucosides and developed technical processes for the production of alkyl polyglycosides (Scheme 1).

In the course of this development, Fischer's early work, which involved the reaction of glucose with hydrophilic alcohols such as methanol, ethanol, glycerol, etc., was applied to hydrophobic alcohols with alkyl chains from C₈ to C₁₆, the typical fatty alcohols. Not pure alkyl monoglucosides but a complex mixture of alkyl mono-, di-, tri-, and oligoglycosides are produced in the industrial processes. Because of this, the industrial products are called alkyl polyglycosides. The products are characterized by the length of the alkyl chain and the average number of glucose units linked to it, the degree of polymerization (DP).

Rohm & Haas (Philadelphia, USA) was the first to market an octyl/decyl (C_{8/10}) polyglycoside in commercial quantities in the late 1970s, followed by BASF (Ludwigshafen, Germany), and later SEPPIC (Paris, France). However, owing to the unsatisfactory performance of this short-chain version as a surfactant and its poor color quality, applications were limited to few market segments, for example industrial bottle cleaning. The product quality of such short-chain alkyl polyglyco-

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Scheme 1. Commercially produced carbohydrate-based surfactants.

sides has been improved in the last few years, and new types of octyl/decyl polyglycoside are currently being offered by various companies, among them, Akzo Nobel (Stenungsund, Sweden), BASF, Henkel (Düsseldorf, Germany), ICI (Middlesbrough, U.K.), SEPPIC, and Union Carbide (Danbury, USA).

At the beginning of the 1980s, several companies started programs to develop alkyl polyglycosides in the longer dodecyl/tetradecyl alkyl chain range ($C_{12/14}$ -alkyl polyglycoside) for application in the cosmetics and detergent industries. According to the number of patent applications,^[3] the

following companies made the major efforts: Procter & Gamble (Cincinnati, USA), Henkel, Horizon (a division of A. E. Staley Manufacturing Company in Decatur, USA, which was acquired by Henkel later), Hüls (Marl, Germany), Kao (Tokyo, Japan), and SEPPIC. In 1988/1989 Henkel built a pilot plant to manufacture alkyl polyglycosides (APG surfactants) in Crosby, USA, with a capacity of 5000 t per year. Between 1990 and 1992 other companies announced their intention to build up industrial plants for the manufacturing of alkyl polyglycosides, among them Hüls, ICI, Kao, and SEPPIC. The final breakthrough in the commercial exploitation of alkyl polyglycosides was reached in 1992 with the inauguration of a production plant for APG surfactants with an annual capacity of about 25 000 t by Henkel in Cincinnati, USA and in 1995 with the opening of a second plant of equal capacity by Henkel in Düsseldorf, Germany.^[2d]

2. Synthesis of Alkyl Polyglycosides

2.1. Glycosylation Reactions

In the synthesis of glycosides, a polyfunctional sugar component is combined with a nucleophile such as an alcohol, a carbohydrate, or a protein. The broad synthesis potential of this reaction, which is very common in nature, has recently been reviewed in articles by R. R. Schmidt and P. Sinaÿ, as well as K. Toshima and K. Tatsuta.^[4]

Selective glycosylation reactions require special activation methods, the use of protective groups, or selective catalysis by enzymes. A selection of the many routes to glycosides is shown in Scheme 2 in a generalized way; the effect of

Wolfgang von Rybinski (1951) studied chemistry at the University of Bochum (Germany) and received his Ph.D. in physical chemistry in 1980. In the same year he joined the Physical Chemical Research at Henkel. After working for some time in the surfactant production site at Düsseldorf and in the product development groups of Surface Technologies in Düsseldorf and Detroit, he returned to corporate research and was appointed Head of Research Physical Chemistry in 1989. The focus of his work is Interface and Colloid Chemistry, especially surfactant properties, dispersions, and emulsions. He teaches Colloid and Interface Chemistry at the University of Düsseldorf and is cochairman of the German Colloid Society.



W. von Rybinski

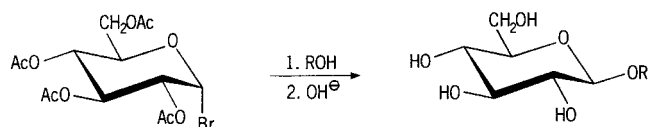


K. Hill

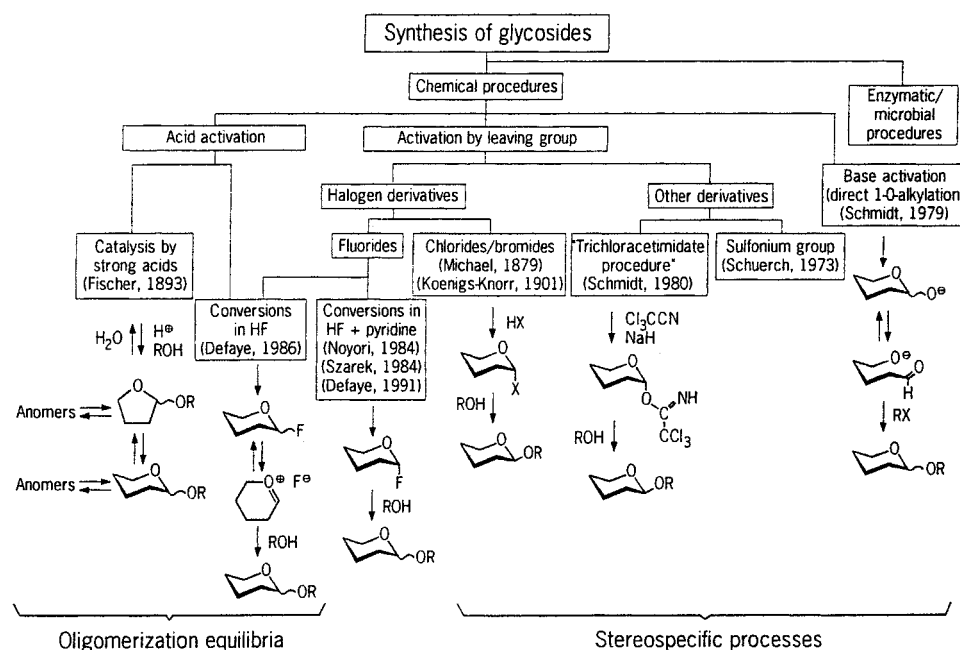
Karlheinz Hill, born 1955 in Bayreuth (Germany), studied Chemistry at the University of Würzburg. After receiving his Ph.D. under the supervision of W. Adam in 1984 he spent one and a half years as a post-doctoral fellow in the Structural Chemistry group of M. Lahav at the Weizmann Institute in Rehovot (Israel). In 1986 he joined Henkel KGaA in Düsseldorf and worked three years in the organic chemistry research group in the field of alkyl polyglycosides. The next two years he spent at the Henkel Research Corporation in Santa Rosa, California, working on carbohydrate derivatives. After returning to Düsseldorf he was involved in various projects in the chemical research division, focusing on organic chemistry, oleochemistry, and surfactants. In 1995 he was appointed head of Research Oleochemistry, and since 1998 he is head of Research Chemical Products at Henkel. He is a member of the German Society for Fat Research (DGF), where he is responsible for the Oleochemistry division.

neighboring groups on the stereo-selectivity of the reaction is not considered.^[4, 5] In principle, enzymatic or microbial procedures, by virtue of their selectivity, can replace complicated chemical protection and deprotection steps where regioselective formation of glycosides is required. Nevertheless, the use of enzymes in glycoside synthesis has not yet been widely enough investigated, and applications are presently limited to the laboratory.^[6] Owing to problems of availability of suitable enzyme systems and the high manufacturing costs anticipated, enzymatic syntheses of alkyl glycosides are not yet ready for upgrading to the industrial level, and chemical procedures are preferred. In general, chemical glycosylations may be divided into two processes: those leading to complex oligomer equilibria in acid-catalyzed glycosyl exchange reactions (Fischer glycosylation^[2a] and reactions in hydrogen fluoride (HF)^[7, 8] with unprotected carbohydrate molecules) and kinetically controlled, irreversible, mostly stereoselective substitution reactions on suitably activated carbohydrate substrates.^[9–13] Procedures of the second type may result in the formation of exclusive products rather than of complex reaction mixtures, especially when combined with protective group techniques. Carbohydrates may be activated at the anomeric carbon by leaving groups (for example, halides,^[7–10] the sulfonium group,^[11] or the trichloroacetimidate group^[12]) or by base activation.^[13]

The history of synthetic routes that eventually led to glycosides began in 1870, when M. A. Colley^[14] reported the synthesis of “acetochlorohydrose” by reaction of dextrose (glucose) with acetyl chloride. Tetra-*O*-acetyl-glucopyranosyl halides (acetohaloglucoses) were later found to be useful intermediates for the stereoselective synthesis of pure alkyl glucoside anomers. In 1879 Arthur Michael^[9] succeeded in preparing well-defined, readily crystallizable aryl glucosides starting from Colley's intermediate and phenolates. The crucial application of Michael's synthesis to a broad range of carbohydrates and hydroxylic aglycons occurred in 1901, when W. Koenigs and E. Knorr introduced an improved stereoselective glycosylation process (Scheme 3).^[10] The reaction, which takes place in the presence of silver or mercury promoters, involves an S_N2 substitution at the anomeric carbon and proceeds stereoselectively with inversion of



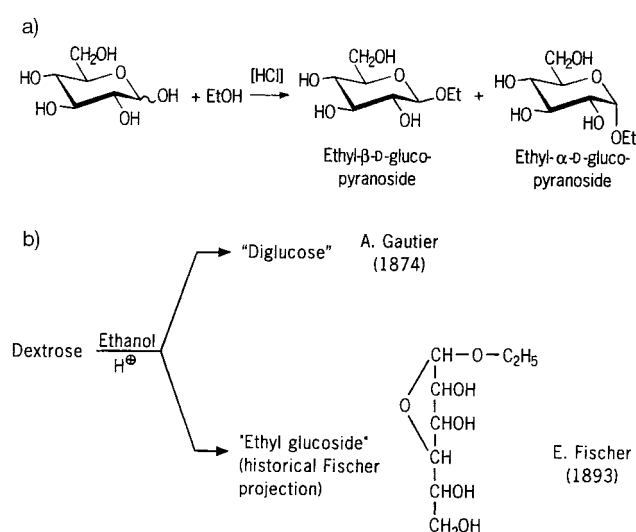
Scheme 3. Stereoselective synthesis of glycosides according to Koenigs-Knorr. R = alkyl.



Scheme 2. Overview of glycosylation reactions.

configuration, producing, for example, the β -glucoside from the α anomer of the acetobromoglucose intermediate.

A fundamentally different approach to the synthesis of alkyl glucosides was chosen by Emil Fischer in 1893, when he discovered the acid-catalyzed reaction of glycoses with alcohols (Scheme 4a). This process is now well known as the “Fischer glycosylation”. Any historical account should nevertheless also include A. Gautier's first reported attempt, in 1874, to convert dextrose with anhydrous ethanol in the presence of hydrochloric acid. Due to a misleading elemental analysis, Gautier believed he had obtained a “diglucose”.^[15] Fischer later demonstrated that Gautier's “diglucose” was in fact mainly ethyl glucoside. The structure of ethyl glucoside was defined correctly by Fischer—as the furanosidic “Fischer projection” (Scheme 4b).^[2a] In fact, the Fischer glycosylation



Scheme 4. Synthesis of ethyl glucoside according to Fischer (a) and their historic formulations by Gautier and Fischer (b).

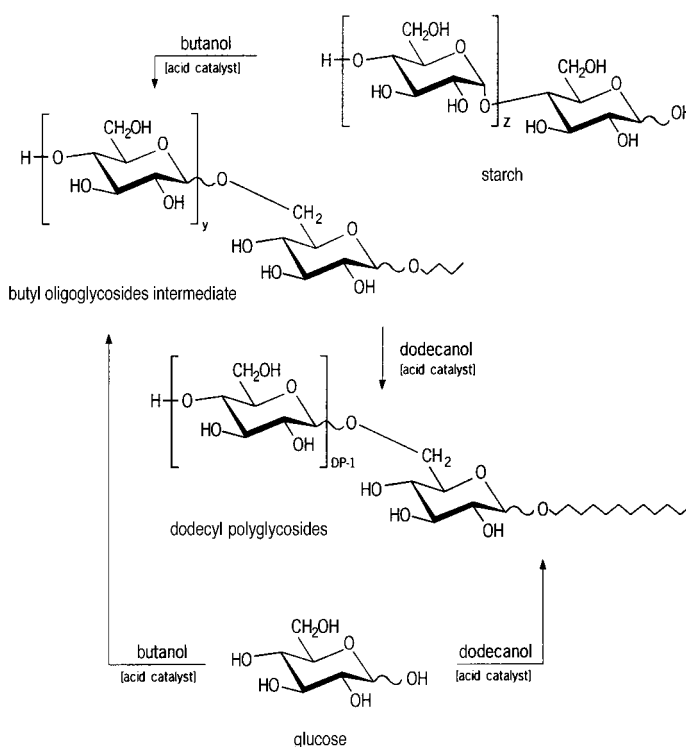
is an equilibrium reaction that on passing through kinetically favored furanoside stages leads to complex product mixtures dominated by pyranosides. The polyfunctionality of the carbohydrates cause the formation of randomly linked glycoside oligomers (isomaltosides, maltosides, maltotriosides, etc.) besides α - and β -anomers of pyranosides and furanosides ($\alpha:\beta \approx 2:1$ in product mixtures from technical processes).^[16] Accordingly, individual molecular species are not easy to isolate from Fischer reaction mixtures. After some improvement of this synthesis method, Fischer subsequently adopted the Koenigs–Knorr synthesis for his investigations.^[17] Using this process, E. Fischer and B. Helferich were the first to report the synthesis of a long-chain alkyl glucoside exhibiting surfactant properties in 1911.^[17c] Other research groups have applied modifications of this method in the recent past to investigate the product properties of these sugar-surfactants further.^[10b, 18]

2.2. Technology for the Manufacture of Long-Chain Alkyl Polyglycosides

Any production process suitable for use on an industrial scale must satisfy several criteria. The ability to produce products with suitable performance properties under economically viable technical conditions is the most important. Some other aspects are the minimizing of side reactions, waste, and emissions. The technology should be flexible enough to allow properties and qualities to be adapted to dynamic market requirements. As far as the industrial production of alkyl polyglycosides is concerned, processes based on the Fischer synthesis have been successfully adopted. Development work over the past decade has enabled the efficiency of this synthesis route to be increased to a level where it has finally become attractive for industrial application, especially with regard to product quality and process economy. Modern production plants built on the basis of the Fischer synthesis are the embodiment of low-waste, virtually emission-free technologies. Another advantage of the Fischer synthesis is that the ratio of alkyl monoglycosides to alkyl oligoglycosides can be precisely controlled over a wide range by adjusting the amounts of glucose and fatty alcohol in the reaction mixture. Relevant performance properties, for example hydrophilicity, can thus be adapted to meet requirements of specific applications without further purification of the final product mixture or isolation of one component.^[5]

In a technical process either a polymeric form of glucose such as starch or glucose syrup with low dextrose equivalent (DE), or monomeric glucose (anhydrous or as the monohydrate) can be used. Fatty alcohols can be obtained either from petrochemical sources (synthetic fatty alcohols) or from natural, renewable resources such as fats and oils, after splitting of the triglycerides with methanol and subsequent hydrogenation of the corresponding fatty acid methyl esters (natural fatty alcohols). Due to its fatty acid composition coconut and palm-kernel oil are the preferred raw materials for the production of dodecanol/tetradecanol blends. The typical ratio formed is 70:30 (hexadecanol < 5%).^[5, 19]

Depending on the type of carbohydrate used, all manufacturing processes for the Fischer synthesis of alkyl polyglycosides can be attributed to two process variants, namely direct synthesis^[20] and the transacetalization process (Scheme 5).^[21] In either case, the reaction can be carried out in batches or



Scheme 5. Reaction pathways for the industrial production of dodecyl polyglycoside.

continuously.^[20c, 22] The two-stage transacetalization process is applied if oligo- and polyglycoses are used and involves more equipment than the direct synthesis. In the first stage the carbohydrate reacts with a short-chain alcohol (for example, *n*-butanol or propylene glycol); polymeric carbohydrates require depolymerization. In the second stage the short-chain alkyl glycoside is transacetalized with a long-chain alcohol ($C_{12/14}OH$) to form the final alkyl polyglycoside. The necessary depolymerization of the polymeric glucose starting materials requires temperatures of $> 140^\circ C$. Depending on the alcohol used, this can create correspondingly higher pressures, which impose more stringent demands on equipment and can lead to higher plant cost. If the molar ratios of carbohydrate to alcohol are identical, the oligomer distribution obtained in the transacetalization process is basically the same as in the direct synthesis.

In the following, the one stage process (direct synthesis) for the manufacturing of dodecyl/tetradecyl polyglycoside is discussed in detail.^[20] In this case glucose is suspended in excess fatty alcohol (2–6 mol), and the reaction is carried out at a temperature of $100\text{--}120^\circ C$ in the presence of an acidic catalyst, typically a sulfonic acid. After removal of water as by-product (1 equiv relative to glucose) under vacuum, the product mixture comprises alkyl mono-, alkyl oligo-, and alkyl polyglycosides. The (average) degree of polymerization (DP)

for such an alkyl polyglycoside is largely dependent on the ratio of glucose to alcohol in the reaction mixture and can be calculated from the mole percent p of the respective oligomeric species n in the glycoside mixture. The composition of a typical product is shown in Figure 1. Several

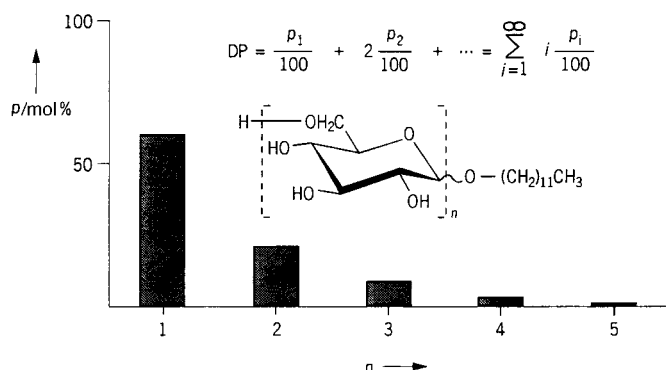


Figure 1. Typical distribution of oligomers in dodecyl polyglycoside (DP = 1.3).

analytical methods have been developed recently to identify and characterize the individual species in the alkyl polyglycoside.^[23] The chromatogram of a high-temperature GC analysis of dodecyl/tetradecyl polyglycoside is shown as an example (Figure 2).

Under the conditions of the acid-catalyzed syntheses of alkyl polyglycoside, secondary products such as glucose polymers,^[24] ethers, and colored impurities, are formed. Glucose polymers are substances of undefined structure formed in the course of the synthesis through the polymerization of glycopyranoses. The type and concentration of the substances formed by secondary reactions are dependent on process parameters such as temperature, pressure, reaction time, and catalyst, which have to be adjusted and controlled exactly.^[19]

The Fischer glycosylation may be described as a process in which, in a first step, the dextrose reacts relatively quickly, and an oligomer equilibrium is reached. This step is followed by slow degradation of the alkyl polyglycoside. In the course of

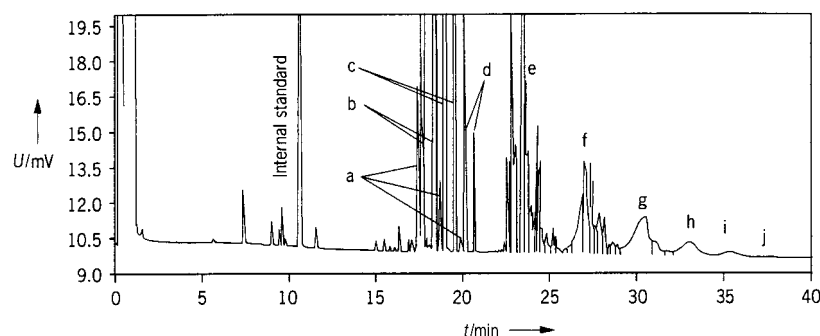


Figure 2. Chromatogram of the high-temperature GC analysis of dodecyl/tetradecyl polyglycoside. a) $C_{12/14/16}$ furanosides, b) C_{12} monoglycosides, c) C_{14} monoglycosides, d) C_{16} monoglycosides, e) diglycosides, f) triglycosides, g) tetraglycosides, h) pentaglycosides, i) hexaglycosides, j) heptaglycosides (detection: FID, 420°C ; hydrogen 30 mL min^{-1} , air 300 mL min^{-1} . Duran glass capillary column, $10\text{ m} \times 0.53\text{ mm ID}$, SIMDIS; injection: on column, $1\text{ }\mu\text{L}$; carrier gas: hydrogen 20 mL min^{-1} ; temperature program: 70°C [4 min], heating rate $10^{\circ}\text{C min}^{-1}$ to 400°C [12 min]).

the degradation, which consists of dealkylation and polymerization steps, the thermodynamically more stable glucose polymer is formed irreversibly in increasing concentrations. Reaction mixtures that have exceeded an optimal reaction time may be described as overreacted. If the reaction is terminated too early, the resulting reaction mixture contains a significant amount of residual glucose (Figure 3). As catalysts,

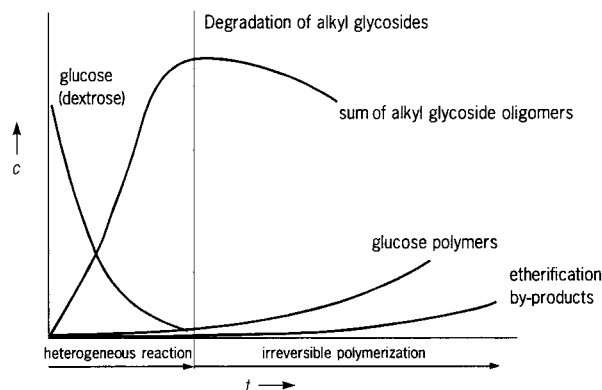
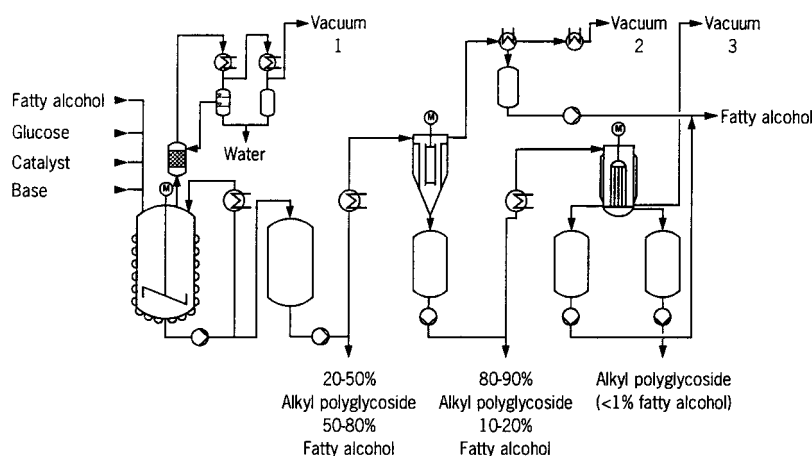


Figure 3. Course of reaction of the technical glycosylation process (dodecyl polyglycoside).

any acids with sufficient strength are suitable for this purpose such as sulfuric acid, *p*-toluenesulfonic acid, alkylbenzenesulfonic acid, and sulfosuccinic acid.^[25] The reaction rate is dependent on the acidity and the concentration of the acid in the alcohol.^[26] Secondary reactions that are also catalyzed by acids such as the formation of glucose polymers mainly take place in the polar phase (traces of water) of the heterogeneous reaction mixture and can be reduced by using hydrophobic acids such as alkylbenzene sulfonic acids, which, through the length of their alkyl chain, mainly dissolve in the less polar phase of the reaction mixtures.

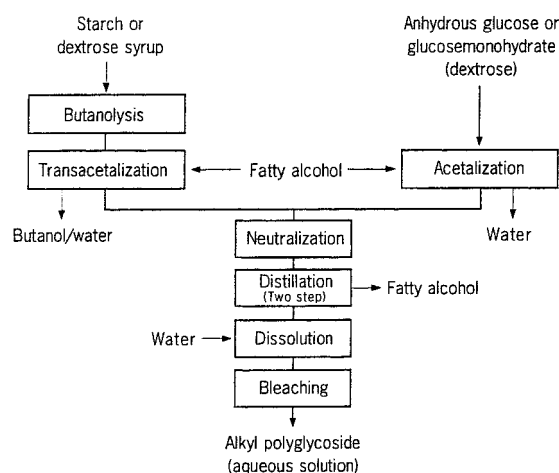
After the reaction the acidic catalyst is neutralized by a suitable base, for example sodium hydroxide or magnesium oxide. The neutralized reaction mixture is a yellowish solution containing less than 1 % of residual glucose and 50 to 80 % fatty alcohol, depending on the fatty alcohol excess used. The fatty alcohol is removed by continuous vacuum distillation to 1 % or below. To minimize the formation of unwanted pyrolysis products or discoloring components during distillation, thermal stressing and residence time of the target product are kept as low as possible. No monoglycoside should enter the distillate, because the distillate is recycled in the reaction as pure fatty alcohol. In case of dodecyl/tetradecyl polyglycoside these requirements are largely satisfied by multistage distillation. It is important to note that there is a distinct increase in viscosity with decreasing fatty alcohol content. This significantly impairs heat and mass transport in the last distillation stage. Accordingly, thin-layer or short-path evaporators are preferred.^[20a, 27] In these evaporators, the mechanically moved film provides for high specific evaporation efficiency and a short product residence time,

and at the same time a good vacuum. The end product after distillation is an almost pure alkyl polyglycoside, which accumulates as a solid with a melting range of 70 to 150°C. Scheme 6 summarizes the main process steps for the synthesis of alkyl polyglycosides.



Scheme 6. Industrial-scale glycosylation process for the direct reaction of glucose with fatty alcohol (dodecanol/tetradecanol).

After removal of the fatty alcohol, the alkyl polyglycoside active substance is directly dissolved in water to form a highly viscous 50 to 70 % alkyl polyglycoside paste. In subsequent refining steps this paste is worked up into a product of satisfactory quality in accordance with performance-related requirements. These refining steps may comprise bleaching of the product, the adjustment of product characteristics such as pH value and active substance content, and microbial stabilization.^[20a] The patent literature includes many examples of reductive^[28a] and oxidative bleaching^[28b-f] and of two-stage processes of oxidative bleaching and reductive stabilization.^[29] For example, treatment with hydrogen peroxide under alkaline conditions leads to a colorless product, which is stable during long storage—an important requirement for high-quality applications in consumer-friendly market products. Scheme 7 summarizes the individual steps of the industrial production of dodecyl/tetradecyl polyglycoside.



Scheme 7. Flow diagram for the production of alkyl polyglycosides based on different carbohydrate sources.

3. Physicochemical Properties of Alkyl Polyglycosides

The favorable performance properties of surfactants, in particular interfacial properties and behavior in solutions (for example, phase behavior), are essentially attributable to specific physicochemical effects.^[30] Alkyl polyglycosides were found to possess remarkable properties which, in some cases, differ clearly from those of other nonionic surfactants. The results obtained so far are summarized in the following sections. Significant differences in relation to the behavior of fatty alcohol ethoxylates in particular are highlighted.

3.1. Interfacial Properties

The surface tension of alkyl (poly)glycosides was investigated as a function of the alkyl chain and the degree of polymerization (DP) on samples differing in purity. Shinoda et al.^[31] and Böcker et al.^[18c] determined the critical micelle concentration (cmc) and the surface tension values at the cmc from surface tension/concentration curves. A few selected values are set out in Table 1. Figure 4 shows the surface

Table 1. Critical micelle concentrations c_M from surface tension measurements.

Substance	T [°C]	c_M [mol L ⁻¹]	Ref.
β -D-C ₈ G ₁	25	2.5×10^{-2}	[31]
C ₈ G ₁	25	1.8×10^{-2}	[32]
β -D-C ₁₀ G ₁	25	2.2×10^{-3}	[31]
β -D-C ₁₂ G ₁	25	1.9×10^{-4}	[31]
C ₁₂ G ₁	25	1.7×10^{-4}	[32]

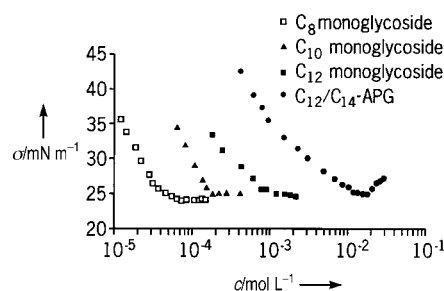


Figure 4. Static surface tension σ of alkyl glycosides with different alkyl chain lengths as a function of the concentration c in distilled water at 60°C.

tension as a function of concentration for three alkyl monoglycosides (C_nG₁, G = number of glycoside units) and a technical C_{12/14} APG at 60°C.^[32] The cmc values of the pure alkyl monoglycosides and the technical alkyl polyglycosides are comparable with those of typical nonionic surfactants and decrease distinctly with increasing alkyl chain length. The alkyl chain length has a far stronger influence on the cmc than the number of glycoside groups of the APG.

A mixture of APG and fatty alcohol sulfate (FAS) was used as example to investigate the surface tension behavior of surfactant mixtures of APG and anionic surfactants.^[32] The values of the mixtures are near the curve for APG even despite a high anionic surfactant content. This corresponds to the normally observed behavior of mixtures of anionic and nonionic surfactants differing considerably in their cmc values.^[33] A weak attractive interaction between these surfactants can be derived on the basis of Rosen's theory.^[34] Similar results are reported for mixtures of alkyl polyglycosides and alkyl benzenesulfonates.^[35]

Figure 5 shows the dynamic surface tension as a function of time for the same surfactant solutions at a concentration of 8×10^{-4} moles L^{-1} at $40^\circ C$.^[36] The curve of the pure FAS falls

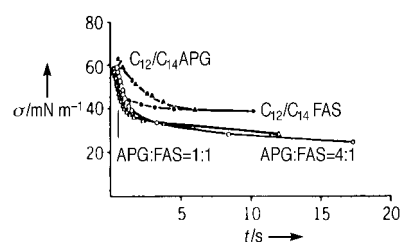


Figure 5. Static surface tension σ of $C_{12/14}$ APG and $C_{12/14}$ FAS and 1:1 and 4:1 mixtures thereof as a function of the time at $40^\circ C$ and a concentration of 8×10^{-4} mol L^{-1} .

more quickly for short times than that of pure APG: the FAS thus diffuses more quickly to the surface of the liquid than the APG with the same alkyl chain length. The mixtures of both surfactants reach lower surface tensions than the pure surfactants. It should be noted that surfactants of technical purity were compared with one another in these investigations. This factor can be important in the interpretation of the results of dynamic surface tension measurements, because the individual components of the technical surfactants can have a different affinity for the surface.^[37]

The interfacial tension between various APGs and three oils (decane, isopropyl myristate, and 2-octyl dodecanol) differing in structure and polarity was investigated by Kutschmann et al.^[38] The influence of oil polarity is clearly illustrated in Figure 6. The interfacial tension between aqueous solutions of alkyl monoglycosides and the three oils is plotted against the logarithm of the surfactant concentra-

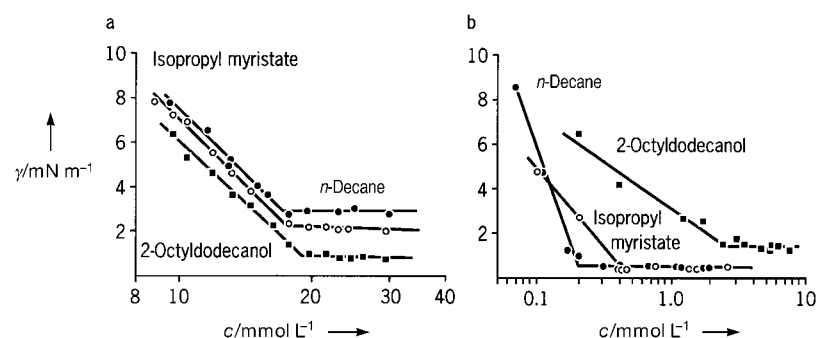


Figure 6. Influence of alkyl glycosides C_8G_1 (a) and $C_{12}G_1$ (b) on oil/water interfacial tension γ for three different oils as a function of the initial concentration c of the surfactant in the water phase.

tion. For each oil there is a pronounced break and a constant plateau value, which decreases in the order decane > isopropyl myristate > octyl dodecanol. For C_8G_1 the break occurs at approximately the same concentration of the surfactant in the water phase for all three oils. The corresponding curves for $C_{12}G_1$ are shown in Figure 13b. For isopropyl myristate and octyl dodecanol, the break of the isotherm distinctly shifts towards higher concentrations of the surfactant. Also, the position of the plateau value lies at far higher values for octyl dodecanol than for the other two oils: the cmc apparently shifts towards higher values with increasing oil polarity. This effect is more pronounced, the longer the alkyl chain length of the glucoside. One possible explanation for this is the increase in the solubility of the surfactant in the oil phase with increasing alkyl chain length and, hence, hydrophobicity or increasing polarity of the oil.

Figure 7 shows the plateau values γ_c of the interfacial tension between C_nG_1 homologues as well as various technical APGs and the three oils as a function of the chain length of

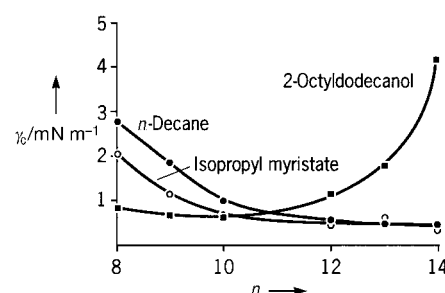


Figure 7. Plateau values of the interfacial tension γ_c in three different oil/water systems as a function of the alkyl chain length of the surfactant n at $60^\circ C$.

the surfactant. For decane/water and IPM/water mixtures, γ_c decreases with increasing alkyl chain length and, hence, increasing hydrophobicity of the surfactant. By contrast, the curve of the octyl dodecanol/water system has a pronounced minimum in the case of $C_{10}G_1$ and increases steeply with increasing alkyl chain length. Since $C_{12}G_1$ is highly oil-soluble in the octyl dodecanol/water system, optimum affinity for the oil phase in this system is actually achieved in the case of $C_{10}G_1$.

Similarly to the liquid/gas and liquid/liquid interfaces, surfactants also influence the interface of liquid systems with solid substrates by virtue of their amphiphilic structure. This affects, for example, dispersions of solids in liquids,^[39] washing and cleaning processes,^[40] and the processing of ores.^[41] The systematic dependence of adsorption on the structure of nonionic surfactants has been summarized.^[42] Nickel et al.^[43] report on the adsorption of alkyl glycosides onto various types of solids and demonstrate a connection with the dispersion of solids.

Figure 8 shows the adsorption behavior of $C_{10}G_1$ for graphitized carbon black at $22^\circ C$.

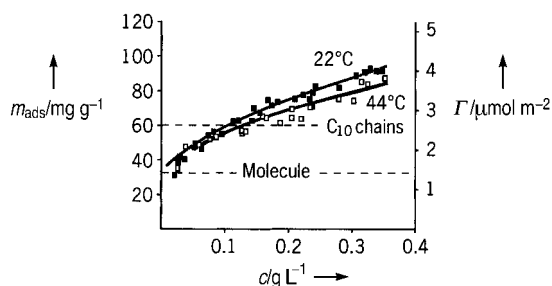


Figure 8. Adsorbed amount m_{ads} and surface concentration Γ of C_{10}G_1 on graphitized carbon black as a function of the surfactant concentration c in water at 22°C and 44°C.

The adsorption isotherms are characterized by a very steep initial slope. This behavior is indicative of a high affinity of the alkyl glycosides for this solid surface. In addition to the adsorption curve, the theoretical values for monolayers on horizontal and vertical arrangements are indicated. The adsorption volume corresponding to a monomolecular layer with a vertical arrangement of the alkyl chain is exceeded at a concentration of around 0.15 g L^{-1} . The dependence of adsorption on temperature is very weak. The 22°C curve is slightly above the 45°C curve.

Comparison with the adsorption behavior of C_{10}E_4 (E = number of oxyethylene glycol groups) on graphitized carbon black at three temperatures (Figure 9) shows clear differences between the surfactant types. A marked dependence on temperature in the upper concentration range can be seen for

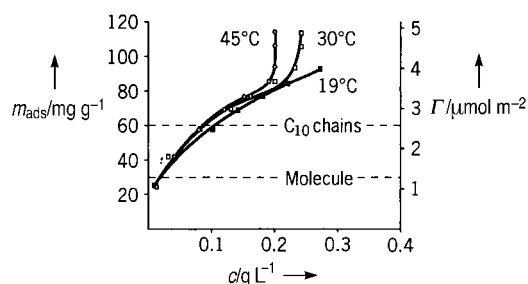


Figure 9. Adsorbed amount m_{ads} and surface concentration Γ of C_{10}E_4 on graphitized carbon black as a function of the surfactant concentration c in water at 19°C, 30°C, and 45°C.

the fatty alcohol ethoxylate. In contrast to the alkyl glycosides, adsorption increases with increasing temperature. The critical parameter for the dependence of the adsorption of C_{10}E_4 on temperature is clearly the cloud point ($T_c = 20^\circ\text{C}$). The adsorption of C_{10}E_4 increases dramatically at temperatures above T_c . On the other hand, however, a C_8E_4 with a cloud point of 40°C also shows significant dependence of adsorption behavior on temperature below the cloud point.^[42]

The influence of surface quality is even clearer on hydrophilic surfaces. Smith et al.^[44] studied the adsorption of technical APGs with different chain lengths on titanium

dioxide. It is known from adsorption studies that lauryl polyglycol ethers are not adsorbed onto the surface of titanium dioxide particles.^[45] The reason was assumed to be that the ether bonds of the nonionic surfactants preferentially form hydrogen bonds with the unbound water molecules than with the hydroxyl groups of the polar titanium dioxide surface. Alkyl glycosides show different behavior on polar solid surfaces.

The adsorption isotherms of three technical alkyl polyglycosides on titanium dioxide are shown in Figure 10. In the identical concentration range investigated, the shapes of the isotherms differ with the chain length of the alkyl polyglyco-

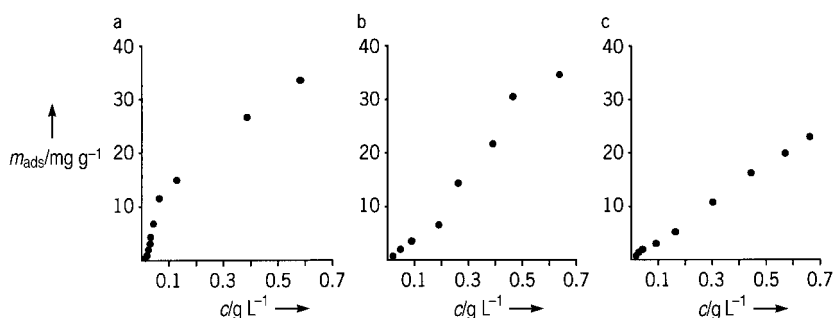


Figure 10. Adsorbed quantity m_{ads} of APGs $\text{C}_{12/14}$ (a), $\text{C}_{9/11}$ (b), and $\text{C}_{8/10}$ (c) on titanium dioxide (R-960) as a function of the surfactant concentration c in water at 25°C.

side mixtures. In the case of the short-chain $\text{C}_{8/10}$ alkyl polyglycoside, the amount adsorbed is almost linearly dependent on the concentration, whereas a tendency towards a pronounced S form of the isotherms is observed with increasing alkyl chain length. A similar isotherm form is also observed for the adsorption of anionic surfactants onto polar solids, for example sodium dodecyl sulfate (SDS) onto titanium dioxide^[46] and aluminium oxide.^[47] By way of explanation, it was stated in these examples that individual surfactant molecules with the polar head directed towards the surface are adsorbed by an acid/base interaction of the basic OH groups of the surface with the SDS anion. If the concentration of the surfactants in solution is increased, two-dimensional aggregates—often referred to as “hemimicelles”^[48]—are formed by hydrophobic interactions of the alkyl chains. Such interactions lead to a marked increase in the quantities adsorbed. A similar mechanism can also be postulated for the adsorption of alkyl polyglycosides with relatively long alkyl chains. The hydroxyl groups of the surfactant have a slightly acidic character and are capable of forming hydrogen bonds with the hydroxyl groups of the titanium dioxide surface. If a sufficient number of alkyl glycoside molecules is adsorbed onto the surface, other molecules are adsorbed onto the surface through an interaction of the alkyl chains. This leads to surface coverages above a theoretical monolayer, which is confirmed by the adsorption measurements. The effects of adsorption on the dispersion of pigments in aqueous solutions of alkyl polyglycosides and the rheology of dispersions were described by Nickel et al.^[43] and by Smith et al.^[44]

3.2. Phase Behavior

In contrast to systematic studies of fatty alcohol ethoxylates, only a few studies have hitherto been conducted into the phase behavior of alkyl polyglycosides. For a pure short-chain *n*-octyl- β -D-glucoside, the phase diagram was investigated in detail by Nilsson and Söderman^[49] and Sakya et al.^[50] The phase sequence is illustrated in Figure 11. At low

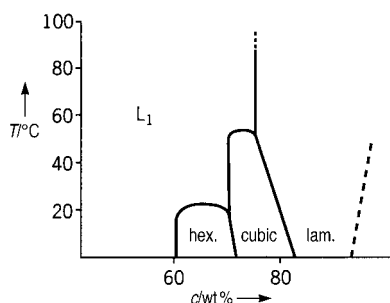


Figure 11. Phase diagram of *n*-octyl- β -D-glucoside in water.

temperatures, a hexagonal, a cubic, and finally a lamellar phase are observed with increasing surfactant content. The phase diagram of the $C_{12/14}$ alkyl polyglycoside/water system (Figure 12) differs clearly from that of a short-chain alkyl

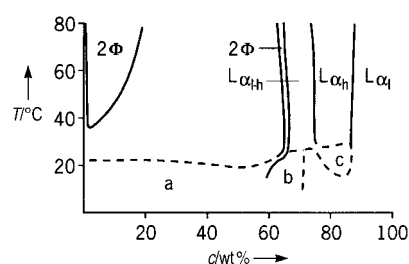


Figure 12. Phase diagram of $C_{12/14}$ alkyl polyglycoside in water.

polyglycoside.^[49] At low temperatures, a region corresponding to a solid/liquid region below the Krafft point is formed over a wide concentration range. With an increase in temperature, the system changes into an isotropic liquid phase. Since crystallization is kinetically retarded to a considerable extent, this phase boundary changes position with the storage time. At low concentrations the isotropic liquid phase changes above 35°C into a two-phase region of two liquid phases, as is normally observed with nonionic surfactants.^[51] At concentrations above 60 % by weight, a sequence of liquid crystalline phases is formed at all temperatures. Investigations into the structure of the liquid crystalline phases were conducted by Platz et al.^[52] According to these investigations, there are three different lamellar regions in concentrated $C_{12/14}$ APG solutions: L_{al} , L_{al-h} , and L_{ah} . Polarization microscopy shows that there are three different textures.

The influence of the degree of polymerization (DP) of alkyl polyglycosides on their phase behavior was described by Fukuda et al.^[53] The region in which the liquid crystalline phases occur is only slightly dependent on concentration with a greater expansion in the case of alkyl polyglycosides with a

higher DP. The two APGs with a low DP have a two-phase region (see also Figure 12) at low concentrations, which is reminiscent of the clouding phenomena of nonionic surfactants of the ethylene oxide type.^[50] Balzer^[54] investigated the clouding phenomena in dependence upon various parameters. He showed that the two-phase region is influenced to a far greater extent by the length of the alkyl chain than in the case of alkyl polyglycol ethers. If increasing quantities of $C_{10/12}$ alkyl polyglycoside are added to $C_{12/14}$ alkyl polyglycoside, the initially broad miscibility gap becomes gradually narrower (Figure 13), the separation zone separates from the Krafft

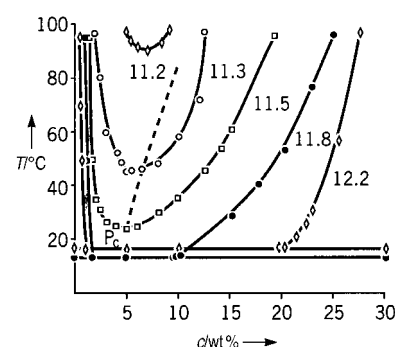


Figure 13. Phase diagrams of alkyl polyglycosides (DP = 1.3) for different alkyl chain lengths in the concentration range to 30 wt %.

point curve, and a lower separation point becomes visible. Accordingly, the dependence of the clouding effect for alkyl polyglycoside is comparable with that of alkyl polyglycol ethers, although the dependence on chain length is extremely strong for alkyl polyglycosides. In order to shift the cloud point from 25°C to 90°C, it is sufficient to change the alkyl chain length from $C_{11.5}$ to $C_{11.2}$. In the case of alkyl polyglycol ethers, a corresponding change in chain length would signify a change in the cloud point of only 2°C. An equally strong influence on the cloud point is observed when the degree of polymerization is changed.^[53]

If small quantities of electrolyte are added to alkyl polyglycosides, clouding phenomena are also observed with relatively short-chain alkyl polyglycosides.^[53] In this case, the electrolyte effect is far more clearly pronounced than in the case of alkyl polyglycol ethers, for which the influence of salt type and concentration has long been known.^[55] The behavior of alkyl polyglycosides resembles mixtures of alkyl polyglycol ethers and anionic surfactants.^[56]

The addition of fatty alcohols as a third component to alkyl polyglycoside/water mixtures leads to the appearance of different lamellar phases over the entire concentration range.^[51] This behavior is typical of the influence of fatty alcohols on the phase behavior of binary surfactant/water systems.^[57] Figure 14 shows the phase diagram determined for the addition of hexanol to various mixtures of $C_{12/14}$ alkyl polyglycoside and water. Three L_{α} phases can be seen: L_{al} , L_{ah} , L_{al-h} . The almost linear trend of the phases as a function of the alkyl polyglycoside and hexanol concentration indicates that the structure formed depends primarily on the alkyl polyglycoside/alcohol ratio. The quantity of alcohol that has to be added to ensure that a certain phase is formed decreases drastically with increasing alkyl chain length of the alcohol.

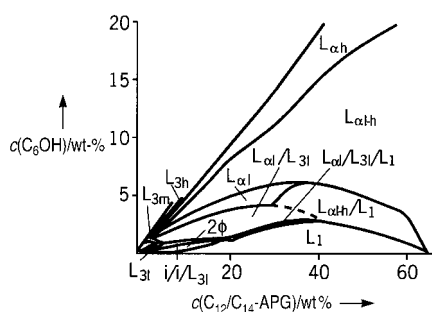


Figure 14. Phase diagram of the $C_{12/14}$ alkyl polyglycoside/hexanol/water system at 25°C.

In principle, the phase sequences observed with mixtures of alkyl polyglycosides and anionic surfactants, which are of particular importance in practice, are similar to those observed with the ternary systems of alkyl polyglycoside, alcohol, and water.^[52] The $L_{\alpha l}$ phase disappears on the addition of fatty alcohol sulfates, and the $L_{\alpha l-h}$ region becomes very dominant. The phases that in addition contain ionic surfactants appear optically more transparent and have a higher viscosity and elasticity than systems consisting solely of alkyl polyglycoside and alcohol. Yield points, which increase considerably with increased concentration of fatty alcohol sulfate, are obtained in the $L_{\alpha l-h}$ and L_{3m} phases of these systems. Dilute lamellar phases can only be obtained in $C_{12/14}$ alkyl polyglycoside solutions on addition of fatty alcohol. Fatty alcohol has to be added for steric reasons. Anionic surfactants have large head groups. Accordingly, in the case of systems containing fatty alcohol sulfates, relatively large quantities of fatty alcohol are required to obtain a lamellar structure. This explains why the lamellar phases in these systems are displaced towards higher fatty alcohol concentrations. It is interesting that the repulsive forces between the charged lamellae and hence the elastic shear moduli are far greater than in uncharged systems. Relatively large viscous and elastic moduli were observed with all the anionic surfactants investigated.

The addition of anionic surfactants also has an influence on the clouding phenomena. The cloud points are considerably increased by small quantities of alkyl sulfates. According to Balzer,^[54] small quantities of alkyl sulfate lead to a change in the electrical charge of the alkyl polyglycoside micelles. This results in a greater repulsive interaction between the micelles and leads to a distinct increase in the cloud point.

3.3. Ecological Evaluation, Toxicology, and Dermatological Properties

Alkyl polyglycosides are mostly used in dishwashing and laundry detergents, cosmetics, and cleaning products, which are discharged into domestic wastewater after use and thus enter the aquatic environment. Generally, the environmental fate of surfactants is inextricably linked with their biodegradation behavior. Thus, quick and complete biodegradability is the most important requirement for an environmentally compatible surfactant. The environmental impact of chem-

icals lies mainly in their ecotoxicity, which is relatively high in the case of surfactants because of their surface activity and the resulting effects on biological membranes. According to broadly accepted risk assessment schemes for chemical substances,^[58] environmental compatibility requires proof that the use of the chemical will not result in environmental concentration levels higher than the ecotoxicological no-effect concentration.

The biodegradation tests with alkyl polyglycosides were carried out by internationally used and accepted standard methods.^[59] The group of discontinuous tests is relatively simple in terms of design but has a high stringency, which, in the case of positive results, allows general conclusions to be drawn as to biodegradability in aquatic and terrestrial environments.^[60] The group of continuous activated sludge tests mainly comprises those tests that simulate the biodegradation process in a municipal sewage treatment plant.

The biodegradability assessment of chemicals normally starts with screening tests. Although alkyl polyglycosides are nonionic surfactants, the routine analytical procedure used to follow the (primary) degradation of nonionic surfactants, namely measurement of bismuth-active substance (BiAS) removal,^[61] cannot be applied, because alkyl polyglycosides do not react as BiAS. Only nonionic surfactants with a polyglycol ether chain form a complex with the barium ion of the added barium iodo bismuthate. Thus, legal biodegradability requirements in Europe for nonionics ($\geq 80\%$ BiAS removal) do not apply to this group of surfactants. However, the OECD ready biodegradability tests (OECD 301 series)^[61] represent a group of broadly applicable screening tests which form the basis for the biodegradability evaluation of most chemicals. These tests determine the ultimate biodegradation of the test compound, that is, the microbial transformation of the parent test substance into the final products of the degradation process such as carbon dioxide, water, and assimilated bacterial biomass. $C_{12/14}$ alkyl polyglycoside was tested in three different ready biodegradability tests, the Closed Bottle Test (OECD 301 D), the Modified OECD Screening Test (OECD 301 E), and the DOC Die Away Test (OECD 301 A). The results obtained reflect a very high degree of ultimate biodegradation over the 28-day test period in all tests.^[59] The Closed Bottle Test, which is the most exact of all OECD 301 tests,^[62] reached mineralization levels of 88% (test concentration 2 mg L^{-1}) and 72% (5 mg L^{-1}), thus far exceeding the OECD limit for the label "ready biodegradability" (60% biological/chemical oxygen demand (BOD/COD)). The "10-day time window" was also easily fulfilled.^[59] To sum up, the results of various OECD ready biodegradability tests show unequivocally that alkyl polyglycosides are readily biodegradable and, according to the conclusions of the OECD,^[60] will undergo rapid and complete biodegradation in the environment.

Today, defined test strategies^[63, 64] are available for characterizing biological properties. After toxicological safety screening, they provide for the direct testing of effects on the skin of volunteers and have also been applied comprehensively to alkyl polyglycosides. Dermatologically, alkyl polyglycosides represent a new class of very mild surfactants, which, depending on the type of product, are eminently

suitable for use as sole surfactant or cosurfactant in the formulation of particularly gentle products. Optimized dermatological compatibility for many cleaning products can be achieved through careful choice of the chain length, the degree of polymerization, the vehicle or solvent, and the particular formulation.

The object of toxicological studies is to assess the hazard potential of chemical products in order—on the basis of these findings—to assess the risks to the health of the user and to prevent possible adverse effects, even after improper use. The main concern of these studies is to determine the toxic potential of a substance and often involves conditions that considerably exceed normal exposure levels. Toxicological studies thus provide information on the inherent toxicological potential of chemical substances. An assessment of the actual risks is only possible if the corresponding exposure conditions, that is, the mode of application, duration, and frequency of contact are included in these considerations. If these principles are disregarded by arbitrarily equating hazard with risk, wrong conclusions will inevitably be drawn.

The toxicological safety strategy for chemical products should be based on the following objectives:

- Correct handling should rule out unwanted side effects.
- Foreseeable improper use should not cause serious health damage.
- Even long-term exposure as a result of long environmental residence times should not involve any health risk.

Alkyl polyglycosides varying in chain length and purity have been subjected to the most relevant toxicological tests necessary for a sound risk assessment. On the basis of the information available, alkyl polyglycosides are not considered as toxic or harmful in acute toxicity tests, but in high concentrations have to be classified as irritating to the skin and eyes. In addition, sensitizing effects are unlikely to occur. A NOAEL (NOAEL = no observed adverse effect level) of 1000 mg kg^{-1} body weight can be estimated for toxicity after repeated oral application. In vitro tests indicated that alkyl polyglycosides have no potential for gene and chromosome mutations.

Safety in use and handling also includes foreseeable improper use such as the accidental swallowing of cosmetic products by children. By virtue of their low acute oral toxicity, alkyl polyglycosides do not contribute to the toxicity of cosmetic and other household products. The acute oral toxicity values (LD_{50}) are of the order of several grams per kilogram body weight. In other words, it is virtually impossible to be seriously poisoned by these products.^[64]

4. Applications

Due to their physico-chemical properties, alkyl polyglycosides show interesting effects for various applications. Specific examples will be given in the following sections.^[64]

4.1. Microemulsions

Various parameters determine whether ternary systems of water, oil, and nonionic surfactants can form microemulsions.

Microemulsions of oil, water, and ethoxylated nonionic surfactants have become particularly interesting.^[65, 66] One characteristic of these systems of oil, water, and ethoxylated nonionic surfactant is their pronounced dependence on temperature, which is the basis of the known phase inversion temperature (PIT) phenomenon.^[65–67] Due to the fact that the phase behavior of simple binary alkyl polyglycoside/water mixtures shows only comparatively weak temperature effects^[68, 69] no temperature-dependent phase inversion can be expected to occur in alkyl polyglycoside-containing emulsions.

Alkyl polyglycosides react similarly to anionic surfactants on the addition of cosolvents that increase the solubility of the surfactant in the oil phase. In the decane/water/APG system the addition of the cosolvent isobutanol results in a drastic reduction in the interfacial tension between oil and aqueous phase, and, hence, in the formation of a third phase, the microemulsion.^[70] As expected, the range in which this three-phase microemulsion exists is only slightly dependent on temperature and, in contrast to anionic surfactants, is also hardly affected by electrolytes.^[70] Systematic investigations of the phase behavior confirm these initial results for a number of simple hydrocarbons from hexane to hexadecane and aromatics.^[71, 72]

Figure 15 shows the known microemulsion phases (in the literature named as “Kahlweit” fish^[65] because of the shape) in a pseudoternary phase diagram. With small alkyl polyglycoside content of 5 to 25 % and small pentanol content of 3

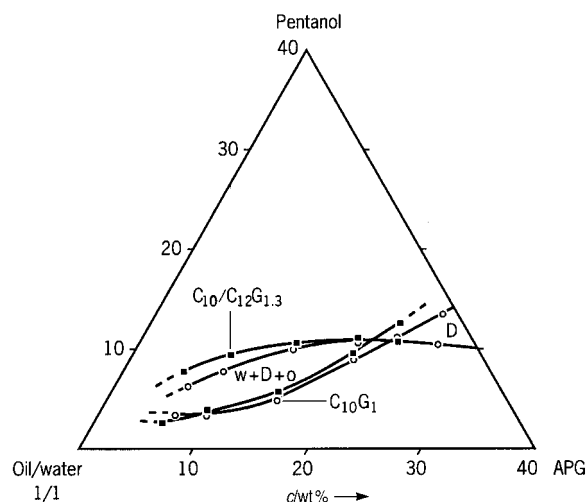


Figure 15. Pseudoternary phase diagram for the systems dodecane/water (1/1), pentanol, C_{10} monoglycoside (C_{10}G_1), and $\text{C}_{10/12}$ alkyl polyglycoside ($\text{DP} = 1.3$; $\text{C}_{10}/\text{C}_{12}\text{G}_{1.3}$) at 40°C .

to 10 %, three-phase microemulsions are formed. Of greater interest for practical applications are single-phase microemulsions, which are formed with an alkyl polyglycoside content of $>25\%$ and a pentanol content of 10% in the system. Figure 15 includes the—almost identical—results for two different alkyl polyglycosides, namely a high-purity C_{10} monoglycoside and a $\text{C}_{10/12}$ alkyl polyglycoside of technical purity with an average degree of polymerization of 1.3. In the technical product, the slightly increased degree of polymer-

ization evidently compensates for the somewhat longer alkyl chain length cut. Another way of achieving balanced hydrophilic/lipophilic properties is to combine the hydrophilic emulsifier alkyl polyglycoside with a hydrophobic coemulsifier.

Representation of the microemulsion phases as a function of formulation parameters (for example, temperature for systems containing fatty alcohol ethoxylate) and emulsifier concentration^[65, 73] has been successful as an aid for establishing practical formulations. A basically similar picture emerges for emulsions of oil, water, and an emulsifier mixture of alkyl polyglycoside and a hydrophobic coemulsifier: instead of temperature as the formulation parameter, the mixing ratio of alkyl polyglycoside to hydrophobic coemulsifier is varied.^[74] In the case of the specific emulsifier mixing ratio of 1:1, the system of dodecane, water, $C_{12/14}$ alkyl polyglycoside, and sorbitan monolaurate (SML) as hydrophobic coemulsifier forms microemulsions (Figure 16). The emulsions formed with a relatively large SML content are water-in-oil (w/o) emulsions while the emulsions formed with a relatively large alkyl polyglycoside content are oil-in-water (o/w) emulsions. By varying the overall emulsifier concentration, a "Kahlweit" fish again appears in the phase diagram with three-phase microemulsions in its body and a single-phase microemulsion in its tail.

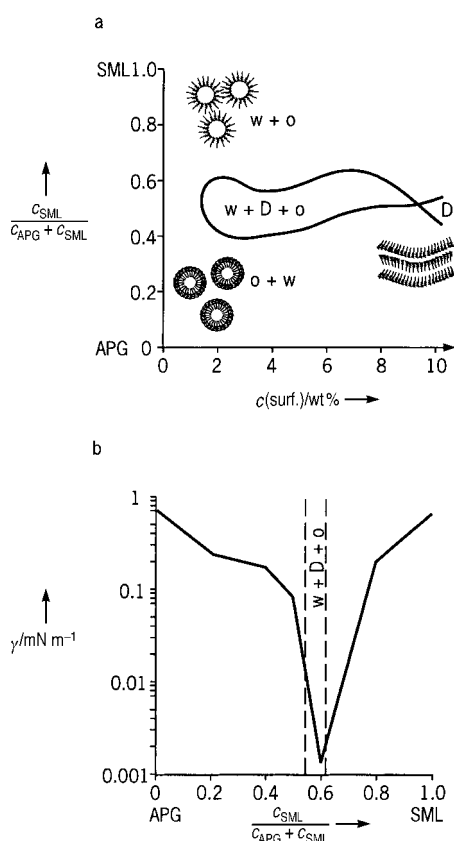


Figure 16. a) Dependence of the phase behavior of the system dodecane/water (1:1), $C_{12/14}$ APG, sorbitan monolaurate upon the ratio of APG to SML as a function of the total surfactant concentration. b) Dependence of the interfacial tension of the system dodecane/water (1:1), $C_{12/14}$ APG, sorbitan monolaurate in dependence upon the ratio of APG to SML for a total surfactant concentration of 1.5 wt %.

The similarity between alkyl polyglycosides and fatty alcohol ethoxylates is not confined to phase behavior but also applies to the interfacial tension of the emulsifier mixture. With an alkyl polyglycoside/SML ratio of 4:6, the hydrophilic/lipophilic properties of the emulsifier mixture are balanced, and the interfacial tension is minimal. It is remarkable that the alkyl polyglycoside/SML mixture produces a very low minimum interfacial tension value (around $10^{-3} \text{ mN m}^{-1}$) which, once again, is lower by one order of magnitude than that observed in the case of the fatty alcohol ethoxylate system.^[33, 65, 75]

In the case of the alkyl polyglycoside-containing microemulsion, the high interfacial activity is attributable to the fact that the hydrophilic alkyl polyglycoside with the large polyglycoside head group is present in exactly the right mixing ratio with the hydrophobic coemulsifier SML with its small head group at the oil/water interface. In contrast to ethoxylated nonionic surfactants, hydration and hence the effective size of the head group are hardly dependent on temperature,^[54, 70, 76] an attribute that can be utilized for formulating temperature-stable microemulsions.^[77]

In order to be able to use alkyl polyglycoside microemulsions for industrial or cosmetic applications, tailor-made formulations with certain desirable performance properties are necessary. Figure 17 shows the pseudoternary phase

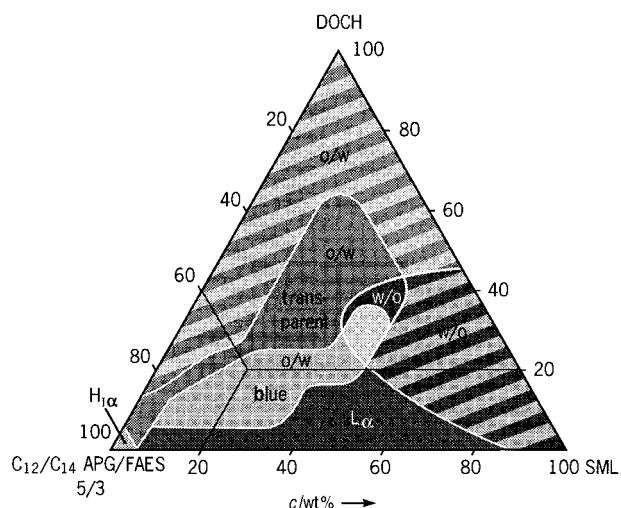


Figure 17. Pseudoternary phase diagram for emulsion systems of 60 wt % water with dioctyl cyclohexane (DOCH), sorbitan monolaurate (SML), and a FAES/APG mixture (sodium laureth sulfate: $C_{12/14}$ APG = 3:5) at 25°C.

triangle of a five-component system of cosmetic raw materials, which may serve as a model system for foaming and simultaneous refatting body-care formulations.^[78] The water content is a constant 60%, the oil component is dioctyl cyclohexane. In this example, the hydrophilic emulsifier is a 5:3 mixture of alkyl polyglycoside and a fatty alcohol ether sulfate (FAES), which, as a high-foaming anionic surfactant, forms the basis of many body-care formulations. Although sorbitan monolaurate (SML) was chosen as the hydrophobic coemulsifier in this case, other coemulsifiers (for example glycerol monooleate^[35]) are, in principle, also suitable.

Accordingly, the indicated formulation in the blue o/w emulsion range contains 15 % alkyl polyglycoside, 9 % FAES, 8 % SML, 8 % dioctyl cyclohexane, and 60 % water.

Starting out from an oil-free and coemulsifier-free system, a 40 % alkyl polyglycoside/FAES mixture in water is present as a viscous hexagonal liquid crystal (H_{1a}). Even the replacement of a small part of the alkyl polyglycoside/FAES mixture by the hydrophobic cosurfactant SML is sufficient to allow a low-viscosity lamellar phase (L_a) to be formed. If the SML content is increased, the lamellar phase remains intact whereas the viscosity increases considerably and reaches levels that are even above those of the hexagonal phase. Like the hexagonal phase, the lamellar phases are also non-Newtonian, in other words their viscosity decreases with increasing shear rate.

The two liquid crystals react very differently to the addition of oil. Whereas the hexagonal liquid crystal is only capable of solubilizing very small quantities of oil, the range in which the lamellar phase exists extends far towards the oil corner. The ability of the lamellar liquid crystal to incorporate oil increases distinctly with increasing SML content. Solubilization of the oil leads to an increase in the lamellar layer spacing, which was measured by small angle X-ray scattering. Accordingly, the oil molecules are incorporated in the hydrophobic interior of the lamellar layers and not in the palisade layer parallel to the emulsifier molecules.

With a relatively high proportion of oil, blue emulsions or transparent microemulsions are formed. With a high percentage of SML (more than 50 % in the emulsifier mixture), these emulsions are of the w/o type. For an optimal mixing ratio of hydrophilic alkyl polyglycoside/FAES compound to hydrophobic SML, the range in which a transparent microemulsion exists extends very far towards the oil corner: a maximum of 60 % of dioctyl cyclohexane can be microemulsified. The microemulsions have low viscosities and are substantially Newtonian, the w/o microemulsions having slightly higher viscosities than the o/w microemulsions.

4.2. Detergents and Cleaners

Alkyl polyglycosides are used in manual dishwashing detergents as well as all-purpose cleaners and laundry detergents. Alkyl polyglycosides show pronounced synergisms with the three primary surfactants linear alkyl benzene

sulfonate (LAS), secondary alkane sulfonate (SAS), and fatty alcohol sulfate (FAS). These synergisms are far more pronounced (Figure 18) than those observed with fatty alcohol ether sulfate (FAES). In contrast to alkyl polyglycosides, other nonionic surfactants such as fatty alcohol polyethylene glycol ether (FAEO) do not show any synergisms with FAES. The synergistic interactions of alkyl polyglycosides with the various primary surfactant systems enables the formulation of even more effective products for the same active substance content or the reduction of the active substance content without affecting the performance level.

Although foam volume and foam structure both in the dishwashing liquor and under running water do not directly determine product performance, they are expected by the consumer and thus lead to purchasing decisions. In APGs the product developer has a nonionic surfactant that improves the foam properties of the product. Both foam height and foam stability under mechanical influence can be investigated by suitable methods. The test results obtained with various commercial concentrates, even in the presence of soil, are set out in Figure 19. The results show that the APG-containing dishwashing detergent produces an elastic foam which is relatively unaffected by soil.

Because of the broad range of soil types found in the home, all-purpose cleaners have to perform efficiently against both emulsifiable oil- and fat-containing soils and against disper-

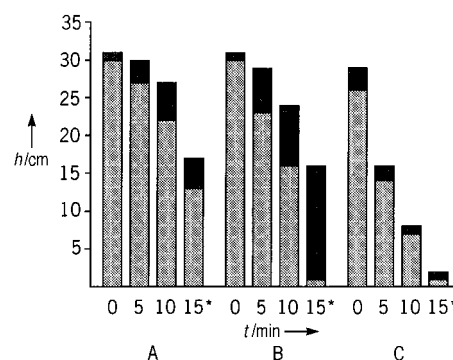


Figure 19. Foaming behavior of concentrated manual dishwashing detergents. Test method: stress stability of foam; concentration of the product 1 g L^{-1} ; $T = 50^\circ\text{C}$, water hardness 16°d . h = foam height; A = APG-containing concentrate, B = glucamide-containing concentrate, C = SAS-based concentrate, * = with mechanical impact. Dark gray column: foam height without soil; light gray column: foam height on addition of vegetable oil.

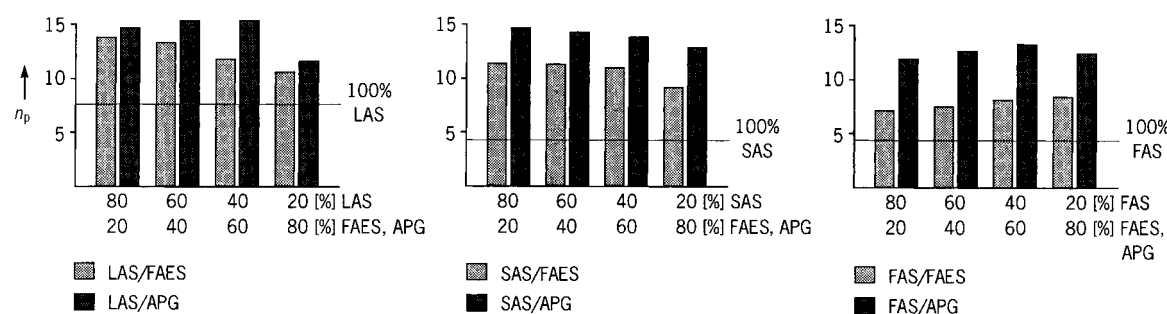


Figure 18. Dishwashing performance of $C_{12/14}$ alkyl polyglycoside in combination with alkylbenzene sulfonate (LAS), secondary alkane sulfonate (SAS), and fatty alcohol sulfates (FAS). Test method: plate test; test soil: beef tallow; concentration of active substance 0.1 g L^{-1} ; $T = 50^\circ\text{C}$; water hardness 16°d . The number of plates n_p washed is plotted against the surfactant composition.

sible solid soil particles. Alkyl polyglycosides themselves have an excellent cleaning performance, which can be determined, for example, in accordance with the IPP quality standard.^[79] The cleaning performance can be further increased by small additions of anionic surfactants and/or polymeric boosters. Thus, it is possible to formulate products comparable in cleaning performance to the market leaders at significantly lower surfactant contents. All-purpose cleaners with particularly good skin compatibility should be slightly acidic rather than alkaline. Alkyl polyglycoside is a surfactant of which the high cleaning performance level is hardly affected by changes in the pH value. Consumers today prefer all-purpose cleaners with moderate or low foaming behavior. The foaming capacity of alkyl polyglycoside-containing cleaners can readily be reduced by using small quantities of soaps or increased by adding small quantities of anionic surfactants. Alkyl polyglycoside has proved to be the problem solver in the formulation of concentrated all-purpose cleaners with excellent ecological compatibility. With alkyl polyglycosides, it is possible to formulate concentrates which have a correspondingly higher content of builders and perfume oils without having to use large quantities of solubilizers (hydrotropes).

The alkyl polyglycosides used in detergent formulations are those with an alkyl chain length of $C_{12/14}$ and a DP value of around 1.42. As a nonionic surfactant, they are particularly effective against fatty soils. Optimized surfactant systems generally based on mixtures of anionic and nonionic surfactants are used in modern detergent formulations. Alkyl polyglycosides occur in these surfactant mixtures preferably as so-called cosurfactants, which have the property of complementing or improving quantitatively the washing performance of the predominant surfactants. Besides performance, the aesthetics play an important part for a detergent. Wool detergents, for example, are intended to produce a rich, stable foam. The consumer associates performance and care with foam. For machine washing, the correct foam height on the one hand determines textile care, because the mechanical action on the wash load is reduced. On the other hand, foam may cause a distinct reduction of the detergency performance. Alkyl polyglycosides in conjunction with anionic surfactants may alter the foaming behavior of the formulations.

APGs were first used in liquid laundry detergents in 1989. The hydrotropes—which do not contribute to cleaning—can be partially replaced by alkyl polyglycosides. Alkyl polyglycosides surprisingly have a positive influence on the low-temperature and storage stability of such formulations. In addition, triethanolamine soaps have been successfully replaced by the similarly acting sodium/potassium soaps.^[80] The diethanolamine contamination of triethanolamine, which may cause the formation of nitrosamines, was thus avoided. In addition, as sodium soaps are less expensive, a net result of the use of alkyl polyglycosides is a price advantage for the formulation. Washing tests show that these new formulations outperform their predecessors (Figure 20). Whereas in the case of liquid heavy duty detergents containing optical brighteners and enzymes, the emphasis is on performance, the aspect of textile care is more dominant in the case of specialty detergents. Liquid specialty detergents are formu-

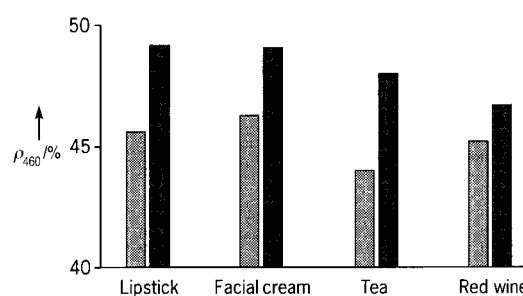


Figure 20. Washing performance of heavy-duty detergents. Test method: washing machine concentration: 180 mL per wash load (Miele-W-760 washing machine), 60°C, water hardness 16°d. The reflectance ρ at 460 nm is plotted against the type of soil; light gray column: triethanolamine soaps; dark gray column: sodium soaps.

lated with pH values less than or equal to 8.5. In order to avoid shifts in color, optical brighteners are avoided in the formulations.^[81]

The storage stability of enzymes in liquid formulations is smaller than in powders. On account of the high surfactant content of certain formulations, the enzymes are partly deactivated and slowly lose their initial activity upon storage. In order to improve the storage stability of enzymes such as proteases, lipases, amylases, and/or cellulases in liquid detergents, stabilizers (borates, phosphates, or special esters) are added, and the surfactant systems are adapted. The storage stability of enzymes in liquid detergents can be distinctly improved by the use of alkyl polyglycosides (Figure 21). The alkyl polyglycosides have the advantage over the otherwise typical stabilizers of enhancing the washing result.

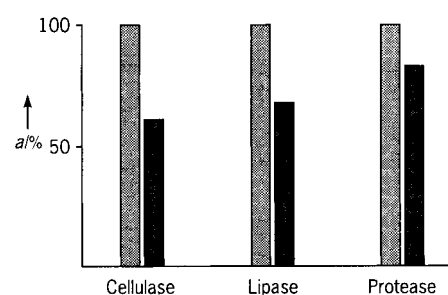


Figure 21. Stability of enzymes in liquid detergents. Test method: relative enzymatic activity a after storage for 56 days at room temperature. Formula: heavy-duty liquid detergent, 42% surfactants, pH = 8. Light gray column: formulation with 5 wt. % $C_{12/14}$ APG; dark gray column: formulation without $C_{12/14}$ APG.

Quantitatively the largest group, namely the heavy duty powder detergents, are based on formulations that remove virtually all the soil types normally encountered. Particular emphasis is placed on washing performance. For this reason, these detergents have a distinctly higher alkalinity (pH value in the range from pH 9.5 to 10.5) to greatly improve soil removal. In addition, heavy duty detergents are provided with a bleaching system. Bleachable stains such as tea, coffee, red wine, etc., are thus effortlessly removed. Fat- and oil-containing soils such as sebum, olive oil, lipstick, and facial cream are difficult to remove, particularly at low temperatures. By using alkyl polyglycosides in powder detergents, these stains in particular can be removed considerably more effectively.

4.3. Personal Care Products

Over the past decade, progress in the development of raw materials for personal-care products has mainly occurred in three areas:

- mildness and protection for the skin
- high-quality standards by minimization of by-products and trace impurities and
- ecological compatibility.

At the same time, the variety of parameters relevant for a new raw material has increased, and their detection by subjective and objective methods has become more precise. In the cosmetic field alkyl polyglycosides show interesting properties. For example, addition of alkyl polyglycosides modifies the rheology of concentrated surfactant mixtures, so that pumpable and readily dilutable concentrates containing up to 60% active substance can be prepared. These concentrated blends of several components may be generally used as cosmetic raw materials or specifically as core concentrates in the production of cosmetic formulations (for shampoos, shampoo concentrates, shower baths, foam baths etc).

The compositions are based on anionics such as alkyl ether sulfate, betaines, and/or nonionic surfactants, and are more gentle on the eyes and the skin than conventional systems. At the same time, they show excellent foam, viscosity, and processing properties. Super concentrates are preferred for economic reasons insofar as they are easier to handle and dilute without containing hydrotropes.

A simple characteristic example is the compound of standard ether sulfate and $C_{12/14}$ alkyl polyglycoside in a ratio of 2:1. Alkyl polyglycoside disrupts the formation of the highly viscous hexagonal phase of the ether sulfate, which, in turn, inhibits the crystallization of alkyl polyglycoside (Figure 22). The mixture is pumpable above 15°C and can be cold-processed with normal mixing units. On dilution, the viscosity passes through a flattened broad maximum at 40–45%.^[78] Foaming is an essential quality feature of cosmetic cleansing formulations. Alkyl polyglycosides foam considerably better than fatty alcohol ethoxylates, the foam volume increasing with increasing percentage of short carbon chains in the alkyl polyglycosides. They are comparable with betaines and

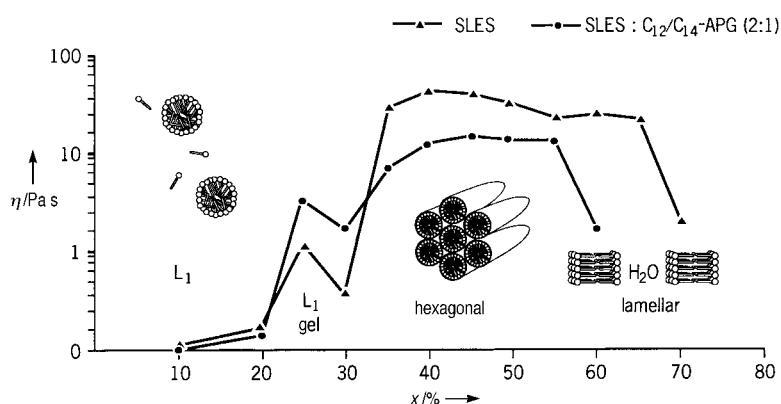


Figure 22. Rheology of standard sodium lauryl ether sulfate (SLES) and C_{12}/C_{14} alkyl lauryl ether polyglycoside in admixture, superimposed on a plot of the viscosity η of the surfactants against the proportion of surfactant in the mixture.

sulfosuccinates but do not match the initial foam behavior or foam volume of alkyl ether sulfates.^[82–84]

On the other hand, alkyl polyglycosides can stabilize the foam of anionics in hard water and in the presence of sebum, so that up to 20% of surfactant can be saved for the same foaming power.^[82, 84] The structure of the foams of alkyl ether sulfates and alkyl polyglycosides was investigated by image analysis and provides a basis for understanding the observed properties.^[82, 84] Alkyl polyglycoside foam consists of finer bubbles and is more creamy than alkyl ether sulfate foam (Figure 23).

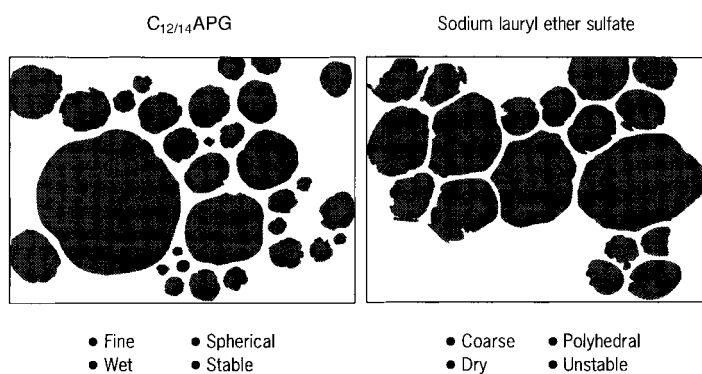


Figure 23. Foam structure of lauryl glycoside and sodium lauryl ether sulfate after 15 min (magnification 30 ×).

Alkyl polyglycosides with carbon chains longer than $n = 12$ assist the build-up of rodlike mixed micelles in solutions of anionics and thus make a considerable contribution towards increasing viscosity.^[82, 85] This effect is somewhat weaker in standard ether sulfate formulations than with alkanolamides, but is more pronounced with sulfosuccinates and highly ethoxylated alkyl ether sulfates, which are very difficult to thicken with alkanolamides. Alkyl polyglycoside formulations without anionics can best be thickened by adding polymeric thickeners such as xanthan gum, alginate, polyethoxylated esters, carbomers, etc.

The mildness of alkyl polyglycosides is also reflected in a caring effect on damaged hair. The tensile strengths of permed hair tresses are reduced far less by treatment with alkyl polyglycosides solutions than by standard ether sulfate solutions.^[82, 84] Direct proof of the adsorption of alkyl polyglycosides onto hair can be qualitatively provided by the XPS technique (X-ray photoelectron spectroscopy). Hair tresses were divided into two halves; both surfactants can be detected on the hair surface by XPS. If the process is repeated several times, no change in the XPS signals is observed in case of ether sulfate between treated and untreated hair. By contrast, slightly increased oxygen contents are measured for alkyl polyglycosides. This result shows that alkyl polyglycoside is more substantive to the hair than standard ether sulfate. The substantivity of surfactants to hair influences combability.

In addition to the mentioned fields of application and the formulation of emulsions and micro-

emulsions alkyl polyglycosides may also be used in soaps, syndets (synthetic detergents), and toothpastes. C_{12/14} alkyl polyglycoside was found to be an effective booster for special antibacterial agents such as chlorohexidine. In the presence of alkyl polyglycoside, the quantity of bactericidal agent can be reduced to about one quarter without losing any bactericidal activity.

5. Summary

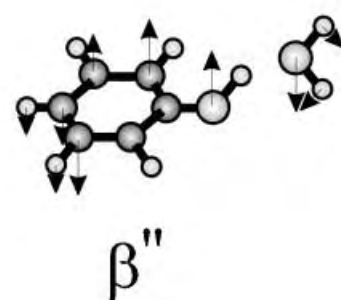
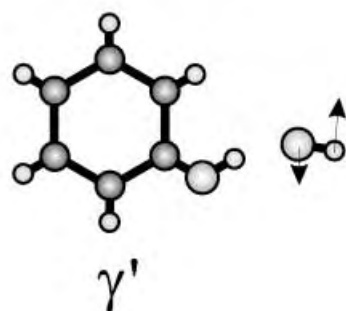
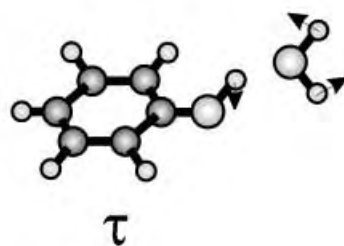
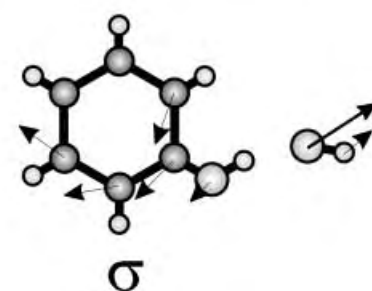
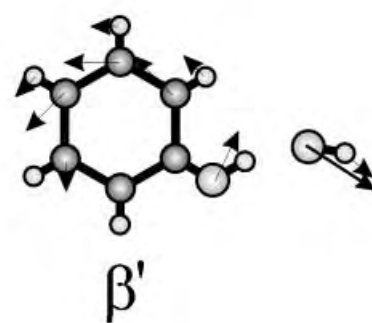
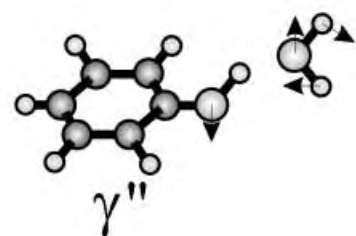
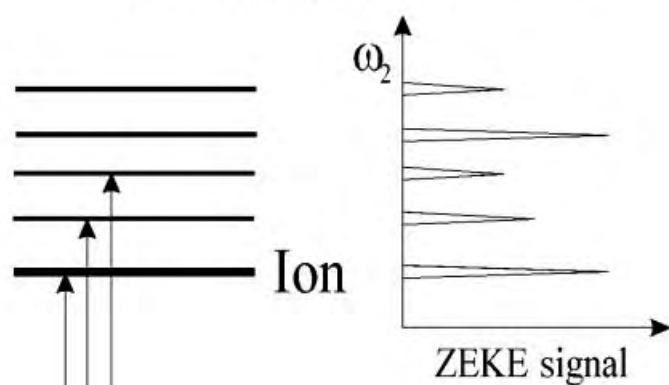
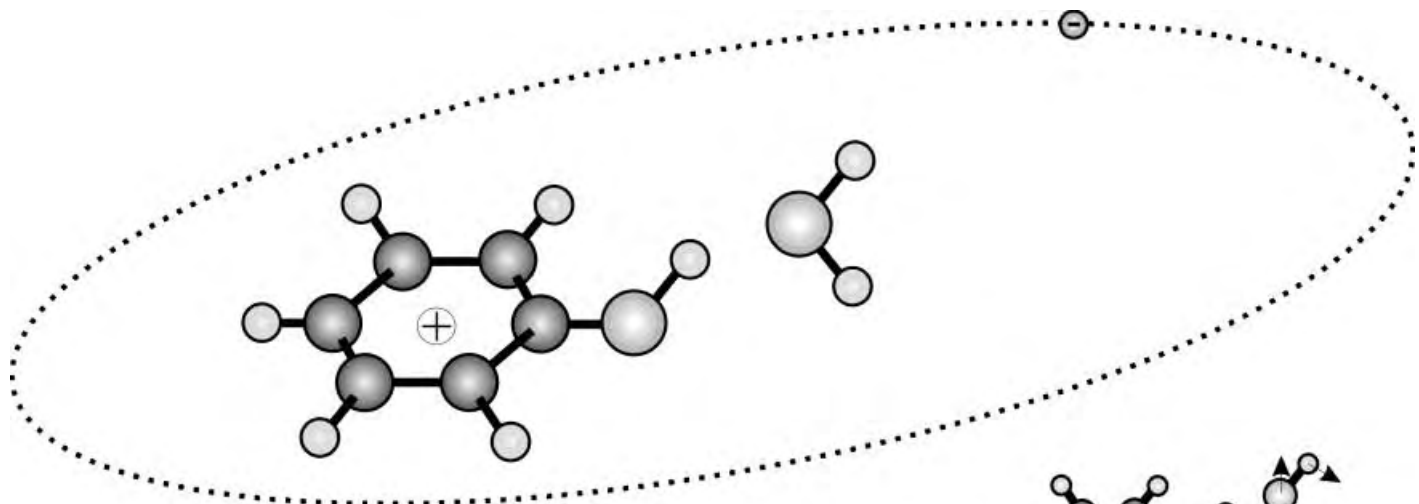
By virtue of their physico-chemical parameters and their performance profile alkyl polyglycosides are a new class of environmentally favorable nonionic surfactants, which represent new concepts in performance, compatibility, and care for various consumer products. Alkyl polyglycosides are multi-functional raw materials that are beginning to make their mark on modern formulation techniques and represent a trend-setting innovation.

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ZEKE spectroscopy shows for the first time the intermolecular vibrational modes of the phenol–water cation.

Chemical Applications of Zero Kinetic Energy (ZEKE) Photoelectron Spectroscopy

Klaus Müller-Dethlefs* and Edward W. Schlag

ZEKE spectroscopy is a new method in chemical spectroscopy which particularly addresses ionic species by measuring (ro)vibronic states of the ion through detection of isoenergetic, stable Rydberg states. These states are extremely long-lived and can therefore be measured with high precision. The new spectroscopy allows very high resolution measurements of positively charged ions. This approach can be

extended to photodetachment of anions, producing information about the corresponding neutral molecule. ZEKE spectroscopy has already been applied to a wide variety of molecular ions, clusters, van der Waals molecules, free radicals, reactive intermediates, and even to elusive transition states of chemical reactions. Compared to conventional photoelectron spectroscopy, ZEKE spectroscopy offers

many advantages, for example, greatly increased spectral resolution. This allows one to obtain the rotational structure of large molecular cations such as the benzene cation and the intermolecular vibrations of molecular clusters such as phenol–water.

Keywords: cations • clusters • photoelectron spectroscopy • Rydberg states • ZEKE spectroscopy

1. Introduction

Spectroscopic techniques such as NMR, IR, or UV/Vis spectroscopy have been crucial for the understanding of the structure and reactivity of molecules.^[1] There remain, however, a plethora of chemical systems—for example, ions, van der Waals complexes, and reactive intermediates—which are difficult if not impossible to probe by these traditional approaches. This review presents the application of a relatively new spectroscopic method, ZEKE spectroscopy (*zero kinetic energy photoelectron spectroscopy*), to such species to further our understanding of the structures of complex chemical systems.

ZEKE spectroscopy is an evolution of the well-known photoionization technique developed in the 1960s, photoelectron spectroscopy (PES).^[2–4] Photoionization can be described as the removal of an electron from the HOMO (*highest occupied molecular orbital*) into the ionization continuum, thus creating a molecular cation in its electronic ground state. Furthermore, removal of an electron from an orbital below the HOMO (with higher ionization energy E_i)

will produce an excited electronic state of the cation. A photoelectron spectrum of benzene obtained with vacuum UV (VUV) radiation is presented in Figure 1 (together with the frontier molecular orbitals); the bands can be assigned to the ground state and electronically excited states of the benzene cation. PES provides quantitative information about the electronic and vibronic states of molecular ions^[4–6] through analysis of the kinetic energy of the ejected photoelectrons. The molecule to be analyzed is irradiated with monoenergetic photons that ionize the molecule, and any excess energy is transformed into kinetic energy of the electron [Eq. (a); n , S , v , and N represent electronic, electronic-spin, vibrational, and rotational quantum numbers, E_i is the ionization energy, and $E_{\text{kin}}(e^-)$ is the kinetic energy of the electron]. Partially

$$E_{\text{neutral}}^{\text{int}}(n, S, v, N) + h\nu - E_i \rightarrow E_{\text{ion}}^{\text{int}}(n^+, S^+, v^+, N^+) + E_{\text{kin}}(e^-) \quad (\text{a})$$

resolved fine structure is visible in the VUV photoelectron spectrum of benzene, and corresponds to rotationally and vibrationally excited levels of the cation which are populated in accordance with Equation (a). As a zero-order approximation (in which electron correlation is ignored), the ionization energies can be equated to the negative orbital energies following Koopmans theorem. Though rarely accurate in practice, Koopmans theorem has proven conceptually that molecular orbitals are more than just a product of the quantum chemist's imagination and has contributed to the understanding of the electronic structure of molecules.

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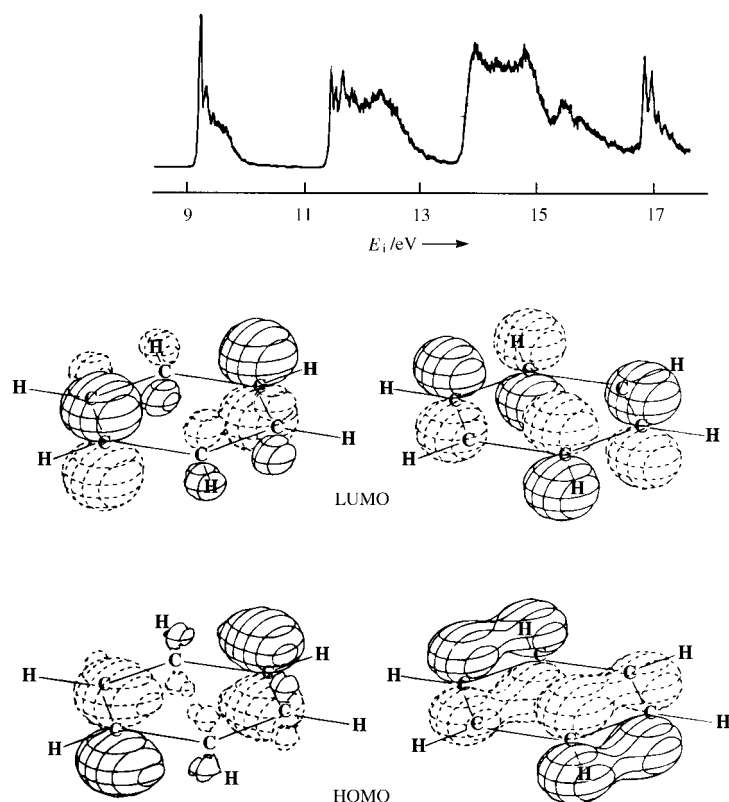


Figure 1. VUV photoelectron spectrum of benzene (top) and comparison of the frontier orbitals of benzene (bottom).^[6]

While there is no fundamental limit to the resolution of PES, since the energy of the ejected electron is quantized (assuming sharp photon energy and molecular states of the cation and the neutral molecule), the practical resolution is limited by the necessity of determining the kinetic energy of the electrons. Firstly, calibration of the detector is necessary, and, secondly, the resolution of commercially available geometrical or time-of-flight (TOF) photoelectron analysers is generally limited to about 10 meV, although it can be improved to 3–5 meV with a combination of a He^I source and a spherical analyzer.^[7] When combined with resonance enhanced multiphoton ionization (REMPI) a similar resolution was achieved in some cases.^[8,9] With the notable exception of hydrogen^[10–12] and some high-lying states of NO^+ ,^[8,9] conventional PES is unable to resolve rotational states of ions. In addition, intermolecular vibrations in van der Waals clusters (whose frequency generally ranges between 10 and 400 cm^{-1}) cannot be elucidated with this approach.

The ZEKE method developed in our laboratory over the last decade overcomes the limitations of PES by producing electrons with no kinetic energy by matching the photon energy exactly to the energy for the transition from the state of the neutral molecule and that of the ion state.^[13–22] This is achieved experimentally by scanning a laser or a VUV light

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K. Müller-Dethlefs



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Edward W. Schlag was born in 1932 in Los Angeles (USA). He studied chemistry at Occidental College (Los Angeles), and received his Ph.D. at the University of Washington (Seattle) in 1958 under the supervision of B. S. Rabinovitch for work on the unimolecular isomerization of cyclopropanes. Since 1971 he has been a Professor for Physical Chemistry at the Technische Universität München. He has received several honors for his diverse research activities, which have been reported in more than 300 original papers and book contributions. He is a full member of the Bavarian Academy of Sciences, of Academia Europaea, and since 1984 a fellow of the American Physical Society. In 1988 he was made an honorary Doctor of the Hebrew University in Jerusalem. His main interests currently focus on the investigation of the structure and dynamics of molecules and molecular complexes with high resolution spectroscopic methods and the laser mass spectrometry of large biomolecules.

source such as synchrotron radiation across an ionization threshold and selectively detecting electrons with zero kinetic energy. ZEKE spectroscopy has been extensively used by many other groups, making it impossible to present a representative cross-section of the present work. The reader is therefore directed to two recent books^[19,153] and a review^[21] for further references. The present review first describes an overview of the ZEKE method and then concentrates on a selection of chemical applications.

In contrast to conventional PES, ZEKE spectroscopy offers a resolution that is essentially limited by the typical bandwidth of a tunable pulsed dye laser (about 0.1 cm^{-1}).^[17,23–25] This enables the resolution of rotational states of larger molecular cations and even the preparation of specific rovibronic states, opening the way to new experiments in chemical reaction dynamics. For molecular transitions between two bound states the selection rule $\Delta J = 0, \pm 1$ must be followed, whereas angular momentum transfers between the ion and molecule that are larger than ± 1 are possible for ionizing transitions. Especially rewarding is the combination of the ZEKE method with resonance enhanced multiphoton ionization (REMPI), where ionization occurs through one or more intermediate states. Owing to the Franck–Condon principle these intermediate states act as a kind of “filter” for the final state, thus further increasing the resolution. REMPI has been extremely successful as a sensitive method for obtaining electronic excitation spectra with rovibronic-state resolution. This has enabled the study of Rydberg-state dynamics,^[15,26] photo-fragmentation processes, and the dynamics of photoionization apparent in the coupling between the molecular ion core (in a certain eigenstate) and the ejected photoelectron.^[19,27]

A further significant improvement in resolution arises from the involvement of Rydberg states. If the photon energy falls just short of the ionization energy, an electron is promoted to a Rydberg state (a state with a high principal quantum number n). Whereas low-lying Rydberg states (with low n) readily interact with the molecular core and rapidly decay through radiationless transitions (i.e., predissociation or autoionization), the higher Rydberg states ($n > 150$) have lifetimes up to some ten microseconds and can be selectively ionized with pulsed-field ionization (PFI).^[24,25,28] This “magic” Rydberg region (typically 1 meV below the ionization threshold) can be used to produce a ZEKE signal with high resolution. The term “magic” was applied to the Rydberg states that exist in this region because of their unexpectedly long lifetimes.^[29] Chupka^[30] originally pointed out that this lengthening in lifetime probably arises due to mixing of the angular momentum l and its projection m_l , which results in a lifetime $\tau \propto n^5$ instead of the usual $\tau \propto n^3$.^[31] ZEKE-PFI^[28] has now become the most widespread experimental realization of ZEKE spectroscopy.

The superiority of the resolution (about three orders of magnitude) of the ZEKE method over traditional PES is illustrated in Figure 2. The vibrationally resolved photoelectron spectrum of NO, excited by a He^I light source,^[4] is compared to the first ZEKE spectrum measured in 1984 with the C²Π state of NO as intermediate resonance in a (3+1) photoionization experiment.^[14] In the ZEKE spectrum (Figure 2, bottom) the rotational structure of the NO⁺ cation is

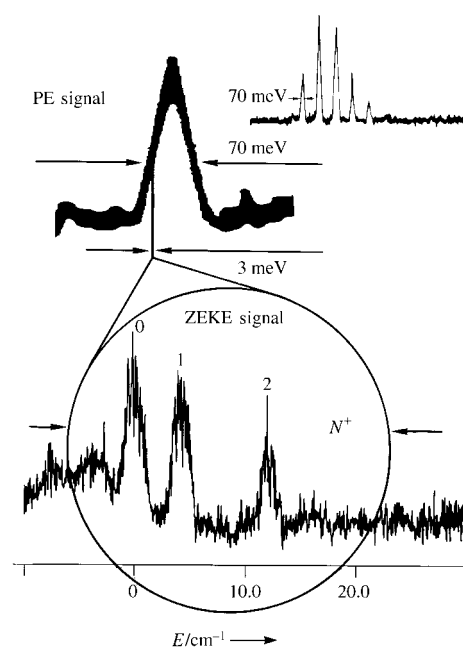


Figure 2. The first VUV photoelectron spectrum of NO^[4] (top) with a vibrational progression from $v^+ = 0$ to $v^+ = 4$ of the ${}^1\Sigma^+$ electronic ground state of NO⁺ and comparison of the $v^+ = 0$ peak with the first ZEKE spectrum obtained.^[14] The ZEKE spectrum shows the lowest rotational states in the vibrational state $v^+ = 0$ with $N^+ = 0-2$.

fully resolved. Recent rotationally resolved ZEKE spectra of the benzene cation^[32,53] were used to settle the debate regarding the structure of the ion, which is, in fact, planar and adequately described in the D_{6h} molecular point group, although it is subject to Jahn–Teller distortion.^[1]

In the field of vibrational spectroscopy the ZEKE method also achieves a major improvement over PES, as illustrated by the ZEKE spectrum of *para*-difluorobenzene (Figure 3, bottom),^[33] which reveals a much clearer vibrational structure than the time-of-flight photoelectron spectrum (Figure 3, top).^[34] ZEKE spectroscopy has now also been successfully

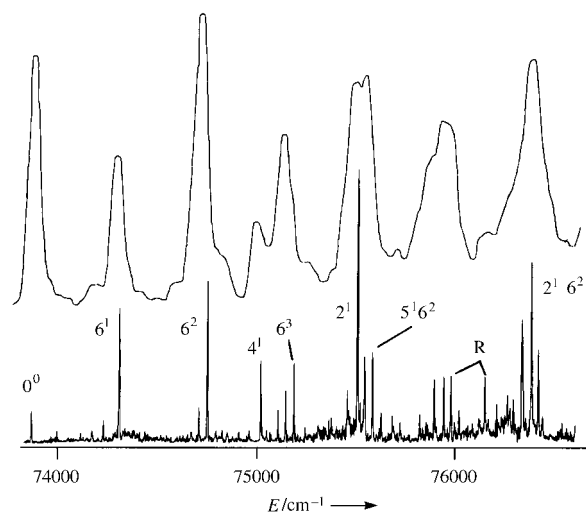


Figure 3. The time-of-flight photoelectron spectrum^[34] (top) and ZEKE spectrum^[33] (bottom) of *para*-difluorobenzene through the $S_1, 6^1$ intermediate state. The improvement in vibrational resolution obtained in ZEKE spectroscopy is illustrated. R = accidental resonances of the second laser in the S_1 state.

applied to studies of the vibrational structure of molecular^[35,36] and metal clusters^[37–39] and systems with hydrogen bonds.^[18,40–46] With ZEKE spectroscopy ionization energies E_i can be determined with an accuracy comparable to that of Rydberg extrapolations but with less experimental effort, even if Rydberg series are not resolved.^[25]

2. Experimental Details of the ZEKE Method

The idea and principles of ZEKE spectroscopy have already been discussed in a number of papers,^[13,14,23,26,47,48] and other reviews.^[15–22,27,51,153] The term ZEKE spectroscopy is now commonly used to describe any experimental technique that detects electrons in a small, experimentally adjustable energy range around (i.e., above and below) a selected ionization threshold with delayed pulsed electric field extraction^[13,14] (for a discussion of the older threshold techniques and their relation to ZEKE spectroscopy, see references [15,19]). In contrast to PES, in which a fixed photon energy is used for ionization, the ZEKE method involves the detection of electrons that are formed with zero kinetic energy when the light source is scanned across the region of the ionic threshold. ZEKE electrons (within a certain bandwidth) are produced when the energy of the incident light matches the energy of a rovibronic transition between the initial state of the neutral molecule and the final state of the ion.^[15] It should be noted that there are two different ways to produce electrons that contribute to the measured ZEKE signal (Figure 4). First, there are electrons with very low

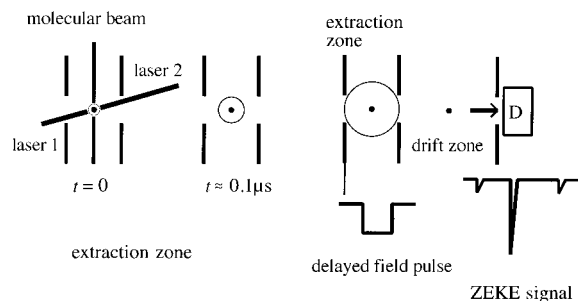


Figure 4. Principle of delayed pulsed field extraction. ZEKE electrons remain at their original position (assuming field-free conditions), whereas kinetic electrons disperse with increasing delay time. The delayed field pulse extracts the ZEKE electrons, which are measured by the detector (D).

kinetic energy, which are generated by photoionization at the threshold (a threshold implies, for molecules, a rovibronic eigenstate of the cation). These “free ZEKE electrons” are discriminated from kinetic electrons with the steradiancy principle^[5,15,49] and time-of-flight separation.^[50] Secondly, as discovered by Reiser et al.,^[28] electrons from long-lived Rydberg levels of high principal quantum number n very close to the threshold contribute significantly to the ZEKE signal or even constitute the observed ZEKE signal (Figure 5). Such electrons are generated by pulsed-field ionization of these high-lying ZEKE Rydberg states from the magic region (see below). The free ZEKE electrons, however, can

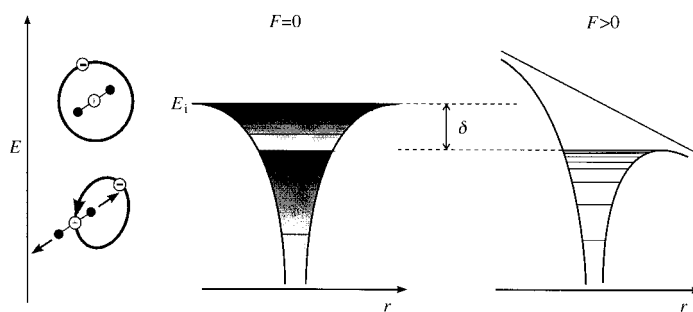


Figure 5. Schematic representation of the magic region of long-lived ZEKE Rydberg states (left) and pulsed-field ionization (right).

contribute to most of the signal when the bandwidth of the ionizing radiation is comparable or larger than the magic region of the long-lived ZEKE Rydberg states. This is typically the case for ZEKE experiments with VUV synchrotron radiation employing a normal incidence monochromator.^[50]

The experimental observation of long-lived (up to tens of microseconds) Rydberg states which converge to rovibronic energy levels of the ion has led to the currently most commonly used ZEKE technique, the detection of pulsed field ionized Rydberg electrons.^[28] Long-lived Rydberg states with a high quantum number n are clearly evident even in large molecules such as benzene^[32] and molecular clusters^[18,40–46,51] as well as in small molecules such as NO. These ZEKE Rydberg states which can be ionized by a pulsed field (by diabatic ionization that is described by $E \approx 4\sqrt{F}$, where E is the energy in wavenumbers and F the field strength in V cm^{-1})^[24] as depicted in Figure 5 owe their longevity to the fact that the electron no longer interacts with the core. For Rydberg states with a low quantum number n (Figure 6) the

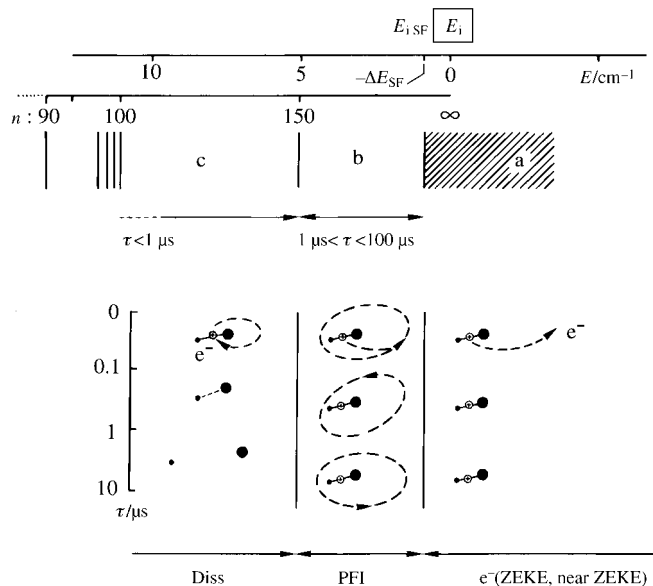


Figure 6. Stabilization of ZEKE Rydberg states in the magic region (b), a few wavenumbers below the ionization threshold (a). The Rydberg states below the magic region (c) predissociate into neutral fragments since the Rydberg electron still collides with the ion core. In the magic region the electron no longer collides with the core, and intramolecular relaxation processes are hence quenched. Diss = dissociation, PFI = pulsed-field ionization, SF = stray field, E_{iSF} = ionization energy in the strong field of the apparatus, τ = lifetime.

Rydberg electron still collides with the core, leading to intramolecular relaxation and particularly to predissociation into neutral products. This accounts for the surprising observation that bandwidths in ZEKE spectroscopy are generally not larger than 5 to 10 cm^{-1} , even when the height of the field pulse is increased, since the lower Rydberg states that would be ionized by the higher field pulse will decay in the field-free delay period (typically several microseconds). From an experimental point of view, this makes it particularly easy to obtain a ZEKE signal if a resolution a few wavenumbers is acceptable.

ZEKE-PFI can be used in combination with a slowly rising electric field extraction pulse (i.e., with a linear or multistep slope)^[17,20,25] to obtain the very high resolution (up to 0.2 cm^{-1}) which is essential for the rotational resolution of larger molecules such as benzene.^[32,52,53] By a variation of the pulse slope, the spectral resolution of the ZEKE-PFI technique can be adjusted in accordance with the laser bandwidth and the needs of the system under study, that is, whether vibrational or rotational resolution is necessary. This is demonstrated in Figure 7, in which the effect of the slope

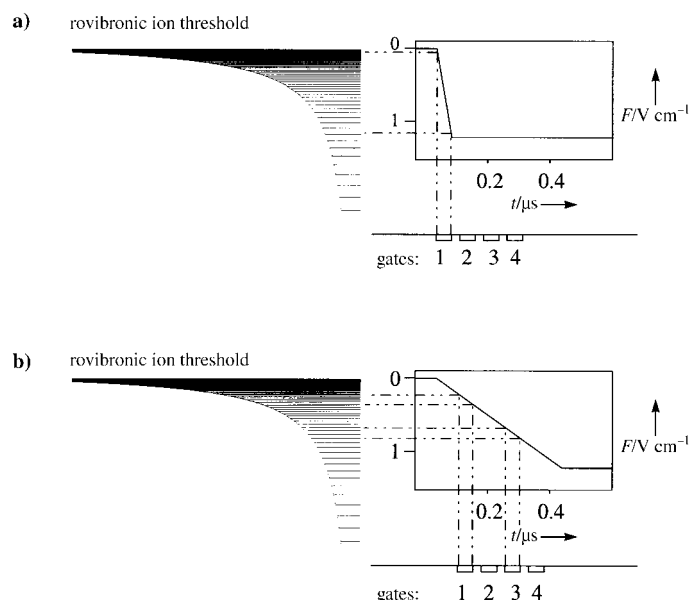


Figure 7. PFI of long-lived ZEKE Rydberg states with a) a fast-rising and b) a slow-rising pulse and detection within a certain time gate.

risetime of the pulse on the time-of-flight of the corresponding electrons produced by PFI is shown. A fast pulse generates the whole signal within a narrow time-of-flight distribution (Figure 7a), whereas a slow pulse spreads the different “slices” of Rydberg states into a broader time-of-flight distribution. By setting a time-of-flight gate and scanning the photon energy of the light source, a smaller spectral “Rydberg slice” is collected for a slow pulse than for a fast pulse. In fact, using a multistep staircaselike extraction pulse provides a method for the exact determination of the ionization energy under field-free conditions.^[25,54] Recently, a new technique which employs an inversion of the orientation of two field pulses to selectively ionize “red” or “blue” Stark states was used to gain a further improvement in

spectral resolution.^[23] An initial (offset) electric pulse selectively ionizes the more easily ionizable red Stark states (lower in energy), while the blue states (higher in energy) survive until a second (probe) pulse is applied in the opposite direction, shifting the blue states to lower energies. The offset:probe ratio can be tuned to produce optimum ZEKE resolution.

The origin of the long lifetime of the ZEKE Rydberg states is still under heavy discussion, and different models have been invoked. Theoretical approaches to these questions can provide new insight into the dynamics of molecular ZEKE Rydberg states.^[55–58] Small fields leading to “*I* mixing” seem to be involved, maybe with some intramolecular coupling.^[59–61] The role of ions in the probe volume,^[62,63] giving rise to inhomogeneous fields, is not yet fully understood since ion densities can vary over many orders of magnitudes in different experiments. Nonetheless, these theoretical concerns are not ultimately important for the experimental chemist, and the overall message that should be stressed is that long-lived Rydberg states exist in the magic region for all neutral systems, the region in which the ion core and the electron no longer interact.

It should be noted that the PFI technique is not applicable to photodetachment studies of anions, because no Rydberg states exist for these species. The original ZEKE method^[13,14] involving the detection of free electrons with negligible kinetic energy must be applied, but it can still yield the vibronic structure of the corresponding neutral molecule.^[38,64–66] The ZEKE photodetachment spectrum of IHI^- (Figure 8) is particularly interesting, as it provides an example

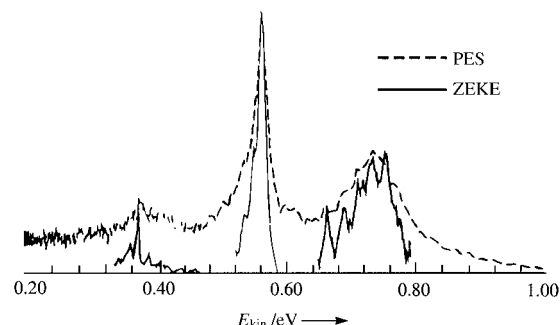


Figure 8. Comparison of the ZEKE spectrum^[65] (solid line) and photoelectron spectrum (dashed line) of IHI^- ^[66] (ν_3 vibration of the $[\text{IHI}]$ transition state).

of transition state spectroscopy. The spectrum displays resolved vibrational structure of the (metastable) activated complex $[\text{IHI}]^\ddagger$ of the reaction of iodine with hydrogen.^[65] This structure was not resolved by PES, as illustrated by the superimposed photoelectron spectrum^[66] in Figure 8.

A schematic representation of the experimental setup for a ZEKE experiment is shown in Figure 9. The apparatus consists of a laser system and a vacuum apparatus that contains a molecular-beam source, extraction plates, and a μ -metal shielded flight tube with an electron detector (i.e., dual multichannel plates) at its end. In a typical two-color experiment both dye lasers (typically frequency doubled) are pumped simultaneously by an excimer laser or a Nd:YAG

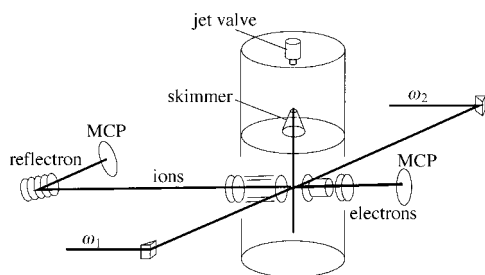


Figure 9. Schematic representation of a ZEKE apparatus for a two-color ZEKE experiment. MCP = multichannel plate (the detector), ω_1 = frequency of the pump laser, ω_2 = frequency of the ionization laser.

laser. The first dye laser excites a specific vibronic or rovibronic level of an intermediate state, and the second dye laser ionizes the molecules or promotes them into long-lived Rydberg states ($n > 150$), which converge to (ro)vibronic levels of the electronic ground state or an electronically excited state of the cation. After a delay time of several microseconds, an extraction pulse is applied by either a simple electric pulsing device or an arbitrary function generator. The electrons are detected with multichannel plates, and their time-of-flight signal is recorded with boxcar integrators or a transient digitizer by setting narrow time gates (10–30 ns).

3. ZEKE Spectra of Small Molecules

3.1. Nitric Oxide

Nitric oxide was chosen in 1984 for the first ZEKE study with the $C^2\Pi$ as intermediate since it was expected to display a clear rotational structure owing to its low moment of inertia. In a subsequent investigation the $A^2\Sigma^+$ state was selected as the intermediate resonance state^[67] and different transitions were used to populate certain rotational levels in the A state. This A state is a $3s$ Rydberg state with a contribution of 94 % s, 5 % d, and 0.2 % p orbitals.^[68] As it shows very small spin-rotation splitting, the state is well described by Hund's coupling case b (the standard case when the electron spin is not coupled to the molecular axis).^[48,67]

The ZEKE spectra for photoionization through the rotation states $N_A = 0$ to 2 (total angular momentum quantum numbers excluding electronic spin) for the A state are presented in Figure 10. A decrease in intensity for ionizing transitions that involve a change in rotational quantum number (i.e., $\Delta N^+ = N^+ - N_A \neq 0$) is observed as the rotational quantum number N_A increases.^[69] This effect is well understood from the theoretical work of Rudolph et al.^[68] in which the matrix elements for the continuum partial wave channels were obtained by an ab initio calculation. The second observation is the dependence of the nondiagonal ionizing transitions on the initial rotational quantum number N_A . For example, for $N_A = 2$ one observes a very strong increase in intensity for rotational transitions with $N^+ = -1$ and -3 . This effect—that is, the higher intensity of transitions involving a negative N^+ compared to a positive N^+ —is observed in other rotationally resolved ZEKE measurements^[19,22,70–74] and has been attributed to coupling between the ZEKE Rydberg states high n and those with low n .^[71]

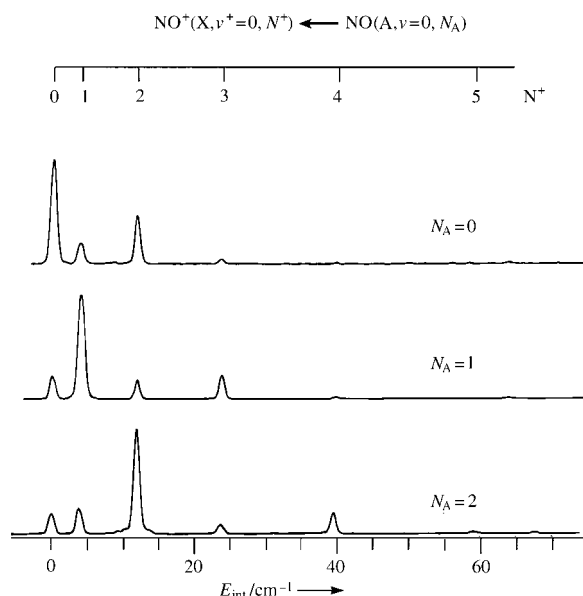


Figure 10. Rotationally resolved ZEKE spectra of NO through different rotational levels ($N_A = 0$ –2) of the $A^2\Sigma^+$ ($v = 0$, N_A) state.^[69] The spectra illustrate the ionization into different rotational states of the NO^+ cation.

3.2. Iodine

An interesting new class of experiments have probed the dynamics of ZEKE electron, for example spin-orbit autoionization. The ZEKE spectrum of I_2 was extensively studied through different intermediate Rydberg states by Cockett et al.^[72–74] A (2+1) REMPI process was used to select the intermediate state, while the energy of the third photon was tuned to obtain the ZEKE spectra. The $[^2\Pi_{3/2}]_{core}5d;2_g$ Rydberg state at around 62 600 cm^{-1} was used as intermediate state for ionization into the lower ionic spin-orbit state, and the $[^2\Pi_{1/2}]_{core}5d;2_g$ Rydberg state at around 68 000 cm^{-1} for ionization into the upper spin-orbit state. In the original work these states are referred to as $7s$ states.^[72,73] However, the assignments given do not conform to a recent reassignment of all ns Rydberg states of I_2 and Br_2 with $n > 6$ to $(n-2)d$ Rydberg states following a band-contour analysis of the REMPI spectra of Br_2 .^[75] One goal of the study was to resolve the question of whether the spin-orbit branching ratios in the ZEKE experiment reflected those observed in a conventional photoelectron spectrum. Spin-orbit autoionization processes can influence the distribution of peak intensities in the ZEKE spectrum, leading to a reduction of spectral intensity in the upper spin-orbit band which is offset by increased intensity in the lower spin-orbit state.

The two-color (2+1') ZEKE spectra of I_2 ionized by the band origin of the $[^2\Pi_{3/2}]_{core}5d;2_g$ Rydberg state at 62 639 cm^{-1} as well as by the first three vibrationally excited levels are presented in Figure 11. For the excitation of the band origin (Figure 11 a) the most intense peak corresponds to the $\Delta v = 0$ transition to the $v^+ = 0$ state of the ion. The total energy for the transition to this level is $75\,069 \pm 2$ cm^{-1} and represents the adiabatic ionization energy to the ion ground state. A weak vibrational progression built upon the origin band extends up

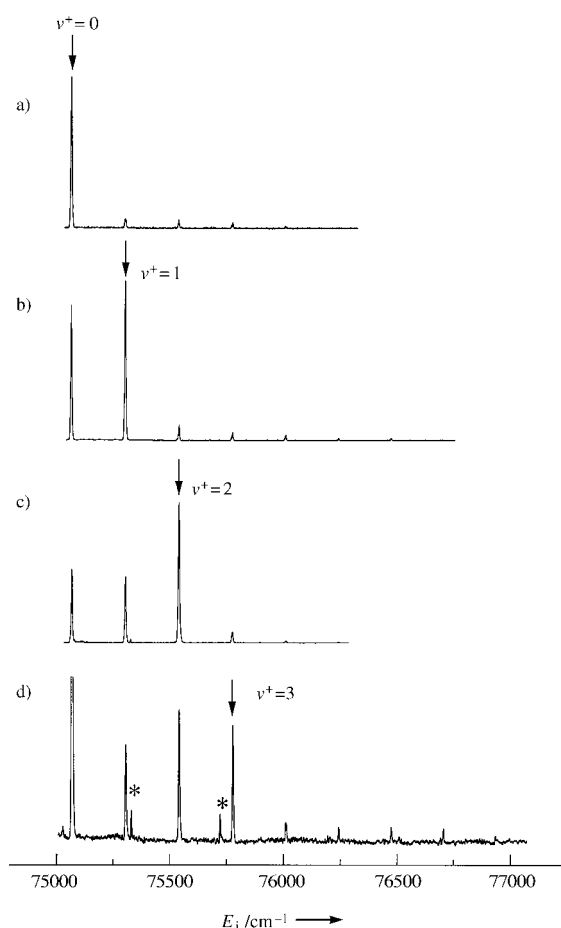


Figure 11. (2+1') ZEKE spectrum of I_2 recorded through the $[^2\Pi_{3/2}]_{\text{core}} 5d;2_g$ Rydberg excited state.^[72] The vertical arrows indicate the $\Delta v = 0$ transitions, and the asterisks accidental $A \leftarrow X$ neutral resonances.

to $v^+ = 4$. The minimal geometry change experienced by the molecule upon ionization is reflected in the dominance of the origin peak; this is exactly what one expects for ionization from a Rydberg state. However, the progression does extend to higher v^+ values than one would expect merely on the basis of Franck–Condon factors. For the $v^+ = 1$ intermediate state (Figure 11b) this behavior is even more pronounced. Again the $\Delta v = 0$ transition dominates, but the $v^+ = 0$ peak appears with nearly the same intensity as the $v^+ = 1$ peak. The stretching progression can be followed up to $v^+ = 7$. For intermediate states $v^+ = 2$ (Figure 11c) and $v^+ = 3$ (Figure 11d), this behavior becomes more and more pronounced. Although there is an emphasis of the $\Delta v = 0$ transition in all the spectra, the distribution of peak intensities cannot be described by a Franck–Condon envelope.

A rather different vibrational pattern was found in the upper spin-orbit state. The two-color (2+1') ZEKE spectra of I_2 ionized through the band origin of the $[^2\Pi_{1/2}]_{\text{core}} 5d;2_g$ Rydberg state at 67992 cm^{-1} as well as through the first two vibrational levels are presented in Figure 12a–c. In the spectrum recorded through the band origin (Figure 12a) the most intense peak corresponds to the $\Delta v = 0$ transition to the $v^+ = 0$ level of the ion. The corrected total transition energy to the origin is $80266 \pm 2 \text{ cm}^{-1}$, which corresponds to the

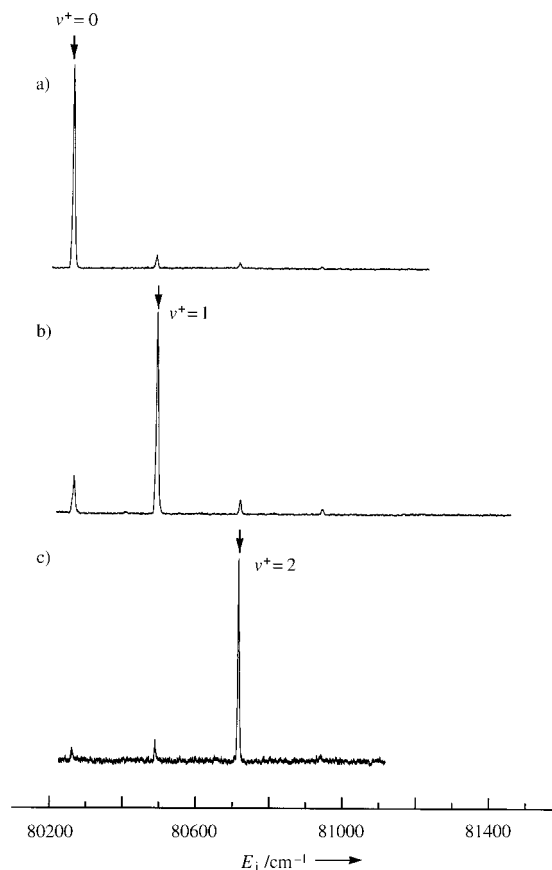


Figure 12. (2+1') ZEKE spectrum of I_2 recorded through the $[^2\Pi_{1/2}]_{\text{core}} 5d;2_g$ Rydberg excited state.^[72] The vertical arrows indicate the $\Delta v = 0$ transitions.

adiabatic ionization energy into the upper $^2\Pi_{1/2}$ spin-orbit state. This result, combined with the ionization energy for the lower $^2\Pi_{3/2}$ spin-orbit state, gives rise to an improved spin-orbit splitting constant for I_2^+ in its ground electronic state of $5197 \pm 4 \text{ cm}^{-1}$. For the upper spin-orbit component, increasing the level of vibrational excitation in the intermediate Rydberg states leads to a marked propensity for the $\Delta v = 0$ transition. This corresponds to classic Franck–Condon behavior.

The intensities in the lower spin-orbit state spectrum that do not correspond to Franck–Condon behavior were interpreted in terms of an autoionization mechanism involving a Rydberg series which converges to a higher ionic vibrational state. The ZEKE states with low n converging to higher thresholds interact with nearly degenerate ZEKE Rydberg states with high n in this region and can be ionized by the pulsed electronic field applied in ZEKE-PFI. There are no comparable states located in the vicinity of the upper spin-orbit state to perturb the intensities.

In an extension of this study, ionization of I_2 was studied through the valence B state. Owing to the valence character of the intermediate state, the ZEKE spectra into both spin-orbit components of the cation exhibit very long Franck–Condon progressions. For the lower spin-orbit component, an extended vibrational progression up to at least $v = 62$ is found, while the progression in the upper state can be followed as far as

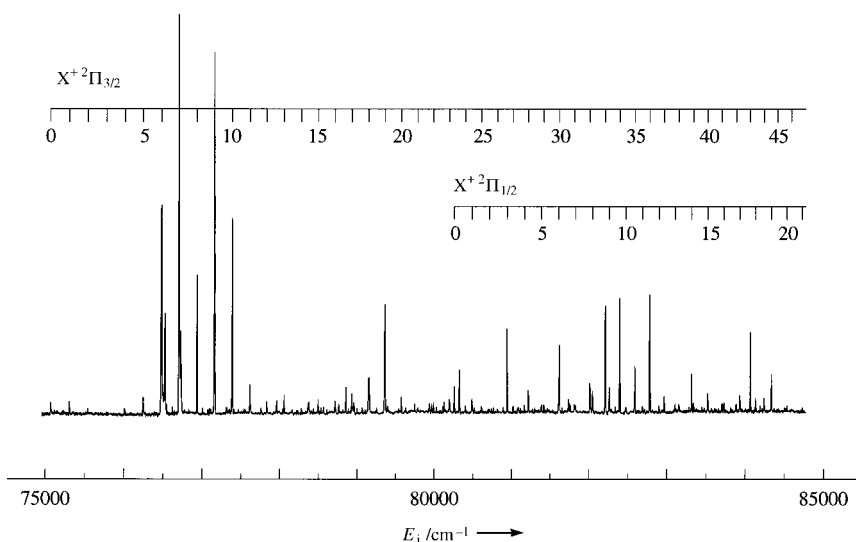


Figure 13. $(1+2')$ ZEKE spectrum of I_2 recorded through $v=15$ of the valence $B^3\Pi_u 0_v^+$ excited state with a long Franck–Condon-forbidden progression in the $X^+ 2\Pi_{3/2}$ state of the iodine cation.^[72]

$v=34$. The $(1+2')$ ZEKE spectrum of I_2 in the energy range 75000 to 85000 cm^{-1} recorded through $v=15$ of the valence B state^[73] is shown in Figure 13. Although the extent of the vibrational progressions can be adequately simulated through the calculation of Franck–Condon factors, the distribution of peak intensities and observed orbit branching ratio reflects the considerable contribution of both spin-orbit and field-induced resonant autoionization processes. In addition, accidental resonances at the two-photon level with ion-pair states further perturb the distribution of peak intensities.

3.3. Hydrogen Bromide

ZEKE spectroscopy has been used to follow the dynamics of photodissociation^[76] and predissociation in a variety of small molecules.^[77–81] Hepburn et al.^[82] recently recorded ZEKE spectra for the $v^+=1–3$ levels of the predissociating $A^2\Sigma^+$ state of HBr^+ by VUV excitation of high Rydberg states of HBr converging to the predissociating level. The ZEKE-PFI spectra were obtained with rotational resolution for both predissociating ($v^+=2,3$) and nondissociative levels. For the dissociating levels, field ionization occurs long after the ion core has fragmented; the Rydberg electron is unperturbed by the dissociation. Therefore, the spectrum results from field ionization of a Br atom in a high Rydberg state, which is produced by predissociation of the initially excited HBr Rydberg state. The intensities and lineshapes of the non-dissociating $v^+=1$ level and the predissociating $v^+=2$ level were comparable, demonstrating that the initially excited Rydberg electron is essentially undisturbed by the dissociating core. The $v^+=3$ level was considerably broadened, however, consistent with a lifetime of only 10^{-13} s. Adiabatic decay of high-lying Rydberg states converging to predissociating levels of the respective ions has also been observed in ZEKE-PFI of van der Waals complexes (see Section 8.1).

3.4. Ammonia

Ammonia, NH_3 , was the first polyatomic molecule studied by ZEKE spectroscopy^[47] for which the full rotational resolution in the cation was achieved in 1991. (An earlier study of benzene by Chewter et al.^[83] showed a partially resolved rotational structure which was not fully assigned.) Ionization was achieved by $(2+1')$ one-color REMPI excitation with the $\tilde{B}$ state as intermediate resonance excited through the two-photon transition $\tilde{B} \leftarrow \tilde{X}$. The excitation spectrum for the 2_0^+ transition obtained by a $(2+1')$ REMPI ion signal measurement shows clearly resolved rotational structure with Coriolis interaction and l -type doubling, allowing for rotational-state selectivity in the intermediate state. Two rotational states corresponding to the *ortho* and *para* nuclear-

spin modifications of NH_3 , that is, $J, K': 3, 1$ (*ortho*- NH_3) and $J, K': 3, 2$ (*para*- NH_3), were chosen as intermediate states for the ZEKE spectra.

The ZEKE spectra obtained from the two selected rovibronic levels of the $2^2\tilde{B}$ state (Figure 14), measured in the energy range between 21800 and 22300 cm^{-1} for the ionizing (probe) laser, correspond to the $v_2^+=1$ vibrational quantum number of the ion. There is a striking difference between the spectra obtained for *ortho*- (top spectrum) and

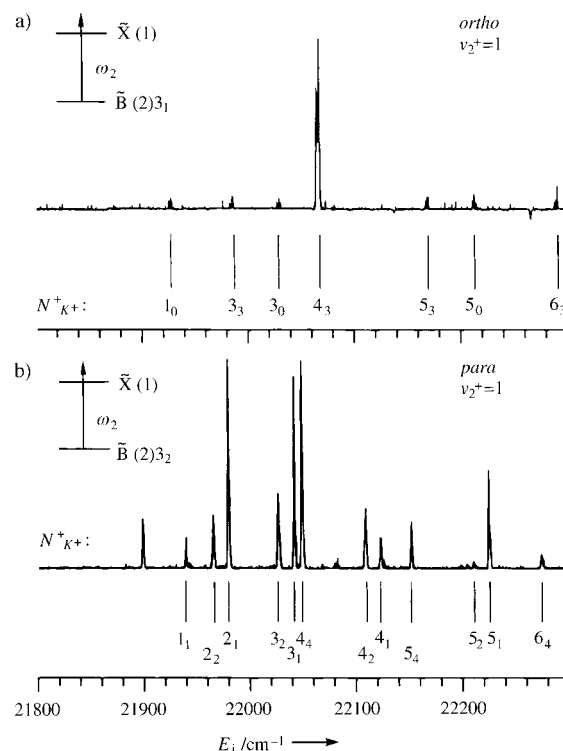


Figure 14. Rotationally resolved ZEKE spectra of the $v^+=1$ band of NH_3 through the $\tilde{B}(v=2)$ state with a) $J=3$, $K=1$ (*ortho*- NH_3) and b) $J=3$, $K=2$ (*para*- NH_3).^[47]

para-NH₃ (bottom spectrum). The ZEKE spectrum of *ortho*-NH₃ shows only a single transition into the ion rotational state with $N^+, K^+ : 4, 3$; there are additional transitions into $K^+ = 0$ and 3 which are weaker by at least an order of magnitude. On first sight this ZEKE spectrum looks as if it originates from the photoionization of an atom. In contrast, the ZEKE spectrum of *para*-NH₃ shows many more transitions with the strongest for $K^+ = 1$ and $N^+ = 4$, $K^+ = 4$ and some weaker transitions into $K^+ = 2$. The symmetry selection rules that apply to ZEKE transitions can account for the main spectral features.^[48]

3.5. The Renner–Teller Effect in the *trans*-Bending Vibration of the Acetylene Cation.

Linear molecules such as acetylene in degenerate electronic states (e.g. the ground state $\tilde{X}^+2\Pi_u$ of C₂H₂⁺^[84]) exhibit a form of vibronic coupling that is termed the Renner–Teller effect.^[1] The acetylene cation is of particular interest because it shows a Renner–Teller interaction that is expected to dominate both the rotational structure and the spin-orbit splitting. Briefly, the vibrational angular momentum l generated by the bending mode leads to a vibronic angular momentum $K = |\lambda + l|$, where λ is the projection of the electronic orbital angular momentum along the internuclear axis. For the $\tilde{X}^+2\Pi_u$ state of the acetylene ion, the spin is coupled to λ giving ω , which is then coupled to l to give $P = \omega + l$, the vibronic angular momentum including spin. A schematic energy level diagram for the Renner–Teller levels of the ν_4^+ *trans*-bending operation of the $\tilde{X}^+2\Pi_u$ state of the acetylene cation is shown in Figure 15. In the ZEKE experi-

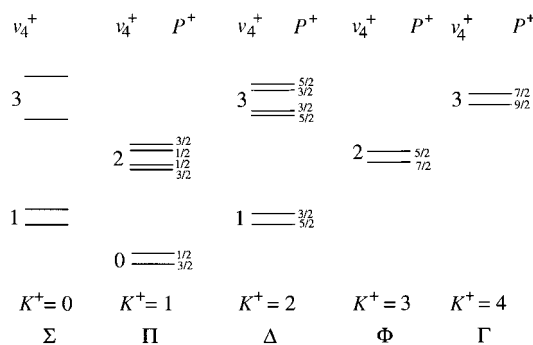


Figure 15. A schematic energy level diagram for the Renner–Teller levels of the ν_4^+ *trans*-bending vibration of the $\tilde{X}^+2\Pi_u$ state of the acetylene cation.^[85]

ments carried out by Pratt et al.^[85] it was not only possible to resolve the Renner–Teller splitting but also the spin-orbit and rotational structure of the $2\Pi_u$ state of the cation. The full level structure of this system and the selection rules, including the parity selection rule, are discussed in reference [85]. The additional vibronic bands that appear in these spectra can be explained by relaxation of symmetry selection rules that arises through the Renner–Teller effect. Figure 16 gives an overview of the ZEKE spectrum in the region between the $2\Sigma_u^+$ and the $2\Sigma_u^-$ components of the $\nu_4^+ = 1$ vibronic band, which are obtained by pumping the $R(1)V_4^0K_0^1\tilde{A}^1A_u \leftarrow \tilde{X}^1\Sigma_g^+$ transition of neutral acetylene.^[86,87]

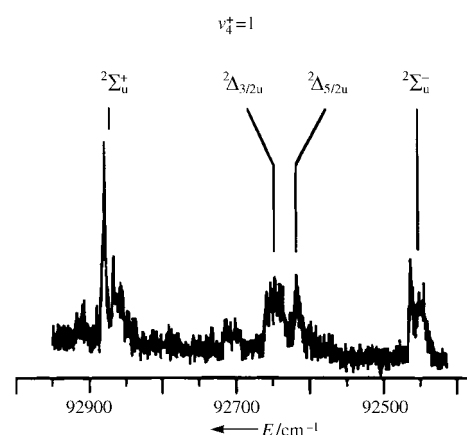


Figure 16. ZEKE spectrum of acetylene in the region of $\nu_4^+ = 1$ through the $R(1)V_4^0K_0^1\tilde{A}^1A_u \leftarrow \tilde{X}^1\Sigma_g^+$ transition in the neutral molecule.^[86,87]

3.6. Carbon Dioxide

The carbon dioxide cation with its $\tilde{X}^+2\Pi_g$ ground state is also subject to a Renner–Teller interaction. A thorough ZEKE study of this molecule with use of VUV single-photon ionization was carried out by Softley et al.^[88] They resolved the different Renner–Teller states ($2\Pi_{g3/2}$, $2\Pi_{g1/2}$, $2\Delta_{u5/2}$, $2\Delta_{u3/2}$, $2\Sigma_u^+$, and $2\Sigma_u^-$) and found that the propensity rules for angular momentum transfer during photoionization are very strongly dependent on the vibronic symmetry of the different ionic states. This has to do with the different Hund's coupling cases that apply to each of the different vibronic cation states. The spectral region studied in these experiments comprises the transitions from the ground vibronic state of CO₂ [$\tilde{X}^1\Sigma_g^+(000)$] to the two spin-orbit components of the ground state of CO₂⁺ [$\tilde{X}^+2\Pi_{g3/2}/\tilde{X}^+2\Pi_{g1/2}(000)$] as well as to the four Renner–Teller

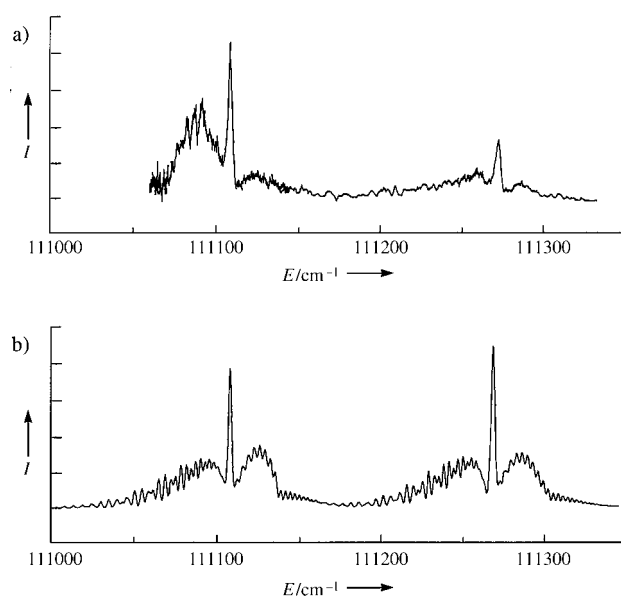


Figure 17. a) Experimental^[88] and b) simulated^[89] one-photon ZEKE spectrum of CO₂ corresponding to the $\tilde{X}^+2\Pi_{g,i}(000)$ ($i = 1/2, 3/2$) $\leftarrow \tilde{X}^1\Sigma_g^+(000)$ transition.

ionic substates which arise when one quantum of the bending vibration is excited ($\tilde{X}^+(010) \mu^2\Sigma_u^+, {}^2\Delta_{u5/2}, {}^2\Delta_{u3/2}, \kappa^2\Sigma_u^-$). The ZEKE spectrum of the $\tilde{X}^+2\Pi_{g3/2}/\tilde{X}^+2\Pi_{g1/2} (000) \leftarrow \tilde{X}^1\Sigma_g^+$ transition is reproduced in Figure 17a. The comparison to the theoretical fit (Figure 17b) using the approach of Buckingham et al.^[89] shows that some channel couplings between the ZEKE Rydberg states with high n and those with low n (converging to higher ionization limits) leads to some deviations in intensity and the enhancement of higher angular momentum transfer transitions. The study also revealed a disagreement with a Rydberg extrapolation to the ionization energy of Cossart-Magos et al.^[90] The disagreement of 10 cm^{-1} is far too large to be explained as experimental error. It may be that a perturbation in the Rydberg series used for extrapolating to $n \rightarrow \infty$ has not yet been properly accounted for.

4. ZEKE Spectra of Larger Molecules

4.1. Benzene

The neutral benzene molecule has a hexagonal, planar structure with D_{6h} symmetry.^[91–94] In the electronic ground state the electron configuration is $(a_{2u})^2(e_{1g})^4$. Upon ionization, one e_{1g} electron is removed from the highest molecular orbital, thus leaving one e_{1g} electron unpaired. This results in a doubly degenerate ${}^2E_{1g}$ electronic ground state of the cation. According to the Jahn–Teller theorem,^[95] for any nonlinear polyatomic molecule in a degenerate electronic state there exists a distortion of the nuclei along at least one nontotally symmetric normal coordinate. This results in a splitting of the potential energy function, so that the potential minimum is no longer at the symmetrical position.^[1,95–97] Several authors have discussed structural distortions of the benzene cation;^[98,99] model calculations predict three equivalent D_{2h} structures.^[98] These structures could be envisaged as locally distorted (elongated or compressed) structures as shown in Figure 18.

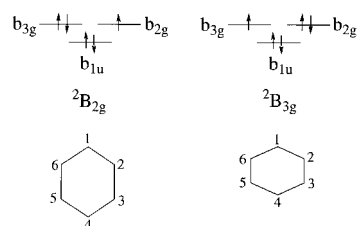


Figure 18. Distorted structures of the benzene cation resulting from removal of an e_{1g} electron from benzene, which corresponds to a reduction in the symmetry from D_{6h} to D_{2h} . The distortion can produce either an elongated (left) or compressed structure (right).

The distortion to D_{2h} symmetry can, in fact, be detected experimentally in a matrix at low temperatures.^[100] The ESR spectra of $C_6H_6^+$ in a freon matrix indicate an increased spin density at atoms C_1 and C_4 at 4.2 K but an equivalent spin density at 100 K (Figure 19). Thus, the question arises whether the D_{2h} structure is static and destabilized at higher temper-

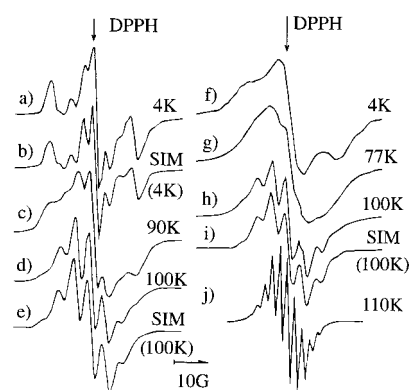


Figure 19. ESR spectra of the benzene cation in freon matrices at temperatures from 4 to 110 K.^[100] Spectra (a)–(e) were recorded in $CFCl_3$, while spectra (f)–(j) were obtained in CF_2ClCF_2Cl at various solute concentrations. SIM = simulated spectrum (at the temperature of the previous spectrum), DPPH = diphenylpicrylhydrazyl (standard). At higher temperatures the spectra support a structure of highest symmetry (D_{6h}), whereas at 4 K two different spin densities with intensity ratio 4:2 are found, which supports a distorted D_{2h} structure.

atures by collisions with the matrix or whether a dynamic D_{2h} structure is stabilized by the matrix lattice.

The experimentally determined value of 266 cm^{-1} for the stabilization energy^[101] is about the half of the zero-point energy of the lowest Jahn–Teller-active normal vibration. For weak Jahn–Teller coupling the stabilization energy for the distorted symmetry is smaller than the zero-point energy of the Jahn–Teller-active mode. Under collision-free conditions, the three equivalent D_{2h} structures of the cation would dynamically interconvert, and the ground state of the cation would still be described in the D_{6h} symmetry group. For strong Jahn–Teller coupling the cation would spend much time in one of the three structures, and would therefore be described in the D_{2h} symmetry group. The knowledge of the structure and the symmetry of the isolated benzene cation is desirable not only for testing quantum-mechanical model calculations, it is also of fundamental importance for organic chemistry. Rotationally resolved ZEKE spectroscopy allows an unambiguous determination of the symmetry of the cation by analysis of the rotational transitions together with group-theoretical considerations.^[1,102]

If one quantum of a Jahn–Teller-active normal vibration (for benzene normal modes with e_{2g} symmetry,^[95] ν_{6-9} according to Wilson's notation^[103]) is excited, the linear dynamic Jahn–Teller coupling leads to a splitting into two vibronic states with vibronic angular momentum $j = \pm 1/2$ and $j = \pm 3/2$.^[1,104] The quadratic dynamic Jahn–Teller coupling further splits the $j = \pm 3/2$ band into two substates, but leaves the $j = \pm 1/2$ state doubly degenerate.^[1] The excitation of an e_{2g} normal vibration in an E_{1g} electronic state leads to vibronic states with $B_{1g} \oplus B_{2g} \oplus E_{1g}$ vibronic symmetry. A first-order interaction lifts the fourfold degeneracy and results in two doubly degenerate vibronic states with $B_{1g} \oplus B_{2g}$ and E_{1g} symmetry, respectively. Higher order interactions can split the $B_{1g} \oplus B_{2g}$ state, but not the inherently doubly degenerate E_{1g} vibronic state. An unambiguous assignment of the individual, split vibronic states and an exact determination of their energies is necessary for a precise determination of

the strengths of the vibronic coupling. Rotationally resolved ZEKE spectroscopy is the suitable method for the unambiguous assignment of the symmetry species of the vibronic states and thus the vibrational modes of the benzene cation, thereby providing reliable values for the vibronic coupling strengths.

A first attempt to resolve the question of whether a static or a dynamic D_{2h} structure is applicable was carried out by gas-phase PES.^[101] The photoelectron spectrum shown in Figure 20 was obtained with a standard time-of-flight technique

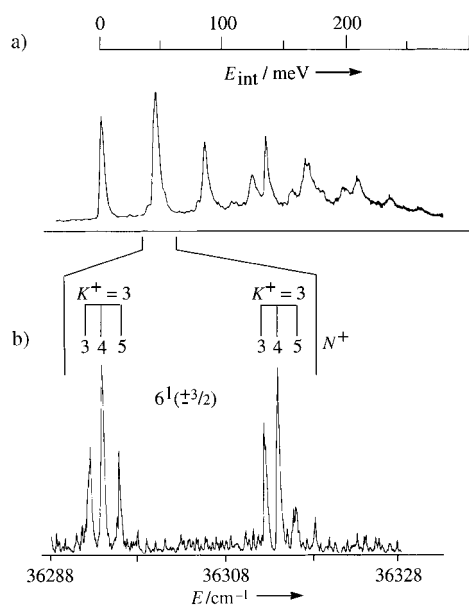


Figure 20. a) Time-of-flight photoelectron spectrum^[101] with limited vibrational resolution and b) ZEKE spectrum^[32] of benzene showing rotationally resolved $6^1(3/2)$ vibronic bands of the benzene cation.

and two-photon, two-color ($1+1'$) ionization with the $S_1 6^1$ state as intermediate resonance. The vibrational structure found in that photoelectron spectrum was assigned to the 0^0 vibrational origin and the 6^1 progression; the $6^1(3/2)$ and $6^1(1/2)$ states show linear Jahn–Teller splitting. No resolution of the quadratic Jahn–Teller splitting of the $6^1(3/2)$ state into the B_{1g} and B_{2g} components nor any resolved rotational structure was observed.

The rotational state of an oblate-symmetric rotor is characterized by two quantum numbers (Figure 21). For the ground state S_0 and intermediate states S_1 of neutral benzene, the relevant quantum numbers are J , the total angular momentum, and K , its projection along the principal axis of the molecule. For the benzene cation with electronic spin $S = 1/2$, the rotational states are characterized (assuming a weak spin-orbit interaction) by the quantum number N^+ , which describes the total angular momentum without electronic spin, and the projection quantum number K^+ . In degenerate vibronic states the rotational states split by Coriolis interactions must be differentiated by an additional quantum number, $\pm l$.^[1]

The determination of the rotational structure of the benzene cation and the assignment of the rotational transitions observed in the ZEKE spectra allow the determination of the vibronic symmetry species of the corresponding

vibrational state. This is done similarly as for ammonia.^[47,48] Starting with the known symmetry species of the intermediate state, in which only one rovibronic state is populated, the possible final states are determined based on group-theoretical considerations. The conservation of symmetry species of the nuclear spin wave function and the selection rules for electronic symmetry species as well as the coupling of angular momenta greatly restrict the possible transitions; depending on the vibronic symmetry species of the final state, only certain rotational progressions can be observed.^[32,48]

Figure 22 shows the ZEKE spectrum for the transitions into the ion ground state from the intermediate states $S_1 6^1$ ($J' = 1$, $K' = 1$, $+l$);^[32] the rotational states in $S_1 6^1$ are assigned according to reference [93]. The most notable feature in the rotational structure is the appearance of progressions in the

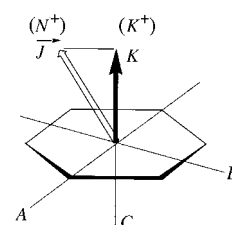


Figure 21. Conventions for benzene as a symmetric rotor. For the neutral molecule the total angular momentum quantum number is denoted J , and its projection onto the highest symmetry axis K ; for the cation electron spin is neglected, and total angular momentum is denoted N^+ with projection K^+ .

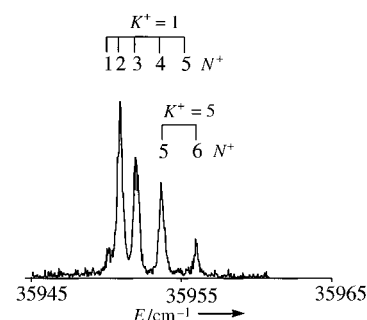


Figure 22. Rotationally resolved ZEKE spectrum of benzene at the vibronic origin (E_{1g}) of the benzene cation through the $S_1 6^1$ ($J' = 1$, $K' = 1$) intermediate state. Two rotational progressions with $K^+ = 1$ and $K^+ = 5$ are observed.^[32]

total angular momentum quantum number N^+ (without electron spin) of the cations with $K^+ = 1$ and $K^+ = 5$. For transitions between bound states, the selection rules $\Delta J = 0, \pm 1$ and $\Delta K = 0, \pm 1$ are valid. However, for a transition from a bound to an unbound state, the ZEKE electron can compensate for the angular momentum by vector coupling depending on the type of the partial wavefunction (s, p, d, ...), thus enabling higher changes in the rotational angular momentum.^[48]

It is interesting to observe the effect of excitation of a Jahn–Teller-active vibrational mode on the structure of the ion and to see how vibronic interactions influence the vibrational structure of the ground state. Because of vibronic coupling, the electronic wave function depends on the vibrational coordinate. According to the Jahn–Teller theorem, excitation of a degenerate vibration in a degenerate electronic state should lift the degeneracy, and splitting into vibronic states of different energies is expected.^[99]

For excitation of ν_6 , the second component of the ν_6 band with vibronic angular momentum $j = \pm 3/2$ is split due to the quadratic, dynamic Jahn–Teller effect into two states with B_{1g} and B_{2g} symmetry.^[104] Since both vibronic states have the same symmetry species B and their rotational constants should be close to each other, very similar rotational structures are expected for the two states. Figure 23 shows the ZEKE

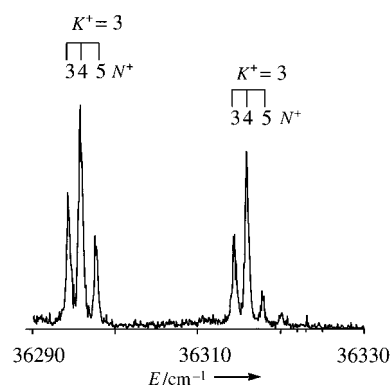


Figure 23. Rotationally resolved ZEKE spectrum of benzene at the lower 6^1 Jahn–Teller manifold $6^1(\pm 3/2)$ through the $S_1 6^1$ ($J=1$, $K'=1$) intermediate state. The two bands correspond to the B_{1g} and B_{2g} vibronic bands, which are split by the quadratic Jahn–Teller interaction. For each band only one rotational progression with $K^+ = 3$ is observed.^[32]

spectrum through the same intermediate state $S_1 6^1$ ($J=1$, $K'=1$, $+$).^[32] Two clearly separated vibronic states with almost identical rotational structures can be seen, which can both be assigned to a progression with $K^+ = 3$. This leads to the vibronic symmetry species B_{1g} and B_{2g} , in agreement with the symmetry selection rules for ZEKE spectroscopy; these components must be assigned to the two Jahn–Teller states $6^1(j = \pm 3/2)$. The separations of each set of two transitions with the same quantum numbers N^+ and K^+ agree to within $\pm 0.1 \text{ cm}^{-1}$. The mean splitting between the two states is 20 cm^{-1} .

The differences in the energies of the band origins of the $6^1(j = \pm 1/2)$ bands and the $6^1(j = \pm 3/2)$ bands is 331 and 311 cm^{-1} , respectively. This corresponds to roughly half of the vibrational energy of the ν_6 mode. Thus, the benzene cation is a good example for intermediate coupling, in which the vibrational frequency of the Jahn–Teller-active mode and the accompanying coupling strengths have almost the same values.^[32,53,104] With the precise energy values for the components of the ν_6 band that are affected by vibronic interaction, the results of quantum-chemical ab initio calculations can be examined very closely. Comparison with values published in 1992 shows how well these latest dynamic Jahn–Teller calculations can take into account several active modes.^[105] The difference between the calculated value for the $6^1(j = \pm 1/2)$ band of 694 cm^{-1} and the measured value of 676.4 cm^{-1} is only three percent.

The determination of the vibronic symmetry species of the vibronic levels of the benzene cation by rotationally resolved ZEKE spectroscopy was recently described for the B_{1g} and B_{2g} bands.^[53] The analysis of the ZEKE spectrum for the ν_6 mode

led to the assignment of the global minimum of the benzene cation as acute D_{2h} , with the caveat that the energy difference between the distortion isomers on the pseudorotation coordinate is only a few percent of the zero-point energy along this coordinate alone. The cation should therefore be viewed as a fluctuational, dynamical D_{6h} structure. The analysis of the full vibrational structure, which is highly irregular due to multiple-mode Jahn–Teller coupling, constitutes a significant contribution to the understanding of the Jahn–Teller effect and vibronic interactions. High-resolution experimental analysis of the cation of benzene, the prototypical aromatic molecule which is frequently the subject of theoretical studies, was not possible previously.

4.2. *para*-Difluorobenzene

The resolution of the vibrational structure of larger molecular ions is also an important application of ZEKE spectroscopy in chemistry. The considerable gain in resolution makes it possible to measure low-frequency vibrations and to analyze combination bands which may be congested in the photoelectron spectrum (see Figure 3). The cation of *para*-difluorobenzene (*p*-DFB), like most large molecular ions, does not fluoresce, making most methods of fluorescence spectroscopy inapplicable. Ab initio calculations from von Niessen et al.^[106] predicted an electronic configuration for the outer molecular orbitals of *p*-DFB of $\dots(b_{2u})^2(b_{3g})^2(b_{3u})^2(b_{1g})^2(b_{2g})^2(a_u)^0(b_{3u})^0$ within the D_{2h} symmetry group. From He^I and He^{II} photoelectron spectra^[4,107,108] it follows that the symmetry of the electronic ground state for the *p*-DFB cation is $^2B_{2g}$.

The ZEKE spectrum obtained from excitation through the vibrationless S_1 state is reproduced in Figure 24.^[33] The scanning region ranges from the ionization energy to approximately 3000 cm^{-1} higher; the majority of the spectral bands have been definitively assigned to vibrational states of the *p*-DFB cation. Aside from the vertical transition into the vibrationless state of the cation, the spectrum is dominated by transitions into totally symmetric modes and their combina-

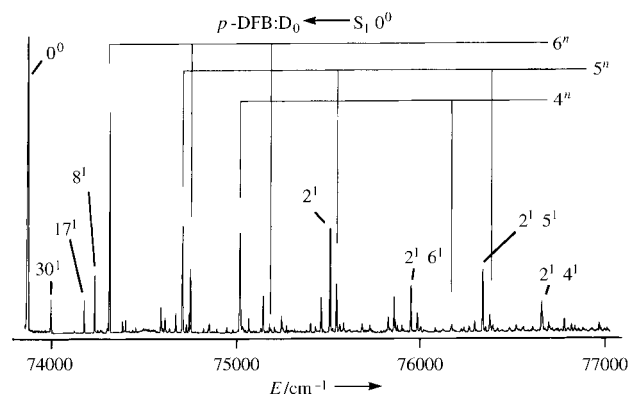


Figure 24. Vibrationally resolved ZEKE spectrum of *para*-difluorobenzene through the S_1 vibrational origin (0^0) as intermediate resonance.^[33] D_0 : cation ground state.

tion bands. The strongest transitions are the 6^1 , 5^1 , 4^1 , and 2^1 and various combinations of these quanta. However, the modes that are not totally symmetric— ν_{30} , ν_{17} and ν_8 —also appear and occur in combination with a_g modes. Several transitions could not be unambiguously identified in the present analysis.

Figure 25 shows the ZEKE spectrum using $S_1 6^1$ as the resonant intermediate state. For the ν_6 mode, a progression with four quanta is observed with the maximum intensity for the 6^2 level. This shift of the Franck–Condon maximum

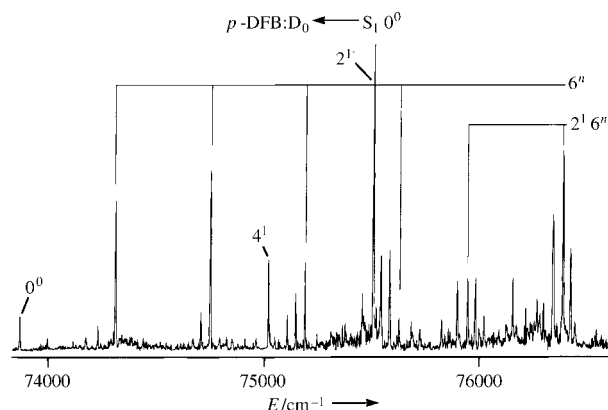


Figure 25. Vibrationally resolved ZEKE spectrum of *para*-difluorobenzene through the $S_1 6^1$ state as intermediate resonance.^[33] D_0 : cation ground state.

towards higher vibrational excitation in the ν_6 mode was also observed in the corresponding time-of-flight photoelectron spectrum.^[34] Again, the ZEKE spectrum mainly displays transitions into symmetric modes. Probable assignments, taking into account the combination bands, have also been given in reference [34]. The most prominent feature of this ZEKE spectrum is the strong activity of the a_g modes ν_2 – ν_6 (the a_g vibration ν_1 has not yet been seen in conventional photoelectron spectra and is, with the exception of the ZEKE spectrum from the $S_1 0^0$ state, outside the scanning range employed in the experiments reported here).

The restricted validity of the $\Delta\nu=0$ propensity rule for *p*-DFB should be noted at this point. This propensity has previously been observed for the ionization of aromatic molecules from their S_1 states.^[109] The failure of the rule is not so surprising though, as it is only expected to hold when the geometries of the S_1 and ionic states are similar (as they are, for example, for Rydberg states and their corresponding ions). Different vibrational excitations of the S_1 state produce some bands in combination with one quantum of mode ν_6 , which are of similar strength as the dominating $\Delta\nu=0$ transitions ($D_0 30^1 6^1 \leftarrow S_1 30^1$, $D_0 9^2 6^1 \leftarrow S_1 9^2$, $D_0 17^1 6^1 \leftarrow S_1 17^1$). The Franck–Condon maximum is observed for the 6^2 vibration of the cation for excitation through the $S_1 6^1$ intermediate state, which is in agreement with the previously published photoelectron spectrum^[34] (the stronger appearance of the 2^1 band in the ZEKE spectrum pumping the $S_1 0^0$ is due to the dye-tuning curve). The shift of the Franck–Condon maximum towards 6^2 implies that the geometries of the S_1 state and the ionic state differ along this mode, so that maximum

overlap is achieved for the first overtone in the ion rather than the fundamental.

Within the Franck–Condon approximation (and in the absence of any other coupling) no transitions should be observed for which the symmetry species of the vibrational wavefunction in the S_1 state is different from that of the ion. The most prominent transitions which violate this symmetry restriction are the ν_8 , ν_{17} and ν_{30} vibrations. Vibronic coupling (to an excited electronic state) in the cation cannot explain the occurrence of these three vibrations of different symmetry, and the origin of such symmetry-forbidden vibrations is still not perfectly clear. A possible mechanism could be channel couplings between Rydberg states with high n and those with low n converging to higher limits.

To aid in the assignment of the observed vibrations in the *p*-DFB cation and to check the experimentally observed vibrational frequencies, *ab initio* calculations were performed.^[33] The calculations support the experimental assignments for the ionic frequencies and lead to a D_{2h} structure for the S_0 and the ionic ground state. For the S_1 state deviations from the D_{2h} symmetry, mainly along the ν_8 coordinate, are indicated.

4.3. Pyrazine

Pyrazine has long served as a model for understanding intersystem crossing, since the S_1 – T_1 gap is small enough that there are a limited number of zero-order triplet states isoenergetic to a given singlet level. The spin-orbit interaction of T_1 and S_1 produces a set of mixed singlet–triplet states (molecular eigenstates). Hillenbrand et al.^[110] used ZEKE spectroscopy to study the degree of singlet–triplet mixing. The ZEKE spectrum they measured as function of energy above the first ionization limit for an excitation wavelength of the first laser corresponding to the S_1 – $S_0 0-0$ transition is reproduced in Figure 26. Surprisingly, they observed not only the expected transitions from S_1 to the electronic ground state of the ion (Figure 26, left) but also transitions from T_1 (Figure 26, right). The population of the triplet state T_1 , under the experimental conditions, is mediated through

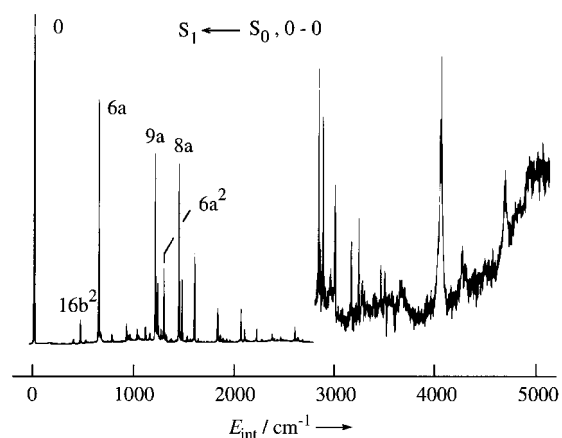


Figure 26. Vibrationally resolved ZEKE spectrum of pyrazine through the $S_1 0^0$ intermediate state.^[110]

pyrazine–argon clusters. The intersystem crossing is enhanced in the cluster, and evaporation of argon molecules produce a cold triplet monomer. With the assignment of the vibrations in the pyrazine ion, the lines associated with ionization of the triplet states were also assigned (including some vibrational structure of the triplet state itself).

5. Torsional Motions Observed in ZEKE Spectroscopy

5.1. Internal Rotation in the Toluene Cation

The occurrence of motion of large amplitudes, for instance in molecular clusters (see below) or in systems with internal rotors (e.g. methyl groups), has been followed with considerable interest in the last few years. The ZEKE spectroscopic measurements of toluene by Weisshaar et al. offer the opportunity to study how such systems behave upon ionization.^[111] The description of the toluene molecule and its torsional states relies on its rigorous classification according to its irreducible representations in the molecular symmetry group G_{12} ,^[102] which is isomorphic to the point group D_{3h} .

The problem of an unhindered, rigid methyl rotor attached to a rigid frame is reduced to a one-dimensional Schrödinger equation. The eigenfunctions are $\Phi_{\text{tor}}(\alpha) = (2\pi)^{-1/2} e^{\pm i m \alpha}$ with the eigenvalues $E_m = Bm^2$, where B is an effective constant for the rotation of the methyl group relative to the rigid molecular framework and $m = 0, \pm 1, \pm 2, \dots$ is the rotational quantum number. In toluene the torsional potential has sixfold symmetry. A small torsional perturbation of the form $V(\alpha) = (V_6/2)(1 - \cos 6\alpha)$ leaves the $m = \pm 1, \pm 2, \pm 4$, and ± 5 states doubly degenerate but lifts the degeneracy of the $m = \pm 3$ and $m = \pm 6$ levels. One defines $\alpha = 0$ when one C–H bond is in the plane of the benzene ring (eclipsed geometry);

when $\alpha = \pi/6$, one C–H bond is perpendicular to the ring (staggered geometry). In order of increasing energy (Figure 27), the rotor states are $0a_1'$, $1e''$, $2e'$, $3a_2''$ and $3a_1''$ (or vice versa), $4e'$, etc. Band intensities in the $S_1 \leftarrow S_0$ and cation- S_1 spectra reveal which $|m| = 3$ state lies lower in energy and thus the absolute phase of the torsional potential. For negative V_6 (potential minimum at $\alpha = \pi/6$) $3a_2''$ lies below $3a_1''$, whereas for positive V_6 (potential minimum at $\alpha = 0$) $3a_1''$ lies below $3a_2''$, as in the ground state of toluene.

In the absence of coupling between torsion and molecular rotation or between torsion and electronic motion, allowed transitions must preserve torsional-state symmetry: $\Gamma'_{\text{tor}} \otimes \Gamma''_{\text{tor}} \supset a_1'$. Accordingly, the $0a_1'$ and $1e''$ states of S_0 populated in the beam allow transitions only to a_1' and e'' states of S_1 . However, next to the

overlapping $0-0(a_1' \leftarrow a_1')$ and $1-1(e'' \leftarrow e'')$ bands the $S_1 \leftarrow S_0$ REMPI spectrum also shows the significantly weaker $2-1(e' \leftarrow e'')$, $3-0(a_1'' \leftarrow a_1')$, and $4-1(e' \leftarrow e'')$ transitions (due to weak torsional electronic coupling). ZEKE spectra of toluene through different intermediate resonances of S_1 are presented in Figure 28. The transition frequencies, referred to the respective origin, of the transitions into torsional states of the toluene cation ($0, 15, 54$, and 75 cm^{-1}) are not very different from those for $S_1 \leftarrow S_0$ ($0, 15, 55$, and 77 cm^{-1}). This leads to the conclusion that the torsional barriers in the cation and in S_1 are quite similar. An additional band at about 45 cm^{-1} was, however, observed in the cation.

For $2e'$ excitation of S_1 , a weak ZEKE band at 0 cm^{-1} (assigned as $1e'' \leftarrow 2e'$) and a stronger band at 16 cm^{-1} ($2e' \leftarrow 2e'$) was observed. For $4e'$ excitation, a weak ZEKE band at 0 cm^{-1} ($1e'' \leftarrow 4e'$) and a strong band at 78 cm^{-1} ($4e' \leftarrow 4e'$) occurs. For excitation of the $3a_1''$ level, one observes a weak ZEKE band at 0 cm^{-1} ($0a_1' \leftarrow 3a_1''$), a strong band at 47 cm^{-1} (tentatively assigned as $3a_1'' \leftarrow 3a_1''$), and a moderately strong band (about 30% of the intensity of the strongest band) at 54 cm^{-1} (tentatively assigned as $3a_2'' \leftarrow 3a_1''$). For ionization through the ground torsional level $0a_1'$ level of S_1 , the band at 47 cm^{-1} is much more intense than that at 54 cm^{-1} .

Under the assumption that coupling between torsion and electronic motion makes $a_2 \leftrightarrow a_1$ torsional transitions allowed but not $a \leftrightarrow e$ transitions and based on the fact that the band at 47 cm^{-1} is three times more intense than that at 54 cm^{-1} for ionization through the $3a_1''$ state of S_1 , the band at 47 cm^{-1} is assigned to the $3a_1'' \leftarrow 3a_1''$ transition and the band at 54 cm^{-1} to the $3a_2'' \leftarrow 3a_1''$ transition. These assignments of symmetry-forbidden transitions in the ZEKE spectra constitute a major step in understanding motions of large amplitude and the role of torsional-electronic couplings.

5.2. Torsional Motion in the Toluene Cation

The $(1+1')$ REMPI ZEKE spectrum of toluene was recorded between $63\,500$ and $66\,500 \text{ cm}^{-1}$ by Okuyama et al.^[112] Figure 29 shows the comparison of the ZEKE spectra through the different intermediate torsional levels (T^n) of the $S_1^1B_{1u}$ state with zero (T^0), two (T^2), and four quanta (T^4). For the origin excited in the S_1 state (Figure 29a) the origin peak of

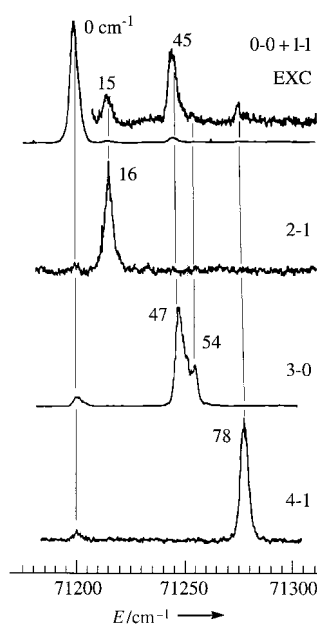


Figure 28. ZEKE spectra of toluene near the origin of the cation ground state $\tilde{X}^{+2}A_2''$ through different rotor states in S_1 (see Figure 27).^[111] EXC denotes the $S_1 \leftarrow S_0$ torsional transition used.

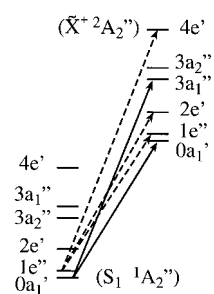


Figure 27. Nearly free rotor states and G_{12} -symmetry species for toluene (S_1) and the toluene cation. The arrows indicate the strongest ZEKE transitions (for $\omega_1 = 37475 \text{ cm}^{-1}$), which correspond to the $0-0$ and $1-1$ rotor transitions of $S_1 \leftarrow S_0$. Note the different order of the $3a_1''$ and $3a_2''$ levels in S_1 state and the cation.^[111]

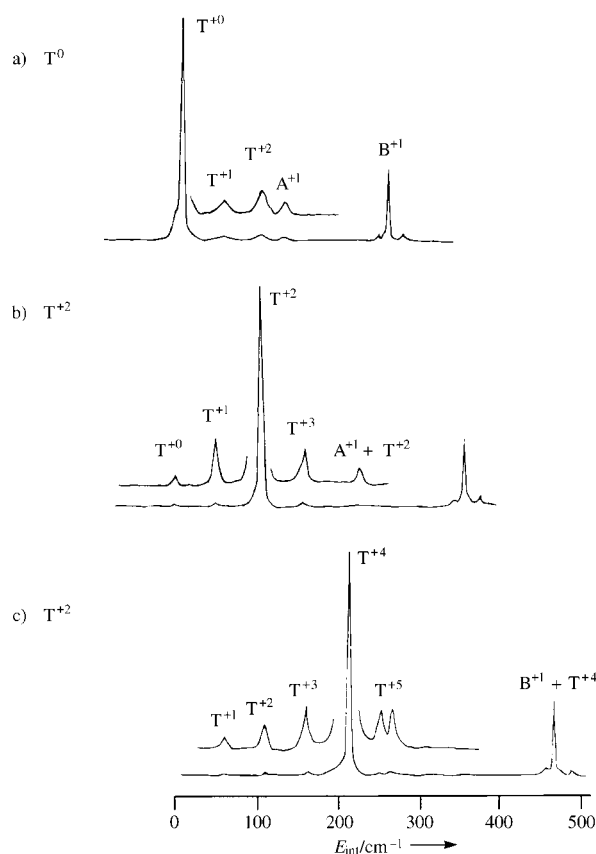


Figure 29. $(1+1')$ ZEKE spectra of tolane obtained through the a) T^0 , b) T^2 , and c) T^4 levels of the S_1 ${}^1B_{1u}$ state.^[112] T =torsional vibration.

the cation dominates along with the totally symmetric vibration B^{+1} . However, there is a signal of lower intensity for the torsional motions with odd quantum numbers (denoted T^{+1}) and even-numbered overtone (T^{+2}). For excitation of two quanta of the torsion S_1 similar results were found (Figure 29b). The strongest transition applies to $\Delta v = 0$ (in this case to T^{+2}). Also the B^{+1} vibration is found in combination with the T^{+2} torsional overtone. Though much less intense, peaks are also found for the cation origin (T^{+0} , symmetry-allowed) with transitions with odd torsional quantum numbers in the ion (T^{+1} and T^{+3} , symmetry-forbidden). A similar observation is made for excitation of the fourth torsional overtone in S_1 where again the $\Delta v = 0$ transition is favored, but torsional overtones with odd quantum numbers (i.e., symmetry-forbidden transitions) are once again observed.

Odd quantum levels of the torsional mode are clearly observed with weak intensities, as seen in Figure 29. Under the D_{2h} point group the torsional mode has a_u symmetry. There is no evidence for a large structural change upon photoionization. Though the intensity of the symmetry-forbidden transitions with odd torsional quantum numbers is weak, these transitions are a clear manifestation of the violation of the Frank–Condon principle. Similar observations have been made for a number of other molecules studied by ZEKE spectroscopy, and may be considered as a common phenomenon in ionization transitions.

6. Radicals

6.1. Benzyl Radical

The first radical studied by ZEKE spectroscopy was the benzyl radical. The ZEKE spectrum obtained by Weisshaar et al.^[113] is reproduced in Figure 30. The vibronic coupling in the intermediate state (the A^1 , A^2 , and A^3 states arising from vibronic coupling of the 1^2A_2 – 2^2B_2 system) allows the

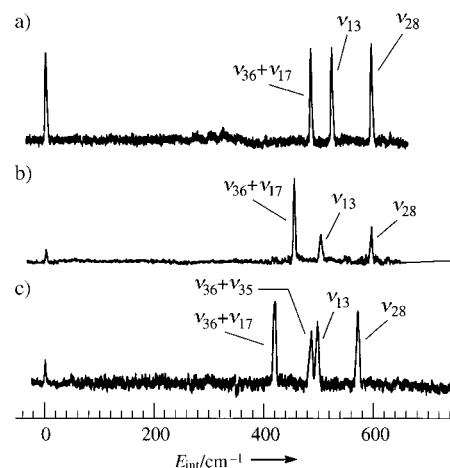


Figure 30. ZEKE spectra of the three isotopomers of benzyl a) (H_7), b) (α - D_2), c) (D_7).^[113]

observation of vibrational states of both a_1 and b_1 symmetry (C_{2v} point group) of the benzyl cation in the ZEKE spectrum. The frequencies of the out-of-plane modes of the benzyl cation, obtained from combination bands and ab initio calculations, show that the bond between the exocyclic CH_2 group and the benzene ring has substantially more double-bond character in the ion than in the neutral molecule. The ZEKE spectra for the three isotopomers of benzyl (H_7 , α - D_2 , and D_7) provide the adiabatic ionization energies 58465 ± 5 , 58410 ± 5 , and 58382 ± 5 cm^{-1} , respectively. The observation of both transitions, $\nu_{13}(a_1)$ and $\nu_{28}(b_1)$, is direct evidence of vibronic mixing in the A^1 , A^2 , and A^3 states and indicates that both electronic components of the 1^2A_2 – 2^2B_2 system are detected in the ZEKE spectrum.

6.2. Methyl Radical

The planar methyl radical, isoelectronic with NH_3^+ , was studied by White, Chen et al.^[114] This effort provided the first rotationally resolved ZEKE measurement of a polyatomic radical. One-photon ionization was achieved by using a tunable VUV laser source. The ZEKE spectrum of the methyl radical is reproduced in Figure 31. The rotational structure is very similar to that observed in parallel ($\Delta K = 0$) transitions between bound electronic states in CH_3 and CD_3 radicals; there is little evidence for $\Delta K = \pm 1$ subbands. Under the assumption that mainly P, R, and Q branches contribute to the spectrum, the simulation (Figure 31, bottom) fits reasonably well with the experimental ZEKE spectrum. The

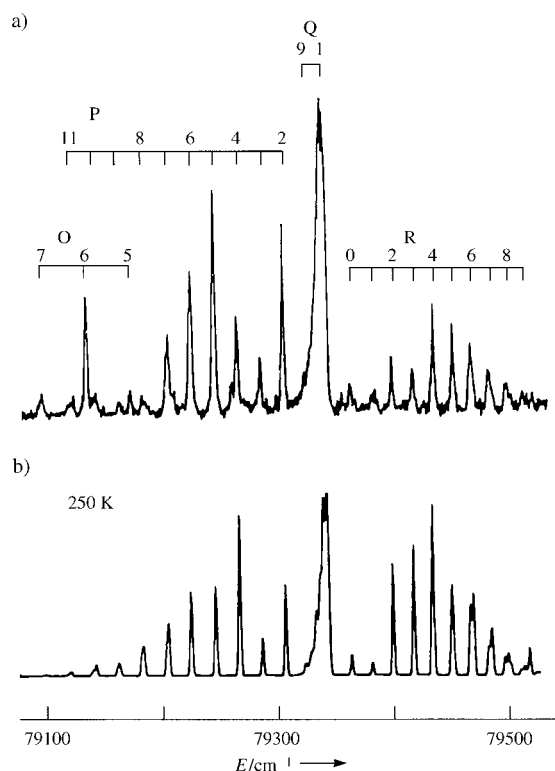


Figure 31. a) Measured and b) simulated one-photon rotationally resolved ZEKE spectra of the methyl radical with assignment of O, P, Q, and R transitions.^[114]

exclusive presence of the $\Delta K = 0$ transition suggests that only the ka'_1 continua account for the transitions. This seems to be in disagreement with the analysis of the Rydberg series.

7. Hydrogen-Bonded Clusters

Hydrogen bonding has received enormous attention over the years owing to its ubiquity in biological systems.^[115] The detailed study of hydrogen bonding in such systems is not straightforward, however, and attention has been focused on smaller systems in environments that are more amenable to interpretation by the chemist. The biggest successes have come from the study of 1:1 complexes in molecular beams.^[116,117] Although numerous studies have been performed on neutral complexes, there are very few studies that have concentrated on ionic species. These species are of great importance, as fundamental processes such as solvation depend on the interaction of ionic species with neutral molecules. The paucity of such studies is a result of the difficulty of producing significant quantities of ionic complexes in the gas phase (although infrared spectroscopy of ions is an extremely active field^[118–120]). Conventional PES does not offer sufficient resolution to determine the soft intermolecular vibrations, as can be seen in Figure 32 for phenol, phenol–water and phenol–(water)_n.

The major study of hydrogen-bonded species with ZEKE spectroscopy took place in one of our laboratories in the mid 1990s. To date, five different hydrogen-bonded species have

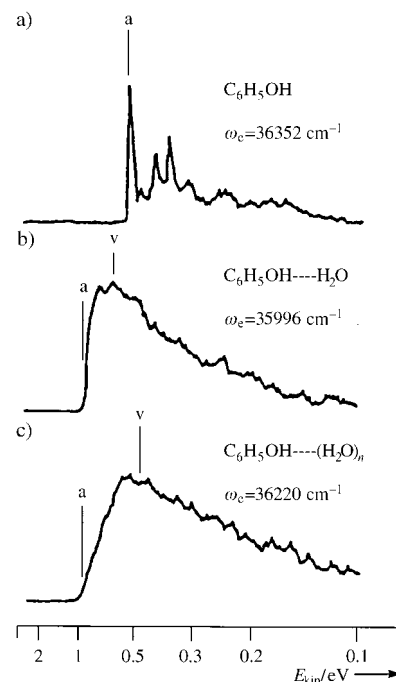


Figure 32. Photoelectron spectra of a) phenol, b) phenol–water, and c) higher pheno–water clusters through the S_1 intermediate state.^[127]

been studied, all containing phenol as the proton-donating moiety: phenol–water ($\text{PhOH}-\text{H}_2\text{O}$),^[40–42,121] phenol–methanol ($\text{PhOH}-\text{MeOH}$),^[43] phenol–ethanol ($\text{PhOH}-\text{EtOH}$),^[44] the phenol dimer ($\text{PhOH}-\text{PhOH}$),^[45] and phenol–dimethyl ether ($\text{PhOH}-\text{DME}$).^[46] The hydrogen-bonded clusters discussed here were recently reviewed in a broader context.^[18] The experimental modifications used to study $\text{PhOH}-\text{H}_2\text{O}$ are discussed in detail in the above-mentioned ZEKE studies. Briefly, phenol (heated up to 100 °C) and water vapor (partial pressure 10–50 mbar) were expanded through a 300 μm nozzle into a vacuum chamber with up to 6 bar of argon or neon as carrier gas to produce the $\text{PhOH}-\text{H}_2\text{O}$ complex. To record a ZEKE spectrum, the first dye laser was fixed resonant with the S_1 intermediate state of the complex, while the second dye laser was scanned through the ionization thresholds to populate the ZEKE Rydberg states; these were subsequently field-ionized by a delayed extraction pulse of 0.7 V cm^{-1} (delay 2 μs).

7.1. Phenol–Water

The $\text{PhOH}-\text{H}_2\text{O}$ complex and the series of complexes $\text{PhOH}-(\text{H}_2\text{O})_n$ ($n = 1-4$) have received much attention over the last 10–15 years. Several experimental techniques have been employed (see reference [18] for a comprehensive review). A number of ab initio studies on the neutral electronic ground state have also been published,^[122–125] all of which agree that the water lies perpendicular to the plane of the phenol and that the water hydrogen atoms are symmetric with respect to the mirror plane of the phenol ring; the complex is thus C_s -symmetric. Experimental studies on the 1:1 complex have concentrated on the first excited

singlet state S_1 (formed by a $\pi^* \leftarrow \pi$ excitation of the phenol ring) in the main, although some information is available on the ground state S_0 . The (1+1') REMPI spectrum of the PhOH–H₂O complex shows only a meager degree of structure.^[126] The transition into the vibrationless state is the most intense, suggesting that the geometries of the S_1 and S_0 states are fairly similar—at least along the hydrogen-bonding coordinates. Two other intermolecular vibrations appear: the reasonably strong stretching vibration (σ) at 156 cm⁻¹ and the weak in-plane wagging vibration (γ') at 121 cm⁻¹. The assignments of these bands have been refined over the years and can now be considered as certain, as shown by comparison of a high-quality (1+1') REMPI spectrum of the PhOH–H₂O complex with ab initio calculations.^[42, 122, 130]

Information about the low-frequency intermolecular vibrations of the ionic complex, in contrast to the neutral states of the 1:1 PhOH–H₂O complex, was rather sparse before the ZEKE studies.^[40–42, 121] A conventional (one-color, two-photon) time-of-flight photoelectron spectrum (REMPI-PES)^[127] measured through the vibrationless S_1 state does not show resolved structure for the vibrations of greatest interest, the intermolecular modes (see Figure 32). Two-color photoionization efficiency (REMPI-PIE)^[128] measurements through the vibrationless S_1 origin and the S_1 level, excited with one quantum of the intermolecular stretching vibration, showed the presence of at least one intermolecular vibration as a progression of steps in the ion-yield spectra. This vibration at 242 cm⁻¹ was assigned to the intermolecular stretching mode of the ionic complex. However, none of the other five possible intermolecular modes were observed.

In 1994 the 1:1 PhOH–H₂O complex was investigated in a more complete ZEKE spectroscopic study^[42] that included the triply deuterated complex (in which all oxygen-bound hydrogen atoms were substituted by deuterium atoms). For the non-deuterated complex, ZEKE spectra were obtained by exciting through three intermediate vibronic states ($S_1 0^0$, $S_1 \sigma^1$, and $S_1 \gamma'^1$; Figure 33). From the ZEKE spectra, the field-free ionization energy (corrected for the extraction field) was determined to be $E_i = 64027 \pm 4$ cm⁻¹. The same value, within experimental error, was obtained from all three intermediate states. The ionization energy of the fully protonated complex is 4601 ± 8 cm⁻¹ lower than that of the isolated phenol molecule^[129] (68628 ± 4 cm⁻¹). In a further work the partially deuterated (d_1)–(d_3) complexes were investigated.^[121]

From recent work, five out of the six possible intermolecular vibrations were extracted. As noted above, the predominant feature is the progression of the intermolecular stretching vibrations, which is also seen in combination with other intermolecular modes. This long progression (consisting of five quanta) of the intermolecular stretching vibration is indicative of the expected large change in the length of the hydrogen bond upon ionization. It is interesting that this progression is so strong (it is also observed in photoionization efficiency measurements),^[128] and a decrease in bond length of 0.018 Å was estimated from a one-dimensional Franck–Condon calculation. The progression itself was found to be quite anharmonic, a general finding from the ZEKE spectra of the different hydrogen-bonded complexes. The increase in frequency of the intermolecular stretching vibration of the

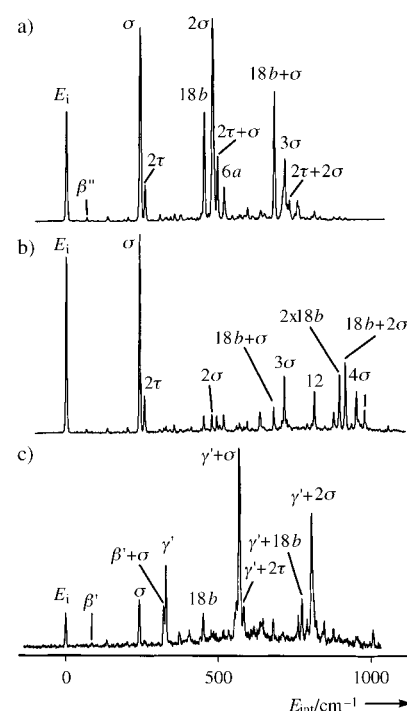


Figure 33. ZEKE spectrum of phenol–water a) through the vibrational origin of S_1 state (0^0), b) through the intermolecular stretching vibration excited in the S_1 state (σ^1), and c) through the intermolecular in-plane wagging excited in the S_1 state (γ'^1).^[42]

cation (240 cm⁻¹) over that in the S_1 state (157 cm⁻¹)^[42] and the S_0 state (155 cm⁻¹)^[122] illustrates the large increase in binding energy upon ionization. The other intermolecular vibrations that were observed are for out-of-plane bending (β'') at 67 cm⁻¹, in-plane bending (β') at 84 cm⁻¹, the first overtone of the torsional mode (2τ) at 257 cm⁻¹, and in-plane wagging (γ') at 328 cm⁻¹. Various features of the spectra were used to assign these modes, including the magnitude of shifts in vibrational frequency on deuteration, comparison with ab initio calculations^[125] that were carried out concurrently, and observation of the changes in intensity as the intermediate S_1 vibronic level was changed. The latter point was supported by Figure 33: In the ZEKE spectrum through the intermolecular $S_1 \gamma'^1$ level (Figure 33c) the ionic intermolecular in-plane wagging (γ') is strongly enhanced (as is the progression of the intermolecular stretching vibration starting on that particular vibrational origin) compared to the other two ZEKE spectra through the $S_1 \sigma^1$ (Figure 33b) and S_1 origin level (Figure 33a). The sixth intermolecular vibration, the out-of-plane wagging γ'' at 261 cm⁻¹, has now been identified from a ZEKE spectrum through the intermediate S_1 state (145 cm⁻¹).^[130]

One final point of interest is that the intramolecular ν_{18b} vibration of the complex at 450 cm⁻¹ couples strongly with the intermolecular stretching vibration. This observation was used to explain why this vibration appeared so prominently in the ZEKE spectrum of this complex, while it was seen only weakly in the ZEKE spectrum of the isolated phenol molecule. The coupling was identified from normal-mode pictures obtained from the ab initio calculations^[125] of the frequencies.

7.2. Phenol–Methanol

The study of the PhOH–MeOH complex was carried out in a similar way as the PhOH–H₂O complex: Phenol was heated, and the resulting vapor and methanol (partial pressure 20–100 mbar) were expanded with argon (up to 6 bar). The (1+1') REMPI spectrum was difficult to interpret owing to the proximity of a number of vibrations.^[18] Vibrational levels in the S₁ state were used as intermediate states on the way to ionization. The ZEKE spectrum^[43] obtained by exciting through the S₁ vibrationless level is particularly striking (Figure 34), as progressions of about ten quanta of a

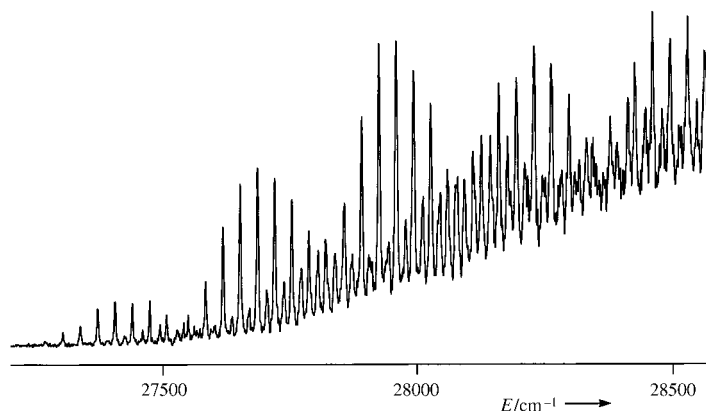


Figure 34. ZEKE spectrum of phenol–methanol through the vibrational origin of S₁(0⁰).^[43]

low-frequency vibrational mode, η_1 ,^[131] of 34 cm⁻¹ appear in combination with components of an anharmonic progression of the intermolecular stretching vibration of 278 cm⁻¹. This pattern clearly suggests a rather substantial change in geometry upon ionization. The adiabatic ionization energy was determined to be $63\,207 \pm 4$ cm⁻¹ (field-free value), which represented a large increase in bonding energy of 5421 ± 8 cm⁻¹ over that in the S₀ state. This is exemplified by the large increase in the intermolecular stretching vibration over the values of 176 cm⁻¹ in the S₁ state^[43] and 162 cm⁻¹ in the S₀ state obtained by dispersed fluorescence spectroscopy.^[132] Additionally, another set of progressions of the intermolecular mode of 34 cm⁻¹ was seen between the latter components, this time in combination with a third intermolecular mode of 52 cm⁻¹. The ZEKE spectrum obtained through the S₁ state which was excited with one quantum of the lowest frequency intermolecular mode showed the same vibrations, but with a substantially changed Franck–Condon envelope. This allowed the identification of a fourth intermolecular mode, η_4 , at 153 cm⁻¹. A slightly different envelope of the vibration at 34 cm⁻¹ was also obtained when exciting through the S₁ state with one quantum of the intermolecular stretching vibration (σ). The other two intermolecular modes of the PhOH–MeOH cationic complex were identified from the ZEKE spectrum obtained through a combination band; their values were 76 and 158 cm⁻¹. Therefore, as for PhOH–H₂O, in PhOH–MeOH all six intermolecular modes of the cationic complex were identified by using different intermolecular vibrational S₁ levels as intermediate resonances.

8. van der Waals Complexes

The first ZEKE study of a van der Waals complex was carried out by Chewter et al.^[133] on the benzene–argon cluster. The ZEKE spectrum revealed only one peak, assigned to the ionization threshold, that was shifted with respect to the benzene origin by 172 cm⁻¹. From that spectrum and the rather small change in ionization energy compared to the benzene monomer, the conclusion was drawn that ionization of the complex does not lead to a drastic increase in the binding energy of the argon atom.

For complexes containing benzene derivatives, an extensive ZEKE study of aniline–Ar and aniline–Ar₂ was carried out by Knee et al.^[134] The ZEKE spectra they measured (Figure 35) were normalized with respect to the origin of the

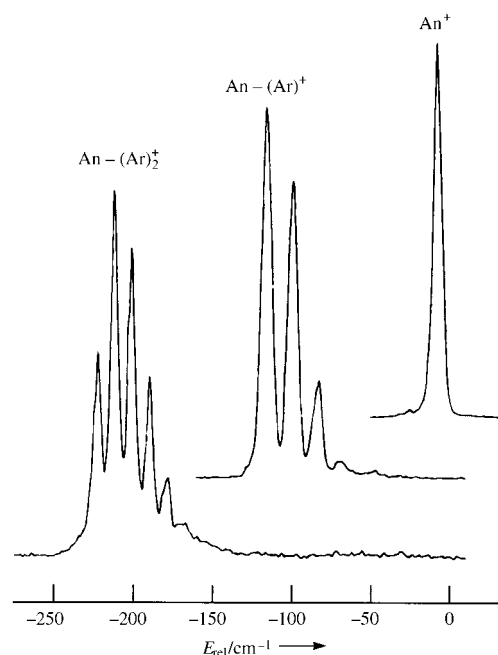


Figure 35. ZEKE spectrum of aniline–argon (An–Ar) complexes at the ionization threshold (with respect to the aniline cation).^[134]

aniline ion. For aniline–Ar the ionization energy was determined to be $62\,168 \pm 4$ cm⁻¹, indicating that the cation is more tightly bound than the S₀ and S₁ states by 113 and 60 cm⁻¹, respectively. From a comparison of the ZEKE spectrum of aniline–Ar and the S₁ ← S₀ transition in the neutral molecule, as investigated by Bieske et al.,^[135] it is apparent that the ZEKE spectrum shows more pronounced vibrational structure, specifically a progression of 15 cm⁻¹ for a single vibration. The analysis of the intermolecular van der Waals modes for the S₁ ← S₀ transition led to the following classification: symmetric stretching s_z (49 cm⁻¹), symmetric bending b_x (22 cm⁻¹), and asymmetric bending b_y (19 cm⁻¹). The motion of argon along the C₂ rotation axis (in C_{2v}-symmetric aniline) corresponds to the symmetric bending. The asymmetric bending motion takes place across the aromatic plane perpendicular to the C₂ axis. Fundamentals and overtones of these two symmetric modes are allowed and have been observed in the S₁ spectrum; however, they are not

very intense, indicating only a slight change in geometry upon $S_1 \leftarrow S_0$ excitation. By comparison with the S_1 spectrum, Knee et al. assigned the mode at 15 cm^{-1} as the symmetric bending vibration in the cation. The relatively long progression observed, according to Franck–Condon arguments, indicates a significant change in the geometry along the coordinations of symmetric bending upon ionization. This was explained by a positive charge on the nitrogen atom, which shifts the equilibrium position of the argon towards the amino group. No ab initio calculations were to support the assignment.

For aniline–Ar₂ a shift of 220 cm^{-1} relative to S_0 and 113 cm^{-1} relative to S_1 , with an ionization energy of $62061 \pm 4\text{ cm}^{-1}$, was obtained. The change in bond energy is almost exactly twice that of the 1:1 complex, producing a considerably extended Franck–Condon envelope. The most intense peak within the vibrational van der Waals progression is not found at the ion origin, but at the second member of the mode at 11 cm^{-1} . Following the symmetry analysis of Bieske et al.^[135] for the S_1 spectrum of aniline–Ar₂ and their classification, the progression observed in the ZEKE spectrum was assigned to the symmetric bending vibration along the C_{2v} axis (b_x). This vibration has a frequency of 15 cm^{-1} in the S_1 state, and upon ionization a reduction in frequency is again observed.

8.1. Transfer of Vibrational Energy and Predissociation in S_1

The excitation of an intramolecular vibration (i.e., in the aniline manifold) can lead to dissociation of the aniline–Ar complex due to the transfer of the intramolecular vibration energy to translational energy.^[136] A potential scheme to probe such S_1 dynamics is shown in, Figure 36. The pump

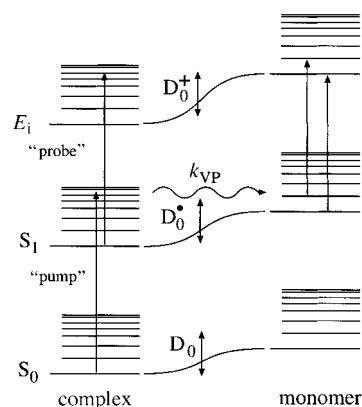


Figure 36. Schematic energy diagram for intramolecular energy redistribution and dissociation in a van der Waals cluster. D_0 = dissociation energy.

photon excites an intramolecular vibration in the S_1 state of the neutral van der Waals molecule. The ionization rate due to the probe laser (ionization laser) then has to compete with the predissociation rate (rate constant k_{vp}). Depending on the timescale of the experiment (i.e., the delay between pump and probe laser) one observes either the vibrations due to the aniline–Ar van der Waals complex or the aniline ion in the

ZEKE spectrum. For small delay times (i.e., the time overlap of pump and probe laser) one expects mainly ionization into the stable van der Waals cluster, whereas vibrations of the monomer cation are observed for longer delays.

Excitation of the overtone of the inversion vibration in the aniline ring (denoted I) is of particular interest. The first overtone of this vibration is clearly seen in the $S_1 \leftarrow S_0$ transition at 762 cm^{-1} . Excitation of this vibration should considerably interfere with the movement of the argon atom sitting on the aniline ring. When pumping the I_0^2 transition, the ZEKE spectrum indeed reveals features that are attributed to both the reactant (aniline–Ar) and the product (aniline). Figure 37 reproduces the ZEKE spectra for different probe laser delay times (with respect to the pump laser). Closer inspection reveals that when both pump and probe laser overlap in time, the spectral features observed are mainly due to the van der Waals aniline–Ar complex. With increasing delay time, features due to the van der Waals complex decrease in intensity, and vibrational features due to the monomer appear (see the arrows in Figure 37) and become prominent at delay times of 4 and 12 ns. Taking into account the energetics, the measured $S_1 \leftarrow S_0$ excitation spectra, and ZEKE spectra of the aniline monomer, Knee et al.^[134] were able to assign these vibrational features in the ZEKE spectrum with an optical delay of 12 ns to the transition into the origin of the aniline cation (denoted 0_0^{0+}) and the transition from the ν_{16a} vibration in which one quantum is excited into the ion that is also excited with one quantum of ν_{16a} (denoted $16a_1^{1+}$). Therefore, these spectra lead to the conclusion that the predissociation channel can leave the monomer either vibrationless or excited with one quantum of the ν_{16a} mode. The peaks attributed to the monomer are much broader than the ZEKE peaks not subject to predissociation. The width of approximately 28 cm^{-1} was attributed to rotational excitation of the monomer produced in the S_1 state by dissociation.

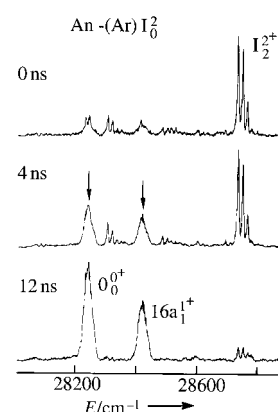


Figure 37. ZEKE spectrum of aniline–argon through the $S_1 I_0^2$ level (762 cm^{-1} ; i.e., ca. 300 cm^{-1} above the dissociation energy of the S_1 state) of the complex as a function of the delay time between pump and probe laser.^[136] The arrows indicate product states of the aniline monomer which grow in with increasing probe delay time and which are a measure of the dynamics in the S_1 state (dissociation and intravibrational redistribution).

9. Mass-Analyzed ZEKE Measurements

The PFI of ZEKE Rydberg states results in the formation of an electron and a cation, which may also be detected by mass analyzed threshold ionization (MATI); this mass-selective technique was originally suggested by Johnson et al.^[137] Compared to detection of the electron, which is very easy, that of cations must take place in the presence of other

spontaneous ions and is considerably more difficult. Hence, for normal ZEKE spectroscopy electron detection is more suitable, but MATI clearly offers additional information about mass. Optimized detection schemes are described in references [23–25].

The advantages of combining mass detection with ZEKE spectroscopy are particularly apparent for systems undergoing dissociation. An experiment by Krause and Neusser^[138,139] gave the following results for the dissociation of the C_6H_6-Ar van der Waals complex (the frequency of the first laser was tuned to the intermediate state of the C_6H_6-Ar complex produced in the seeded supersonic jet): The 6_0^1 transition is red-shifted by 21 cm^{-1} from the corresponding transition in benzene. Under these conditions the selectivity of excitation of the intermediate state is very good, and it is possible to ionize only the C_6H_6-Ar complex. The threshold ion, $[C_6H_6-Ar]^+$ and the fragment $C_6H_6^+$ were detected; the resulting mass-selected ZEKE spectra are shown in Figure 38. The spectrum in Figure c was obtained by selecting mass 78 u for a photon energy in resonance with the 6^1 state of benzene; it shows the vibronic structure of the monomer benzene cation.

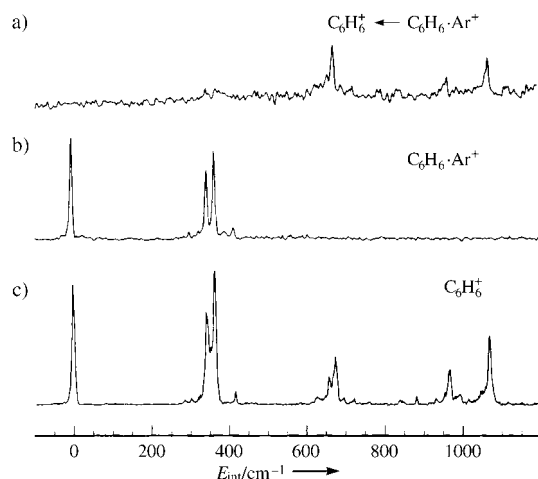


Figure 38. Mass-resolved ZEKE spectra in three different mass channels. a) ZEKE spectrum of benzene–argon measured in the benzene mass channel (78 u). The benzene ions are produced by PFI of fragment ZEKE Rydberg states of benzene originating from fragmentation of the benzene–argon complex.^[138] b) ZEKE spectrum of benzene–argon through the $S_1, 6^1$ intermediate state, measured by detecting benzene cations produced from PFI of ZEKE Rydberg states of benzene–argon (118 u). c) ZEKE spectrum of the benzene monomer through the $S_1, 6^1$ intermediate state, measured by detecting benzene cation produced from PFI of ZEKE Rydberg states of benzene (78 u).

Figure 38b shows the corresponding ZEKE spectrum for which mass 118 u was selected and the photon energy is in resonance with the 6^1 intermediate state of the neutral C_6H_6-Ar van der Waals complex. The resulting ZEKE spectrum is red-shifted by 127 cm^{-1} with respect to ZEKE spectrum of benzene due to the increased binding energy in the ion compared to the neutral molecule. A comparison of the ZEKE spectra of C_6H_6-Ar and benzene clearly shows that vibrational states above the 4^1 vibronic state have disappeared in the former. Those higher energy vibrations that disap-

peared in the ZEKE spectrum for mass 118 u appear in the ZEKE spectrum at mass 78 u (Figure 38a), which originates from the dissociation of $[C_6H_6-Ar]^+$ since the intermediate state of the neutral cluster is pumped and selected in the experiment. The experimental finding that the spectral signature of the cluster cation is actually found for the mass of the fragment (daughter ion) is quite astonishing. The dissociation of $[C_6H_6-Ar]^+$ by evaporation of the argon atom occurs within less than 100 μs and at an internal energy lower than 629 cm^{-1} (position of $16^1 6^1 \pm 3/2$).

This leads to the striking conclusion that the electron in the ZEKE Rydberg state does not notice dissociative processes in the ion core since it is bound by the positive Coulombic charge of the ion core. Higher multipole moments and even dissociative dynamics of the core do not constitute a sufficient perturbation to eject the ZEKE Rydberg electron. Hence, after the dissociation process of the core the ZEKE Rydberg electron is still bound by the positive charge now sitting on the fragment daughter ion. When a pulse field is applied this electron can be removed to produce an ion, and this ion is subsequently separated and measured in the MATI experiment. Similar results were also observed in the $p\text{-DFB}-Ar$ system.^[140] These measurements allow the determination of the lower and upper limits for the dissociation energy. In an additional study on benzene–krypton this dissociation energy could be determined within narrower ranges, and a comparison to the most advanced theoretical predictions could be made.^[141,142]

Much higher dissociation energies were reached in an experiment in which benzene ZEKE Rydberg states^[143] were excited about 4 eV above the ionization limit, leading to strong fragmentation.^[144] In spite of the high translational energy of the fragments, it was clearly established that the Rydberg electron once again follows the ionic core of the fragment. The ZEKE Rydberg state of the daughter fragment, with the fragment ion core, was then pulsed-field ionized in these mass-resolved ZEKE experiments.^[145] This result came as a big surprise and will have important implications for experimental studies of the dynamics of reaction in which fragments are “parked” in long-lived ZEKE Rydberg states.

MATI experiments on the $PhOH-H_2O-Ar$ complex, which shows hydrogen van der Waals bonds, should prove interesting for studying the interplay between different types of intermolecular bonds during fragmentation. Rapid intermolecular redistribution (IVR) of vibrational energy initially localized at the intermolecular hydrogen bond into the weaker van der Waals bond has already been observed in this system,^[146] leading to dissociation of the weaker van der Waals bond. The photoionization efficiency (PIE) curve for $[PhOH-H_2O-Ar]^+$ displays steps that correlate to each strong peak in the PFI-ZEKE spectrum. Notably, the steps in the PIE spectrum are rather broadened since the low-frequency intermolecular van der Waals vibrations of the argon atom and their combinations with the equally low-frequency vibrations of the hydrogen bond produce a high density of vibrational states close to each ionization threshold. Above a certain photoionization energy, the intensity of the $[PhOH-H_2O-Ar]^+$ signal remains constant,

while that of the $[\text{PhOH}-\text{H}_2\text{O}]^+$ signal increases, reflecting fragmentation of the parent cluster by ejection of argon. The energy difference between the appearance potential becomes constant in the $[\text{PhOH}-\text{H}_2\text{O}]^+$ channel and the point at which the $[\text{Ph}-\text{H}_2\text{O}-\text{Ar}]^+$ signal provides an upper limit for the dissociation energy of $[\text{PhOH}-\text{H}_2\text{O}-\text{Ar}]^+$ to $[\text{PhOH}-\text{H}_2\text{O}]^+$. This value should be reasonably close to the true dissociation energy as the density of optically accessible vibrational states close to the dissociation threshold is high.^[146]

10. Metals, Metal Oxides, and Metal–Carbide Clusters

A new field that has developed over recent years is the application of ZEKE spectroscopy to metal carbides and metal oxides. Analogous systems are believed to play a vital role in catalysis, and it is of great interest to prepare these compounds in a mass-selected way to study their structure and potentially their reactivity as a function of known composition.

Németh et al.^[147] obtained a well-resolved ZEKE spectrum of the silver dimer and thus improved values for the vibrational frequencies and ionization. More importantly, the ZEKE spectrum of Ag_2 revealed excitation in the cation up to very high vibrational quantum numbers ($v^+ = 10$). This completely non-Franck–Condon vibrational envelope was interpreted by channel couplings of the ZEKE Rydberg states with high n with those with low n . This results in anomalous intensities for the transitions that are forbidden by Franck–Condon rules.^[148]

Small vanadium, niobium, and yttrium clusters were studied by Yang et al.^[149–151] For the vanadium dimer, transitions were observed from the A state to two spin-orbit components with $\Omega = 1/2$ and $\Omega = 3/2$ ^[150,151] confirming that the cation ground state has $^4\Sigma_g^-$ symmetry, in accordance with previous experimental and theoretical work. For the rotational distributions in the $^4\Sigma_g^- \leftarrow \text{A}^3\Pi_{1u}$ and $^4\Sigma_g^- \leftarrow \text{A}^3\Pi_{2u}$ transitions striking differences were observed for the rotational propensity rules. The adiabatic ionization potential was determined to be $51\,271.1\text{ cm}^{-1}$.

The metal clusters probed in these experiments were produced by laser ablation of the metal with a supersonic expansion of helium gas over the target from a pulsed beam valve.^[149] The clusters were then excited in a two-color experiment. The geometric structures of the niobium and niobium oxide clusters are important (but unsolved) problems in cluster science as models for reactive systems in heterogeneous catalysis. To take full advantage of the cluster-surface analogy it is necessary to establish the structure of metal clusters containing several transition metal atoms, both in the presence and absence of ligands. It has proved difficult to address this problem in a satisfactory way with conventional spectroscopic techniques. The dense manifold of vibronic states that exists for even fairly small groupings of transition metal atoms has been a major impediment to the use of most forms of electronic spectroscopy for this purpose.

Given the lack of experimental data on the structure of small transition metal clusters, one often has to rely on

geometries determined from electronic-structure calculations. Density functional theory (DFT) calculations and other ab initio techniques have been used; the validity of the different theoretical approaches is under intense, even controversial, discussion. The DFT results presented by Yang et al.^[149,151] seem quite reasonable considering the difficulties encountered in such systems. It would be interesting if it can provide structures for transition metal clusters containing up to seven or eight atoms and bond lengths, including those for metal–ligand and metal–metal bonds.

The structures of transition metal systems can therefore be elucidated with a combination of ZEKE spectroscopy and ab initio calculations. This is a very promising development since it would allow ab initio calculations for large chemical systems. For Nb_3O the ground electronic configuration of the Nb atom is $4d^45s^1$. The electronic structure of a molecule containing three Nb atoms is very complex since the Nb atom has 15 electronic terms below 2 eV. Remarkably, the ZEKE spectrum of Nb_3O ^[151] (Figure 39) shows a completely resolved

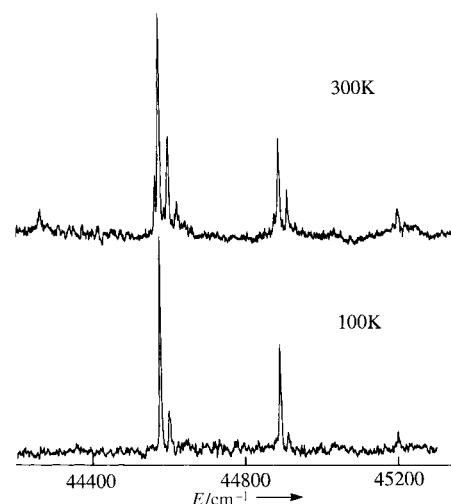


Figure 39. ZEKE spectra of Nb_3O at 300 K and 100 K.^[151]

vibrational structure, which can readily be assigned and simulated with multi-dimensional Franck–Condon factors. The Franck–Condon factors were calculated with use of the stable geometries and harmonic frequencies obtained from DFT calculations for the neutral Nb_3O molecule and the Nb_3O^+ ion. The remarkable agreement between the experimental and simulated ZEKE spectrum establishes the power of the ZEKE approach, coupled with DFT electronic structure and Franck–Condon calculations for resolving questions concerning the structure of these small transition metal clusters.

Figure 40 presents the minimum-energy structures and their relative energies for Nb_3O and Nb_3O^+ . These geometries were obtained by minimization of the total energy without symmetry constraints.^[151] The most stable structure for both Nb_3O and Nb_3O^+ is planar with C_{2v} symmetry. The oxygen atom is bound with equal bond lengths to two Nb atoms, and there are two distinct Nb–Nb bond distances in the cluster. The observed ZEKE spectra are in perfect agreement with this structure, as indicated by a simulation with the C_{2v}

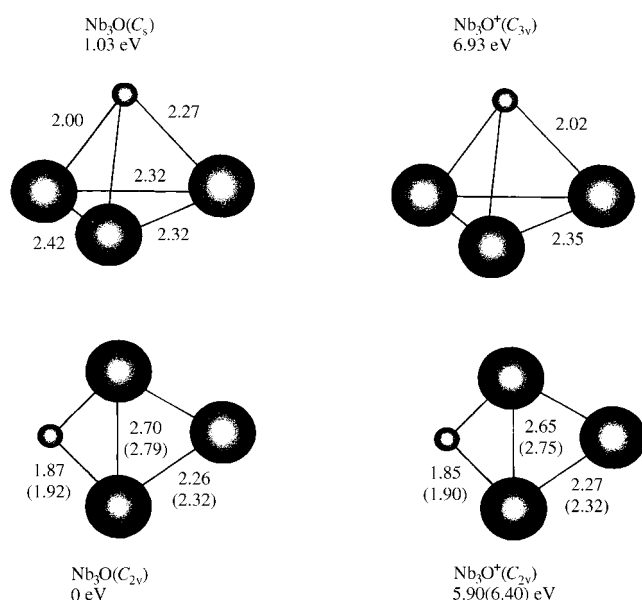


Figure 40. Geometries and relative energies for Nb_3O and Nb_3O^+ calculated with density functional theory.^[151]

structure (Figure 41). This confirms that three-dimensional structures like the ones in Figure 40 are associated with excited states, which play no role here.

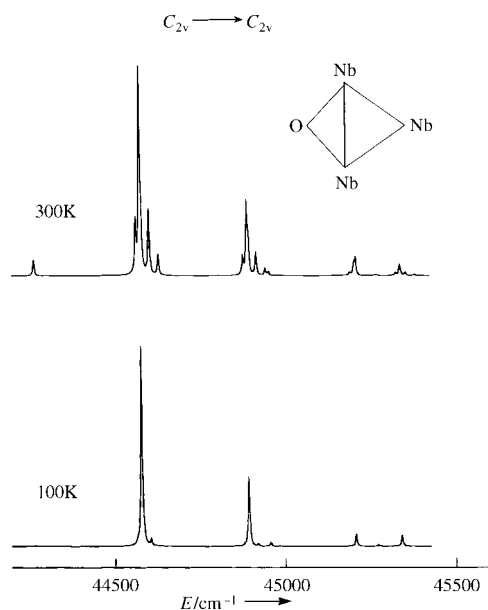


Figure 41. Simulation of the ZEKE spectra shown in Figure 39 with use of the structures shown in Figure 40.^[151]

An even richer spectroscopic structure can be seen for the cluster Nb_3C_2 . The ZEKE spectrum showing several vibrational progressions is reproduced in Figure 42.^[152] For this cluster, again with use of the DFT formalism, agreement was obtained for a C_1 structure of the neutral molecule and a D_{3h} structure for the cation (Figure 43b). The simulation of the ZEKE spectrum, again taking into account a multi-dimen-

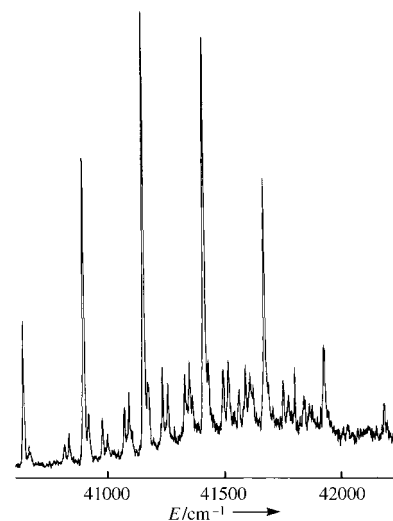


Figure 42. ZEKE spectrum of Nb_3C_2 .^[152]

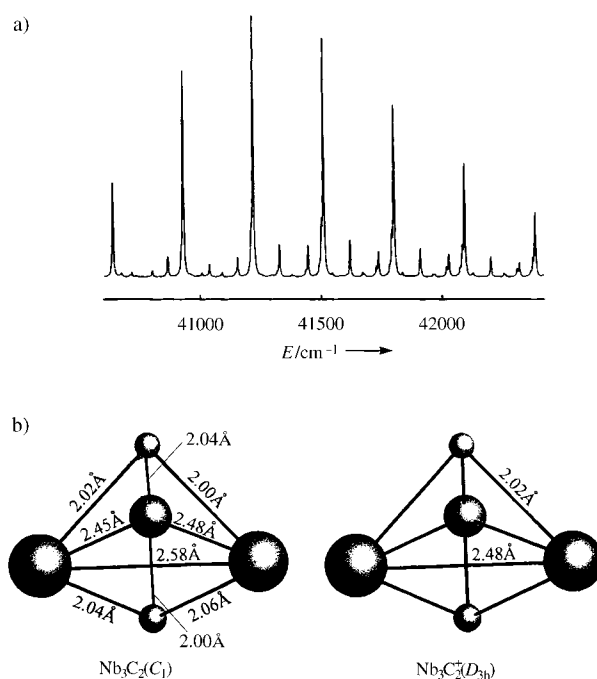


Figure 43. a) Simulated ZEKE spectrum of Nb_3C_2 . b) Structures obtained from DFT calculations.^[152]

sional Franck–Condon approach, is quite reasonable, though not all features of the spectrum appear (Figure 43a).

In conclusion, ZEKE spectroscopy combined with the sensible application of a suitable ab initio calculations reveals vibrational information on small transition metal clusters. The quality of the agreement between the experimental and the simulated spectra is sufficient to assign the geometry of a complex transition metal cluster.

11. Anions

The study of anions by ZEKE spectroscopy poses significant problems since the PFI variant of the ZEKE method (see

Figures 5–8) does not quite provide the same improvement (since the requisite Rydberg states do not exist), and electrons are detected just above threshold within a very small energy range (see Figure 4). This, in turn, implies that significantly more care must be taken to shield the ionization region from stray electric and magnetic fields. Neumark et al. first applied the ZEKE method to photodetachment spectroscopy^[64] and have been very active in this field. They have successfully performed studies on clusters of germanium,^[154] silicon,^[155] and halide ion molecules^[156,157] as well as transition state complexes.^[65] Their first ZEKE photodetachment spectrum was obtained in 1989 for the SH^- anion (Figure 44).^[64] It shows the clearly resolved rotational structure of the corresponding neutral molecule, the SH radical. More recently,

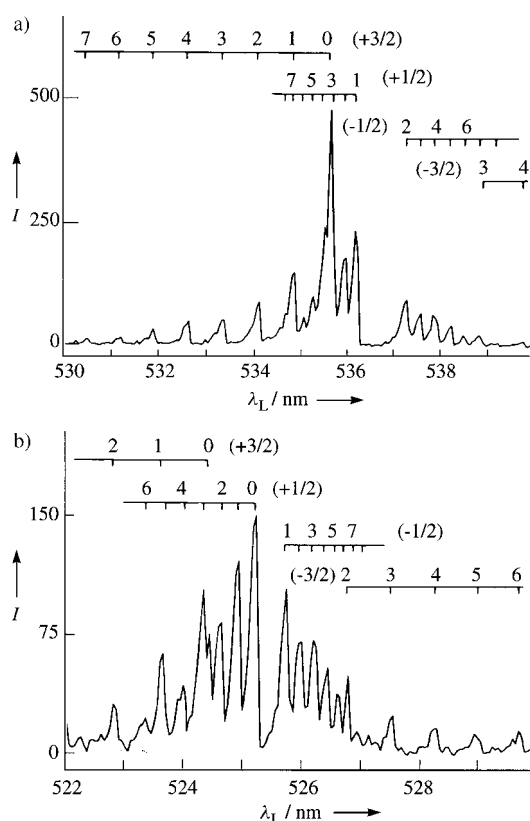


Figure 44. ZEKE photodetachment spectrum of SH^- with rotational resolution for a) $\text{SH}(^2\Pi_{3/2}) \leftarrow \text{SH}^-(^1\Sigma^+)$ and b) $\text{SH}(^2\Pi_{1/2}) \leftarrow \text{SH}^-(^1\Sigma^+)$. The SH^- J'' values are given; the ΔJ values are in parenthesis.^[64]

Bässman et al.^[158] constructed a high-resolution ZEKE spectrometer for anions (resolution 1.5 cm^{-1}) and obtained spectra of the $\text{I}^- - \text{H}_2\text{O}$ cluster. The spectra are dominated by two low-frequency modes at 45 and 210 cm^{-1} , which were assigned to the $\text{I}-\text{H}_2\text{O}$ stretching and in-plane bending modes, respectively. The fine structure was tentatively assigned to rotational excitation around the $\text{I}-\text{O}$ axis. In the future it may be possible to significantly increase the resolution of anion spectra for such complexes between halides and polar molecule by employing novel “dipole-bound” excited states,^[159,161] which have recently been discovered in such clusters. Excitation of the complex from the

ground state to the weakly bound excited state could be followed by PFI to give an anionic version of ZEKE-PFI.^[160]

The other main area of application, to metals and mixed clusters, was first carried out by Ganteför et al.^[39,162,163] and further developed by Drechsler et al.^[164,165] Photodetachment spectroscopy of anionic clusters is a useful technique, as mass selection of the charged clusters may be achieved. The information gained from the photodetachment spectrum gives direct information on the neutral species.

11.1. Transition States

According to long-standing common belief, it seemed impossible to directly measure the transition state of a chemical reaction. ZEKE spectroscopy, however, has been successfully used for this purpose from a rather different angle than for recent femtosecond pump–probe experiments.

During the hydrogen-exchange reaction $\text{A} + \text{HB} \rightarrow \text{AH} + \text{B}$ a transition state is formed in which the hydrogen atom is partway between the A and B molecules.^[166] This reaction has been probed by photodetachment of AHB^- complexes by Neumark et al.^[167–169] The ClHCl^- , BrHBr^- , IHI^- , and H_2F^- ^[170] complexes have been studied by conventional photodetachment spectroscopy. Ab initio calculations were also performed on these species; the work up until the beginning of 1993 has been summarized by Klepeis et al. in their extensive study of the FHCl^- complex.^[171] To date, only one experimental study has looked at these complexes with ZEKE spectroscopy, namely, that of Waller et al. on IHI^- .^[65] This complex has attracted a significant amount of attention recently, and an ab initio study was performed by Schatz et al.^[172]

Weaver et al.^[168] looked at the IHI^- and IDI^- complexes in the conventional photodetachment study. One of the stimulations for this investigation was a matrix-isolation study of IHI^- by Ellison and Ault,^[173] which indicated that IHI^- was linear and centrosymmetric, as was expected for the transition state of the reaction $\text{I} + \text{HI} \rightarrow \text{IH} + \text{I}$. Since calculations had predicted that bound states of the IHI complex existed,^[174] it was anticipated that the vertical (most intense) region of the photodetachment spectrum would give direct information on the IHI transition state. A simplified potential for the IHI^- anion and the corresponding neutral molecule is shown in Figure 45. The photoelectron photodetachment spectrum (see

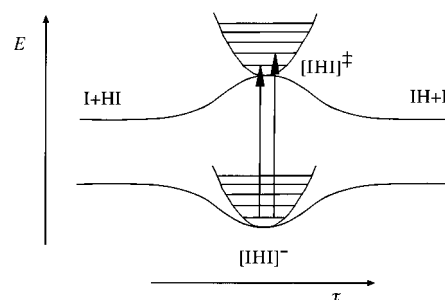


Figure 45. Schematic representation of a part of the $[\text{IHI}]$ reaction coordinate with the level structure of the ν_3 vibration in the IHI^- ion and in the activated complex.

Figure 8 including the comparison to the ZEKE spectrum) was obtained by photodetachment of mass-selected anions by the fourth harmonic vibration of a Nd:YAG laser. The resulting electrons were analyzed with respect to their kinetic energy; a spectral resolution of approximately 8 meV was obtained. A series of three peaks was assigned to a progression of double quanta of the asymmetric stretching vibration ν_3 .

The simulation of the spectrum indicated that a symmetric stretching vibration quanta should also be associated with each of the transitions in the asymmetric mode, but these were not resolved in this experiment. Owing to the poor spectral resolution, it was not possible to be certain that any of the states of IHI accessed in the photodetachment were bound. The most likely candidate for a bound state was a narrow peak in the spectrum of IDI^- . The ZEKE spectrum^[65] (see Figure 8) was more definitive, however, and contained peaks with a width of 30 cm^{-1} . The IHI^- ions were produced and selected as in the previous experiment, but on this occasion they underwent photodetachment by the output of a tunable dye laser; the experimental resolution was between 1 and 2 meV. At this higher resolution, the expected symmetric stretching vibration of the IHI complex was observed for the transitions $\nu_3=0, 2$, and 4. They exhibited significantly different widths, which were taken to be indicative of the different lifetimes of the levels in the neutral complex. For example, in the $\nu_3=4$ level two components of a symmetric stretching vibrational progression ($93 \pm 5\text{ cm}^{-1}$) were observed and assigned to $\nu_1=0$ and 1; these spectral widths indicated lifetimes of 180 and 120 fs, respectively. The “hot bands” in the latter feature showed vibrational structure that basically agreed with the data from matrix-isolation experiments.^[173] For the $\nu_3=2$ feature the peaks were somewhat broader (100 cm^{-1}) and had spacings of about 100 cm^{-1} . In contrast, the $\nu_3=0$ level showed a series of peaks whose spacing varied from 160 to 200 cm^{-1} (for higher laser energy). However, this was expected as, calculations had suggested that photodetachment to this level would only access direct-scattering wavefunctions and not quasi-bound levels. Interestingly, comparison of the ZEKE experiment and the calculations showed that only high rotational energy levels of the IHI complex have significant amplitude near the threshold. Also of note is that both a three-dimensional adiabatic model^[175] and a recent *ab initio* calculation^[172] indicate a sharp feature at the threshold, which does not appear in the ZEKE spectrum.

11.2. Metallic Clusters

A number of anionic metallic clusters have been studied by Ganteför et al.^[161–163] They produced the metal clusters by laser vaporization of a metal target in rare gas jet molecular expansion; the mixture of anions, cations, and neutral molecules passes through a skimmer. The anions are accelerated, which results in the separation of clusters of different mass. Cluster of a particular mass are then irradiated in a ZEKE photodetachment experiment. The first study looked at the gold dimer and the silver trimer.^[161]

For Au_2^- the results showed a progression in the vibrational frequency of the neutral molecule of 146 cm^{-1} . There were also hot bands in the spectrum, which indicate a vibrational frequency as about 188 cm^{-1} for the anionic ground state. The 0–0 band in the ZEKE spectrum was taken as the electron affinity and led to a value of $1.9400 \pm 0.0005\text{ eV}$. An analysis of the Franck–Condon factors led to a vibrational temperature of $165 \pm 30\text{ K}$ for the sample gas.

For Ag_3^- only one peak was observed in the ZEKE spectrum.^[162] At first sight this may be a little surprising, as the geometry of Ag_3^- is linear whereas Ag_3 is an equilateral triangle. However, there is a linear state of Ag_3 that lies 0.05 eV above the triangular state,^[176] and it is detachment to this state that was thought to be responsible for the ZEKE spectrum. The gold hexamer Au_6^- was also studied.^[163] The ZEKE spectrum showed a vibrational progression of 107 cm^{-1} , which was also present in the electron total yield spectrum. These studies demonstrate that fundamental information on metal clusters can be quite clearly ascertained from the ZEKE photodetachment spectra. The mass selectivity possible for anions, together with the sensitivity of the ZEKE method, combine to provide a powerful tool for gaining information on neutral species which is difficult to obtain by other means.

11.3. Silicon Clusters

The ZEKE spectrum of the Si_3^- complex was acquired by Arnold and Neumark^[155] with a resolution of 10 to 15 cm^{-1} . Only the broad, higher energy band (X) gave rise to a ZEKE spectrum. The structure in this spectrum was dominated by a progression with a spacing of 337 cm^{-1} ; there were also weaker features and a peak that was red-shifted by 385 cm^{-1} with respect to the origin of the progression at 337 cm^{-1} .

In order to discuss the assignment of the bands, the electronic structure of the Si_3 molecule needed to be considered. The electronic configuration of the first two states (D_{3h} symmetry) is $(1a_1')^2(1e')^4(2a_1')^2(1a_2')^2(2e')^2$ giving rise to three electronic states: $^3A_2'$, $^1E'$, and $^1A_1'$. The $^1E'$ state is distorted owing to the Jahn–Teller effect and gives rise to two states. The $^1A_1$ and $^1B_2$ states arise from the lifting of the degeneracy of the e' orbitals into a_1 and b_2 orbitals upon going to C_{2v} symmetry. Under D_{3h} symmetry, the anion has $^2E'$ symmetry and is thus also subject to Jahn–Teller distortion—to a $^2A_1$ and a $^2B_2$ state.

According to QCISD(T) calculations^[177] the $^2A_1$ state is the ground state (QCISD(T) = quadratic configuration interaction singles doubles (triples)). Large calculated differences in the bond angle between the anion and the neutral molecule led Arnold and Neumark to consider the assignment of the vibration at 337 cm^{-1} to the symmetric bending mode ν_2 of the $^1A_1$ state. However, calculations suggested that this assignment could not be correct since the calculated vibrational frequency was far too low; thus, the assignment to the $^3A_2'$ state was favored. QCISD(T) and self-consistent field (SCF) calculations gave a value that was in poor agreement with the measured frequency, whereas values from DFT calculations^[178] were in much better agreement. Therefore, band X

was assigned to the $^3A_2' \leftarrow ^2A_1$ transition, and the progression at 337 cm^{-1} was assigned to the ν_2 vibration of the neutral molecule. Some of the weaker features were assigned to combinations of the ν_2 progression with one quantum of the ν_1 vibration (measured at $501 \pm 10\text{ cm}^{-1}$); other features in the spectrum were assigned to hot band structure. Simulations were then performed to understand the spectrum in more detail. The best agreement was obtained under consideration of the quadratic Jahn–Teller effect, although there were still inconsistencies between the experimental data and calculations.

The conventional photodetachment spectrum of Si_4^- showed a large amount of vibrational structure. Assignment of this spectrum was originally tentative, but recently confirmed by ZEKE spectra and ab initio calculations.^[179] Band X did not give rise to any ZEKE intensity, whereas band A gave a rich vibrational structure. Only part of band B and band C gave rise to any ZEKE structure. Band A is shown in Figure 46; it displays additional resolved structure

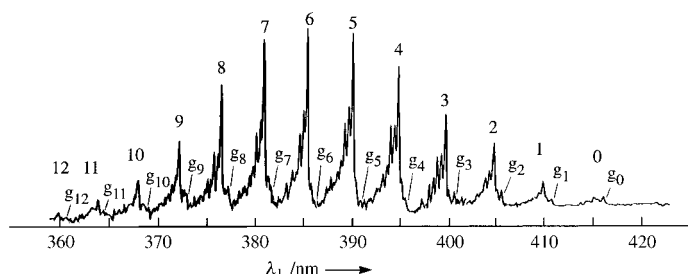


Figure 46. ZEKE photodetachment spectrum of Si_4^- illustrating resolved vibrational structure in band A.^[179]

on the individual vibrational components (spacing 312 cm^{-1}). The intensities of the weak features to either side of the most intense feature vary with the conditions of molecular expansion, indicating that they were due to hot bands arising from vibrational excitation in the anion. The weaker features that are blue-shifted with respect to the intense peaks were separated into two progressions of about 50 and 30 cm^{-1} ; the two red-shifted features had spacings of about 25 and 53 cm^{-1} . Band A could be assigned to the $^3B_{3u} \leftarrow ^2B_{2g}$ photodetachment by considering the ab initio calculation^[177] with regard to energy and vibrational frequency (the ν_2 mode was calculated to have a harmonic frequency of 306 cm^{-1} for the $^3B_{3u}$ state) as well as expectations based upon the changes in geometry between the neutral and anionic states. Locating the origin of this progression proved difficult owing to the low intensity at the onset of the band. Franck–Condon simulations together with ab initio calculations led to the conclusion that band marked 0 in Figure 46 was indeed the origin of the band. The weak features were assigned by further Franck–Condon calculations and by comparison with the results of ab initio calculations.

Band B' again showed a main progression ($300 \pm 6\text{ cm}^{-1}$) flanked by weaker features. The

assignment of this band was based upon the fact that the only state calculated^[177] to be in this energy region, and that also could be formed by s-wave photodetachment from the anionic state, was the $^1B_{3u}$ state. The irregular vibrational structure of the weaker features was postulated as being due to vibronic coupling between the electronic states, which were calculated to lie within the range of band A (Figure 46) but that could not be formed by photodetachment of an s wave.

Band C' was rather broad owing to only partial discrimination of electrons with higher kinetic energy (with a view to increasing the intensity of the rather weak feature). The structure consisted of a progression of about 430 cm^{-1} . The assignment to the $^3B_{1u} \leftarrow ^2B_{2g}$ photodetachment transition^[177] was deemed most likely.

11.4. Metal–Carbide Clusters

As part of a study of catalytically active species, FeC_2^- was studied by Drechsler et al.^[164,165] They obtained a very highly resolved ZEKE spectrum, as can be seen from the comparison to the photodetachment photoelectron spectra for excitation at 532 nm and 355 nm (Figure 47). The work gave a greatly improved value for the electron affinity of FeC_2 (15955 cm^{-1}). The vibrational constants associated with the Fe–C vibration were determined to be $\omega_e = 561.6\text{ cm}^{-1}$ and $\omega_e x_e = 2.1\text{ cm}^{-1}$. There was also an indication for another vibration attributed to the C–C vibration at 1975 cm^{-1} . Furthermore, there was evidence of hot bands originating from excitation in the mother anion. The particular significance of these experiments lies in the fact that a resolution of 1.5 cm^{-1} was obtained, the record for ZEKE photodetachment so far.

12. Conclusions

Owing to its unprecedented resolution, ZEKE spectroscopy provides a unique tool for studying a large variety of molecular systems. In this review we have presented some typical examples, mainly focusing on the high-resolution

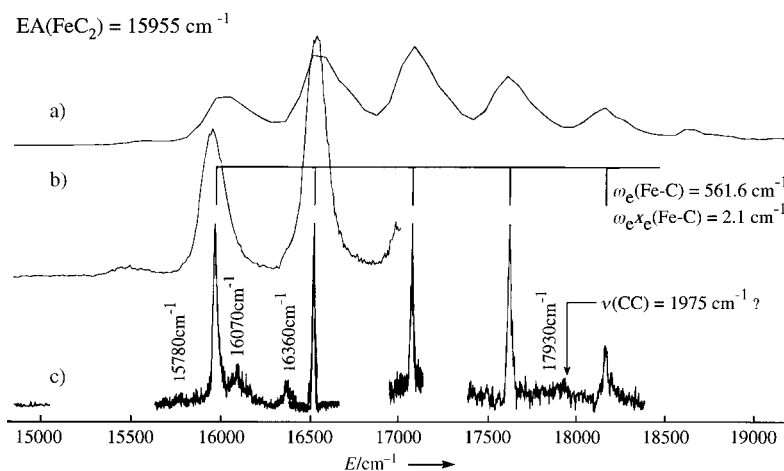


Figure 47. Photodetachment photoelectron spectra (fixed photon energy) of FeC_2^- ; a) 355 nm , b) 532 nm . c) ZEKE photodetachment spectrum of FeC_2^- .^[164]

spectra of molecular cations that can be obtained by ZEKE spectroscopy. The extension of the technique to free radicals, anions, and thence neutral molecules is still an emerging field. Many laboratories across the world are contributing to the rapid development of this spectroscopy, as documented by four European research conferences at Kreuth in 1991, Giens in 1993, Lenggries in 1995, and Emmetten in 1997. Future experiments will no doubt help to further elucidate the nature of ZEKE Rydberg states and extend applications to anion spectra and neutral molecules. In addition, the method also lends itself to the study of transient species such as radicals or complexes, thus continuing on the lines of the first direct measurements of transition states in chemical reactions.^[65] All these initial examples will certainly be followed, as is the case for any emerging spectroscopy, by a rich body of examples, which then forms the broad basis for this new spectroscopy.

Another important chemical aspect concerns the dynamics of hydrogen-bonded clusters. Proton transfer has been probed in such systems by short pulse lasers in the femto- to picosecond regime.^[180] The combination of this pump-probe technique with ZEKE detection^[181] should be particularly suitable to project out the proton-transfer coordinate^[182] from the excited S_1 state of the ion. Combined with mass-selected ZEKE detection, the proton transfer and fragmentation channel of the ion can also be monitored.

In conclusion, one can say that we are standing at the beginning of a rich new spectroscopy which will provide new insights into the chemistry of cations, elusive neutral molecules, and metastable species that are present in reactive mixtures, clusters, van der Waals complexes, and free radicals.

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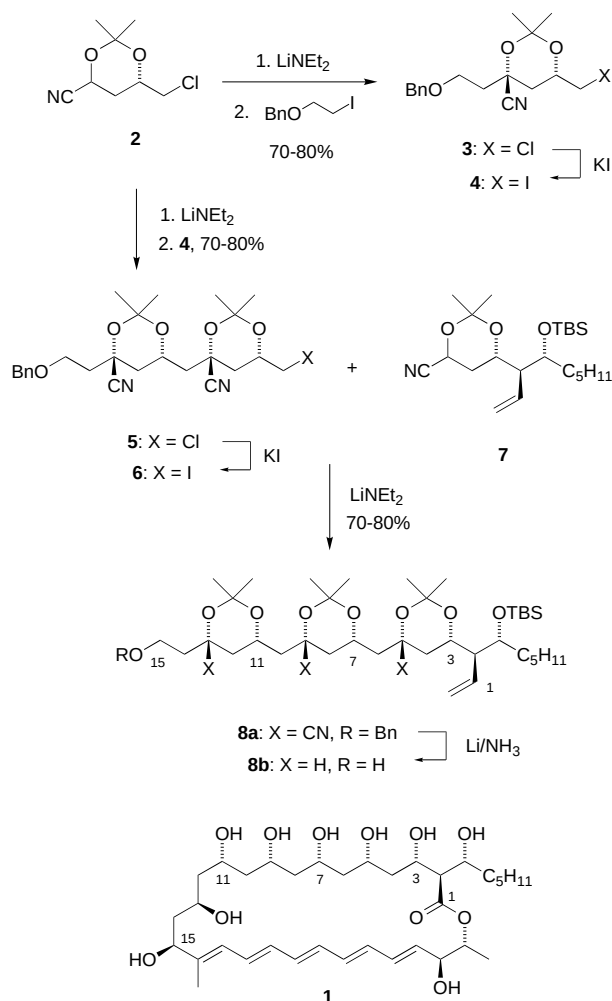
New Polyol Syntheses

Christoph Schneider*

Owing to their biological action and chemical structure, certain natural products have always fascinated biologists and chemists. In addition to the cytotoxic epothilones and taxol and the antihypercholesterolemic squalenstatins (zaragossic acids), the highly fungicidal polyene macrolides are attracting increasing attention.^[1] More than 200 polyene macrolides have been identified, but the constitution and configuration of many have only been partially elucidated. Best known are probably amphotericin B and nystatin, which are used clinically for the treatment of systemic fungal infections. Their biological activity rests on their ability to damage cytoplasmic membranes of eukaryotic cells by various mechanisms with consequent loss of ions, amino acids, and carbohydrates. Structurally they consist of a polyene moiety with up to seven, mostly conjugated double bonds and a polyol moiety with nine secondary, mainly 1,3-orientated hydroxy groups. New strategies for the stereoselective synthesis of the polyol structures are of great interest to synthetic chemists.

Rychnovsky and his group have recently developed new synthetic methods that lead to the total syntheses of the polyene macrolides roxaticin,^[2] roflamycoin,^[3] and filipin III.^[4] The polyol chains of all three natural products were constructed by iterative, stereoselective alkylation of lithiated cyanohydrin acetonides and subsequent reductive decyanation, illustrated here by the synthesis of the polyol framework of filipin III (**1**) (Scheme 1). The bifunctional cyanohydrin acetonide **2**, prepared by ruthenium/BINAP catalyzed enantioselective hydrogenation of the corresponding β -keto ester (BINAP = [1,1'-binaphthyl]-2,2'-diylbis(diphenylphosphane)), is deprotonated with LiNEt₂ and alkylated with 2-benzyloxy-1-iodoethane. The alkylation product **3** is converted by a Finkelstein reaction into the iodide **4**, which is used to alkylate a second molecule of **2**. After a second Finkelstein reaction, the protected tetraol **6** is coupled with the lithiated cyanohydrin acetonide **7** in a third alkylation to form the complete polyol segment **8** of filipin III.

Each alkylation step proceeds in good yield (70–80%), and the 1,3-dioxanes **9**, in which the “slim” cyano group assumes the axial position, are formed with high stereoselectivity. Once they have fulfilled their role for the alkylations, the

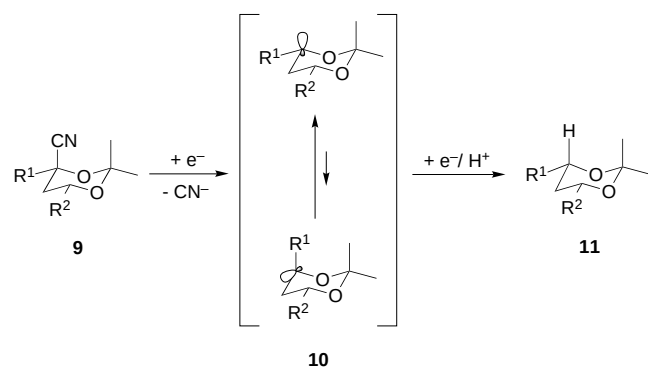


Scheme 1. Synthesis of the C₁–C₁₅ polyol fragment **8b** of filipin III (**1**) according to Rychnovsky et al. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

three cyano groups are removed with Li/NH₃ with retention of configuration to afford the 1,3-*syn*-diol acetonides **11** (Scheme 2). Control experiments revealed, however, that the reductive decyanation always gives 1,3-*syn* configured diol acetonides irrespective of the cyanohydrin acetonide configuration. The reason is that the intermediate radical **10** prefers a configuration in which the unpaired electron assumes the axial position at the anomeric center. The carbanion formed by the next electron transfer is protonated at this position so the H atom is also in an axial position.

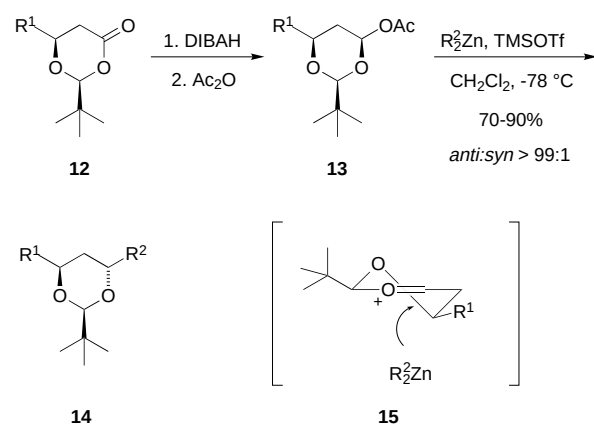
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Scheme 2. Reductive decyanation of the cyanohydrin acetone **9** according to Rychnovsky et al.

Protected 1,3-*anti*-diols **14** are accessible by the highly stereoselective Lewis acid promoted addition of dialkylzinc compounds to 4-acetoxy-1,3-dioxanes **13** (Scheme 3).^[5] The

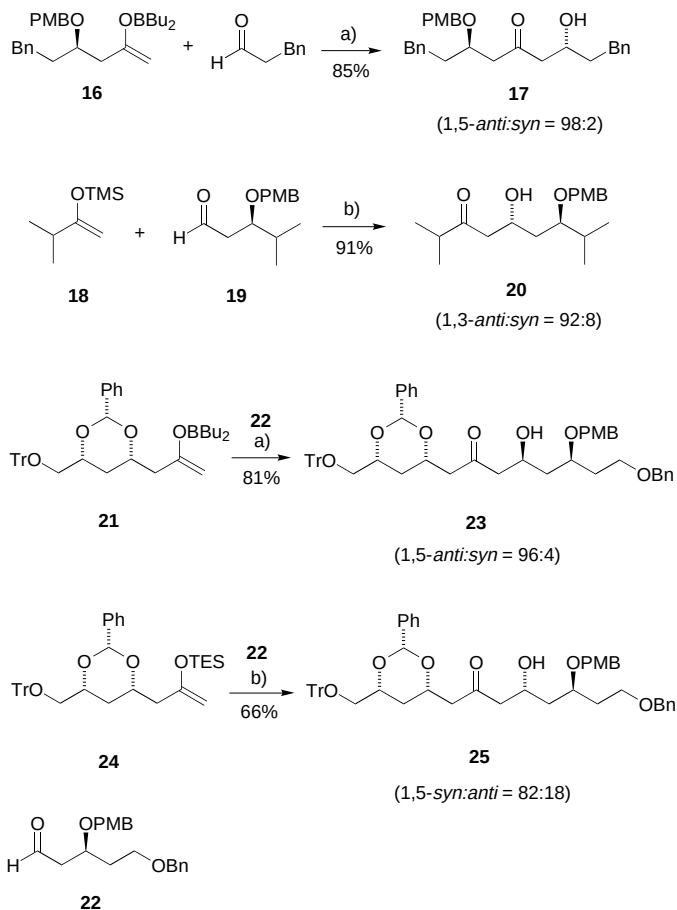


Scheme 3. Preparation of the 1,3-*anti*-diol acetal **14** by dialkylzinc addition to 4-acetoxy-1,3-dioxanes **13** according to Rychnovsky et al. TMSOTf = trimethylsilyltrifluoromethyl sulfonate.

two *cis*-orientated alkyl substituents at C2 and C6 fix the carboxonium ion **15** in the half chair conformation, which undergoes preferential axial attack by the dialkylzinc under stereoelectronic control. The 4-acetoxy-1,3-dioxanes **13** may be synthesized from the Seebach 1,3-dioxan-4-ones **12** by reduction with diisobutylaluminium hydride (DIBALH) and acetylation. Since dialkylzinc compounds are now readily available and are compatible with many functional groups, this method should be widely applicable to the preparation of 1,3-*anti*-diols.

The most direct method for the preparation of polyol frameworks is without doubt the aldol reaction. The diastereofacial selectivity of the reaction can be controlled by β -alkoxy groups in both the methylketone enolate and the aldehyde. As investigations by Evans^[6] and Paterson^[7] and their groups have demonstrated, the correct selection of enolization conditions and the protective group for the β -hydroxy group are important for the stereocontrol of the reaction.

Boron-aldol reactions of the *p*-methoxybenzyl(PMB)-protected methylketone **16** proceeds with excellent 1,5-*anti*-selectivity (Scheme 4). The asymmetric induction may be

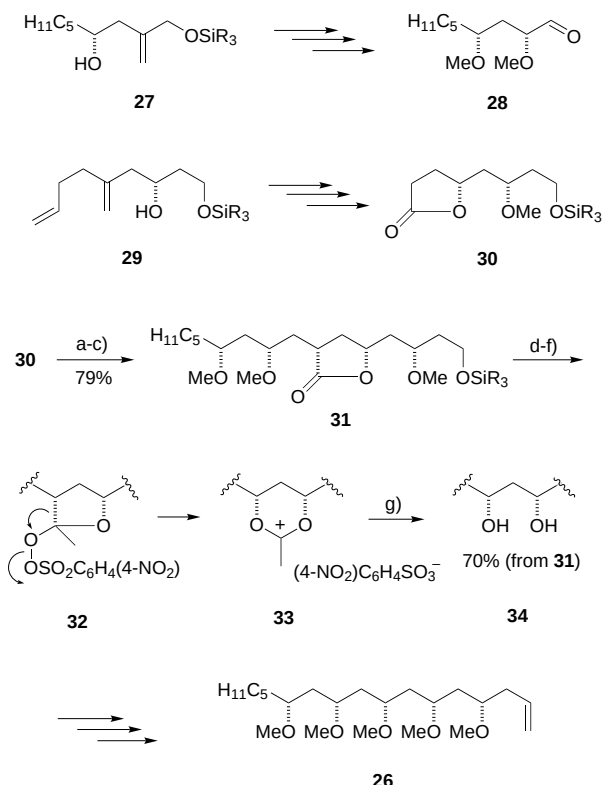


Scheme 4. Stereocontrolled aldol reaction according to Evans et al. a) Et₂O, -115 °C; b) BF₃·OEt₂, CH₂Cl₂, -78 °C. TES = triethylsilyl, Tr = triphenylmethyl.

improved by a double stereodifferential aldol reaction with chiral boron ligands.^[7] The reason for this high stereoselectivity is currently unknown. Ab initio calculations suggest the involvement of twisted boat structures rather than chair transition states.^[6]

If the chiral information is contained within the aldehyde, a Mukaiyama aldol reaction is the method of choice.^[8] The BF₃-catalyzed addition of the silyl enol ether **18** to the chiral aldehyde **19** affords the 1,3-*anti* product **20** in high yield and stereoselectivity. Evans has developed a modified Felkin–Anh model as a working hypothesis in which repulsive interactions between the carbonyl group and the β -alkoxy group, and steric interactions between the carbonyl group and the β -alkyl group are minimized. The complementary reaction conditions permit selective product formation in a double stereodifferential aldol reaction of a chiral ketone and a chiral aldehyde, even in the mismatched situation.^[6] Thus the boron enolate **21** adds to the aldehyde **22** with excellent stereoselectivity and forms almost exclusively the 1,5-*anti* product **23** (enolate control). In the Mukaiyama reaction of the corresponding silyl enol ether **24**, however, the aldehyde **22** exercises stereochemical control, and the 1,5-*syn* product **25** is the main product. The ketone carbonyl function of the aldol products can be reduced with high diastereoselectivity to the 1,3-*syn*-diols with Et₂BOMe/NaBH₄^[9] and DIBALH,^[10] and to the 1,3-*anti*-diols with Me₄NBH(OAc)₃^[11] and SmI₂/RCHO.^[12]

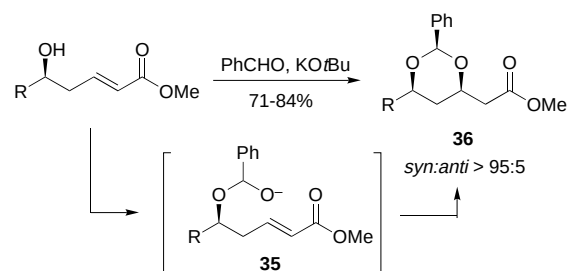
Brückner et al. use the oxidative degradation of butyrolactones by a Criegee rearrangement as the key step in the synthesis of different polyol systems (Scheme 5).^[13] In



Scheme 5. Synthesis of the *Tolypothrix* pentamethyl ether **26** according to Brückner et al. a) 2 equiv LDA, 1 equiv MePh₂SiCl, $-78^{\circ}\text{C} \rightarrow \text{RT}$; b) **28**, $-78^{\circ}\text{C} \rightarrow \text{RT}$; c) Rh/C/H₂; d) MeLi, -78°C ; e) H₂O₂, PPTS; f) (4-NO₂)C₆H₄SO₂Cl, NEt₃; g) H₂O, K₂CO₃, MeOH. LDA = lithium diisopropylamide, PPTS = pyridinium toluene-4-sulfonate.

their convergent route to the pentamethyl ether **26** from *Tolypothrix conglutinata* they synthesize the homoallylic alcohols **27** and **29** by catalytic, enantioselective allylstannane additions and convert them into the two central building blocks **28** and **30** by ozonolysis and *syn*-selective ketone reduction. Coupling of these two fragments to form the complete carbon framework **31** of the polyol chain is achieved by Peterson olefination and stereoselective hydrogenation of the conjugated double bond. The butyrolactone **31** is now converted into the peroxosulfonate **32** by addition of MeLi, oxidation with H₂O₂, and reaction with *p*-nitrobenzenesulfonyl chloride. This sulfonate undergoes a Criegee rearrangement at room temperature to form the resonance-stabilized, cyclic carboxonium ion **33** by cleavage of the unstable peroxo compound and stereospecific migration of the neighboring carbon atom. Alkaline hydrolysis yields the *syn*-diol **34**, and standard methods then give the natural product in a few steps.

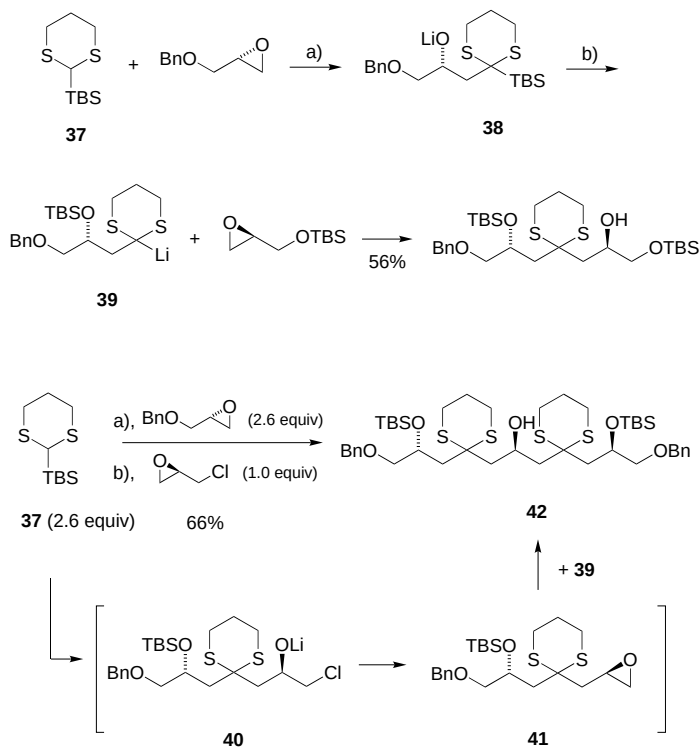
α,β -unsaturated δ -hydroxy esters and amides are excellent starting materials for the synthesis of 1,3-diols. Protected 1,3-*syn*-diols may be prepared with high stereoselectivity by intramolecular Michael addition of the hemiacetal alkoxides **35** derived from them (Scheme 6).^[14] The thermodynamically controlled reaction gives almost exclusively the all-equato-



Scheme 6. Preparation of the 1,3-*syn*-diol acetals **36** by intramolecular Michael addition of a hemiacetal alkoxide according to Evans et al.

rially substituted 1,3-dioxanes **36**, which are readily deprotected by hydrogenolysis or acid hydrolysis. Evans made repeated use of this strategy that he developed in his recently completed synthesis of althoyrtin C.^[15]

Smith et al. have developed a very elegant route to complex polyol structures by sequential dithiane–epoxide coupling reactions (Scheme 7).^[16] Following the work of Tietze,^[17]



Scheme 7. Sequential dithiane–epoxide coupling according to Smith et al. a) *t*BuLi, Et₂O, $-78^{\circ}\text{C} \rightarrow -45^{\circ}\text{C}$; b) HMPA, Et₂O, $-78^{\circ}\text{C} \rightarrow -25^{\circ}\text{C}$.

2-silyl-1,3-dithianes **37** are deprotonated with *t*BuLi in ether and converted into the stable lithium alkoxides **38** with enantiomerically pure epoxides. A fast 1,4-Brook rearrangement occurs only after the addition of 0.3 equivalents of hexamethylphosphoramide (HMPA) or 1,3-dimethylhexahydro-2-pyrimidone (DMPU) to the reaction mixture. A new lithiated dithiane **39** that can undergo nucleophilic addition to a second epoxide is formed. Thus, careful tuning of the reaction conditions allows unsymmetrical bisalkylation of dithianes with two different epoxides. The suitable selection of stoichiometric ratios and the insertion of an additional

leaving group into the second epoxide allows a third dithiane–epoxide coupling to be achieved. The new epoxide **41** which is formed from the doubly alkylated product **40** by intramolecular S_N reaction, is opened by unreacted Brook rearrangement product **39**. Thus a C_{11} -polyol chain (**42**) with five free or protected secondary alcohol functions is formed from five components in a one pot reaction. However, this remarkable efficiency is achieved only if the complete stereochemical information of the polyol chain has already been introduced by the chiral epoxides.

Although the absolute configuration has only been established for a few polyene macrolide antibiotics, the search for new, efficient, and selective strategies for the synthesis of their polyol structures is in full swing. A number of the synthetic procedures presented here will certainly be used in future syntheses of this class of natural products.

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Keywords: aldol reactions • asymmetric syntheses • macrolides • polyenes • polyols

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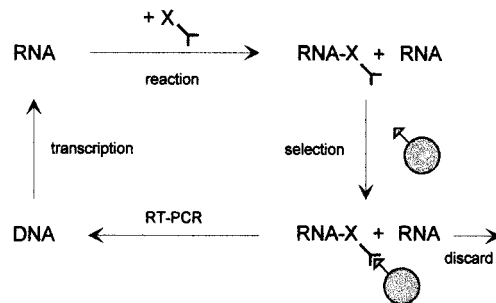
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Catalysis of Organic Reactions by RNA

Christian Frauendorf and Andres Jäschke*

It has been known since the early 1980s that ribonucleic acids (RNAs) do not only participate in the flow of genetic information, but may also have catalytic properties.^[1] This discovery, which was honored with the Nobel Prize in 1989, stimulated earlier hypotheses about the existence of a prebiotic “RNA world” in which both the storage of genetic information and the control of chemical reactions were carried out by RNA.^[2] While the search for other naturally occurring ribozymes has not led to substantial discoveries in recent years, the use of in vitro selection and evolution techniques has provided significant contributions to the exploration of the catalytic potential of RNA.^[3]

To isolate catalytically active RNA molecules, catalysis must be coupled with some other event that allows a selection. The most successful method for the selection of RNA catalysts is direct selection in which those members are selected from RNA libraries that can modify themselves in the absence of an external catalyst (Scheme 1). A combina-



Scheme 1. General principle of direct selection with a combinatorial RNA library.

torial RNA pool is incubated with a substrate X, which contains an anchor group that is not present in unmodified RNA (e.g., a thiol group or biotin). After incubation, those RNAs are isolated by affinity chromatography that have been covalently linked to the anchor group. These RNA molecules are reverse transcribed into DNA and then amplified by polymerase chain reaction (PCR). The double-stranded DNA is subsequently used to generate RNA by transcription, and the next cycle starts with the incubation step. This cycle is repeated until the active RNA molecules dominate the pool.

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While the exploration of the catalytic potential of RNA initially focussed on reactions at the functional groups present in RNA (acylations, alkylations, phosphorylations of RNA molecules^[4]), several studies have recently been published in which the limitation on self-modifying reactions has been overcome by using linker-coupled reactants. Herein we will discuss studies that deal with reactions central to the synthetic chemist—the Diels–Alder reaction, the synthesis of amides and esters, and peptide bond formation.

By using direct selection with linker-coupled reactants, Eaton and co-workers identified catalysts for the formation of carbon–carbon bonds by the Diels–Alder reaction.^[5] Despite its minor biochemical significance,^[6] this key reaction of organic synthesis was often chosen for innovative approaches in catalysis research, and several laboratories have attempted, but with little success so far, to generate RNA catalysts for Diels–Alder reactions by selecting RNA molecules with high affinity to transition state analogues.^[7]

The selection scheme employed by Eaton started with a pool of 10^{14} different RNA molecules; all of them containing a region of 100 completely randomized positions and flanked by two constant sequences (Scheme 2a). Hexadienol was coupled through a carbamate linkage to poly(ethylene glycol) (PEG), average molecular weight 2000, which was enzymatically linked to the pool RNA molecules. The highly flexible

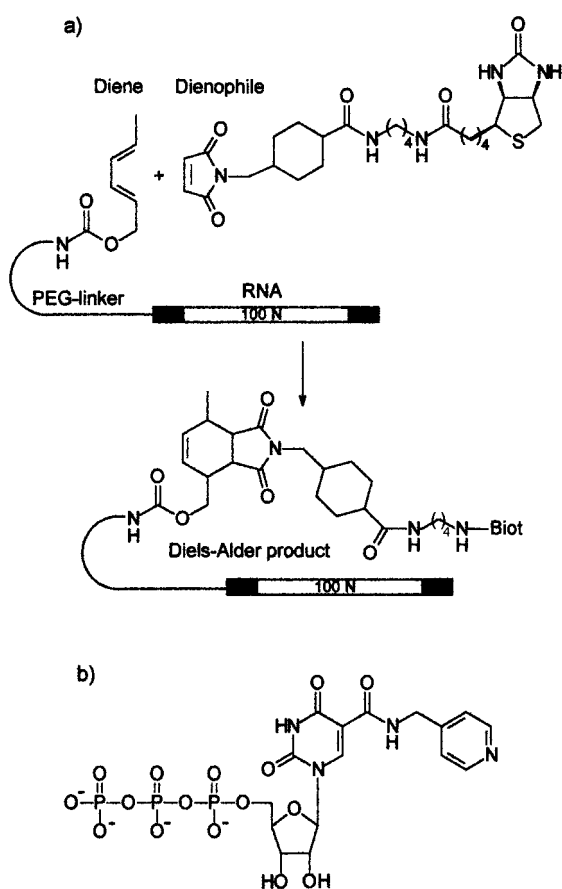
PEG linker made it possible for the diene to act like a free species in solution and thus interact with all parts of a folded RNA molecule. This pool of RNA-linker-diene conjugates was incubated with the dienophile, a biotinylated maleimide, in the presence of various metal ions. RNA-coupled biotinylated cycloaddition products were separated from unmodified RNA by streptavidin (a biotin-binding protein) and enzymatically amplified. This enriched pool was then subjected to further rounds of selection and amplification.

The introduction of additional functionalities into RNA was important for catalysis.^[8] Instead of uridine-5'-triphosphate (UTP), the modified analogue 5-[(4-pyridylmethyl)carbamoyl]-UTP (Scheme 2b) was used in enzymatic RNA synthesis, allowing additional interactions like hydrogen bonding, hydrophobic and dipolar interactions, and metal ion coordination.

After 12 rounds of selection and amplification, functionally active molecules were enriched and eight sequence families were identified that were capable of accelerating the reaction up to 800-fold with respect to the uncatalyzed background reaction. The catalytic activity was shown to depend on the presence of the pyridyl modification; as expected, unmodified RNA molecules of the same nucleotide sequence had no activity, since they fold into different three-dimensional structures and lack the additional interaction sites. The most thoroughly characterized catalyst had an absolute requirement for Cu^{2+} ions, and the authors discuss that Diels–Alder reactions are known to be catalyzed by Lewis acids,^[9] and RNA may coordinate these copper ions, presumably by the pyridyl moieties.

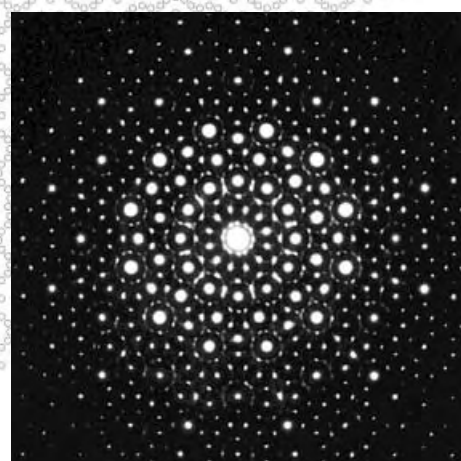
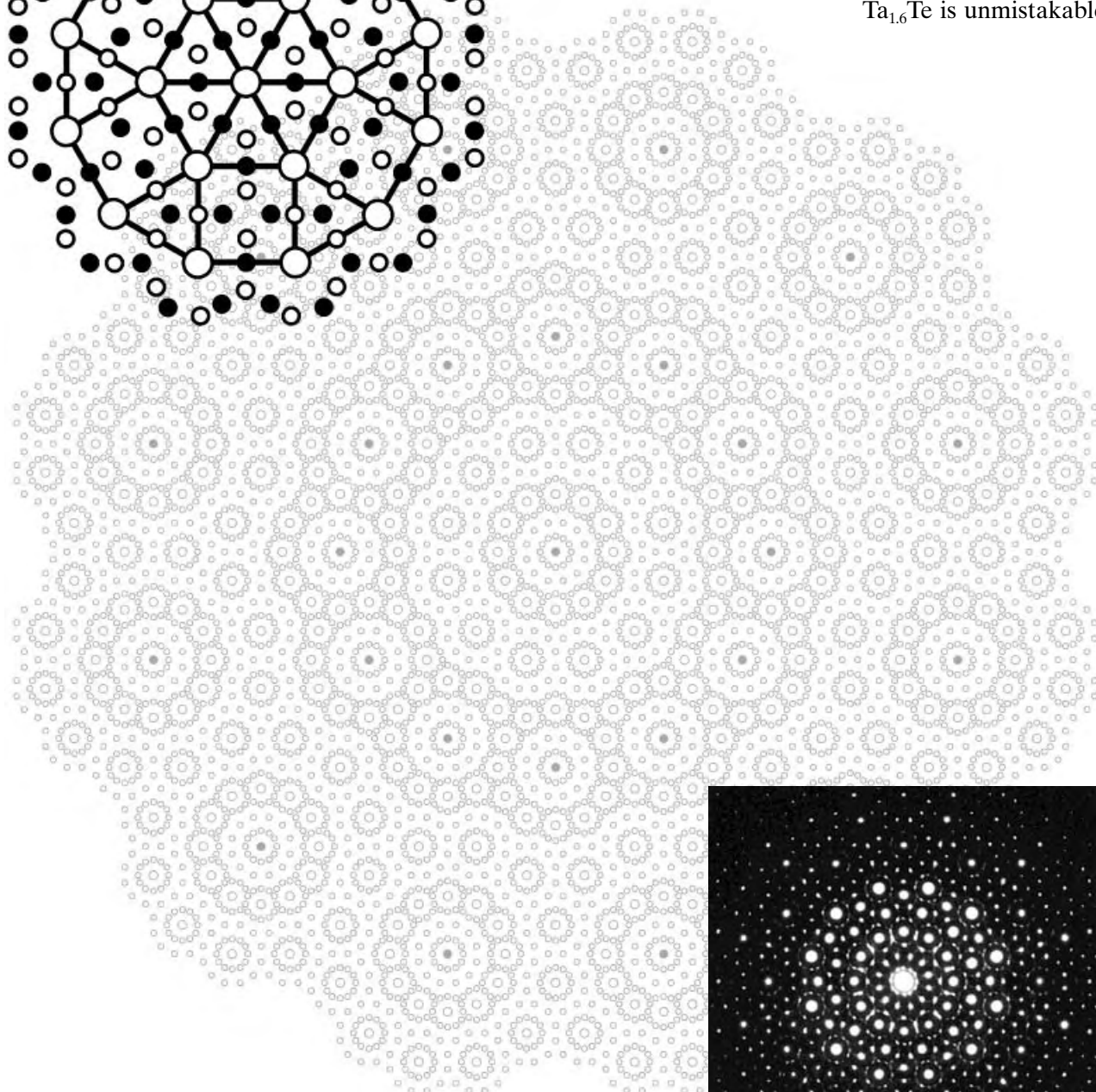
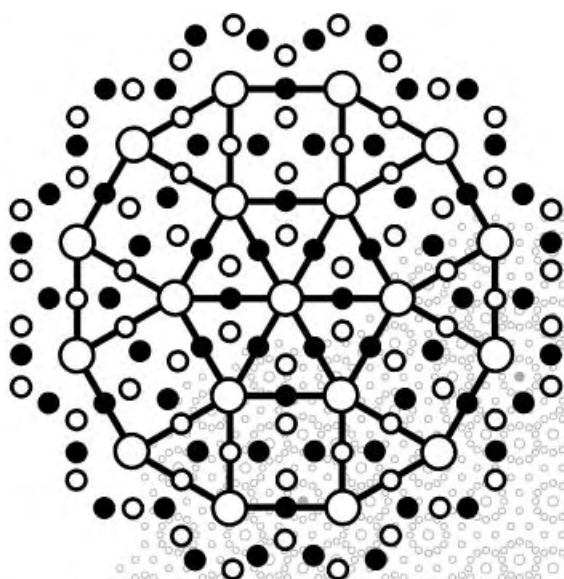
Eaton and co-workers have also recently described the catalysis of another important reaction by RNA that uses a similar selection scheme.^[10] This time, a primary aliphatic amine was coupled to the end of the PEG linker, and the resulting RNA pool was allowed to react with the asymmetric anhydride of biotin and adenosine monophosphate (AMP, Scheme 3a). Again, modified nucleotides were used; the 5-position of uracil was derivatized with imidazole, which was expected to help improve properties in general acid/base catalysis and metal ion coordination (Scheme 3b). To select the most active RNA species, the selection pressure was gradually increased from round to round by reducing the concentration of reactants and the reaction time. After 16 rounds, the kinetic characterization of individual selected species revealed rate accelerations of up to 110 000-fold. Again, the RNA species chosen for detailed characterization showed a strong dependence on the presence of the modified nucleotides and on the concentration of different metal ions. Remarkably, the adenosine moiety present in the free reactant biotin-AMP was not required for substrate recognition. The kinetic constants measured with the analogues uridine monophosphate-biotin and ribose-5-phosphate-biotin were almost identical to that measured with biotin-AMP.

These two studies demonstrate the successful application of direct selection to synthetically relevant reactions. A number of interesting questions raised by this work indicate that more detailed studies are still required. For instance: Can the selected RNAs act as true catalysts with two free reactants



Scheme 2. a) Reaction step in the selection of a Diels–Alderase from a combinatorial RNA library. Biot–OH = biotin. b) 5-[(4-Pyridylmethyl)carbamoyl]-UTP, which was used instead of uridine triphosphate (UTP) in enzymatic RNA synthesis.

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More about this quasicrystalline chalcogenide is described by Harbrecht et al. on pages 1384 ff.

A Dodecagonal Quasicrystalline Chalcogenide**

Matthias Conrad, Frank Krumeich, and Bernd Harbrecht*

Quasicrystals have their own particular type of order.^[1] This leads to diffractograms with discrete intensity maxima, which indicates that there is long-range order. However, unlike in crystals this does not result from a periodic arrangement of the atoms in three dimensions; the particular type of order is expressed by a special symmetry in the diffractograms: characteristic for the quasicrystalline state are Fourier spectra with crystallographically forbidden five-, eight-, ten-, or twelvefold rotational symmetry.

The diffraction patterns from dodecagonal (dd) quasicrystals exhibit the symmetry of a regular dodecagon. This rare ordering was discovered by Ishimasa, Nissen, and Fukano in their investigations with electron diffraction and high-resolution transmission electron microscopy (HRTEM) of very small (≤ 100 nm) particles of a Cr–Ni alloy produced by chemical vapor deposition (CVD) in a flow of xenon.^[2] Areas with dd symmetry have also been detected in extremely rapidly solidified Ni–V and Ni–V–Si melts as well as in thermally treated Bi–Mn double layer films, which had originally been amorphous.^[3, 4]

The nickel-containing metastable dd phases appear to consist of columnar hexagonal-antiprismatic clusters,^[2, 5] which occur as characteristic building blocks in some Frank–Kasper phases,^[6] for example, the σ -phase. Frequently, microdomains of such crystalline phases are interspersed in the dd regions. The brightest spots in the HRTEM images are the vertices of a tiling comprising squares and triangles, whose edge length of about 0.45 nm corresponds to the shortest distance between the central atoms of neighboring hexagonal-antiprismatic columns. The tilings of squares and triangles in the dd phases are similar to those of the crystalline regions, however, they are irregular and aperiodic. Further experimental investigations of this ordering could not be conducted due to the insufficient stability and the limited access to these phases. This situation has changed with the discovery of a dd phase, which, according to all the results obtained so far, is stable and which we found in attempts to produce tantalum-rich tellurides.^[7] Here we report on the synthesis, properties, and structural characterization of this first quasicrystalline chalcogenide.

dd-Ta_{1.6}Te is accessible in preparative quantities as the final product of the stepwise reduction of TaTe₂ with tantalum at

temperatures of 1270–1770 K and reaction times of between eight hours and several weeks. The compound is obtained as a black powder with lubricant-like mechanical properties. It decomposes in air to give an amorphous solid, which has not been further characterized. The synthesis was carried out in gas-tight sealed tantalum tubes to ensure the exclusion of further components during the formation of dd-Ta_{1.6}Te. The use of molybdenum as the crucible material allowed control and thus limitation of the composition of the phase. Energy dispersive X-ray spectroscopic (EDX) analyses (DSM-940, Zeiss, PV-9800, Edax) of various samples gave no indication of the inclusion of molybdenum or other possible impurities. The statistical evaluation of 20 EDX analyses (CM30ST, 300 kV, Philips, Tracor-Voyager-System) of a pure sample (by X-ray analysis) prepared in a molybdenum crucible (1.6 g, molar ratio Ta:TaTe₂ = 2.5), by using Ta₂Te₃^[8] as the standard, gave a molar tantalum content of 63.2(4)%. Traces of iodine promote the formation of fine platelets, some of which contain pores, and which are extremely easily cleaved perpendicular to the main symmetry axis. The lamellar structure, atypical for metal-rich compounds, is clearly evident in Figure 1. Thermal treatment for several weeks at

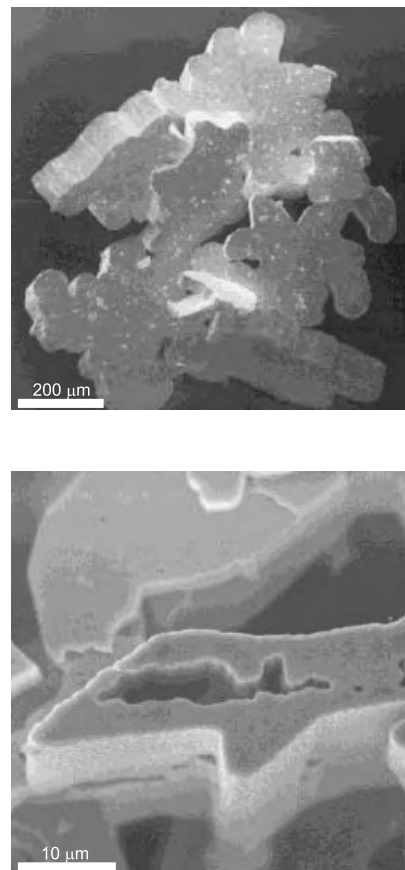


Figure 1. Scanning electron micrographs of dd-Ta_{1.6}Te in two different magnifications.

1070 K did not produce any change in the diffractogram. However, above 1870 K, dd-Ta_{1.6}Te transforms, with loss of the high rotational symmetry, into crystalline compounds that have almost the same chemical composition and structures in which

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the dodecagonal long-range order is relinquished to differing degrees in favor of translational periodicity.^[9]

Characteristic for dd-Ta_{1.6}Te are X-ray diffractograms (precession goniometer FR504, Enraf-Nonius) and electron diffractograms (CM30ST, 300 kV, Philips) with Laue symmetry 12mm. The intensity modulation of the electron diffractograms is dependent on the thickness of the sample. In the reflection-poor diffractogram (Figure 2 a), which was taken of

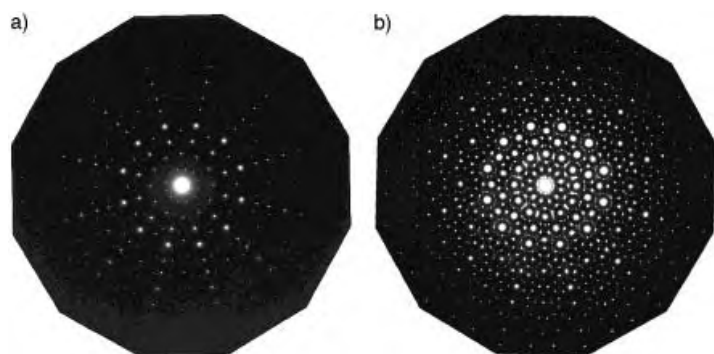


Figure 2. Reflection-poor (a) and reflection-rich (b) electron diffractograms of dd-Ta_{1.6}Te.

a thinner layer (ca. 10 nm), the intensity sequence is essentially in agreement with that of the precession photograph of the zeroth layer (Figure 3 a). Although the reflections do not show a latticelike arrangement, they can still be

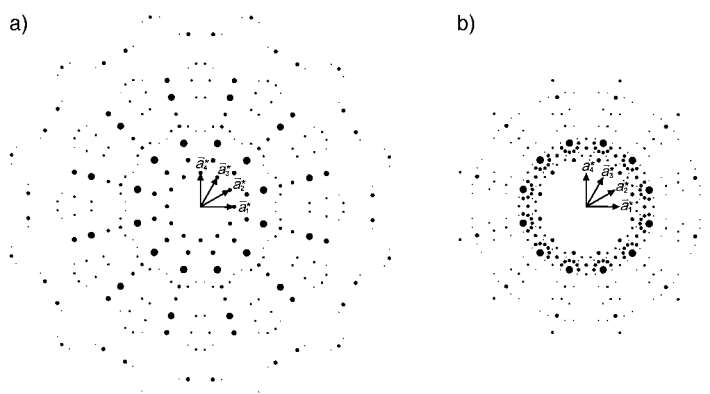


Figure 3. Schematic representation of the precession diffractograms of the zeroth (a) and fourth layer (b) perpendicular to the twelvefold axis. The size of the circles corresponds to the visually estimated intensity of the reflections.

indexed with integers, as for crystals, if instead of two, four base vectors are chosen $\vec{a}_i^*$ ($i = 1-4$). These four vectors point away from the center of a regular dodecagon towards four neighboring corners (Figures 3 a and b). In precession photographs, which were taken perpendicularly to the dodecagonal layers, the reflections parallel to the twelvefold symmetry axis are equidistant, that is, the structure shows translational periodicity only in this direction. The location of all the measured reflections can therefore be given with suitable integral linear combinations of five base vectors; the fifth, independent vector $\vec{a}_5^*$ is perpendicular to the four coplanar

vectors $\vec{a}_i^*$ ($i = 1-4$). In an equation analogous to the Bragg equation [Eq. (1)], they can be related to the experimentally

$$\frac{4 \sin^2 \theta}{\lambda^2} = (a_1^*)^2 \left[\sum_{i=1}^4 h_i^2 + h_1 h_3 + h_2 h_4 + \sqrt{3}(h_1 h_2 + h_2 h_3 + h_3 h_4) \right] + (a_5^*)^2 h_5^2 \quad (1)$$

found diffraction angles θ for the dodecagonal quasicrystal system.

λ is the wave length of the X-ray radiation, and h_1 to h_5 are five integers for addressing the points on the reciprocal quasilattice (corresponding to the three Miller indices h , k , and l for the three-dimensional reciprocal lattice). The evaluation of two chosen Guinier photographs (FR552, Enraf-Nonius, $\lambda(\text{Cu}_{K\alpha 1}) = 154.051$ pm) using the least-squares method gave the following values: $a_1^* = 2.1391(3) \text{ nm}^{-1}$ ($i = 1-4$), $a_5^* = 0.481(2) \text{ nm}^{-1}$, which gave $a_1 = \sqrt{2/3}/a_1^* = 0.38171(6) \text{ nm}$ and $a_5 = 1/a_5^* = 2.079(9) \text{ nm}$.^[10]

Since only two of the four base vectors $\vec{a}_1^*$ to $\vec{a}_4^*$ within the set of the real numbers are linearly independent, integral linear combinations of the four vectors do indeed give discrete points, however, in the dd plane they lie infinitely close together. Reflections can be perceived in the diffractograms only at particular positions. This subset shows some remarkable geometric characteristics. The possible locations of the reflections can be generated as follows (Figure 4): for the

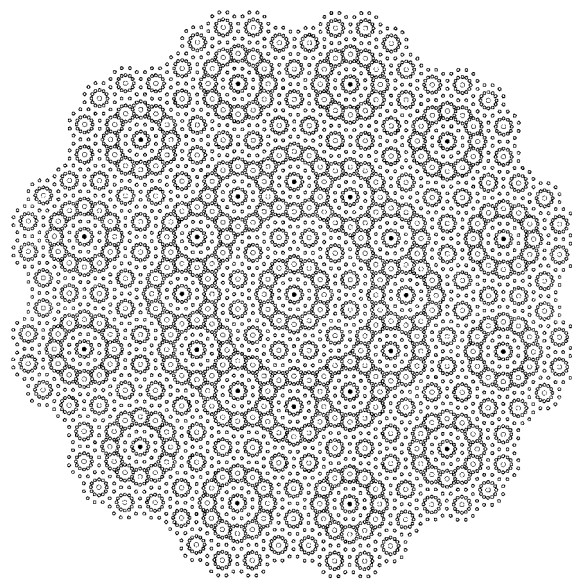


Figure 4. Result of an algorithm for the generation of a self-similar dodecagonal dot pattern.

generator we chose two concentric dodecagons of different size; the larger of the two is expanded by the square irrational factor $\sqrt{\xi} = \sqrt{2 + \sqrt{3}}$ and is also rotated by $\alpha = 15^\circ$ ($2 \cos \alpha = \sqrt{\xi}$) relatively to the smaller one. In the next step we replace the center and the corners of the two dodecagons (large, open circles) by a copy of the original ordering, scaled down by a factor of $2 - \sqrt{3} = 1/\xi$ (small, solid circles). If we repeat this step we obtain the pattern already described by Gähler in its third generation.^[11] It corresponds to a section from an infinite pattern, which repeats itself in a similar manner on scale of lengths differing by the factor ξ . Thus, this pattern is invariant

of scales with regard to the factor ξ , which represents the dodecagonal symmetry. In Figure 4 all the positions of the reflections can be seen that are visible in the diffractograms 2a and 2b as well as in that of 3a. Additional reflections appear in the precession photograph of the fourth layer ($h_1h_2h_3h_44$, Figure 3b), the positions of which are only obtained in the pattern of the fourth generation. The finding that the reflections group together in this characteristic way in the X-ray diffractograms of higher dodecagonal layers is significant in that it clearly demonstrates the strange ordering upon which this tantalum-rich telluride is based.

Direct structural information on dd-Ta_{1.6}Te can be obtained from HRTEM images recorded with the electron beam parallel to the main axis of symmetry. With favorable focal lengths (~ 80 nm) the motif of the diffractogram can be recognized locally (Figure 5); however, it is somewhat out-of-focus and organized differently. In the micrographs with

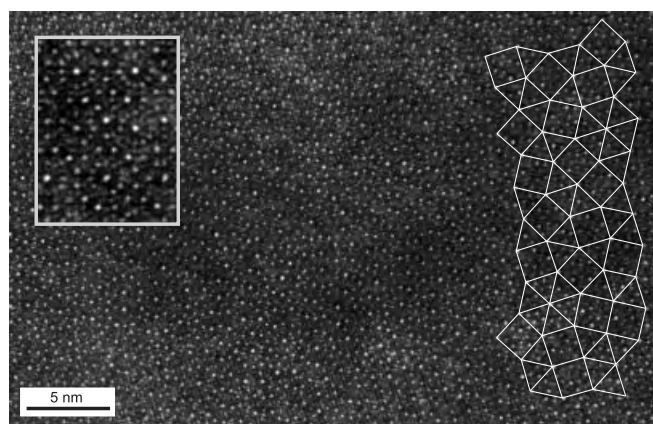


Figure 5. HRTEM image of dd-Ta_{1.6}Te. The inset (top left) shows an enlarged section.

almost atomic resolution, groups of 25 bright spots can be recognized that are arranged at the vertices of two concentric dodecagons, which are rotated by 15° to each other and which exhibit an area ratio of ξ . Some of the outer dodecagons are connected, mostly by five, sometimes by four or six, common edges in such a way that the central contrasts of these groups define an aperiodic, probably random tiling of triangles and squares along a length scale of almost 2 nm. Since such dodecagons may also penetrate to such an extent that interior dodecagons are also edge-connected, the pattern is not unambiguously established. At the level of the aperiodic tiling, the dodecagonal telluride and the intermetallic dd phases are similar; however, there is a marked difference in the length scale upon which this pattern is based. Whilst the characteristic length in the nickel-containing dd phases corresponds to the size of the hexagonal-antiprismatic M₁₃ clusters (M = metal atom) (ca. 450 pm), the corners of the pattern in dd-Ta_{1.6}Te are almost 2 nm apart. In order to explain this result, we assume that dd-Ta_{1.6}Te is also formed of hexagonal-antiprismatic M₁₃ clusters. The distance between neighboring centers of these clusters can be estimated from the lattice constants of the σ -phase of AuTa₂^[12] to be $a(\text{AuTa}_2)/\sqrt{\xi} = 521$ pm. Since the length scale for the square-triangle

tiling of dd-Ta_{1.6}Te is almost exactly extended by ξ compared to this value, it appears sensible to assume that correspondingly larger dodecagonal building blocks of 19 concentrically condensed Ta₁₃ clusters pave the plane. The sandwiching of these aperiodically ordered dodecagonal clusters by tellurium atoms leads to lamellar structural units consisting of five atomic layers (thickness: ca. 1 nm). These arrange themselves along the stacking direction through weak chalcogen-chalcogen interactions, in a similar manner to the metal-rich layered structures of Ta₂Te₃^[8] or Ta₂Se₃^[13]. This structural model is in agreement with the information obtained from diffraction experiments and HRTEM images, explains the unusual morphological and mechanical properties of this quasicrystalline phase, and also gives a geometric and structural chemical interpretation of the scaling factor ξ .

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KH(O₂)CO₂·H₂O₂—An Oxygen-Rich Salt of Monoperoxocarbonic Acid**

Arnold Adam* and Mathias Mehta

“...speculation about the structure of these compounds is less profitable than X-ray crystallographic examination.”

A. F. Wells^[1a]

The existence of peroxocarbonate or hydrogen peroxocarbonate anions in saltlike compounds has so far not been proven by structural methods.^[1b–e] The reported compositions of alkaline and alkaline earth metal peroxocarbonates and hydrogen peroxocarbonates, for example, have been derived either from analytical methods or from the preparative route and the ability to give off oxygen.^[2] Models of the structure of such moieties have been developed by using data from vibrational spectroscopy on microcrystalline materials.^[3] The commercially used product incorrectly labeled as “percarbonate” is in fact a hydrogen peroxide adduct of sodium carbonate, Na₂CO₃·1.5H₂O₂.^[4]

Our studies on hydrogen carbonates^[5] and structurally related carbonic acid derivatives, such as monoalkylcarbonates,^[6] led to the following questions for the acidic salts of the unknown peroxocarbonic acid H₂CO₄: what structural characteristics are exhibited by a hydrogen peroxocarbonate ion, how does it participate in hydrogen bonding, and how do the resulting anion blocks fit into the general system of hydrogen carbonates?^[7]

KH(O₂)CO₂·H₂O₂ is the first compound of a new class of substances^[8] for which “true” peroxocarbonate ions have been shown to exist in the form of [H(O₂)CO₂][−] ions by X-ray crystal structure analysis (Figure 1 and Table 1). These can be formally derived by replacing the OH group of a hydrogen

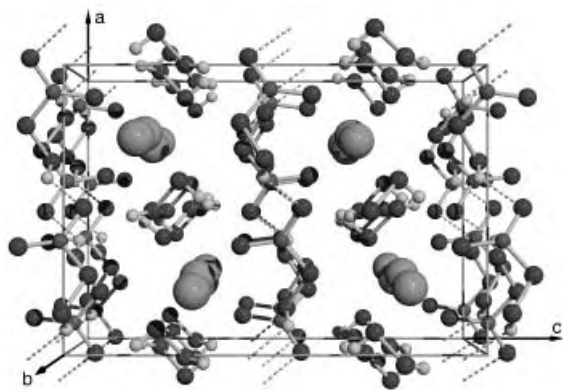


Figure 1. Crystal structure of KH(O₂)CO₂·H₂O₂ with unit cell, shown along [010]. The hydrogen bonds between the [H(O₂)CO₂][−] ions and the H₂O₂ molecules have been omitted for clarity.^[18]

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Table 1. Atomic coordinates and equivalent isotropic displacement parameters for KH(O₂)CO₂·H₂O₂.

Atom	x	y	z	U _{eq} /U _{iso} ^[a]
K	0.23463(4)	0.09434(9)	0.81255(3)	171(3)
C	0.3971(2)	0.1733(3)	0.5126(1)	133(7)
O1	0.3788(2)	0.1624(2)	0.4187(1)	178(5)
O2	0.5066(1)	0.2248(2)	0.5621(1)	206(5)
O3	0.2857(2)	0.1245(2)	0.5793(1)	254(6)
O4	0.1649(2)	0.0443(3)	0.5251(1)	293(6)
O5	0.5980(2)	0.3499(2)	0.7768(1)	197(6)
O6	0.4963(2)	0.4425(2)	0.7119(1)	196(6)
H1	0.108(9)	0.139(9)	0.529(7)	29(5)
H2	0.544(4)	0.341(4)	0.823(2)	4(1)
H3	0.481(5)	0.367(5)	0.668(3)	6(1)

[a] [pm²]; H atoms: 10² [pm²]. U_{eq} is in the form exp{−8π²U_{ij}²(sin²θ/λ)²}.

carbonate ion by an OOH group. The C atom is surrounded in an approximately trigonal-planar fashion by O1, O2, and O3 (C–O: 122.9(2)–138.1(2) pm; O–C–O: 110.4(2)–129.6(2)°). The deviations are caused by the fact that O3 belongs to the peroxo grouping. Within experimental error, the C atom is in the plane defined by O1, O2, and O3, while the O4 atom of the peroxo group is displaced from this plane by 18.5(4) pm. The O3–O4 distance (145.7(2) pm) is comparable to that in solid H₂O₂.^[9] The C–O3–O4 angle of 111.9(1)° corresponds closely to a tetrahedral angle, while the torsion angle C–O3–O4–H1 is 101(6)°. The angle between the hydrogen-bond donor O4, H1, and the hydrogen-bond acceptor O2 is 138(8)°, while the angle O3–O4–H1 is 88(5)°, again comparable to that found in solid H₂O₂. The hydrogen bond lengths of 268.0(3) pm for O2...O4 agree well with those found in Na₂CO₃·1.5H₂O₂.^[4] The hydrogen peroxocarbonate anions are linked by the hydrogen bonds into zigzag-shaped ∞¹[H(O₂)CO₂] chains, which run along the [100] direction. A similar structural feature is found for sodium hydrogen carbonate^[10] and ammonium hydrogen carbonate,^[11] which are characterized by stacks of ∞¹[HCO₃] chains. Thus the hydrogen peroxocarbonate structural unit fits readily into the system developed for hydrogen carbonates.^[7] In contrast to the hydrate-free NaHCO₃, the ∞¹[H(O₂)CO₂] chains found in KH(O₂)CO₂·H₂O₂ are linked by H₂O₂ molecules to form ∞²[[H(O₂)CO₂](H₂O₂)] layers, which run parallel to the ac plane (Figure 2). The potassium ions are embedded between these layers and exhibit a 7 + 2 coordination by nine oxygen atoms (seven O atoms at distances ranging between 274.7(2) and 283.1(2) pm, and two O atoms at 306.2(2) and 312.7(2) pm), which belong to three H₂O₂ molecules and four hydrogen peroxocarbonate anions.

The high content of releasable oxygen is remarkable. According to the decomposition reaction of KH(O₂)CO₂·H₂O₂ in Equation (a), this released oxygen constitutes



21.3% by mass, which is substantially higher than the values found for commercially used peroxo species such as (H₂N)₂CO·H₂O₂ (17.0 wt %),^[12] Na[BO₂(OH)₂] (16.0 wt %),^[13] and Na₂CO₃·1.5H₂O₂ (theory: 15.2 wt %, practice: 14.5 wt %). While KH(O₂)CO₂·H₂O₂ is not stable at room temperature, further experiments^[14] have shown that

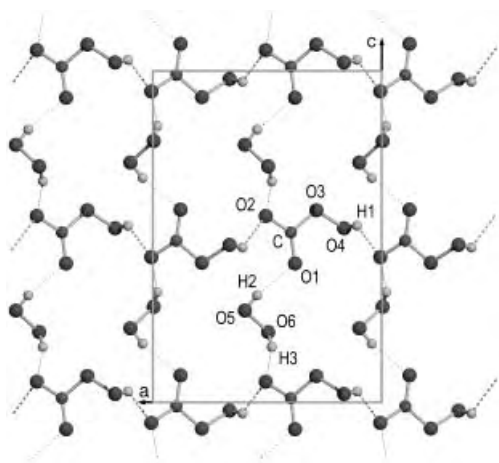


Figure 2. Section of the crystal structure of $\text{KH}(\text{O}_2)\text{CO}_2 \cdot \text{H}_2\text{O}_2$ along $[010]$, showing the linkage of the $[\text{H}(\text{O}_2)\text{CO}_2]^-$ ions and the H_2O_2 molecules through hydrogen bonds to give $\infty^2[[\text{H}(\text{O}_2)\text{CO}_2](\text{H}_2\text{O}_2)]$ layers.^[18]

varying the cation leads to increased thermal stability. Therefore, a temperature-dependent decomposition might be feasible that can be adjusted for various applications.

This is of great importance for the large industrial demand for readily accessible and easily manageable compounds with a high content of releasable oxygen. In this context, peroxo compounds such as hydrogen peroxide, perborates, persulfates, organic hydrogen peroxide derivatives as well as hydrogen peroxide adducts are employed on large scales, for example, as bleaching and oxidizing agents, components of detergents, antiseptic agents and disinfectants, oxygen reservoirs, radical initiators for polymerizations, catalysts. The growing market for water, sewage, and exhaust treatment systems is also of increasing importance.^[15]

Experimental Section

$\text{KH}(\text{O}_2)\text{CO}_2 \cdot \text{H}_2\text{O}_2 \cdot \text{H}_2\text{O}_2$ (ca. 30% solution) was cooled to -10 to -15°C and saturated with solid KHCO_3 . The resulting solution was layered with ethanol (approximately half the volume of the solution) and stored at -15 to -20°C . After a few days the desired product formed in the aqueous phase in the form of crystalline needles. Initial studies indicated that with increased reaction time, potassium carbonate (tris)peroxohydrate^[16] was also obtained.

Crystal structure data for $\text{KH}(\text{O}_2)\text{CO}_2 \cdot \text{H}_2\text{O}_2$: orthorhombic, space group $Pbca$ (no. 61), $a = 891.3(2)$, $b = 857.4(1)$, $c = 1293.7(2)$ pm, $V = 988.6(3) \times 10^6$ pm³, $\rho_{\text{calc}} = 2.017$ g cm⁻³, $Z = 8$, crystal dimensions $0.1 \times 0.15 \times 0.35$ mm³, $T = 173(2)$ K, $F(000) = 608$, $\mu(\text{MoK}\alpha) = 1.018$ mm⁻¹, $\lambda = 71.073$ pm, Enraf-Nonius-CAD4-diffractometer, graphite monochromator, $\omega/2\theta$ scan, 1797 measured, 918 symmetry-independent reflections, 732 reflections with $F_o > 4\sigma|F_o|$, 85 refined parameters; structure solution with direct methods and successive Fourier- and difference Fourier syntheses.^[17] All atomic positions were refined anisotropically (K, C, O) or isotropically (H) against $|F^2|$ to yield $R = 0.036$ and $wR2 = 0.082$; largest residual electron densities $-0.574 \leq \delta \leq 0.990$ near the potassium atom ($GooF = S = 1.061$ for all data). Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-407779.

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Living and Controlled Anionic Polymerization of Methacrylates and Acrylates in the Presence of Tetraalkylammonium Halide – Alkylaluminum Complexes in Toluene**

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Block copolymers of methacrylates and acrylates have the potential to combine thermoplastic–elastomeric, impact-modifying, or emulsifying properties with excellent resistance to weathering. An industrial-scale synthesis of polymers of this type with high molecular weights and narrow molecular-weight distributions would require use of a living and controlled^[1] anionic, coordinative, or radical polymerization reaction, preferably carried out at ambient or elevated temperature in a hydrocarbon solvent or in bulk. Only a few anionic and coordinative polymerization processes have been reported that might fulfill these demands. Examples include anionic polymerization with lithium as the counterion in the presence of lithium alkoxoalkoxides^[2] or alkylaluminum compounds,^[3] polymerization with metal-free counterions,^[4, 5] Lewis acid catalyzed group-transfer polymerization,^[6] and coordinative polymerization with aluminum porphyrins^[7] or lanthanocenes^[8] as initiators. However, either the rates of polymerization are so high that the reaction can be controlled only in a flow-tube reactor,^[9] or the copolymerization of methacrylates and acrylates fails to proceed satisfactorily for other reasons. Thus, molecular weights of the resulting polyacrylates are often limited to 20 000 g mol⁻¹, or the initiators are very expensive, complicated to prepare, and difficult to remove from the polymer. The controlled anionic polymerization of primary acrylates continues to be a particularly great challenge for polymer scientists.

Anionic polymerization of methyl methacrylate with lithiated initiators in the presence of alkylaluminum compounds in toluene has recently been shown to possess the required living character, but it does not follow conventional first-order kinetics, and the resulting polymers display fairly broad molecular-weight distributions.^[10] These circumstances have been attributed to the formation of a coordinative polymer network in which lithium ions at living-chain ends are coordinated to in-chain ester carbonyl groups (Figure 1).^[11] The formation of such a polymer network can be suppressed by the use of Lewis bases such as methyl pivalate or diisooctyl phthalate as cosolvents,^[12] an approach that results even at 0 °C in linear first-order time–conversion plots and syndio-

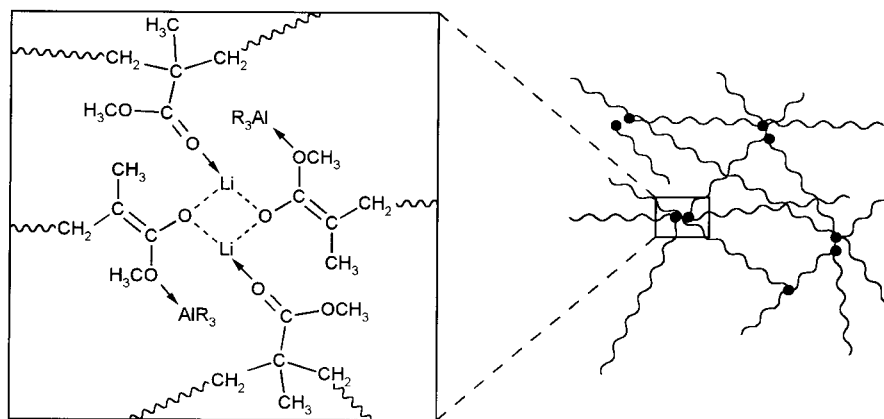


Figure 1. Structure of the coordinative network of living polymer chains.

tactic polymers with narrow molecular-weight distributions. However, since the half-life of the polymerization is usually in the range of several hours, use of this method is restricted to the synthesis of polymethacrylates with molecular weights < 20 000 g mol⁻¹. Moreover, only at –78 °C can primary acrylates such as *n*-butyl acrylate be polymerized in a controlled way.^[13]

We report here a different approach to the prevention of polymer-network formation in pure toluene. The underlying scheme is to substitute a less electropositive cation for lithium—for example, a tetraalkylammonium ion. Ziegler et al.^[14] reported that tetraalkylammonium halides NR₄X form hydrocarbon-soluble complexes with alkylaluminum compounds AIR₃ of the type NR₄⁺[AlR₃X]⁻ (R = Me, Et, *n*Bu; X = Cl, Br, I; R' = Me, Et; *n* = 1, 2). We have found that these complexes support living and controlled polymerization of methyl methacrylate (MMA) initiated by ethyl α -lithioisobutyrate (EiBLi) in toluene.^[15] At or below 0 °C this polymerization usually follows first-order kinetics, the number-average molecular weight *M_n* of the polymer increases linearly with monomer conversion, and the observed molecular-weight distributions are both unimodal and narrow (polydispersity index *M_w/M_n* < 1.2). The half-life of the reaction is reduced to a few minutes, which permits even polymers with molecular weights up to 250 000 g mol⁻¹ to be synthesized within a convenient amount of time. The polymethacrylate (PMMA) products are highly syndiotactic with racemic (*rr*) and mesoy (*mm*) triad fractions of about 0.75 and 0.01, respectively. In the absence of added alkylaluminum compounds, however, introduction of tetraalkylammonium halides leads predominantly to isotactic PMMAs (*mm* fraction ca. 0.65) with broad and multimodal molecular-weight distributions (*M_w/M_n* > 3).^[16] Similarly, initiation with tetrabutylammonium malonates in THF leads to uncontrolled polymerization of MMA (with *M_w/M_n* > 2).^[17] It is thus clear that the combination of tetraalkylammonium halides and alkylaluminum compounds is essential for obtaining a living and controlled polymerization.

Kinetic investigations show that the rate of propagation increases with the size of the tetraalkylammonium ion (NMe₄⁺ < NEt₄⁺ < NBu₄⁺; Figure 2), but that it remains at least two orders of magnitude lower than one might expect for an active species with a large tetraalkylammonium counterion.^[18]

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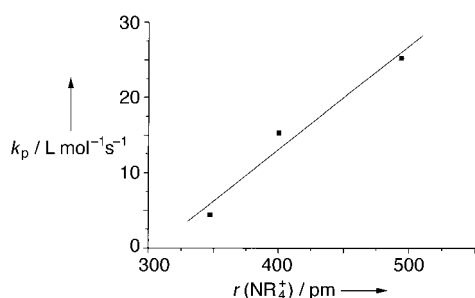


Figure 2. Dependence of the rate constant for propagation k_p on the radius r of the NR_4^+ ion during polymerization of MMA with EiBLi in the presence of $\text{NR}_4^+[\text{Al}_2\text{Et}_6\text{Cl}]^-$ in toluene at -20°C .

The rate of propagation increases also with decreasing ionic radius of the halide ($\text{I}^- < \text{Br}^- < \text{Cl}^-$; Figure 3). Ab initio calculations^[19] suggest that **1** is a possible active species, in which the lithium ion is coordinated to a complex trialkyl-

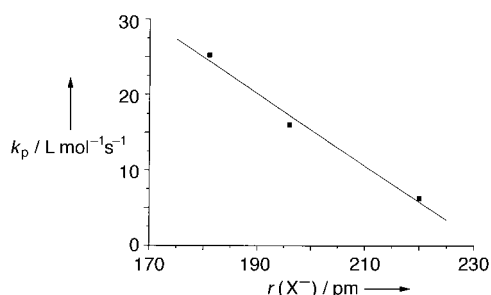
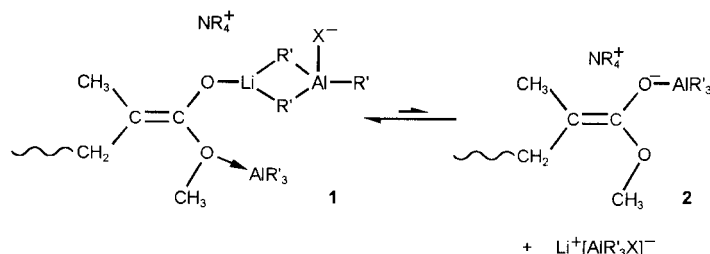


Figure 3. Dependence of k_p on the radius r of the X^- ion during polymerization of MMA with EiBLi in the presence of $\text{NBu}_4^+[\text{Al}_2\text{Et}_6\text{X}]^-$ in toluene at -20°C .

aluminum halide anion, and the tetraalkylammonium ion serves as the counterion. Structure **1** could explain the effect of tetraalkylammonium ions of different sizes upon the reactivity of the active species, but not the effect of the halide. Therefore, we assume that **1** can dissociate into the considerably more reactive ester enol aluminate **2** (with a tetraalkylammonium counterion) and a $\text{Li}^+[\text{AlR}_3\text{X}]^-$ complex (Scheme 1). Because the heat of formation of



Scheme 1. Postulated equilibrium between two active species with differing reactivities in anionic polymerization with $\text{NR}_4\text{X}/\text{AlR}_3$ complexes.

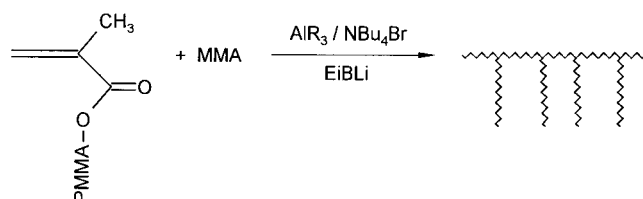
$\text{Li}^+[\text{AlR}_3\text{X}]^-$ increases as the radius of the halide decreases,^[14] the equilibrium in Scheme 1 would be shifted toward the active species **2**, which would lead to the observed acceleration of polymerization. With regard to the low values for

the rate constants of propagation, equilibrium should lie predominantly on the side of the less reactive species **1**. A detailed kinetic study will appear elsewhere.^[20]

It is interesting to note that tetraalkylammonium salts have also been used successfully by Inoue et al. in the ring-opening polymerization of cyclic ethers, lactones, and anhydrides with aluminum porphyrins.^[21] The mechanism proposed by these authors involves two polymer chains bound to the aluminum atom on opposite sides of the porphyrin ring, and the tetraalkylammonium salt enhances the reactivity of the aluminum porphyrin.

Like the polymerization of MMA, the polymerizations of *tert*-butyl methacrylate (*t*BMA) and *tert*-butyl acrylate (*t*BuA) are also living and controlled in the presence of $\text{NR}_4^+[\text{Al}_2\text{R}_6\text{X}]^-$ at -20°C . This makes it possible to prepare block copolymers PMMA-*block*-PtBMA and PMMA-*block*-PtBuA of high molecular weight by sequential monomer addition. Hydrolysis of the *tert*-butyl ester groups results in amphiphilic block copolymers with narrow molecular-weight distributions ($M_w/M_n < 1.2$). The content of residual PMMA precursors is 1–5 wt %.

Random copolymerization of MMA with methacryloyl-functionalized PMMA macromonomers leads to comb-shaped polymers of the type PMMA-*graft*-PMMA (Scheme 2 and



Scheme 2. Synthesis of comb-shaped PMMA through the use of a macromolecular PMMA monomer (macromonomer method).

Figure 4). It is usually difficult to obtain such polymers by anionic polymerization, because the macromonomers cannot be sufficiently purified; the presence of the alkylaluminum compound makes the polymerization system in this case self-cleaning.

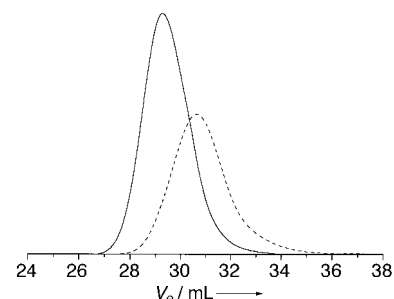


Figure 4. Elution diagram for gel permeation chromatography (GPC) of a PMMA-*graft*-PMMA comb polymer (—; $M_n = 86500$, $M_w/M_n = 1.33$) obtained in the copolymerization of MMA and a macro PMMA monomer (MM) (---; $M_n = 19400$, $M_w/M_n = 1.81$) initiated by EiBLi and $\text{NBu}_4^+[\text{Al}_2\text{Et}_6\text{Br}]^-$ at -20°C . The mass ratio of MMA to MM was 1:2.3; monomer conversions: 1 (MMA) and >0.95 (MM). V_e = elution volume.

Controlled polymerization of primary acrylates such as *n*-butyl acrylate (*n*BuA) or 2-ethylhexyl acrylate (EHA) is achieved at -78°C . Conversion of the monomer is quantitative, and the resulting polymers have molecular weights as high as $120\,000\text{ g mol}^{-1}$ and narrow molecular-weight distributions ($M_w/M_n < 1.2$; Figure 5).

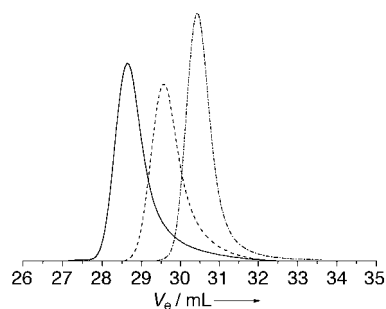


Figure 5. GPC elution diagram for PtBuA (---; $M_n = 70\,800$, $M_w/M_n = 1.15$), PnBuA (---; $M_n = 30\,500$, $M_w/M_n = 1.11$), and PEHA (—; $M_n = 119\,000$, $M_w/M_n = 1.20$), prepared in a polymerization initiated at -78°C with EiBLi and $\text{NMe}_4[\text{Al}_2\text{Me}_6\text{Cl}]^-$.

In summary, we have discovered a new initiating system that takes advantage of readily accessible and inexpensive reagents to produce polymethacrylates and polyacrylates of high molecular weight.

Experimental Section

Reagents: Ethyl α -lithioisobutyrate was prepared from ethyl isobutyrate and lithium diisopropylamide in hexane by described methods.^[22] Alkylaluminum compounds were purchased from Aldrich as solutions (25 wt %) in toluene and used without further purification. Tetraalkylammonium halides (Aldrich) were suspended in benzene and freeze-dried. (Meth)acrylic monomers obtained from BASF AG were fractionally distilled from CaH_2 at reduced pressure through a column (1 m) with Sulzer packing, stirred over CaH_2 , degassed, and distilled under high vacuum. Methacryloyl-terminated PMMA macromonomers donated by Röhm GmbH were used as received. Toluene (BASF AG) was fractionally distilled through a 1.5-m column, stirred twice over Na/K alloy, degassed, and distilled under high vacuum.

Polymerizations: All polymerizations were carried out in a stirred tank reactor under a nitrogen atmosphere. The initiator ethyl α -lithioisobutyrate was added to a solution of tetraalkylammonium halide and alkylaluminum compound in toluene, and the mixture was stirred for 5 min, after which the monomer was introduced. Polymerization was quenched with methanol/acetic acid (9/1) and the monomer conversion was determined by GC with octane or decane as internal standard. After evaporation of the solvent, the polymer was dissolved in benzene, the solution was filtered, and the polymer was freeze-dried.

Polymer characterization: Gel permeation chromatography (GPC) was used for molecular-weight distribution analysis, with THF as eluent (flow rate: 1 mL min^{-1} ; columns: 60 cm, $5\text{ }\mu\text{m}$ PSS-SDV gel, $100\text{ }\text{\AA}$ and linear $10^2\text{--}10^5\text{ }\text{\AA}$; detectors: JASCO-UVIDEC100III and Bischoff RI8110). Appropriate methacrylate and acrylate polymer standards were used to calibrate the columns. The molecular weights of comb-shaped polymers were determined with GPC (on-line viscosity detection) by universal calibration. ^1H and ^{13}C NMR spectra (Bruker AM-400) of the polymers were recorded at room temperature in CDCl_3 . The $\alpha\text{-CH}_3$ and C=O signals were used for the determination of triad tacticities.

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Polyhomologation: Synthesis of Novel Polymethylene Architectures by a Living Polymerization of Dimethylsulfoxonium Methylide**

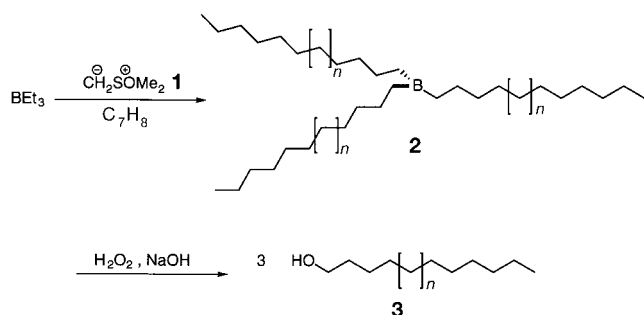
Kenneth J. Shea,* Brett B. Busch, and Manuel M. Paz

We recently reported a new polymerization reaction for the synthesis of polymethylene, the simplest carbon-backbone polymer constructed one methylene group at a time.^[1, 2] The ylide dimethylsulfoxonium methylide (**1**)^[3] is the monomer in this reaction and serves as the source of methylene. Polymerization is initiated by trialkylboranes. All three alkyl groups

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on boron participate in the reaction, which gives rise to the star polymethylene organoborane **2** (Scheme 1). Polyhomologation is a living polymerization reaction in which the length

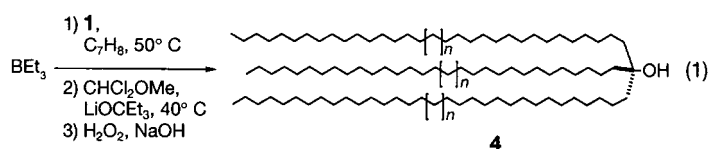


Scheme 1. Polyhomologation and subsequent oxidative cleavage.

of the polymethylene chain is determined by the initial molar ratio of ylide to organoborane. Polydispersities (PDs) that approach the Poisson distribution ($PD = M_w/M_n \approx 1.02 - 1.01$) have been obtained. These oligomeric and polymeric organoboranes are amenable to a number of synthetic transformations that can be used to functionalize the ends of the polymethylene chains. For example, peroxide cleavage of the carbon–boron bonds in star molecule **2** results in linear polymethylene **3** with terminal hydroxyl groups in yields over 90 % (Scheme 1).^[1]

The star-tris(polymethylene)borane can participate in a number of chemical transformations that result in novel polymethylene architectures not available through conventional ethylene polymerization. We demonstrate this by the synthesis of tris(polymethylene) methanols and polymethylene-substituted cyclooctanes. Our implementation takes advantage of “stitching” transformations available to organoboranes through which all three of the alkyl groups on boron are joined to a new carbon atom.^[4] These transformations, when applied to polyhomologated organoboranes, result in the synthesis of star-polymethylene methanols. We also present evidence that the polyhomologation reaction can be initiated by bridged bicyclic organoboranes. Use of these initiators results in cyclic architectures that contain multiple polymethylene substituents.

Two examples serve to illustrate the first strategy. Polymethylene methanols **4** were synthesized by the polyhomologation–chain stitching–oxidation sequence shown in Equation (1). Triethylborane was introduced into a preheated



solution of **1** in toluene under N_2 (ratio of ylide: trialkylborane = 60:1). The ylide was consumed within three minutes. To this heated mixture was added α,α -dichloromethyl methyl ether (DCME),^[5] followed by dropwise

addition of a solution of $LiOCt_3$ in hexane.^[4] After 2 h at $40^\circ C$ the resulting polymethylene derivative was oxidized (aqueous $NaOH$ and 30 % H_2O_2 , heating at reflux for 1 h). Addition of acetonitrile and methanol to the reaction mixture caused precipitation of **4**.^[6] In experiments in which the molar ratio of ylide to organoborane was varied from 25 to 60, 90, and 120, the experimentally determined number-average molecular weights (M_n) of the products were 530, 775, 1682, and 1982, respectively, in close agreement with the calculated molecular weights (Table 1). The PDs ranged from 1.02 to

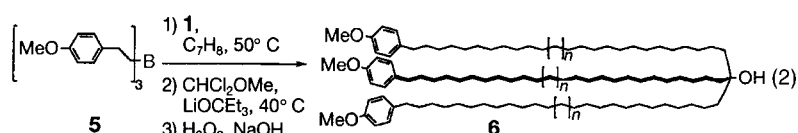
Table 1. GPC analysis of **4**.

Entry	Ylide: Initiator	M (calcd) ^[a]	M_n ^[b]	M_w	PD ^[b]
1	25	453	530	541	1.02
2	60	873	775	817	1.05
3	90	1380	1682	1853	1.10
4	120	1801	1982	2243	1.13

[a] The calculated molecular weight is based on the theoretical degree of polymerization for the initial ratio of ylide to borane. [b] Determined by GPC analysis.

1.13. Careful examination of material eluted during gel permeation chromatography (GPC)^[7] revealed the absence of straight-chain oligomer. The melting temperature (T_m) for the sample listed in entry 4 was approximately $85^\circ C$ [Eq. (1)].

The preparation of ω -substituted tris(polymethylene) methanols **6** was also accomplished by the polyhomologation–stitching–oxidation sequence. Tris(*p*-methoxyphenyl)borane (**5**), prepared by hydroboration of *p*-methoxystyrene,



was used to initiate polyhomologation of ylide **1**. After complete reaction of the ylide and treatment with DCME under basic conditions, polymethylene **6** was obtained in 74 % yield [Eq. (2)]. Both NMR spectroscopy^[8] and molecular-weight data from GPC^[9] were consistent with the assigned structure. In three experiments with molar ratios of ylide to initiator of 45, 90, and 120, the experimentally determined M_n values were 758, 1349, and 1741, respectively (Table 2), again

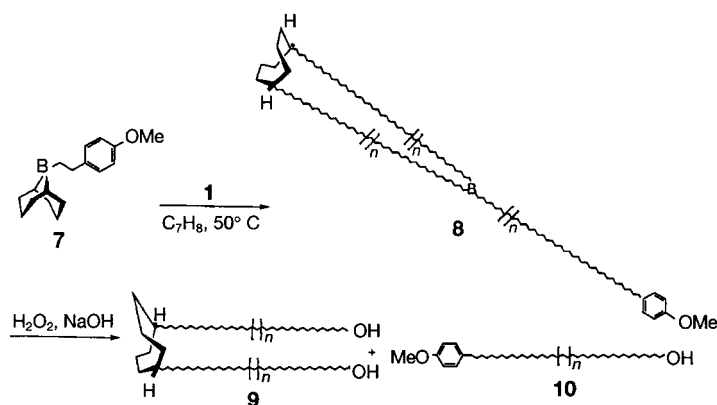
Table 2. GPC analysis of **6**.

Entry	Ylide: Initiator	M (calcd.) ^[a]	M_n ^[b]	M_w	PD ^[b]
1	30	897	714	776	1.08
2	45	1066	758	844	1.11
3	90	1698	1349	1545	1.14
4	120	2119	1741	2155	1.20
5	150	2539	2784	3313	1.19

[a] The calculated molecular weight is based on the theoretical degree of polymerization for the initial ratio of ylide to borane. [b] Determined by GPC analysis.

in close agreement with calculated molecular weights. These polymeric methanols exhibited PD values in the range of 1.08–1.20.

Particularly interesting polymethylene systems can be derived from bridged bicyclic organoboranes. This is illustrated by the synthesis of *cis*-1,5-bis(α -hydroxypolymethylene)cyclooctanes **9**. The starting material, *B*-*p*-methoxyphenylethyl-9-BBN (**7**), is prepared by the hydroboration of *p*-methoxystyrene with 9-BBN (9-BBN = 9-borabicyclo[3.3.1]nonane). The polyhomologation reaction was accomplished by addition of a solution of **7** in THF to ylide **1** in toluene at 50 °C (Scheme 2). After oxidation of the macrocyclic organoborane, the polymethylene product was isolated in 80–90 %



Scheme 2. Polyhomologation of **7** and subsequent oxidative cleavage of **8**.

yield. Based on prior observations of migratory insertions in 9-BBN derivatives, initial methylene insertion reactions are expected to occur at the bridgehead positions.^[10] However, once ring expansion has progressed, insertion reactions should take place readily at all three alkyl positions. The polyhomologation reaction is therefore expected to produce greatly expanded borabicyclic structures **8**. Subsequent oxidative cleavage of the carbon–boron bond yields two polymethylene structures. Analysis by GPC^[11] and NMR spectroscopy of the resulting product are consistent with a 1:1 mixture of α -*p*-methoxyphenyl- ω -hydroxypolymethylenes **10** and *cis*-1,5-bis(ω -hydroxypolymethylene)cyclooctanes **9**.^[12] Interestingly, because narrow distributions of oligomers are generated it is possible to separate the two polymethylene systems by simple chromatography over silica gel. Separation of telechelic **10** from **9** was carried out at 55 °C with a toluene/hexane/EtOAc mixture (8/2/1).^[13] Pure **9** was isolated and characterized independently.^[14]

The PDs for polymethylene derivatives **9** were in the range of 1.04–1.15 (Table 3). Initiator **7** does not restrict control over the length of the polymethylene chain. Despite differences in initial insertion rates, molecular-weight results obtained from GPC appear to be a function of the initial ratio of initiator to ylide.

We have described here the preparation of two new polymethylene topologies, polymethylene methanols **4** and **6** and *cis*-1,5-bis(α -hydroxypolymethylene)cyclooctanes **9**. Their syntheses were achieved by polyhomologation of readily available organoborane starting materials. The length of

Table 3. GPC analysis of **9**.

Entry	Ylide: Initiator	M_n	M_w	PD
1	30	682 ^[a]	750	1.04
2	35	836 ^[a]	957	1.07
3	102	1298	1497	1.15
4	163	4151	4453	1.07
5	330	10675	11861	1.11

[a] Substance **9** was analyzed after chromatographic separation from **10**.

the methylene chain can be controlled by the initial ratio of trialkylborane to ylide. Both **4** and **6**, as well as **9**, can be prepared with PD values less than 1.10. Physical properties of these interesting new polymethylene structures are currently under investigation.

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- [7] GPC was carried out at 100 °C with ultrastryragel columns and a refractive-index (RI) detector. *o*-Xylene was used as the eluent, and polymethylene samples were prepared as 0.5–0.6 % solutions. The GPC calibration curve was prepared with polyethylene standards obtained from Polymer Laboratories and Scientific Polymer Products. For the calibration curve, R^2 = 0.99978.
- [8] ¹H NMR (500 MHz, CDCl₃): δ = 7.08 (d, J = 8.4 Hz, 6H), 6.82 (d, J = 8.4 Hz, 6H), 3.78 (s, 9H), 2.53 (t, J = 7.7 Hz, 6H), 1.56 (t, J = 8.0 Hz, 6H), 1.25 (s); ¹³C NMR (500 MHz, CDCl₃): δ = 135.1, 129.3, 113.7, 74.5, 55.3, 35.1, 31.8, 29.7, 29.6, 23.5; IR (KBr): ν = 3448, 2920, 2850, 1469, 1246 cm⁻¹.
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- [14] ¹H NMR (500 MHz, C₇D₈): δ = 1.35 (s), 1.53 (m, 4H), 1.65 (m, 4H), 1.80 (m, 2H), 3.36 (t, J = 6 Hz, 4H); ¹³C NMR (500 MHz, C₆D₆): δ = 27.9, 30.1, 30.6, 33.3, 34.2, 38.1, 39.3, 62.8; ¹³C NMR (500 MHz, CDCl₃): δ = 25.5, 29.7, 30.0, 32.9, 33.7, 38.9, 63.1; IR (KBr): ν = 3448, 2920, 2850 cm⁻¹; GPC: M_n = 972, M_w = 1008, PD = 1.03; elemental analysis calcd for C₆₇H₁₃₄O₂ (M_n = 972.01): C 82.78, H 13.92; found: C 82.78, H 13.90.

The Twin-Excited State as a Probe for the Transition State in Concerted Unimolecular Reactions: The Semibullvalene Rearrangement**

Shmuel Zilberg,* Yehuda Haas, David Danovich, and Sason Shaik

Transition-state (TS) characterization is a central theme in contemporary chemistry, and new experimental methods are constantly being devised to achieve that goal.^[1] This paper offers an approach based on the “twin-state” concept,^[2] which predicts that the TS of a chemical reaction possesses a twin-excited state^[3] that under certain conditions is bound and has a geometry virtually coincident with that of the TS region. Since it is bound, the twin state is, in principle, observable; hence, it is a possible source of information about the TS. This idea is in the spirit of Bersuker’s^[4] suggestion that every TS should be accompanied by a bound excited state with a similar structure, the properties of which should in principle be measurable by spectroscopic methods and can thus constitute a source of information about the TS. Indeed, extensive discussions in the literature emphasize the ubiquity of the situation in which a transition state is accompanied by an excited-state minimum of similar geometry.^[5] We show here that this is a fingerprint of twin states, and demonstrate the idea computationally through the example of the degenerate Cope rearrangement of semibullvalene^[6] (henceforth, “the semibullvalene rearrangement”). These ideas, together with the present computational support, provide a physical rationale for the intriguing experimental discovery of Quast et al.^[7] that substituted semibullvalenes are colored and thermochromic even though they lack a long-wavelength chromophore.

The twin-state concept, which is based on the valence bond (VB) approach to reactivity,^[3, 8] was found^[2] to provide a physically lucid explanation for the apparently “anomalous” frequency increase of the b_{2u} ^[9] mode of benzene and generally in acenes upon excitation of the molecules from the $S_0(1^1A_{1g})$ ground electronic state to the 1^1B_{2u} electronically excited state. This exaltation was shown to be a natural consequence of the fact that the two electronic states can be considered essentially to arise from in-phase and out-of-phase combinations of two Kekulé structures,^[2a, c, d] other VB structures

being less important.^[10] The twin-state concept is depicted in Figure 1 for a degenerate rearrangement reaction of two mirror-image molecules represented by corresponding VB structures that differ only by bonds that have shifted. The

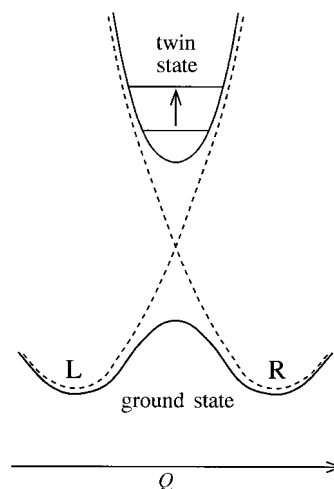
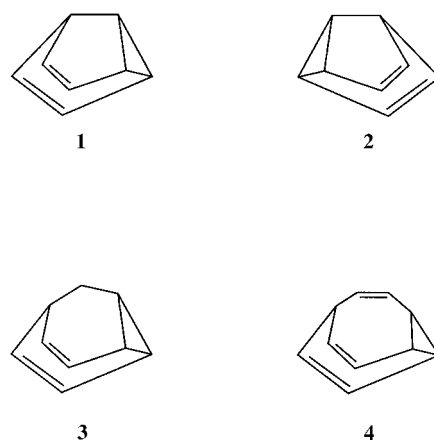


Figure 1. Schematic representation of a degenerate valence isomerization reaction, and the associated energy-level diagram that shows the avoided crossing.

semibullvalene rearrangement is a pertinent example, as evident from the two degenerate mirror-image structures **1** and **2**, but the arguments apply also to other Cope rearrangements and other thermally allowed^[11] degenerate rearrangements such as *i,j*-hydrogen shifts.^[12]



We denote the ground-state wave function of the reactant by $|L\rangle$ and that of the product by $|R\rangle$. As the system moves along the reaction coordinate Q it is assumed that the wave function can be expressed as a linear combination [Equation (1)]. By symmetry, the transition state is located at $Q = 0$,

$$\Psi(Q) = c_L(Q)|L\rangle + c_R(Q)|R\rangle \quad (1)$$

where $|c_L| = |c_R|$. For a case like semibullvalene, in which an odd number of electron pairs^[2e] rearrange during the reaction, the ground state electronic wave function transforms as the totally symmetric irreducible representation of the molecular

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point group. Thus, apart from a normalization factor, the ground state may be written as the in-phase combination [Equation (2)].

$$\Psi^+(Q=0)=|L\rangle+|R\rangle \quad (2)$$

$$\Psi^-(Q=0)=|L\rangle-|R\rangle \quad (3)$$

The state $\Psi^-(Q=0)$ represented by the negative linear combination [Equation (3)] is the excited state that arises from an avoided crossing along the isomerization reaction coordinate (see Figure 1); as such, it is the twin state of $\Psi^+(Q=0)$. By construction, the two zero-order VB states $|L\rangle$ and $|R\rangle$ are degenerate at $Q=0$, while the avoided crossing leads to the nondegenerate combinations $|L\rangle+|R\rangle$ and $|L\rangle-|R\rangle$. Thus, based on Figure 1, the TS of the thermal reaction has a twin-excited state that is bound and possesses a geometry virtually coincident with that of the TS region.

At $Q=0$ the system has an additional symmetry element; as a result, the two linear combinations $\Psi^+(Q)$ and $\Psi^-(Q)$ must have different symmetries. Since $\Psi^+(Q)$ transforms as the totally symmetric irreducible representation, the out-of-phase combination $\Psi^-(Q)$ must transform as some other irreducible representation of the point group.^[2a, 13] By analogy with the case of benzene,^[2] the model predicts the following properties for the twin-excited state:

a) The electronic wave function of the twin state belongs to the same irreducible representation as the coordinate that interchanges the L and R structures.

b) Because of the common “parentage” of the two states, the electric dipole transition between states will be small, even if the transition is formally allowed by symmetry.^[14]

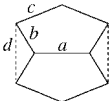
c) There will be a selective increase in the frequency of one vibrational mode in the excited state relative to the ground state. This mode corresponds to motion along the coordinate that interchanges the two VB structures used to construct the twin pair.

Figure 1 represents an ideal situation; it must be recognized that the minimum of the twin state may collapse^[15] as a result of mixing with other states and distortion along the other degrees of freedom. It is therefore essential to ascertain first the conditions for survival of the energy minimum of the twin state. From previous experience, avoidance of situations typified by strong mixing with ionic structures,^[2] while conferring some structural rigidity on the system,^[15] is likely to lead to survival of the twin-state minimum. This is the reason for our choice of the particular target molecule in question, which seems to meet the basic requirements. Thus, molecules that undergo Cope rearrangements—such as semibullvalene (**1**, **2**), barbaralane (**3**), and bullvalene (**4**)—appear to be natural candidates for this scheme because of their structural rigidity and the fact that reactants and products are properly represented by a single covalent VB structure. In addition, these systems have been extensively studied both experimentally and theoretically. Barriers for the reactions involving **1/2**, **3**, and **4** were found experimentally to be rather small (4.8, 8.6, and 12.8 kcal mol⁻¹, respectively).^[16] Recent high-level ab initio calculations,^[17] as well as experimental evidence,^[18] favor a concerted mechanism. If the concerted

mechanism applies, the TS and its twin-excited state should both belong to the C_{2v} point group. Based on the twin-state model [Eq. (2) and (3)] the in-phase combination of the two VB structures **1** and **2** corresponds to the TS and transforms as the A_1 representation, while the out-of-phase combination corresponds to the twin (excited) state and should possess B_2 symmetry.

To test the twin-pair concept for the semibullvalene rearrangement we carried out quantum-chemical calcula-

Table 1. Calculated bond lengths for semibullvalene in the ground state of the TS (1^1A_1) and in the excited twin state (1^1B_2).

	1^1A_1			1^1B_2		
	3-21G	MP2/ 6-31G*	CISD/ 3-21G	CIS/ 3-21G	CIS/MP2/ 6-31G*	UCISD/ 3-21G
						
a	1.562	1.555	1.572	1.562	1.551	1.554
b	1.506	1.496	1.514	1.504	1.491	1.510
c	1.379	1.392	1.388	1.409	1.409	1.426
d	2.049	2.042	2.064	2.190	2.205	2.240

tions^[19] on the two lowest electronic states. Table 1 summarizes geometries for the transition state and the first excited state, calculated at several levels of theory. The excited state is found to have B_2 symmetry, as predicted by the twin-state model. The geometry of the stable ground state (not listed) reproduces fairly closely the experimentally observed geometry, with C_s symmetry,^[20] whereas the TS and the twin-excited states have C_{2v} symmetry. It is apparent from Table 1 that, apart from a slight expansion of the excited state, the two states have very similar geometries. This expansion is analogous to that found both experimentally and computationally for the C–C bonds in the 1^1B_{2u} state of benzene relative to the ground state (1.44 vs. 1.39 Å)^[2]. The CISMP2 results were confirmed by more extensive CISD calculations, which, apart from minor changes, reproduce the CISMP2 data. Thus, quantum-chemical calculations support the idea that the twin state has a geometry virtually coincident with that of the TS region.

The calculated energy profile along the reaction coordinate is found to have the form shown in Figure 1. In accord with the qualitative model, the twin-excited state is calculated to have an energy minimum in the TS region, and the calculated oscillator strength for optical transition between the two states is small: 0.0271. The energy gap between the two twin states at $Q=0$ is calculated to be 5.16 eV, while the barrier height for isomerization in the ground state is 13.1 kcal mol⁻¹. Figure 2 depicts the reaction coordinate mode, which has an imaginary frequency for the TS and an exalted real frequency ($8b_2$) in the twin-excited state; both modes are of b_2 symmetry, as is required by the model. (The value obtained for the imaginary frequency, calculated at the harmonic approximation, may be too high, because the transition region is expected to be rather anharmonic.^[21]) Calculations thus support the notion that the 1^1B_2 state is the twin state of the

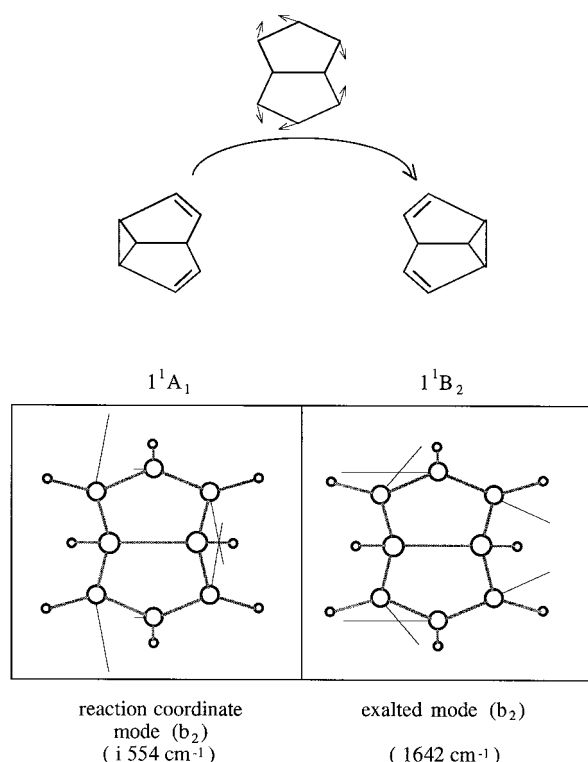


Figure 2. Vector representation of the calculated b_2 mode that exchanges the two VB structures of semibullvalene. Left: the imaginary vibrational mode at the transition state (ground state 1^1A_1); right, the real vibrational mode of the bound 1^1B_2 state.

transitionstate for the isomerization reaction of semibullvalene, because all three criteria identified above are fulfilled. The two states may be considered to be the in-phase and out-of-phase combinations of **1** and **2**.

An experimental link to the above ideas is found in the work of Quast et al.,^[7] who prepared a number of semibullvalene and barbaralane derivatives that are reversibly thermochromic—that is, they become colorless when cooled, and colored when warmed. This phenomenon was interpreted by the authors as being due to the low activation barrier in a system with the energy-level diagram shown in Figure 1. Subsequently, Manz et al.^[22] used the same picture and suggested that the semibullvalene rearrangement could be laser-induced, and that the TS population could be monitored simultaneously as a result of the optical transition to the bound excited state. Our twin-state concept, supported by computational results, proves that the excited state does indeed have the deep potential well *assumed* by both Quast et al.^[7] and Manz et al.^[22] More important, the work provides a clear characterization of the excited state as the twin state of the TS with the properties specified in Equations (1)–(3) above. Thus, consistent with the findings of Quast et al.^[7] and as predicted by the twin concept, the molecule is colorless at low temperatures because it resides near the bottom of the ground-state well where levels of the excited state accessible by the Franck–Condon principle are extremely high lying. When warmed, a significant fraction molecules is able to overcome the barrier; the substance thus acquires color, because now some light absorption is due to transitions from

vibrationally excited levels of the TS region to the low-lying twin-excited state. We emphasize, however, that the existence of a relatively low-lying bound excited state is not a property of *any* double-well potential system with a low barrier in the ground state, but arises from the fact that this is a twin-state situation.^[2, 3]

Our treatment shows that Bersuker's^[4] suggestion (that a TS should be accompanied by a bound excited state of a similar structure) is valid for the twin states in the present study. However, the contention that *every* TS must have such a bound excited state cannot be justified in general. Thus, in cases that are not geometrically constrained, or those with high ionicity,^[15] the twin-excited state will find alternative geometries in which it is more stable (e.g., H_3 , H_3^+ , the S_N2 TS^[15]). Similarly, it does not apply to conformational interconversion, as we recently verified for the conformational isomerization of cycloheptatriene: An exhaustive search for an excited state with B_1 symmetry and a planar structure did not reveal any bound state.^[13]

An experimental verification of the model could be initiated by probing the 1^1B_2 state with two-photon absorption spectroscopy. By analogy with the benzene case, a high-frequency $8b_2$ vibration should be prominent in the spectrum.^[9a] Since a transition from the TS to the twin-excited state is weakly allowed by the Franck–Condon principle, the signal itself may be weak, and the actual lifetime of the state could be shortened by a radiationless process that connects it with the ground state, which could smear out the vibrational structure of the transition. If these difficulties were circumvented (e.g., by a proper sequence of IR and visible-laser pulses) then spectral information (excitation and emission) might be transformed ultimately into structural information about the twin state, hence also about the TS region.

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An Artificial Regulatory System with Coupled Molecular Switches**

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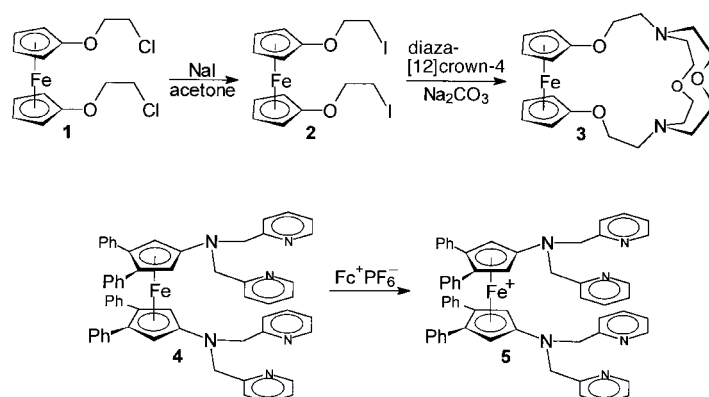
Living organisms rely on an efficient yet complex array of multiply interrelated molecular machines.^[1] Recently synthetic chemists have been imitating some of the very basic functions realized in biological systems. This activity has resulted in a number of artificial systems, such as molecular switches,^[2–9] sensors,^[10] ratchets,^[11] wires,^[12] artificial enzymes,^[13] and self-assembled species^[14] to name but a few.^[15] We set out to increase the complexity of such systems by designing an artificial regulatory unit in which several molecular components are coupled in a well-adjusted man-

ner.^[16, 17] Here, we demonstrate that the interaction of a redox-responsive chelating aminoferrocene, a redox-switchable oxaferrrocene cryptand, a Zn^{2+} and a Na^+ salt, and a polyazamacrocyclic leads to a system in which the availability of sodium ions can be controlled.

The basic components of the artificial regulatory system described here are two types of redox-active chelating ligands based on ferrocenes. Chelating aminoferrocenes form very stable complexes with soft transition metal ions and respond to the incorporation of metal ions by an anodic shift of the ferrocene redox potential.^[18] Complexes of oxaferrrocene cryptands with hard alkali and alkaline earth metal ions can become severely destabilized when the ferrocene is oxidized (redox-switching).^[19, 20] The efficiency of redox-active ligands in general, crucially depends on the electronic communication between the metal centers involved,^[21] and we have recently shown that it is very favorable when donor atoms of a chelating ligand are directly attached to the ferrocene unit.^[22]

The construction of an artificial regulatory system based on such ferrocenes requires the careful assembly of several individual components: a redox-responsive ligand (chelating aminoferrocene), a cofactor (Zn^{2+} salt), a redox-switched ligand (oxaferrrocene cryptand), a mediator (redox-equivalent), and a deactivator (cyclam = 1,4,8,11-tetraazacyclotetradecane). The individual tasks performed by these subunits are as follows: the redox-responsive ligand binds a cofactor (Zn^{2+}) to become an oxidizing agent, thus generating a redox-equivalent to act as a mediator. This mediator triggers the redox switch and strongly reduces the affinity of the redox-switched ligand for Na^+ ions. The removal of the cofactor by an added deactivator results in the reversal of the switching event and the reactivation of Na^+ binding. In the process as a whole, the availability of Na^+ ions is controlled indirectly by Zn^{2+} ions, by means of electron transfer.

The two types of ferrocenes needed for the artificial regulatory system were synthesized as described in Scheme 1. The dichloride **1** was treated with NaI in acetone to yield the



Scheme 1. Syntheses of the redox-active chelating ferrocenes. $\text{Fc}^+ = [\text{Fe}(\text{C}_5\text{H}_5)_2]^+$.

diiodide **2** in 90% yield. The subsequent reaction of **2** with diaza[12]crown-4 generated the oxaferrrocene cryptand **3** (Fcrypt) in 80% yield.^[23] The simple addition of NaCF_3SO_3 to Fccrypt in acetonitrile, followed by evaporation of the

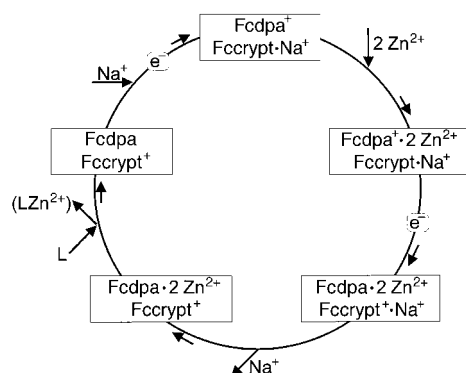
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solvent, resulted in the quantitative formation of the corresponding sodium complex. Oxidation of the aminoferrocene **4** (Fcdpa; dpa = di(2-picolyl)amine)^[18a] was performed with Fc^+PF_6^- to generate the corresponding cation **5**. The identity of compounds **1–5** was established by ^1H , ^{13}C NMR spectroscopy, EI mass spectrometry, and elemental analysis.

The thermodynamics of our artificial regulatory system are governed by the redox potentials of the chelating ferrocenes Fcdpa, Fccrypt, and their respective metal complexes, and it is essential that all four redox potentials are separated by more than 200 mV.^[24] The following redox potentials were measured by cyclic voltammetry (CH_3CN , $n\text{Bu}_4\text{NPF}_6$, with reference to ferrocene ($E = +0.40$ V) or cobaltocene ($E = -0.94$ V)): $E(\text{Fccrypt}) = +0.15$ V, $E(\text{Fccrypt} \cdot \text{NaCF}_3\text{SO}_3) = +0.395$ V, $E(\text{Fcdpa}) = -0.13$ V, $E(\text{Fcdpa} \cdot 2\text{Zn}(\text{CF}_3\text{SO}_3)_2) = +0.665$ V. It is apparent from these data that Fcdpa^+ is a very weak oxidant, while $\text{Fcdpa}^+ \cdot 2\text{Zn}^{2+}$ is a fairly strong oxidizing agent. Accordingly only $\text{Fcdpa}^+ \cdot 2\text{Zn}^{2+}$ is able to oxidize $\text{Fccrypt} \cdot \text{NaCF}_3\text{SO}_3$, which results in a drastic decrease in the Na^+ ion affinity of the ferrocene cryptand.^[25] For strong complexes it is possible to calculate (to a reasonable approximation) the decrease in the stability constant K for $\text{Fccrypt}^+ \cdot \text{Na}^+$ compared to K for $\text{Fccrypt} \cdot \text{Na}^+$ from the difference of the redox potentials $\Delta E = E_{\text{LM}} - E_{\text{L}}$ (L = ligand, M = metal).^[26] In the case of Fccrypt and $\text{Fccrypt} \cdot \text{Na}^+$, the value of $\Delta E = 245$ mV corresponds to a decrease in the stability of the sodium complex by at least 1.6×10^4 upon oxidation of Fccrypt.

Once the thermodynamic requirements have been satisfied by the selection of suitable redox partners, the actual experiment is very simple (Scheme 2). Starting from an equimolar



Scheme 2. Electron-transfer mediated regulation of the Na^+ concentration by Zn^{2+} ions. L = cyclam. The compounds in the boxes only indicate the elementary steps and do not imply isolated intermediates.

mixture of $\text{Fccrypt} \cdot \text{NaCF}_3\text{SO}_3$ and $\text{Fcdpa}^+\text{PF}_6^-$ in acetonitrile, the addition of two equivalents of $\text{Zn}(\text{CF}_3\text{SO}_3)_2$ leads to the complexation of Zn^{2+} by Fcdpa. The aminoferrocenium salt is thus converted into a strong oxidant, which is capable of oxidizing $\text{Fccrypt} \cdot \text{Na}^+$ quantitatively. The oxidized oxoferrocenium cryptand then displays a drastically decreased affinity for Na^+ ions. Finally the ability to bind Na^+ ions by the ferrocene cryptand can be re-established by adding a strong ligand to the reaction mixture that is capable of removing Zn^{2+} ions from the $\text{Fcdpa} \cdot \text{Zn}^{2+}$ complex. Consequently, upon

addition of two equivalents of cyclam, the much more stable Zn^{2+} -cyclam complex is formed. At this point—that is without complexed Zn^{2+} —Fcdpa becomes a reducing agent that can be easily oxidized by Fccrypt^+ to form Fcdpa^+ . The neutral Fccrypt species can now form a stable complex with a Na^+ ion and one finally returns to the situation given at the top of Scheme 2, in which Fcdpa^+ and $\text{Fccrypt} \cdot \text{Na}^+$ coexist.

However, it should not be forgotten that the redox potentials listed above only prove the thermodynamic feasibility of our regulatory device; it is important to check by NMR competition experiments that Zn^{2+} ions alone cannot displace Na^+ ions from the oxoferrocene cryptand. Thus, one equivalent of $\text{Zn}(\text{CF}_3\text{SO}_3)_2$ was titrated to a solution of $\text{Fccrypt} \cdot \text{NaCF}_3\text{SO}_3$ in CD_3CN . In the presence of two equivalents of Et_3N , the ^1H NMR spectrum remained unchanged when the zinc salt was added, indicating a the Na^+ selectivity of Fccrypt. However, in the absence of base, the addition of $\text{Zn}(\text{CF}_3\text{SO}_3)_2$ immediately leads to marked changes in the ^1H and ^{13}C NMR spectra characteristic of monoprotonated Fccrypt, since zinc ions can easily acidify adventitious water in the reaction mixture.

The reactions shown in Scheme 2 can be monitored easily by UV/Vis spectroscopy, since the spectra of Fcdpa, Fcdpa^+ , $\text{Fcdpa} \cdot 2\text{Zn}^{2+}$ and $\text{Fcdpa}^+ \cdot 2\text{Zn}^{2+}$ display very characteristic absorptions. Fccrypt and associated species could not be observed spectroscopically in the reaction mixture since their extinction coefficients are almost two orders of magnitude weaker. To verify the process described in Scheme 2 experimentally, two equivalents of $\text{Zn}(\text{CF}_3\text{SO}_3)_2$ were titrated to an equimolar solution of $\text{Fcdpa}^+\text{PF}_6^-$ and $\text{Fccrypt} \cdot \text{NaCF}_3\text{SO}_3$, with two equivalents of Et_3N , all dissolved in CH_3CN . It is apparent from the UV/Vis spectra (Figure 1) recorded after

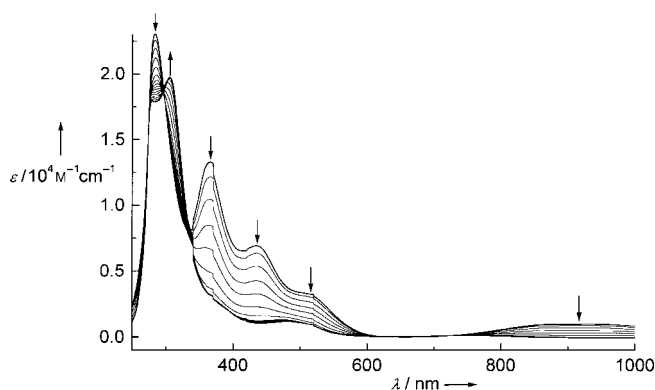


Figure 1. UV/Vis spectra of the titration of $\text{Fcdpa}^+\text{PF}_6^-$, $\text{Fccrypt} \cdot \text{NaCF}_3\text{SO}_3$, and Et_3N with $\text{Zn}(\text{CF}_3\text{SO}_3)_2$ in CH_3CN ($c = 10^{-4}$ M). Arrows indicate increasing or decreasing extinction during the course of the experiment. The initial UV/Vis spectrum is identical to that of Fcdpa^+ , while after addition of $\text{Zn}(\text{CF}_3\text{SO}_3)_2$ the resulting spectrum is identical to that of $\text{Fcdpa} \cdot 2\text{Zn}(\text{CF}_3\text{SO}_3)_2$.

each titration step, that the prominent absorptions associated with Fcdpa^+ disappear during the course of the experiment giving way to the simple spectrum of $\text{Fcdpa} \cdot 2\text{Zn}(\text{CF}_3\text{SO}_3)_2$. Finally two equivalents of cyclam were added to the reaction mixture, leading to the reappearance of the characteristic UV/Vis spectrum of Fcdpa^+ .

Since the UV/Vis experiments only provide information on different Fcdpa species, the titration was monitored in a further experiment by ^1H NMR spectroscopy to obtain information on the ferrocene cryptand and its sodium complex (Figure 2). Addition of $\text{Zn}(\text{CF}_3\text{SO}_3)_2$ in CD_3CN to

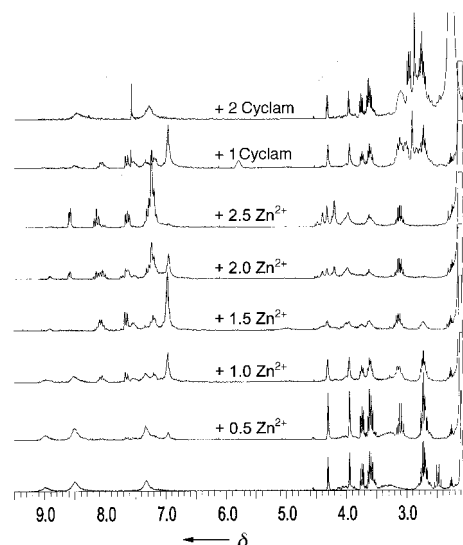


Figure 2. ^1H NMR titration experiment of $\text{Fcdpa}^+\text{PF}_6^-$, $\text{Fccrypt} \cdot \text{NaCF}_3\text{SO}_3$, and Et_3N (in CD_3CN , $c = 10^{-3} \text{ M}$) with the addition of four times 0.5 equivalents of $\text{Zn}(\text{CF}_3\text{SO}_3)_2$ followed by two times one equivalent of cyclam. Characteristic resonances associated with Fcdpa species are found between $\delta = 6.8\text{--}9.1$ (hatched in gray); characteristic resonance signals associated with Fccrypt species are found between $\delta = 3.4\text{--}4.6$ (hatched in gray).

an equimolar solution of $\text{Fcdpa}^+\text{PF}_6^-$ and $\text{Fccrypt} \cdot \text{NaCF}_3\text{SO}_3$ with two equivalents of Et_3N , leads to the disappearance of the ^1H NMR resonances associated with $\text{Fccrypt} \cdot \text{Na}^+$ (instead several broad humps are observed because of paramagnetic line broadening) and the appearance of signals assigned to $\text{Fcdpa} \cdot 2\text{Zn}^{2+}$. The reversal of the electron transfer after addition of two equivalents of cyclam is indicated by the reappearance of $\text{Fccrypt} \cdot \text{Na}^+$ resonances. We have not yet investigated the rates of the respective metal ion and electron transfer processes, however, no induction periods were observed in the above-mentioned titration experiments.

The experiments described here show that the combination of two redox-active ligands enables a regulatory event to be modeled. However, the artificial regulatory system described here is only operative when *all* individual components cooperate and are well adjusted in their binding and redox behavior. It should be noted that the simple addition of a Zn^{2+} salt as a redox-inactive cofactor is sufficient to initiate the electron transfer process and to switch the Na^+ complexation. The removal of the cofactor by addition of cyclam initiates the reverse electron transfer, and restores the binding ability of the oxaferrrocene cryptand.

Keywords: coordination modes • electron transfer • metal-locenes • molecular devices • supramolecular chemistry

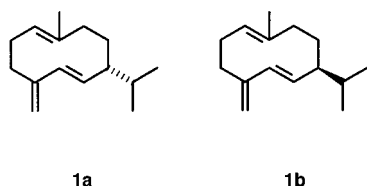
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Biosynthesis of (+)- and (–)-Germacrene D in *Solidago canadensis*: Isolation and Characterization of Two Enantioselective Germacrene D Synthases**

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Sesquiterpenes are synthesized by plants, fungi, bacteria, and marine invertebrates.^[1] Especially the oxygenated sesquiterpenes are important fragrances,^[2] and they also act as antibiotics,^[3] insect repellents, and pheromones;^[4, 5] they are also produced in response to attack by microorganisms.^[6] The biosynthesis of sesquiterpenes is initiated by cyclization of farnesyl diphosphate (FPP) and catalyzed by synthases (cyclases).^[7] Most sesquiterpenes are chiral, and plants usually synthesize only one of the two enantiomers. However, sometimes both enantiomers of a sesquiterpene are present in the same plant.^[8] Germacrene D is considered an important intermediate in the biosynthesis of sesquiterpenoid compounds.^[9] Most higher plants produce only (–)-germacrene D (**1b**), but the essential oils of various *Solidago* species contain similar amounts of both (+)- (**1a**) and (–)-germacrene D (**1b**).^[10, 11] Furthermore, germacrene D is not a precursor for oxygenated products in these plants.



Our aim was to investigate whether one or two synthases are involved in the biosynthesis of **1a** and **1b** in *S. canadensis*.

The major constituents of the essential oil of *S. canadensis* are **1a** and **1b**, and in many cases cyclocolorenone (**2**). The enantiomers **1a** and **1b** can be resolved and quantified by enantioselective gas chromatography^[12] (Figure 1a).

For the isolation of the germacrene D synthases, enzyme extracts were prepared and incubated with radiolabeled FPP. Product formation was monitored by radio gas chromatography (Figure 1b–d).

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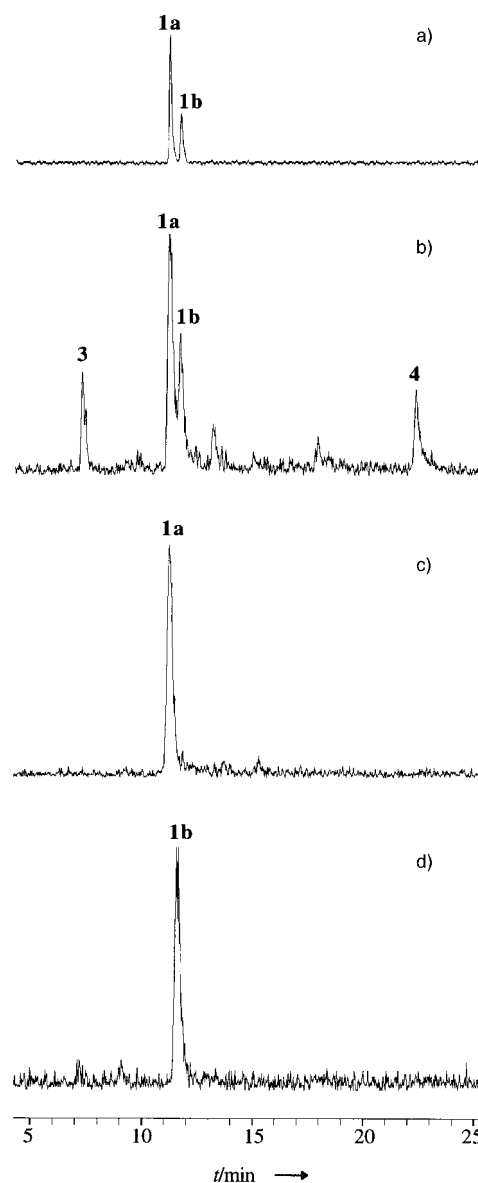
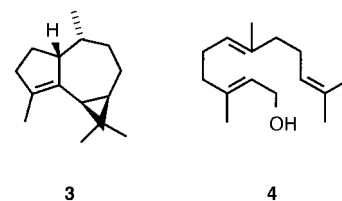


Figure 1. Gas chromatograms on a 25 m fused silica capillary column with heptakis(6-*O*-*tert*-butyldimethylsilyl)-2,3-di-*O*-methyl- β -cyclodextrin (50 wt % in OV 1701); temperature program: 116°C for 14 min, heating to 170°C at 15°C min⁻¹, 20 min at 170°C; flame ionization (a) or radioactivity detector (b–d). a) Separation of a (+)/(–)-germacrene D standard (obtained by preparative GLC from the essential oil of *S. canadensis*); b) Incubation products of the crude enzyme extract (assay 2); c) [³H](+)-germacrene D as the incubation product of the purified (+)-germacrene D synthase (assay 2); d) [³H](–)-[³H]germacrene D as the incubation product of the purified (–)-germacrene D synthase (assay 2).

Incubation of the crude enzyme extract with (*E,E*)-[³H]FPP gave four major products: enantiomerically pure (–)- α -gurjunene (**3**), **1a**, **1b**, and (*E,E*)-farnesol (**4**) (Figure 1b). Since (–)- α -gurjunene occurs only in small amounts in



essential oils of *S. canadensis*, the high (–)- α -gurjunene content of the crude enzyme extract suggests that it is the in vivo precursor of **2**. The formation of farnesol is due to the high phosphohydrolase activity of the crude enzyme extract.

The enzymes were isolated by ion-exchange chromatography (DEAE-52), dye–ligand chromatography (Red 120), and fast protein liquid chromatography (FPLC) on a MonoQ column. The final purification step yielded two active fractions. On incubation with [^{3} H]FPP, one fraction produced only **1a** (Figure 1c), while the other produced only **1b** (Figure 1d). Both enzymes were purified by a factor of 123 (Table 1). These results prove that the biosynthesis of **1a** and **1b** in *S. canadensis* is controlled by two enantioselective synthases. For the first time it was shown that

Table 1. Isolation of the (+)- and (–)-germacrene D synthases.

Fractionation step	Total protein [mg]	Total activity [nmol h ^{–1}]	Specific activity [nmol h ^{–1} mg ^{–1}]	Yield [%]	Purification
crude enzyme extract	63.2	834.1	13.20	100	1.0
DEAE-52 eluate	7.1	714.9	100.7	86	7.63
Dye Red 120	1.5	226.9	151.3	27	11.5
MonoQ					
(+)-germacrene D synthase	0.04	64.7	1618	7.8	123
(–)-germacrene D synthase	0.06	97.3	1622	12	123

one plant species contains two enzymes for the biosynthesis of sesquiterpene enantiomers. Previously the involvement of separate enzymes in the formation of enantiomers has only been demonstrated in the biosynthesis of monoterpenes.^[13]

Analytical SDS-PAGE gel electrophoresis showed the molecular mass of both synthases to be 51 kDa. The native molecular mass of both synthases as determined by gel filtration^[14] was also 51 kDa. Thus, both synthases appear to be monomers. The optimum pH for (+)-germacrene D synthase activity was 7.0, and for (–)-germacrene D synthase 7.1. The K_M values for (*E,E*)-[^{3} H]FPP were 9.97 μ M for (+)-germacrene D synthase and 4.24 μ M for (–)-germacrene D synthase. The results are comparable to those reported for other sesquiterpene synthases.^[15]

The cyclization mechanisms of the two synthases are still unknown. One hypothesis^[10] is that (*E,E*)-FPP is cyclized to a germacrene cation, which can undergo a 1,3-hydride shift to give (**1b**) or a double 1,2-hydride shift to form **1a**. Other authors^[16] demonstrated that (2*Z*,6*E*)-FPP is a substrate for the biosynthesis of **1a** in the liverwort *Heteroscyphus planus*. We have now shown that in *S. canadensis*, (*E,E*)-FPP is the substrate for the formation of both **1a** and **1b**.

Further investigations are aimed at establishing the cyclization mechanism for both synthases by using deuterium-labeled FPP and ^{2} H NMR spectroscopy^[17] and mass spectrometry and at determining the primary structure of both enzymes.

Experimental Section

[^{3} H]FPP was obtained from Amersham (England). During enzyme isolation and preparation of the assays all operations were carried out on ice or at 4°C.

Crude enzyme extract:^[18] 15 g of young leaves of an *S. canadensis* plant (collected near Hamburg, Germany) and 1.5 g polyvinylpyrrolidone (PVPP, Sigma) were ground in buffer A (25 mM 3-(*N*-morpholino)-2-hydroxypropanesulfonic acid (Mopso, Sigma), 25 mM Na₂S₂O₅, 10 mM MgCl₂, 5 mM dithiothreitol, 25 mM ascorbic acid, 20% (v/v) glycerol, pH 7.0). The extract was carefully stirred with 7.5 g XAD-4 resin and then filtered through cheesecloth. The filtrate was centrifuged at 20000g for 20 min (pellet discarded), and then at 100000g for 90 min. The 100000g supernatant was purified further.

Ion-exchange chromatography on diethylaminoethyl cellulose (DEAE, preswollen DE-52, Whatman):^[18] The 100000g supernatant was loaded onto a DEAE-52 column that had been preequilibrated with buffer B (15 mM Mopso, 10 mM MgCl₂, 2 mM Na₂S₂O₅, 10% (v/v) glycerol, pH 7.0). The column was eluted with a linear gradient of 0.0–0.5 M KCl in buffer B. Fractions were collected and assayed for cyclase activity (assay 1). The active fractions were combined and desalted in buffer C (15 mM Mopso, 10 mM MgCl₂, 10% (v/v) glycerol, pH 7.0) on an Econo-Pac 10 DG column (Biorad).

Dye–ligand chromatography:^[19] The desalted DEAE-52 eluent was loaded onto a Reactive Red 120 column (Sigma) that had been preequilibrated with buffer C. The column was then eluted with 1.5 M KCl in buffer C. Active fractions were combined and desalted in buffer C.

FPLC on MonoQ:^[18b] The desalted Red 120 eluate was loaded onto a MonoQ column (Pharmacia) that had been preequilibrated with buffer C. The column was eluted with a linear gradient of 0.0–0.5 M KCl in buffer C. Both active fractions were used separately for the enzyme characterizations.

Assay 1:^[18] 20 μ L enzyme preparation was diluted with 80 μ L buffer C, and 20 μ M [^{3} H]FPP (50 Ci mol^{–1}) was added. The reaction mixture was overlaid with 1 mL of hexane. After incubation for 30 min at 30°C, the reaction was stopped. The hexane phase was mixed with 40 mg of silica gel to remove farnesol, centrifuged, and an aliquot used for liquid scintillation counting.

Assay 2:^[18] 1 mL of enzyme preparation was mixed with 20 μ M [^{3} H]FPP (50 Ci mol^{–1}), layered with 1 mL of pentane, and incubated for 60 min at 30°C. The reaction mixture was extracted with diethyl ether, and the organic phase was removed and passed through a short column of aluminum oxide. The mixture was slowly concentrated under a stream of N₂ and used for radio-GLC analysis.

Radio-GLC^[18a, 20] was performed on a Carlo-Erba 4160 Series gas chromatograph equipped with a RAGA 93 radioactivity detector (Raytest, Straubenhardt, Germany).

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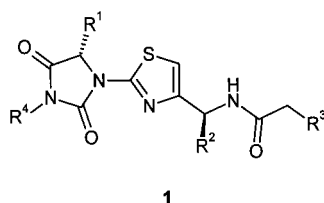
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Combinatorial Solid-Phase Synthesis of Structurally Complex Thiazolyhydantoines**

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In the past few years combinatorial chemistry^[1] and the related solid-phase synthesis^[2] of nonpeptide substance libraries have become established as valuable tools in pharmaceutical research for the discovery and optimization of lead compounds. We have developed a synthetic strategy that allows efficient construction by solid-phase synthesis of libraries of structurally complex thiazolyhydantoines of the general formula **1**. At the

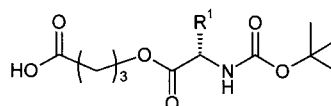


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same time, exploitation of an intrinsic purification principle has led to products with excellent purity after nine synthetic steps and subsequent removal of the target from the polymer support.

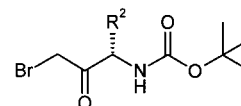
Derivatives **2a–c**,^[3] prepared from amino acids with *N*-butoxycarbonyl (Boc) protecting group, served as building blocks for the synthesis of a representative substance library



2a R¹ = CH₂C₆H₅

2b R¹ = CH₂-cyclo-C₆H₁₁

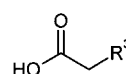
2c R¹ = CH₂C(O)N(CH₂CH₂)₂O



3a R² = H

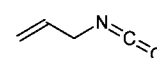
3b R² = CH₃

3c R² = CH₂CH(CH₃)₂



4a R³ = 4-FC₆H₄

4b R³ = H₃CC₆H₄O

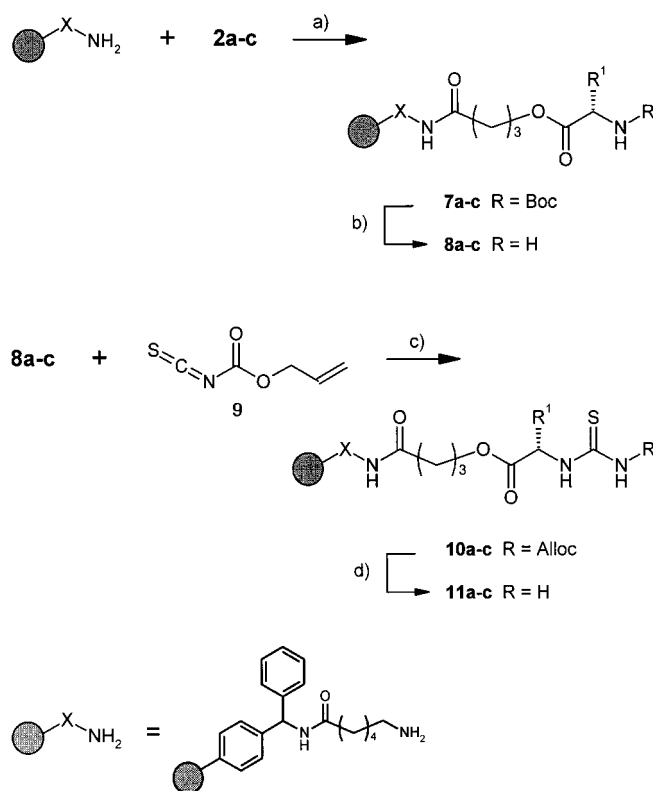


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(note the strategic importance of the ester functionality for detachment of the target compounds from the polymer support). Other key components were α -bromoketones **3a–c**^[4] derived from *N*-Boc-protected amino acids, carboxylic acids **4a, b**, and allyl isocyanate (**5**), which can be seen as a representative of isocyanates in general.

In a first reaction step, building blocks **2a–c** were linked through their free acid functionalities to a benzhydrylamine resin modified with 6-aminoheptanoic acid. 1,1,3,3-Tetramethyl-*O*-(2-oxo-1,2-dihydropyridin-1-yl)uronium tetrafluoroborate (TPTU)^[5] served as the coupling reagent to give derivatives **7a–c**. After cleavage of the Boc protecting group, free amines **8a–c** were transformed by reaction with allyloxycarbonyl isothiocyanate (**9**)^[6] into the thiourea derivatives **10a–c**, which contain the allyloxycarbonyl (Alloc) protecting group. Pd⁰ catalyzed removal of the Alloc group^[7] yielded thioureas **11a–c** as starting materials for the subsequent construction of 2-aminothiazole templates (Scheme 1).

2-Aminothiazoles **12aa–12cc** were obtained by the reaction of aliquot portions of resins **11a–c** with α -bromoketones **3a–c**. Free amines **13aa–13cc** were isolated after removal of the Boc protecting group. Once again, aliquots of resins **13aa–13cc** were coupled through their amino groups with carboxylic acids **4a, b** to give amides **14aaa–14ccb**. Preliminary experiments in solution had shown that coupling with carboxylic acids takes place exclusively at the primary amino group. Under the chosen reaction conditions the amino group attached to the heterocycle does not react with carboxylic acids. Reaction of compounds **14aaa–14ccb** with allylisocyanate (**5**) led finally to urea derivatives **15aaa–15ccb**, which were removed from the polymeric supports by a base-induced cyclization reaction specific to the ester function (the importance of which was alluded to earlier)^[8] to give the



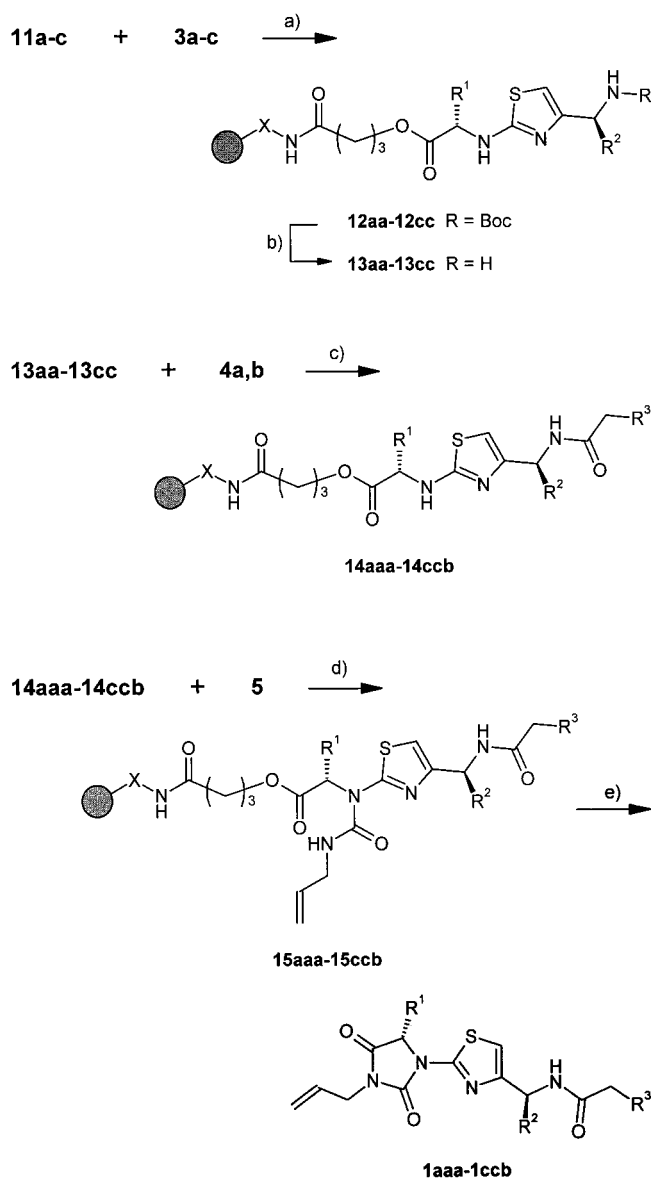
Scheme 1. a) TPTU, *i*PrNEt₂, DMF, 15 min; b) trifluoroacetic acid (TFA)/CH₂Cl₂ 1/2, 30 min; c) toluene, 60 min; d) Me₂NSiMe₃, CF₃COOSiMe₃, [Pd(PPh₃)₄], CH₂Cl₂, 6 h.^[6]

desired hydantoins **1aaa–1ccb**^[9] (Scheme 2). All compounds were tested for purity and identity by HPLC and MS (Table 1).

Table 1. Yields and physical data for **1aaa–1ccb**.

Compound	Building blocks	Yield ^[a]	<i>m/z</i> [<i>M</i> + H ⁺]	<i>R</i> _t (HPLC) [min] (intensity) ^[b]
1aaa	2a,3a,4a	130	479	4.26 (96.0)
1aab	2a,3a,4b	137	491	5.03 (90.0)
1aba	2a,3b,4a	69	505	4.78 (99.7)
1abb	2a,3b,4b	165	493	5.59 (98.7)
1aca	2a,3c,4a	111	535	6.02 (99.8)
1acb	2a,3c,4b	88	547	6.76 (96.5)
1baa	2b,3a,4a	80	485	5.57 (98.6)
1bab	2b,3a,4b	122	497	6.26 (97.2)
1bba	2b,3b,4a	113	499	6.03 (99.3)
1bbb	2b,3b,4b	117	511	6.81 (95.1)
1bca	2b,3c,4a	105	541	7.16 (94.1)
1bcb	2b,3c,4b	121	553	7.42 (5.8)
				8.19 (82.8)
				8.52 (6.1)
1caa	2c,3a,4a	134	516	2.14 (97.9)
1cab	2c,3a,4b	142	528	2.67 (82.1)
1cba	2c,3b,4a	91	530	2.44 (99.0)
1cbb	2c,3b,4b	191	542	3.19 (94.8)
1cca	2c,3c,4a	140	572	3.85 (96.4)
1ccb	2c,3c,4b	166	584	4.68 (97.9)

[a] Yields are based on milligrams of product per gram of resin. [b] Retention time *R*_t; relative intensity is indicated in parentheses in area percent; diastereomers arise in the case of **1bca** and **1bcb** due to partial racemization of the amino acid building blocks.



Scheme 2. a) Dioxane, 60 °C, 16 h; b) TFA/CH₂Cl₂ 1/2, 30 min; c) TPTU, *i*PrNEt₂, DMF, 15 min; d) dioxane, 70 °C, 16 h; e) dioxane/Et₃N 95/5, 60 °C, 6 h.

The high purity of the desired products, especially after a nine-step solid-phase synthesis, can be understood in the context of an intrinsic purification principle that accompanies the process. Thus, after the final reaction with isocyanates, only molecules that have taken part in the prior construction of 2-aminothiazole templates will be detached from the resin.

We have therefore demonstrated that, with careful choice of the reaction sequence, a multistep solid-phase synthesis can be an appropriate tool for the preparation of structurally complex, high-quality substance libraries.

Experimental Section

HPLC: LiChroCART 125-4, Lichrospher, RP-select B; solvent system: CH₃CN/H₂O 1/1 (1 min), CH₃CN/H₂O 1/1 → 3/1 (4 min), CH₃CN/H₂O 3/1 (3 min); flow rate 1 mL min⁻¹.

2a–c: Prepared by esterification of benzyl 4-hydroxybutyrate^[3] with appropriate *N*-Boc-protected amino acids (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), 4-dimethylaminopyridine (DMAP), CH₂Cl₂) followed by hydrogenolysis of the benzyl ester (H₂, 10% Pd on C, EtOH).

Modified benzhydrylamine resin: Benzhydrylamine resin (0.9 mol -NH₂ per gram) was coupled with Fmoc-6-aminoheptanoic acid (TPTU, *i*PrNEt₂, DMF; Fmoc = 9-fluorenylmethoxycarbonyl), and the Fmoc protecting group was subsequently cleaved (20% piperidine in DMF). Excess reagents were used in all solid-phase reactions (1.2–1.5 mmol g⁻¹). After the reactions were complete, the resins were repeatedly washed with DMF, *i*PrOH, and Et₂O. Solutions of product obtained after detachment of the resins were filtered through a minimal amount of neutral alumina (activity grade 3) and evaporated to dryness under reduced pressure.

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Structural Diversity in the Solid-State Structures of the Rubidium and Cesium Salts of 2,6-Dimesitylphenylphosphane**

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Dedicated to Professor Wolfgang A. Herrmann on the occasion of his 50th birthday

We recently focused our interest on the heavier alkali metal derivatives of primary and secondary phosphanes with the general formula MPR₂ and MPRH, respectively. In light of numerous reports on lithium derivatives^[1] and a few examples of sodium^[2] and potassium^[2c, 3] derivatives of MPR₂ and MPRH species, the dearth of structural data available on derivatives of rubidium and cesium is surprising. Recently, the solid-state structure of a sterically congested cesium silyl-(fluorosilyl)phosphanide aggregate was reported.^[2d] Heavier alkali metal phosphides are important because of their enhanced reactivity over their lithium counterparts, and also with respect to the structural diversity of their solid-state structures. We presented earlier a preliminary^[3] and a full report^[4] on the molecular structures of [MP(H)Mes*]_x species (M = K–Cs; Mes*PH₂ = 2,4,6-*t*Bu₃C₆H₂PH₂, “supermesitylphosphane”^[5]) as well as several different base adducts of these compounds. We also reported crystal structure determinations of three different base adducts of an asymmetrically substituted potassium phosphide, KP(*t*Bu)Ph.^[6] All of these alkali metal derivatives exhibit infinitely extended, one-dimensional polymeric M–P ladder-type arrangements in the solid state.

Motivated by our recent findings, we have now extended our studies to heavier alkali metal derivatives of other sterically demanding primary phosphanes. We decided to employ the 2,6-dimesitylphenyl (Dmp) substituent,^[7] since earlier work has suggested that this ligand is even more bulky than the Mes* ligand.^[8] However, recent studies have indicated that the steric relationship between Dmp and Mes* is not as simple as once thought.^[9] The preparation of the corresponding phosphane, DmpPH₂, was described recently.^[10]

Reaction of equimolar amounts of rubidium or cesium metal with DmpPH₂ in THF at room temperature produced the yellow-orange RbP(H)Dmp and yellow CsP(H)Dmp complexes, respectively. Even in the presence of excess alkali

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metal, bismetallation was not observed. Both RbP(H)Dmp and CsP(H)Dmp were fully characterized by ^1H and ^{31}P NMR, IR, and UV/Vis spectroscopy, and elemental analysis. Crystals suitable for an X-ray crystal structure determination were obtained by slow evaporation of a solution of RbP(H)Dmp in toluene. Crystals of CsP(H)Dmp were obtained from toluene/THF/*N*-methylimidazole (*N*-MeIm). The composition of both species was determined crystallographically as $[\{\text{RbP(H)Dmp}\}_4 \cdot \text{C}_7\text{H}_8]$ (**1**) (Figure 1) and $[\{\text{Cs}^+\text{Cs}_2[\text{P(H)Dmp}]_3\} \cdot 1/3 \text{C}_7\text{H}_8]_x$ (**2**) (Figures 2 and 3).

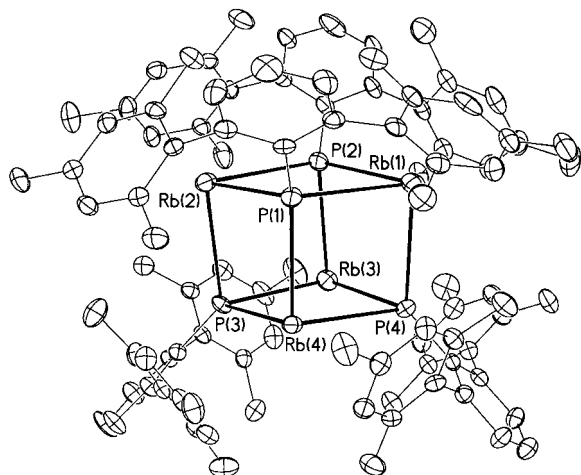


Figure 1. ORTEP diagram of the structure of **1** in the crystal. The hydrogen atoms and the toluene molecule are omitted for clarity. Selected bond lengths [Å] and angles [°]: Rb(1)–P(1) 3.756(2), Rb(1)–P(2) 3.411(2), Rb(1)–P(4) 3.399(2), Rb(2)–P(1) 3.520(2), Rb(2)–P(2) 3.473(2), Rb(2)–P(3) 3.558(2), Rb(3)–P(2) 3.579(2), Rb(3)–P(3) 3.425(2), Rb(3)–P(4) 3.516(2), Rb(4)–P(1) 3.454(2), Rb(4)–P(3) 3.412(2), Rb(4)–P(4) 3.480(2); P(1)–Rb(1)–P(2) 84.32(5), P(1)–Rb(1)–P(4) 96.00(5), P(2)–Rb(1)–P(4) 83.62(5), P(1)–Rb(2)–P(2) 87.10(5), P(1)–Rb(2)–P(3) 101.66(5), P(2)–Rb(2)–P(3) 79.31(5), P(2)–Rb(3)–P(3) 79.67(5), P(2)–Rb(3)–P(4) 79.57(5), P(3)–Rb(3)–P(4) 87.86(5), P(1)–Rb(4)–P(3) 106.11(5), P(1)–Rb(4)–P(4) 100.28(5), P(3)–Rb(4)–P(4) 88.64(5).

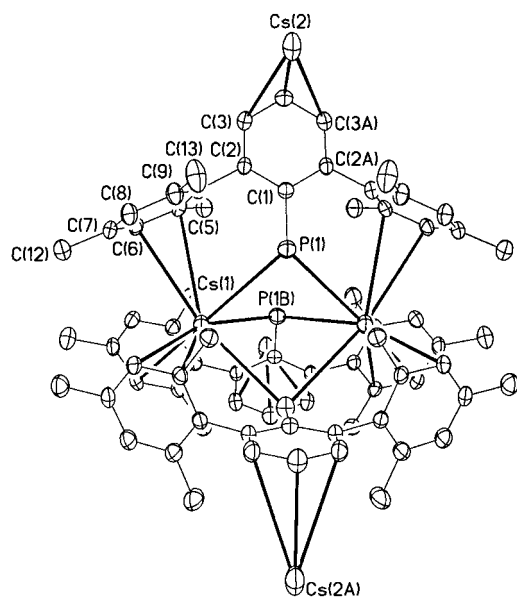


Figure 2. ORTEP diagram of the asymmetric unit of **2**. The hydrogen atoms and the toluene molecule are omitted for clarity. Selected bond lengths [Å] and angles [°]: Cs(1)–P(1) 3.6254(14), Cs(1)–Cs(1A) 4.8959(9), P(1)–Cs(1)–P(1A) 79.40(3), Cs(1)–P(1)–Cs(1A) 84.94(4), C(1)–P(1)–Cs(1) 117.33(13).

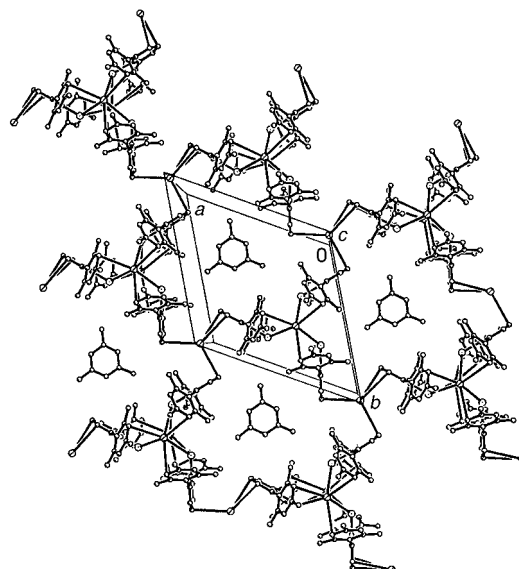


Figure 3. Unit-cell packing diagram of **2** showing the two-dimensional extension of the polymeric framework.

RbP(H)Dmp is slightly soluble in toluene at room temperature, which enabled crystallization from this solvent. It is noteworthy that CsP(H)Dmp is insoluble in toluene and can only be dissolved in the presence of classical Lewis bases such as THF, pyridine, or *N*-MeIm.

The molecular structure of **1** in the crystalline state (Figure 1) features a cubic arrangement of rubidium and phosphorus atoms with both mesityl rings of all four Dmp ligands “solvating” neighboring rubidium atoms with different degrees of π -interaction. Each rubidium cation in the Rb_4P_4 cube is therefore surrounded by three phosphide ligands and, additionally, “solvated” through π -bonding of two adjacent mesityl rings (from different Dmp ligands). The shortest Rb–C(ring) distances are Rb(1)–C(20) 3.216(7), Rb(2)–C(120) 3.401(7), Rb(3)–C(209) 3.425(7), and Rb(4)–C(318) 3.299(7) Å. The Rb–P interatomic separations range from 3.399(2) Å to 3.756(2) Å and can be compared to the corresponding distances found in polymeric $[\text{RbP(H)Mes}^*]_x$ (3.381(1)–3.504(1) Å).^[4] The deviation from ideal cubic geometry is most readily seen by inspecting the interatomic angles within the Rb_4P_4 cube. The P–Rb–P angles range from 79.31(5)° to 106.11(5)°, the corresponding Rb–P–Rb angles from 75.91(4)° to 101.17(5)°, and the Rb–Rb distances from 4.2896(10) Å to 5.3954(12) Å. It is noteworthy that both the ^1H and the ^{31}P NMR spectra of **1** appear to be more or the less solvent-independent, indicating that the heterocubane framework of **1** may be retained in solution.

The solid-state structure of **2** (Figures 2 and 3) differs significantly from the cubic arrangement in **1**, exhibiting a novel and rather peculiar structural motif that also differs significantly from polymeric arrangements in other MP(H)R and MPR₂ species. In contrast to the infinitely extended parallel M–P ladder-type polymers of $[\text{MP(H)Mes}^*]_x$ (M = K–Cs) or the cubic arrangement in **1**, the extended structure of **2** consists of a polymeric two-dimensional framework of $\text{Cs}^+[\text{Cs}_2[\text{P(H)Dmp}]_3]^-$ contact ion pairs. Contrary to the coordination behavior of polymeric $[\text{CsP(H)Mes}^*]_x$, there

are no *N*-MeIm ligands coordinated to the cesium cations in the solid-state structure of **2**.

The molecular structure of **2** in the crystalline state was solved in the hexagonal space group $P6_3/m$. The polymeric two-dimensional network of **2** shows two types of cesium cations, Cs(1) and Cs(2). Cs(1) and Cs(1A) lie on a threefold axis and are bridged by three phosphide ligands (Figure 2) with a Cs–P interatomic separation of 3.6254(14) Å, a P–Cs–P angle of 79.40(3)°, and a Cs–P–Cs angle of 84.94(4)°. Atom P(1) lies on a mirror plane. The interatomic Cs–P separation in **2** compares well with the corresponding distances found in polymeric $[\text{CsP(H)Mes}^*]_x$ (3.577(1)–3.642(1) Å), and the Cs–P interatomic separations in the recently reported cesium silyl(fluorosilyl)phosphanide (3.517(6) and 3.536(7) Å).^[2d] In addition to three Cs(1)–P bonds, each Cs(1) cation is encapsulated by two ring carbon atoms (C(5) and C(6)) of three neighboring mesityl ligands with Cs(1)–C distances of 3.569(4) Å and 3.532(4) Å, respectively. These distances can be compared to the corresponding Cs–C interatomic separations in $[\text{CsP(H)Mes}^*]_x$ that range from 3.219(5) to 3.710(5) Å.^[4]

Atom Cs(2) lies on a $\bar{6}$ axis and appears to be a bare cesium cation, “solvated” only by π -coordination of three arene ligands, each of them coordinated to the metal center in an η^3 -fashion with Cs(2)–C distances of 3.655(5) Å (C(3) and C(3A)) and 3.332(8) Å (C(4)). The interaction of the large cesium cation Cs(2) with three separate $[\text{Cs}_2\text{P(H)Dmp}]_3^-$ ions gives a coordination environment reminiscent of a paddle-wheel. It is unique, has no precedence in organo-cesium chemistry, and differs considerably from the coordination environment around cesium observed in the molecular structures of the bent cesiocene triple-decker anion $[\text{Cp}_3\text{Cs}_2]^-$,^[11] as well as the π -solvates $\text{CsC}(\text{SiMe}_3)_3 \cdot 3.5 \text{C}_6\text{H}_6$ ^[12a] and $\text{CsSi}(\text{SiMe}_3)_3 \cdot 1.5 \text{PhMe}$.^[12b] π -Interaction of aromatic systems with the heavier alkali metal cations has wide precedence in the literature,^[2d, 6, 12] and was also observed in the molecular structures of the potassium, rubidium, and cesium derivatives $[\text{MP(H)Mes}^*]_x$.^[3, 4] It should be noted that the Cs(2)–C distances in **2** are significantly shorter than the corresponding distances in the previously reported π -solvates $\text{CsC}(\text{SiMe}_3)_3 \cdot 3.5 \text{C}_6\text{H}_6$ (av 3.81(2) Å)^[12a] and $\text{CsSi}(\text{SiMe}_3)_3 \cdot 1.5 \text{PhMe}$ (av 3.80(2) Å).^[12b]

Crystals of **2** contain one toluene molecule per asymmetric unit with the methyl carbon atom equally disordered over three positions. The packing diagram of **2** (Figure 3) shows how every Cs(2) atom bridges three anionic $\text{Cs}_2[\text{P(H)Dmp}]_3^-$ moieties, thereby forming what appears to be a host–guest solid-state arrangement. Each molecule of toluene lies on a $\bar{6}$ axis in the center of a cavity formed by three $\text{Cs}^+[\text{Cs}_2\text{P(H)Dmp}]_3^-$ units.

This work demonstrates that the structural motifs found in the phosphides of the heavier alkali metals vary widely, determined both by the steric bulk of the phosphide ligand as well as the alkali metal cation employed.

Experimental Section

The compounds described below were handled under nitrogen using Schlenk line double-manifold, high-vacuum, glovebox (M.Braun, Labmaster 130) techniques. All solvents were dried before use.

RbP(H)Dmp (1): In the glovebox, a solution of DmpPH_2 ^[10] (200 mg, 0.58 mmol) in THF (10 mL) was added to one equivalent of rubidium (50 mg, 0.58 mmol) in THF (5 mL), which resulted in a slow color change to orange. The reaction mixture was stirred for 4 h, centrifuged, the solvent removed, and the residues washed with hexane. The product crystallized from hot toluene and was dried under vacuum to afford **1** as a yellow-orange powder (150 mg, 60%). Compound **1** is well-soluble in THF and pyridine, slightly soluble in toluene at room temperature, and insoluble in aliphatic hydrocarbons. ¹H NMR (400 MHz, $[\text{D}_6]\text{benzene}$, 25 °C, TMS): δ = 1.75 (d, ¹J(P,H) = 180 Hz, 1H), 2.24 (s, 6H), 2.25 (s, 12H), 6.80 (d, ³J(H,H) = 7 Hz, 2H), 6.85 (s, 4H), 6.95 (t, ³J(H,H) = 7 Hz, 1H); ¹H NMR (400 MHz, $[\text{D}_8]\text{THF}$, 25 °C, TMS): δ = 1.67 (d, ¹J(P,H) = 176 Hz, 1H), 2.13 (s, 12H), 2.26 (s, 6H), 6.27 (d, ³J(H,H) = 7 Hz, 2H), 6.34 (t, ³J(H,H) = 7 Hz, 1H), 6.78 (s, 4H); ³¹P NMR (161.9 MHz, $[\text{D}_6]\text{benzene}$, 25 °C): δ = –115.7 (d, ¹J(P,H) = 180 Hz); ³¹P NMR (161.9 MHz, $[\text{D}_8]\text{THF}$, 25 °C): δ = –117.0 (d, ¹J(P,H) = 176 Hz); elemental analysis: $\text{C}_{24}\text{H}_{26}\text{PRb}$: calcd: C 66.90, H 6.08; found: C 66.30, H 5.90; IR (Nujol): $\bar{\nu}$ = 2250 (s), 1882 (w), 1704 (w), 1569 (s), 1277 (w), 1243 (m), 1040 (s), 1014 (m), 999 (w), 853 (vs), 786 (w), 720 (m), 592 (w) cm^{-1} ; UV/Vis (THF): λ_{max} (ϵ) = 212 (25000) nm.

CsP(H)Dmp (2): Compound **2** was prepared in a similar way to **1** with equimolar amounts of DmpPH_2 ^[10] (200 mg, 0.58 mmol) and cesium (77 mg, 0.58 mmol). A slow color change to orange was observed. Workup of the reaction mixture gave **2** after crystallization from THF/hexane (1/1) at –30 °C as a yellow powder (166 mg, 60%). Compound **2** is well-soluble in THF and pyridine, but insoluble in toluene and aliphatic hydrocarbons. ¹H NMR (400 MHz, $[\text{D}_8]\text{THF}$, 25 °C, TMS): δ = 1.79 (d, ¹J(P,H) = 173 Hz, 1H), 2.12 (s, 12H), 2.26 (s, 6H), 6.26 (d, ³J(H,H) = 7 Hz, 2H), 6.33 (t, ³J(H,H) = 7 Hz, 1H), 6.78 (s, 4H); ³¹P NMR (161.9 MHz, $[\text{D}_8]\text{THF}$, 25 °C): δ = –99.9 (d, ¹J(P,H) = 173 Hz); ¹³³Cs NMR (52.46 MHz, $[\text{D}_8]\text{THF}$, 25 °C): δ = 34.8; elemental analysis: $\text{C}_{24}\text{H}_{26}\text{CsP}$: calcd: C 60.26, H 5.48; found: C 60.04, H 5.25; IR (Nujol): $\bar{\nu}$ = 2260 (s), 1605 (w), 1571 (s), 1243 (m), 1176 (w), 1110 (w), 1087 (m), 1040 (s), 1010 (m) 990 (m), 850 (s), 784 (m), 730 (s), 720 (s), 593 (m) cm^{-1} ; UV/Vis (THF): λ_{max} (ϵ) = 213 (26500), 247 (sh, 6100) nm.

Crystal structure data for **1**: $\text{C}_{103}\text{H}_{112}\text{P}_4\text{Rb}_4$, M_r = 1811.66, triclinic, space group $P\bar{1}$, a = 14.2999(2), b = 15.9550(2), c = 23.3811(1) Å, α = 93.2838(1), β = 103.6992(2), γ = 107.0832(2)°, V = 4907.66(9) Å³, Z = 2, ρ_{calcd} = 1.226 g cm^{–3}, $F(000)$ = 1868, $\text{MoK}\alpha$ radiation (λ = 0.71073 Å), T = 228(2) K, $\mu(\text{MoK}\alpha)$ = 2.090 mm^{–1}, R_1 = 0.0720, wR_2 = 0.2280 for 14890 independent observed reflections ($I > 2\sigma(I)$, $1.8^\circ \leq 2\theta \leq 48.0^\circ$), GOF = 1.043.

Crystal structure data for **2**: $\text{C}_{79}\text{H}_{86}\text{Cs}_3\text{P}_3$, M_r = 1527.12, hexagonal, space group $P6_3/m$, a = 14.65280(10), b = 14.65280(10), c = 19.9405(3) Å, V = 3707.73(7) Å³, Z = 2, ρ_{calcd} = 1.368 g cm^{–3}, $F(000)$ = 1540, $\text{MoK}\alpha$ radiation (λ = 0.71073 Å), T = 218(2) K, $\mu(\text{MoK}\alpha)$ = 1.571 mm^{–1}, R_1 = 0.0540, wR_2 = 0.1414 for 2940 independent observed reflections ($I > 2\sigma(I)$, $3.2^\circ \leq 2\theta \leq 56.5^\circ$), GOF = 1.257.

The structures were solved by direct methods and refined by full-matrix least-squares procedures on F^2 . Semiempirical ellipsoid absorption corrections were applied to the data sets. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The hydrogen atom on the phosphorus atoms in **1** and **2** could not be located from the difference map and were ignored. All other hydrogen atoms were treated as idealized contributions. All scattering factors are contained in the SHELXTL (5.3) program library (G. M. Sheldrick, Siemens XRD, 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-100686. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Self-Assembly of Lamellar and Expanded Lamellar Coordination Networks**

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The construction of infinite solid-state arrays by employing coordinate covalent bonding and the principles of self-assembly has resulted in numerous metal–ligand networks with fascinating structural topologies.^[1] Among the framework types that have resulted are PtS analogues,^[1a] honeycomb structures,^[1b] α -Po analogues,^[1c] diamondoid networks,^[1d, j] and SrSi_2 analogues.^[1g] With these metallo-organic networks, one hopes to realize the wealth of applications known for solely inorganic frameworks, which range from separations^[2] to catalysis^[3] to devices.^[4] The preponderance of infinite arrays formed by metal coordination chemistry employ either aromatic N-donor ligands^[1a, d, i, j, 5] or cyano-derived ligands^[1b, e, 6] as the metal-chelating point of contact. Thioethers have been largely neglected as ligands in this

sense,^[7] probably due to the relatively poor metal-complexing ability of nonchelating thioethers.^[8] Herein, we introduce a family of layered coordination networks, structurally reminiscent of anionic clays,^[9] generated by the self-assembly of a novel dithia ligand with AgBF_4 . Single-crystal data on two lamellar arrays are presented which illustrate the formation and expansion of the layers. Differential scanning calorimetry (DSC) results reveal thermal stability to over 180 °C, which is attributed to a “lamellar chelate effect.”

The dithia ligand **1** contains two sulfurs linked by a rigid durene unit, which prohibits chelation of both donors to a single metal center. The ligand **1** was synthesized in excellent yield by the reaction of tetrabromodurene with sodium sulfide. An equimolar mixture of **1** and AgBF_4 was stirred for three hours in MeCN, and then benzene was diffused into this solution to afford colorless platelike crystals of $[\{\text{Ag}(\mathbf{1})(\text{MeCN})_2\}_\infty][\text{BF}_4]_\infty$ (**2**), suitable for X-ray diffraction analysis. An infinite two-dimensional layered structure is formed by the cationic $\{\text{Ag}(\mathbf{1})(\text{MeCN})_2\}$ building blocks while the BF_4 anions reside between the parallel layers (Figure 1).

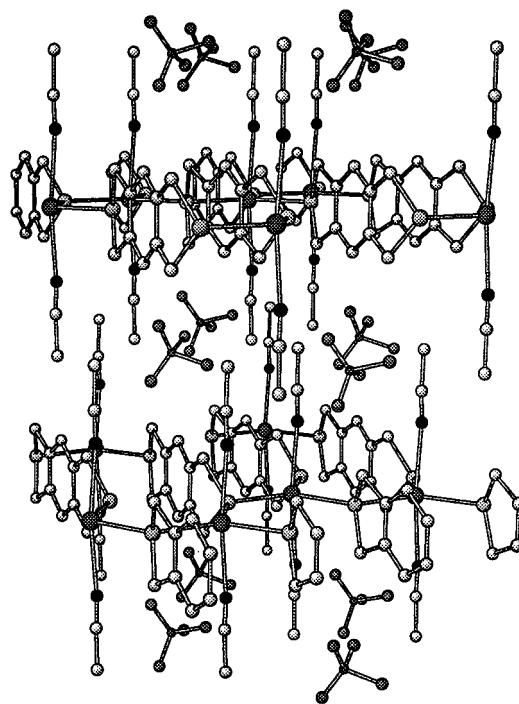
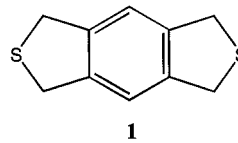


Figure 1. Structure of **2** in the crystal, showing the lamellar network with interlayer BF_4 ions and MeCN molecules that point into the interlayer region. Hydrogen atoms are omitted for clarity.

The coordination geometry about the Ag^{I} ions is a trigonal bipyramid comprising three equatorial sulfur donors and two axially bound MeCN molecules. Remarkably, in order to achieve such a structure, it is necessary for the highly symmetrical **1** to be asymmetrically coordinated to three Ag^{I} ions. Figure 2 clearly shows that one thioether group of **1** coordinates a single Ag^{I} center, while the sulfur atom on the

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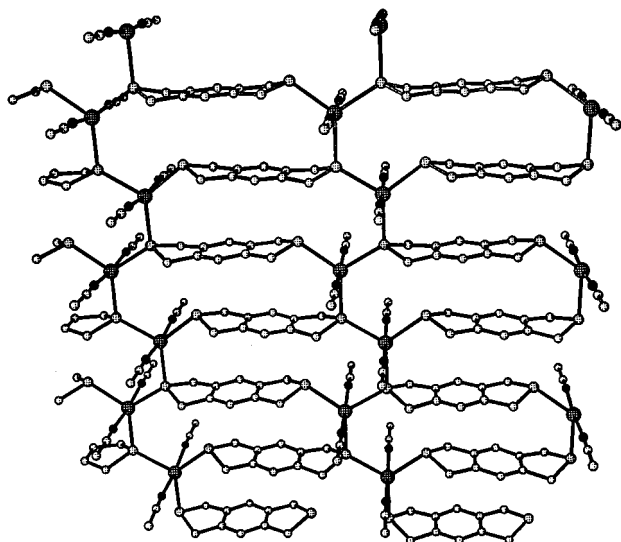


Figure 2. View down onto a single lamella of the structure of **2**. BF_4 ions and hydrogen atoms are omitted for clarity.

opposite side of the ligand employs both lone pairs to coordinate to two different Ag^{I} centers.

The cationic layers lie perpendicular to the crystallographic c axis with an interlayer separation of $10.085(1) \text{ \AA}$.^[10] The axial MeCN molecules are ligated in a linear fashion and protrude directly into the interlayer region. The ligand **1** may adopt either a *syn* or *anti* conformation with respect to the orientation of the sulfur donors, owing to inversion at the benzylic carbon atoms, but **1** is observed exclusively in the *syn* conformation. Throughout the structure, the *syn* sulfur atoms are oriented towards the same crystal face. Adjacent layers are offset by $3.672(2) \text{ \AA}$ along the b axis. The calculated surface area of the layered structure ($S_t = 1160 \text{ m}^2 \text{ g}^{-1}$)^[11] and the fixed charge density ($(\text{fcd}) = 5.58 \times 10^{13} \text{ e}^{-1} \text{ cm}^{-2}$)^[12] are both comparable to other classes of layered compounds.^[13]

As with any layered material, the prospect of “swelling” the structure to afford greater access to the interlayer region is highly appealing.^[14] The presence of labile coordination sites on the metal directed into the interlamellar region makes the use of a larger coordinating ligand, such as PhCN, a logical choice. Therefore, a dried sample of **2** was dissolved in PhCN, and then benzene was diffused into this solution to give colorless, needlelike crystals of $[\{\text{Ag}(\text{1})(\text{PhCN})\}_\infty][\text{BF}_4]_\infty \cdot \infty \text{ PhCN}$ (**3**), where one molecule of PhCN is coordinated to the silver ion and the second is present as a guest molecule. The structure of **3** (Figure 3) is a remarkable illustration of a swelled lamellar solid. It is noteworthy that only a single molecule of PhCN is coordinated to each Ag^{I} ion, necessitating a shift in metal ion geometry from a five-coordinate trigonal bipyramid to a severely distorted four-coordinate tetrahedron ($\text{N1-Ag-S1} = 93.9(1)^\circ$, $\text{N1-Ag-S2} = 102.2(1)^\circ$, $\text{N1-Ag-S2}' = 79.8(1)^\circ$). The individual $\{\text{Ag}(\text{1})\}$ lamellae of **3**, however, are completely planar and identical to the individual layers observed in **2**. Therefore, despite the strained geometry at the metal and the change in metal coordination number, an analogous lamellar structure is retained. The coordinated PhCN molecules, which serve to swell the layers, are coordinated to the metal in a bent orientation (Ag-N1-

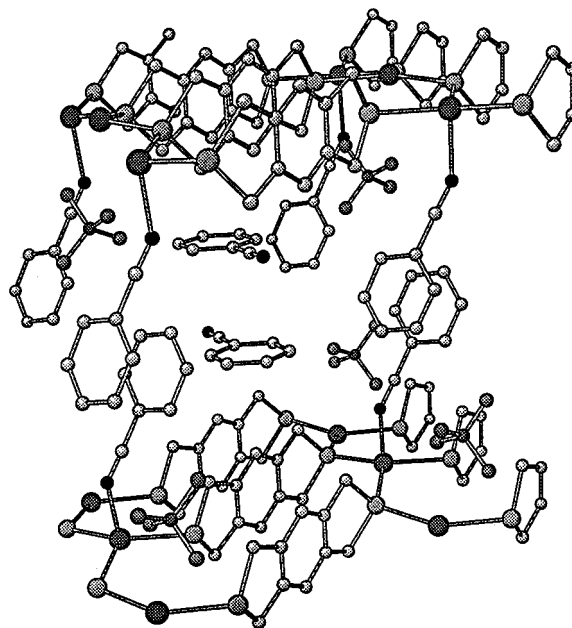


Figure 3. The “swelled” interlayer region in the structure of **3**. The π -stacked PhCN pseudo-pillars and the PhCN guest molecules^[15] are clearly visible.

$\text{C11} = 141.3(4)^\circ$). Furthermore, the phenyl moiety of each coordinated PhCN molecule participates in a π -stacking interaction with another PhCN molecule from an adjacent layer to form a “pseudo-pillar”. This results in a swelling of the interlayer region and an increase in the d spacing from $10.085(1) \text{ \AA}$ to $13.890(1) \text{ \AA}$.^[10, 15] The void space generated by this interlamellar expansion is occupied by a single PhCN molecule per repeat unit.^[16] An additional effect of the pseudo-pillar is to align adjacent layers in the crystal structure. The lamellae are offset by only $0.624(2) \text{ \AA}$, primarily in the a direction, which is considerably different from the $3.672(2) \text{ \AA}$ offset observed in **2**. Interestingly, all molecules of **1** are again in a *syn* conformation, but the ligands in adjacent layers are oriented in opposite directions.

The individual cationic lamellae formed by AgBF_4 and **1** are quite robust in nature. DSC and thermogravimetric (TG) measurements reveal the loss of the nitrile molecules for both **2** and **3** below 100°C ; however, the desolvated complexes do not undergo any further phase changes until an endothermic transition with an onset temperature of 188°C is observed in both complexes.^[17]

Monodentate thioethers are notoriously poor ligands for transition metal ions.^[8] In fact, homoleptic transition metal complexes of Me_2S are quoted as “virtually impossible to prepare”.^[18] Thus, it is interesting to note that **1**, which can be pictured as two molecules of Me_2S linked by a benzene ring, forms complexes stable to over 180°C with the air- and light-sensitive AgBF_4 salt. As this stability stems from the regimented coordination environment about the Ag^{I} center enforced by the layered structure, we refer to this as a “lamellar chelate effect”. Work in progress has shown that these complexes undergo anion exchange reactions and that some of these anions serve to pillar the interlayer region.^[19] This observation further extends the analogy of these lamellar networks to claylike solids.

Experimental Section

1:^[20] Tetrabromodurene (1.99 g, 4.44 mmol) was added to a solution of Na₂S · 9H₂O (2.14 g, 8.88 mmol) in ethanol (100 mL) and refluxed for 6 h. Removal of solvent resulted in an off-white residue that was partitioned between CH₂Cl₂ (100 mL) and H₂O (50 mL). The aqueous layer was separated and further extracted with CH₂Cl₂ (2 × 100 mL). The organic fractions were combined and dried (MgSO₄). Yield: 0.84 g (4.34 mmol, 97 %), >95 % purity by ¹H NMR; m.p. 220–223 °C; ¹H NMR (200 MHz, CDCl₃): δ = 7.08 (s, 2H, arom.), 4.19 (s, 8H, CH₂S); ¹³C{¹H}: δ = 139.66, 120.50 (arom.), 37.31 (CH₂S); CPMAS SS ¹³C NMR (75 MHz): δ = 140.6, 120.7 (arom.), 39.1 (CH₂S); FAB-MS: *m/z*: 194.2 [*M*⁺]; C, H analysis: calcd: C 61.81, H 5.19; found: C 61.59, H 5.14.

2: A solution of **1** (48.3 mg, 0.249 mmol) in MeCN (40 mL) was added to a solution of AgBF₄ (48.3 mg, 0.249 mmol) in MeCN (10 mL). The solution was stirred for 12 h and then concentrated to about 10 mL. Diffusion of benzene into this solution resulted in the growth of platelike crystals suitable for an X-ray analysis. C, H analyses:^[21] calcd: C 35.70, H 3.42; found: C 32.97, H 2.99. Crystal data:^[22] C₇H₈Ag_{0.5}B_{0.5}F₂N₂S, *M*_r = 235.54, colorless plates, orthorhombic, space group *I*2cm, *a* = 7.6520(2), *b* = 11.7135(4), *c* = 20.1711(7), *V* = 1808.0(1) Å³, *Z* = 8, ρ_{calcd} = 1.731 g cm⁻³, *R* = 0.033, *R*_w = 0.041 and GOF = 3.14 for 113 parameters, 1287 reflections with *F*_o > 2.5σ(*F*_o).

3: Benzene was diffused into a saturated, filtered solution of **2** in PhCN. This resulted in the growth of colorless needles suitable for X-ray analysis. C, H analyses:^[21] calcd: C 48.43, H 3.39, found: C 45.82, H 3.15. Crystal data:^[22] C₂₄H₃₀AgBF₄N₂S₂, *M*_r = 595.23, colorless needles, monoclinic, space group *P*2₁/c, *a* = 10.1909(5), *b* = 27.780(1), *c* = 8.6870(5), β = 94.96(1), *V* = 2450.1(2) Å³, *Z* = 4, ρ_{calcd} = 1.600 g cm⁻³, *R* = 0.051, *R*_w = 0.038 and GOF = 2.11 for 387 parameters, 4032 reflections with *F*_o > 2.5σ(*F*_o).

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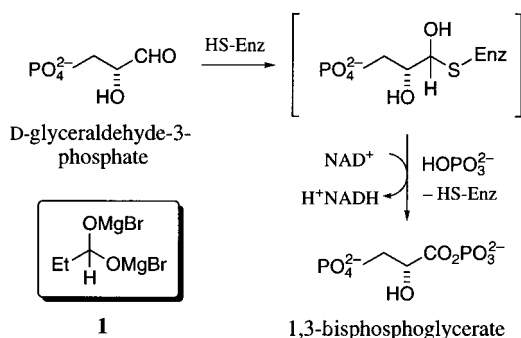
Keywords: coordination modes • layered compounds • self-assembly • silver • S ligands

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- [17] For **2**, a steady loss of MeCN is observed between room temperature and 95 °C. For **3**, loss of PhCN occurs, as expected, in two stages. The first, steady loss from room temperature to 52 °C corresponds to the unbound PhCN, followed by a second mass change from 62–97 °C for the Ag-bound PhCN. No further changes in the DSC or TG are observed for both **2** and **3** until a transition with an onset temperature of 188 ± 1 °C occurs. All mass changes are within reasonable limits (5 %) of the expected values given that the room temperature desolvation of **2** and **3** made an accurate determination of the initial mass impossible. The value of 188 °C is comparable to other Ag coordination arrays with ligands generally accepted to be better donors than thioethers. See: F.-Q. Liu, T. D. Tilley, *Inorg. Chem.* **1997**, *36*, 5090–5096.
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Biomimetic Oxidation of Aldehyde with NAD⁺ Models: Glycolysis-Type Hydrogen Transfer in an NAD⁺/NADH Model System**

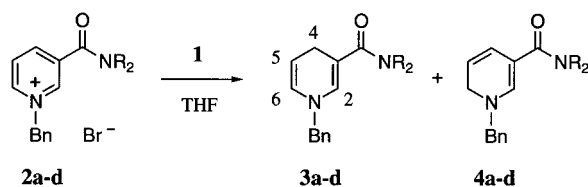
Nobuhiro Kanomata,* Masayuki Suzuki, Mamiko Yoshida, and Tadashi Nakata

Coenzyme NAD⁺ and its reduced form, NADH, function as redox reagents for biological reactions that are catalyzed by L-lactate and D-glyceraldehyde-3-phosphate dehydrogenases (LDH and GAPDH) in anaerobic glycolysis.^[1] A number of synthetic NADH analogues have been reported, including our bridged NADH models^[2a] for LDH-type asymmetric reduction,^[2, 3] but few have been studied in biomimetic oxidation. Although some NAD⁺ models oxidize alcohol/alkoxide^[4, 5] or formate^[6] with formation of the NADH analogues and the corresponding oxidation products, GAPDH oxidation of aldehyde to carboxylate has not been mimicked so far.^[7] To realize this unprecedented model reaction, we focused our attention on the aldehyde equivalent **1**,^[8] which is an analogue of the hemithioacetal intermediate^[1, 9] formed from D-glyceraldehyde-3-phosphate and a cysteine residue of GAPDH (Scheme 1). Here we describe the first GAPDH-analogous oxidation of aldehyde to carboxylate in combination with highly selective 1,4-reduction of NAD⁺ to NADH model compounds and its application to GAPDH- and LDH-type model transfer reactions.



Scheme 1. GAPDH oxidation and structure of **1**.

The diolate **1** was prepared according to the known procedure.^[8] The regioselective hydrogen transfer from **1** proceeds most efficiently with *N*-benzylpyridinium salts (**2**) that contain tertiary amide groups (Table 1; see Table 2 for spectroscopic data for **2–4**). The reaction of **2a** with **1** (5 or



a: R₂ = -(C₄H₈)-; b: R₂ = -(C₅H₁₀)-; c: R₂ = -(C₂H₄OC₂H₄)-; d: R = Me

Table 1. Reactions of **2a–d** with **1**.^[a]

Entry	2	<i>T</i> [°C]	<i>t</i> [h]	3 : 4 ^[b]	Yield [%] ^[c]
1	2a	RT	5	> 95: < 5	58
2 ^[d]	2a	RT	5	> 95: < 5	87
3	2a	50	3	91: 9	73
4	2a	90	1	91: 9	92
5 ^[d]	2b	RT	5	93: 7	61
6	2b	90	1	95: 5	90
7	2c	90	1	91: 9	72
8	2c	90	4	84: 16	62
9	2d	90	1	93: 7	69
10	2d	90	4	73: 27	59

[a] All reactions were carried out in THF under argon with 5 equiv of **1** unless otherwise stated. [b] Ratios determined from the integrals of the ¹H NMR spectra. [c] Yields are of crude mixtures of **3** and **4** after extraction. [d] 10 equiv of **1**.

10 equiv) was carried out in THF at room temperature for 5 h to give 1,4-dihydronicotinamide **3a**^[10] almost exclusively (entries 1 and 2). The reactions at higher temperatures were complete within 1–3 h and led to preferential formation of **3a** and a small amount of 1,6-dihydronicotinamide **4a**^[11] (ratio ca. 9:1; entries 3 and 4). Propionic acid, the product of the oxidation of **1**, was isolated from acidic aqueous solution and identified by means of its ¹H NMR spectrum. High 1,4-selectivity was also exhibited by the other NAD⁺ models **2b**, **2c**,^[4d] and **2d**,^[12] which gave predominantly the desired NADH analogues **3b**, **3c**,^[4d] and **3d**^[13] together with the corresponding 1,6-isomers **4b–d**^[11] in a ratio greater than 9:1 (entries 5–7 and 9). The 1,4-selectivity decreased with increasing reaction time (entries 8 and 10); this is probably due to isomerization of **3c**, **d** to **4c**, **d** in the presence of the pyridinium salts **2c**, **d**.^[14]

An isotope experiment unequivocally proved that these selectivities are the result of kinetic control: The reaction of **2a** with the deuterated diolate [D₁]-**1** (prepared from [D₂]formic acid) was carried out in THF at 50 °C for 3 h. The 1,4-dihydronicotinamide obtained after column chromatography on aluminum oxide was a mixture of **3a** and its mono- and dideuterated compounds [D₁]-**3a** and [D₂]-**3a** in a 28:60:12 ratio (Scheme 2). This is ascribed to deuterium/hydrogen exchange by **2a**-catalyzed transhydrogenation.^[15] The ²H NMR spectrum of the mixture indicated that the deuterium atom is attached exclusively at the C4 position (δ = 3.18). Therefore, in the model reactions, the reactive hydrogen atom of **1** is transferred to the C4 position of NAD⁺ model compounds **2a–d**. This process is comparable to the direct hydrogen transfer^[16] from the hemithioacetal intermediate to coenzyme NAD⁺ in natural GAPDH oxidation.

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Table 2. Melting points and NMR for **2–4**.

2a: White solid; m.p. 172–175 °C; ¹H NMR (270 MHz, CDCl₃): δ = 1.93–2.01 (m, 4H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.69 (t, *J* = 6.3 Hz, 2H), 6.44 (s, 2H), 7.34–7.41 (m, 3H), 7.68–7.71 (m, 2H), 8.15 (dd, *J* = 7.9, 5.9 Hz, 1H), 8.60 (d, *J* = 7.9 Hz, 1H), 9.53 (s, 1H), 9.71 (d, *J* = 5.9 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 24.0, 26.3, 46.9, 49.6, 64.0, 128.4, 129.5(2C), 129.6(2C), 129.9, 132.6, 136.9, 143.2, 143.8, 145.7, 161.5.

2b: White solid; m.p. 202–204 °C; ¹H NMR (270 MHz, CDCl₃): δ = 1.51–1.75 (m, 6H), 3.45 (m, 2H), 3.66 (m, 2H), 6.40 (s, 2H), 7.36–7.42 (m, 3H), 7.66–7.69 (m, 2H), 8.13 (dd, *J* = 7.9, 6.3 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H), 9.27 (s, 1H), 9.74 (d, *J* = 6.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 23.9, 25.2, 26.5, 43.6, 49.3, 64.4, 128.4, 129.6(2C), 129.8(2C), 130.1, 132.4, 136.7, 142.8, 143.4, 145.6, 162.3.

[D₁]-3a: Oil; ¹H NMR (500 MHz, CDCl₃): δ = 1.81 (tt, *J* = 6.8, 3.0 Hz, 4H), 3.16 (brs, 1H), 3.45 (tt, *J* = 6.8, 3.0 Hz, 4H), 4.23 (s, 2H), 4.63 (dd, *J* = 8.1, 3.4 Hz, 1H), 5.74 (dt, *J* = 8.1, 1.5 Hz, 1H), 6.44 (brs, 1H), 7.24 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.27 (tt, *J* = 7.7, 1.7 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 2H).

3b: Oil; ¹H NMR (500 MHz, CDCl₃): δ = 1.49 (quint, *J* = 5.6 Hz, 4H), 1.61 (quint, *J* = 5.7 Hz, 2H), 3.14 (dd, *J* = 3.2, 1.7 Hz, 2H), 3.47 (t, *J* = 5.7 Hz, 4H), 4.22 (s, 2H), 4.59 (dt, *J* = 8.1, 3.2 Hz, 1H), 5.76 (dq, *J* = 8.1, 1.7 Hz, 1H), 6.17 (d, *J* = 1.7 Hz, 1H), 7.26 (dd, *J* = 7.2, 2.1 Hz, 2H), 7.28 (tt, *J* = 7.2, 2.1 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ = 24.0, 24.8, 26.1, 46.1, 57.0, 100.7, 102.6, 127.2(2C), 127.6, 128.7(2C), 129.9, 134.8, 137.9, 171.6.

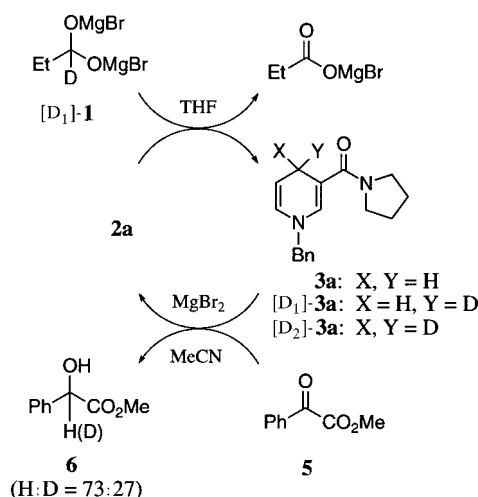
4a:^[a] ¹H NMR (270 MHz, CDCl₃): δ = 1.80–1.92 (m, 4H, overlapped), 3.44–3.53 (m, 4H, overlapped), 3.93 (dd, *J* = 3.6, 1.6 Hz, 2H), 4.18 (s, 2H), 4.94 (dt, *J* = 9.9, 3.6 Hz, 1H), 6.22 (dq, *J* = 9.9, 1.6 Hz, 1H), 7.14 (brs, 1H), 7.25–7.40 (m 5H, overlapped).

4b:^[a] ¹H NMR (500 MHz, CDCl₃): δ = 1.41–1.73 (m, 6H, overlapped), 3.38–3.55 (m, 4H, overlapped), 3.93 (dd, *J* = 3.6, 1.5 Hz, 2H), 4.17 (s, 2H), 4.93 (dt, *J* = 9.8, 3.6 Hz, 1H), 5.98 (dq, *J* = 9.8, 1.5 Hz, 1H), 7.06 (brs, 1H), 7.18–7.40 (m, 5H, overlapped).

4c:^[a] ¹H NMR (270 MHz, CDCl₃): δ = 3.50–3.75 (m, 8H, overlapped), 3.95 (dd, *J* = 3.6, 1.5 Hz, 2H), 4.19 (s, 2H), 4.94 (dt, *J* = 9.7, 3.6 Hz, 1H), 5.96 (dq, *J* = 9.8, 1.5 Hz, 1H), 7.12 (brs, 1H), 7.28–7.42 (m, 5H, overlapped).

4d:^[b] ¹H NMR (270 MHz, CDCl₃): δ = 3.01 (s, 6H), 3.93 (dd, *J* = 3.6, 1.5 Hz, 2H), 4.17 (s, 2H), 4.93 (dt, *J* = 9.9, 3.6 Hz, 1H), 6.06 (dq, *J* = 9.9, 1.5 Hz, 1H), 7.07 (brs, 1H), 7.20–7.40 (m, 5H, overlapped).

[a] Data from the spectra of mixtures that were obtained by reduction of **2a–c** with NaBH₄ and contained large amounts of **4a–c**. [b] Data from the spectrum of the mixture with **3d**.



Scheme 2. GAPDH- and LDH-type model transfer reactions.

Finally, we performed sequential GAPDH- and LDH-type model reactions in a one-pot reaction (Scheme 2). After removal of the THF solvent, the crude deuterated dihydro-

nicotinamides (**3a**, **[D₁]-3a**, and **[D₂]-3a**) from the GAPDH-type reaction of **2a** with **[D₁]-1** (5 equiv) were used for the following LDH-type reaction with methyl benzoylformate (**5** (5 equiv) in acetonitrile without further addition of Mg²⁺.^[17] After the reaction mixture was stirred for four days at room temperature, the lactate analogue methyl mandelate (**6**) was obtained in 47 % yield (based on **2a**) with an H:D ratio of 73:27, as determined by ¹H NMR spectroscopy. We then investigated the reduction of **5** with **[D₁]-3a** that was prepared independently from **2a** and sodium dithionite in D₂O in the presence of Mg(ClO₄)₂.^[18] Partially deuterated **6** was obtained with an H:D ratio of 75:25. This value is in good agreement with that obtained in the model transfer reactions, in view of the ratio of the amounts of **3a**, **[D₁]-3a**, and **[D₂]-3a** formed in the preceding reaction. These findings clearly show that this preferential deuterium/hydrogen transfer from **[D₁]-1** to **6** was mediated by a redox cycle of the NAD⁺/NADH model system, as in the real coenzyme system in anaerobic glycolysis.

Consequently, we have accomplished, to the best of our knowledge, the first GAPDH-type oxidation of aldehyde to carboxylate in an NAD⁺/NADH model system and have demonstrated its application to model transfer reactions of the GAPDH- and LDH-type. Biomimetic oxidation involving such simple model compounds as **1** and **2a–d** is virtually equivalent to the corresponding biological reaction in terms of mechanism and selectivity. The details of the mechanism, the scope and limitation of the reaction, and the application to catalytic model system are under investigation.

Experimental Section

Reaction of **2a–d** with **1** (representative procedure): A solution of **1**, prepared from formic acid (18.9 μL, 0.50 mmol) and a solution of EtMgBr in THF (1.0 M, 1.0 mL, 1.00 mmol), was added dropwise by syringe to a suspension of **2a** (34.7 mg, 0.10 mmol) in THF (0.3 mL) at room temperature. The mixture was heated at 90 °C for 1 h under an argon atmosphere. Water was added, and the mixture was extracted three times with diethyl ether. The combined organic phase was dried over MgSO₄ and concentrated in vacuo to give a 91:9 mixture of **3a** and **4a** (24.7 mg, 92 %). The mixture was further purified by column chromatography on aluminum oxide with deoxygenated hexane/ethyl acetate (1/1); yield: 16.6 mg, 62 %.

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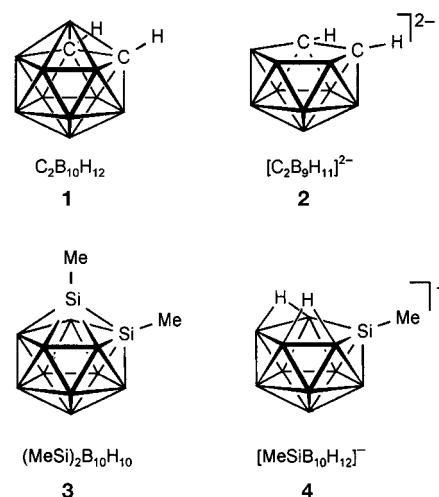
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- [18] The NADH model compound **3a** did not reduce **5** to **6** in the absence of magnesium ions. Therefore, the preceding GAPDH-type model reaction must provide an activator such as MgBr₂ for the following LDH-type model reaction.

A Surprising Adduct of a *closo* Cluster**

Lars Wesemann,* Yves Ramjoie, Michael Trinkaus, Beate Ganter, and Jens Müller*

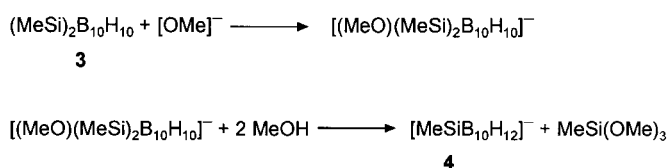
In 1968 Hawthorne et al. published the preparation and characterization of 7,8-dicarba-*nido*-undecaborate(1–) (**2**), the product of the nucleophilic degradation of *o*-carborane (**1**) (Scheme 1).^[1] The reaction of dicarba-*closo*-dodecaborane(12) with potassium hydroxide in ethanol gave the



Scheme 1. *o*-Carborane and *o*-silaborane and their degradation products.

eleven-vertex cluster anion **2**. An adduct formed from the attacking ethoxide anion and the neutral *closo* cluster was formulated as a possible reaction intermediate. In *o*-silaborane(²) (**3**), the silicon atoms are unique in that they are incorporated in the skeleton of a borane cluster framework. We are interested in the reactivity patterns of this icosahedral cluster and especially in the silicon centers. The first reaction of *o*-silaborane to be explained was the nucleophilic degradation.^[3] Removal of a silicon vertex from the icosahedral cluster results in almost quantitative isolation of the sila-*nido*-undecaborate(1–) (**4**). This eleven-vertex cluster is a versatile starting material for the synthesis of transition metal complexes with interactions between the silicon and the metal.^[4, 5]

In this paper we present first insights into the nucleophilic degradation of *o*-silaborane. Attack of one equivalent OH[–] in H₂O, MeO[–] in MeOH, or pure NH₃, results in the removal of a silicon vertex from the *closo* cluster **3**.^[3] According to a plausible mechanism for the degradation, in the first step an adduct is formed comprising the nucleophile and the *closo* cluster (Scheme 2). This adduct should then react with a protic solvent to form the isolated reaction product.



Scheme 2. Nucleophilic degradation of *o*-silaborane **3** to sila-*nido*-undecaborate(1–) **4**.

In order to verify the existence of the adduct, we studied nucleophilic attack on **3** in an aprotic solvent by NMR spectroscopy. The cluster **3** was treated with one equivalent of LiNEt₂ in THF, and the ¹¹B NMR spectrum (Figure 1) of the reaction mixture shows the quantitative formation of a new compound. Four signals in the ¹¹B NMR spectrum corresponding to ten boron atoms indicate that the product still has C_{2v} symmetry. A shift of the ²⁹Si signal from –38 to –76 ppm

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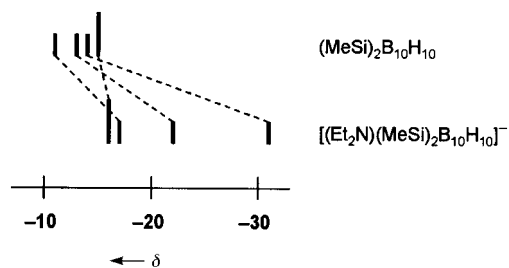
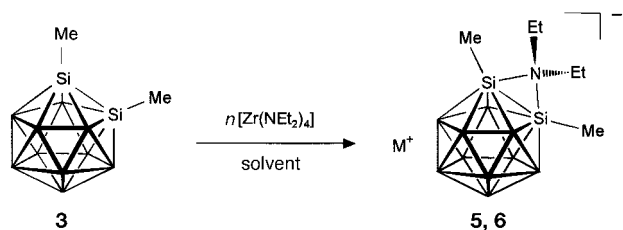


Figure 1. ^{11}B NMR spectra of *o*-silaborane (from left to right: B8/10, B9/12, B3/6, B4/5/7/11) and the anionic adduct with diethylamide (from left to right: B4/5/7/11, B8/10, B9/12, B3/6).

can be interpreted as an increase of the coordination number for the silicon atoms in the cluster. The silicon resonance signal was detected indirectly with the HMQC $^1\text{H}/^{29}\text{Si}$ NMR pulse sequence. As expected, the two-dimensional NMR spectrum shows a correlation between the silicon signal and the signal for the methyl groups attached to the silicon atoms. Interestingly, a second correlation with the CH_2 signal of the diethylamido group is also observed. From these spectroscopic features, it can be concluded that the diethylamido group is connected to both silicon atoms. The solid-state structure of the anionic adduct was determined by investigation of the $[\text{Zr}(\text{NEt}_2)_3(\text{thf})_2][(\text{Et}_2\text{N})(\text{MeSi})_2\text{B}_{10}\text{H}_{10}]^-$ salt (**5**).^[6] This adduct was obtained quantitatively from the reaction of **3** with an excess of $[\text{Zr}(\text{NEt}_2)_4]$ (Scheme 3a). The stoichiometric reaction, in contrast, resulted in an equilibrium between



Scheme 3. Reaction conditions and products: a) THF, $n > 1$ (excess), $\text{M}^+ = [\text{Zr}(\text{NEt}_2)_3(\text{thf})_2]^+$, **5**; b) THF, $n = 1$, equilibrium mixture of **3** and **5**; c) CH_2Cl_2 , $n = 1$, 2py , $\text{M}^+ = [\text{Zr}(\text{NEt}_2)_3(\text{py})_2]^+$, **6** (py = 4-*tert*-butylpyridine).

starting materials and product (Scheme 3b). The same ratio was observed after dissolution of the crystalline adduct **5**, which had been previously characterized by elemental analysis. Use of a stronger donor ligand such as 4-*tert*-butylpyridine in a stoichiometric reaction results in almost complete formation of the adduct (Scheme 3c). In all cases, the initial *closo* cluster **3** was recovered by the reaction of the adduct **5** with methyl iodide.

The solid-state structure of the anion in **5** is shown in Figure 2.^[6] As indicated by NMR spectroscopy, the Si–Si cluster edge is bridged by a diethylamido group. The Si–N distances of 1.999(2) and 1.967(2) Å are slightly longer than the sum of the covalent radii and can be compared with the Si–N distance of 1.95 Å in cyclic $[(\text{Me}_2\text{N})\text{SiH}_3]_5$.^[9] To our surprise, the B–B, Si–B, and Si–Si distances show only small differences from those in **3**. Thus the Si–Si distance in the adduct (2.332(1) Å) is only 0.024 Å longer than in the

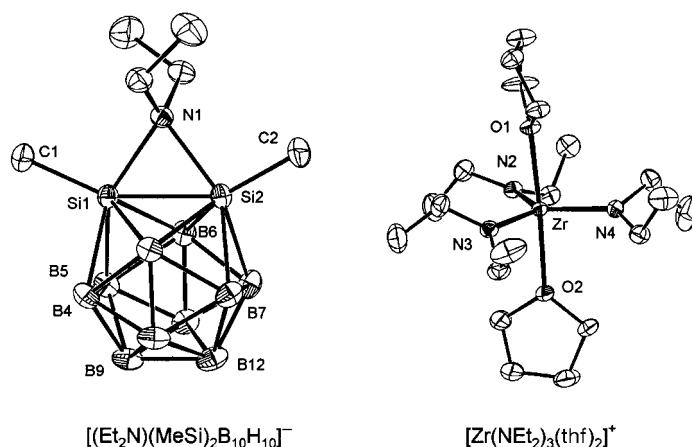


Figure 2. Structures of the anion (left) and the cation (right) of **5** in the crystal (PLATON representation,^[8] ellipsoids at 30% probability level). Selected distances [Å] and angles [°]: Si1–Si2 2.332(1), Si1–N1 1.999(2), Si2–N1 1.967(2), Si1–B3 2.091(3), Si1–B4 2.082(3), Si1–B5 2.091(3), Si1–B6 2.103(3), Si2–B3 2.108(3), Si2–B6 2.114(3), Si2–B7 2.089(3), Si2–B11 2.079(3), B3–B4 1.866(5), B3–B7 1.869(4), B3–B8 1.777(4), B4–B5 1.777(4), B4–B8 1.757(5), B4–B9 1.769(5), B5–B6 1.866(4), B5–B9 1.770(5), B5–B10 1.774(5), B6–B10 1.764(4), B6–B11 1.860(4), B7–B8 1.772(5), B7–B11 1.768(4), B7–B12 1.759(5), B8–B9 1.765(5), B8–B12 1.786(4), B9–B10 1.786(4), B9–B12 1.738(5), B10–B11 1.765(4), B10–B12 1.780(5), B11–B12 1.766(4), Zr–O2 2.246(2), Zr–N2 2.024(2), Zr–N3 2.028(2), Zr–N4 2.027(2); C1–Si1–Si2 152.3(1), C2–Si2–Si1 154.3(1); Zr–O1 2.245(2).

unbridged *o*-silaborane (2.308(2) Å). The biggest structural change is the enlargement of the C–Si–Si angle by 28°. The structure of the cation is related to the published structure of the $[\text{Ti}(\text{NMe}_2)_3\text{py}_2]^+$ cation (py = pyridine).^[10]

In order to understand the properties of silaboranes better, we performed ab initio calculations.^[11] There are two equivalent solutions for the $^{11}\text{B}/^{11}\text{B}$ COSY NMR spectra for the starting compound **3** and the anion in **5**. In order to make an unambiguous assignment, we calculated the chemical shifts with the GIAO method^[12] at the B3LYP/6-311 + G(d, p) level^[13] based on B3LYP/6-31G(d) geometries.^[14] Table 1 summarizes the observed and calculated bond lengths and angles, and Figure 3 depicts the ab initio geometries and the ^{11}B and ^{29}Si NMR chemical shifts. The calculated structural

Table 1. Selected bond lengths [Å] and angles [°] for **3** and the anion in **5**. Calculated (B3LYP/6-31G(d)) and mean observed values (figures in parentheses).

	3 ^[a]	Anion in 5 ^[b]
Si–N		2.03 (1.98)
Si–C	1.87 (1.83)	1.91 (1.87)
Si–Si	2.32 (2.31)	2.38 (2.33)
Si–B3, 6	2.14 (2.11)	2.11 (2.10)
Si–B4, 5	2.03 (2.02)	2.08 (2.09)
B3–B4, 7	1.86 (1.85)	1.89 (1.87)
B3–B8	1.78 (1.77)	1.79 (1.77)
B4–B5	1.88 (1.86)	1.79 (1.77)
B4–B8	1.77 (1.77)	1.78 (1.77)
B4–B9	1.77 (1.77)	1.77 (1.77)
B8–B9	1.79 (1.78)	1.79 (1.78)
B9–B12	1.79 (1.78)	1.75 (1.74)
C–Si–Si	126 (124)	152 (153)

[a] Values in parentheses were taken from ref. [2]. [b] Calculations were performed on a $\mu\text{-NH}_2$ group (see Figure 3).

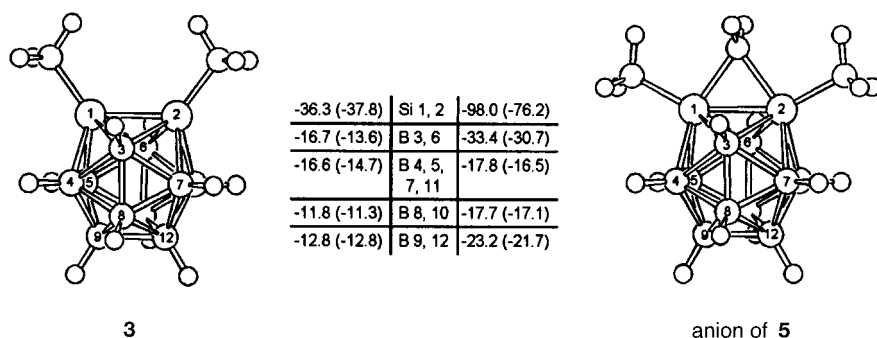


Figure 3. Calculated (B3LYP-GIAO/6-311 + G(d, p)//B3LYP/6-31G(d))^[12–14] and observed ²⁹Si and ¹¹B NMR chemical shifts (figures in parentheses).^[18]

data matches the measured data well (Table 1), and there is also good agreement between the theoretical and experimental NMR data.

The greatest differences are found for ¹¹B NMR shifts for the vertices B3 and B6: $\delta = 3.1$ for **3** and 2.7 for the anionic cluster in **5**. The calculated value of $\delta(^{29}\text{Si}) = -36.3$ for the *o*-silaborane deviates by only 1.5 ppm from the experimental shift. In contrast, the predicted $\delta(^{29}\text{Si})$ value for the amino-bridged species is shifted 21.8 ppm upfield in comparison with the measured value of -76.2 . Evidently, this difference must be mainly due to the alkyl groups of the bridging N atom since the ab initio calculation was performed on a $\mu\text{-NH}_2$ instead of a $\mu\text{-NEt}_2$ group.

The relationship between the empirical formula, the electron count, and geometry of an electron-deficient cluster has been reported by Williams and Wade.^[15] As expected from these cluster rules, aza-*closo*-dodecaborane reacts with nucleophiles to form twelve-vertex *nido* compounds.^[16] A Et_2N^- group in a bridging position donates four electrons to a cluster framework. Therefore, the *closo*-silaborane **3** should form an *arachno* compound after reaction with $[\text{Zr}(\text{NEt}_2)_4]$. Surprisingly, the twelve-vertex cage of **3** is almost unchanged by addition of Et_2N^- . Although the structural effects are small, the NMR properties of the anion in **5** are distinctively different from the starting borane **3**; the upfield shift and the enlargement of the range of the ¹¹B resonances (see Figures 1 and 3) are a result of electron donation to the cluster. In short, the anion of **5** exhibits a *closo* cluster framework with an *arachno* electron count. Evidently the disila unit has acceptor properties reminiscent of silicon compounds that can act as inverse chelate ligands.^[17]

Experimental Section

5: $[\text{Zr}(\text{NEt}_2)_4]$ (1.876 g, 4.94 mmol) was added to **3** (0.460 g, 2.25 mmol) in THF (25 mL) at room temperature. The solution turned slightly yellow and was stirred overnight. The yield of **5** was quantitative relative to **3**, as shown by NMR spectroscopy. Crystals suitable for elemental analysis and X-ray crystallography were obtained from a mixture of THF and toluene at room temperature in a yield of 85.0% (1.393 g, 1.91 mmol).^[19] NMR spectra were recorded in $[\text{D}_8]\text{THF}$ at 25 °C with an excess of $[\text{Zr}(\text{NEt}_2)_4]$, which has been omitted from the spectra. ¹H [¹¹B] NMR (500 MHz, TMS): $\delta = 0.66$ (s, 2H, H3/6), 0.70 (s, 6H, SiMe), 1.01 (t, 6H, $\mu\text{-NCH}_2\text{CH}_3$), 1.04 (s, 2H, H8/10), 1.13 (tr, 18H, $\text{ZrNCH}_2\text{CH}_3$), 1.27 (s, 4H, H4/5/7/11), 1.31 (s, 2H, H9/12), 1.77 (m, 8H, coord. THF, $\text{O}(\text{CH}_2\text{CH}_2)_2$), 3.08 (q, 4H, $\mu\text{-NCH}_2\text{CH}_3$), 3.49 (q, 12H, $\text{ZrNCH}_2\text{CH}_3$), 3.62 (m, 8H, coord. THF, $\text{O}(\text{CH}_2\text{CH}_2)_2$); ¹¹B NMR (160 MHz, $\text{Et}_2\text{O} \cdot \text{BF}_3$): $\delta = -16.5$ (d, $^1J = 122$ Hz, B4/5/7/11), -17.1 (d,

$^1J = 147$ Hz, B8/10), -21.7 (d, $^1J = 134$ Hz, B9/12), -30.7 (d, $^1J = 122$ Hz, B3/6); ¹³C [¹H] NMR (125 MHz, TMS): $\delta = 8.1$ (MeSi), 12.4 ($\mu\text{-NCH}_2\text{CH}_3$), 14.9 ($\text{ZrNCH}_2\text{CH}_3$), 26.2 (coord. THF, $\text{O}(\text{CH}_2\text{CH}_2)_2$), 37.8 ($\mu\text{-NCH}_2\text{CH}_3$), 41.8 (ZrCH_2CH_3), 68.0 (coord. THF, $\text{O}(\text{CH}_2\text{CH}_2)_2$); ²⁹Si NMR (100 MHz, TMS): $\delta = -76.2$.

6: $[\text{Zr}(\text{NEt}_2)_4]$ (0.522 g, 1.375 mmol) and a slight excess of 4-*tert*-butylpyridine (600 μL , ca. 3 equiv) were added to **3** (0.281 g, 1.375 mmol) in CH_2Cl_2 (30 mL) at room temperature. The reaction mixture was stirred for 14 h during which time the color changed to orange-brown. The solvent was changed to THF, 30 mL of toluene was added and the solution was slowly evaporated at 10^{-1} mbar. Yellow crystals were obtained which were filtered and washed several times with toluene. Recrystallization from THF/toluene gave **6** in 90.0% yield (1.058 g, 1.24 mmol).^[19] NMR spectra were recorded in $[\text{D}_8]\text{THF}$ at 25 °C; ¹H [¹¹B] NMR (500 MHz, TMS): $\delta = 0.66$ (s, 2H, H3/6), 0.70 (s, 6H, SiMe), 0.99 (tr, $^3J = 7.3$ Hz, 6H, $\mu\text{-NCH}_2\text{CH}_3$), 1.04 (s, 2H, H8/10), 1.10 (br., $\text{ZrNCH}_2\text{CH}_3$), 1.27 (s, 4H, H4/5/7/11), 1.31 (s, 2H, H9/12), 1.32 (s, 18H, *t*Bu), 3.08 (q, $^3J = 7.3$ Hz, 4H, $\mu\text{-NCH}_2\text{CH}_3$), 3.47 (q, $^3J = 6.4$ Hz, 12H, $\text{ZrNCH}_2\text{CH}_3$), 7.30 (br., 4H, *ppy*), 8.46 (br., 4H, *opy*); ¹¹B NMR (160 MHz, $\text{Et}_2\text{O} \cdot \text{BF}_3$): $\delta = -16.4$ (d, $^1J = 122$ Hz, B4/5/7/11), -17.0 (d, $^1J = 147$ Hz, B8/10), -21.6 (d, $^1J = 134$ Hz, B9/12), -30.4 (d, $^1J = 122$ Hz, B3/6); ¹³C [¹H] NMR (125 MHz, TMS): $\delta = 8.1$ (MeSi), 12.4 ($\mu\text{-NCH}_2\text{CH}_3$), 14.7 ($\text{ZrNCH}_2\text{CH}_3$), 30.3, 30.5 (*t*Bu), 37.8 ($\mu\text{-NCH}_2\text{CH}_3$), 42.0 ($\text{ZrNCH}_2\text{CH}_3$), 123.9, 150.5 (*py*), (the signal for C4 was not observed); ²⁹Si NMR (100 MHz, TMS): $\delta = -76.0$.

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- [19] Correct C,H analyses for **5** and **6** were obtained.

Cationic Gold(I) Complexes: Highly Efficient Catalysts for the Addition of Alcohols to Alkynes**

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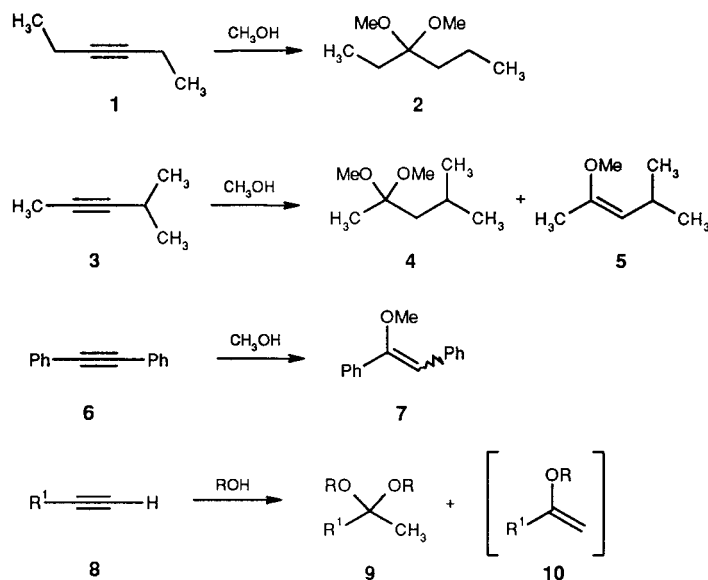
In memory of Dr. Marco Häser

The mercury(II)-catalyzed addition of alcohols to alkynes has been known for almost three-quarters of a century.^[1] The original catalyst has been further developed,^[2] but its preparation by the heating of red mercury(II) oxide with boron trifluoride etherate and trichloroacetic acid in methanol still retains a touch of alchemy, and very little is known about the reaction mechanism.^[2g] This material catalyzes the addition of primary, secondary, and even some tertiary alcohols to

acetylene^[2a] as well as to mono-^[2b] and disubstituted alkynes.^[2c] However, it has the serious drawback that under the reaction conditions the mercury(II) is quickly reduced to metallic mercury, which is catalytically inactive, so 100 moles of product at most can be produced per mole of mercury(II) salt introduced.

An alternative mercury-free catalyst for this reaction has long been sought, but with little success.^[3] Two recent papers describe the use of gold(III) catalysts (NaAuCl_4) for the addition of water and methanol to nonactivated alkynes,^[4] but this catalyst shows the same disadvantage: It is quickly reduced to inactive metallic gold, so no more than 50 moles of product can be synthesized per mole of gold. The fact that the literature on homogeneous catalysis with gold complexes is extremely sparse,^[4, 5] and that until recently gold was thought to be “catalytically dead,”^[6] made the quest for an efficient gold(I) catalyst all the more interesting.

Here we report a new, very efficient class of gold(I) catalysts for the addition of alcohols to alkynes under mild conditions ($T = 20\text{--}50^\circ\text{C}$, H^+ as cocatalyst).^[7] In numerous studies carried out in our laboratory we have found that cationic gold(I) complexes of the general type $[\text{L}-\text{Au}^+]$ (where L is a phosphane, a phosphite, or an arsine)^[8] are excellent catalysts for the addition of alcohols to alkynes. These catalysts achieve total turnover numbers of up to 10^5 moles of product per mole of catalyst, with turnover frequencies of up to 5400 h^{-1} . They are neither water nor air sensitive, and the reaction can usually be conducted without a solvent. Scheme 1 shows examples of the addition of alcohols to unsubstituted alkynes with methyl(triphenylphosphane)gold(I) and methanesulfonic acid as precursors for in situ generation of the catalyst.



- a) $\text{R}' = \text{Me}$, $\text{R} = \text{Me}$
 b) $\text{R}' = \text{Me}$, $\text{R} = \text{Et}$
 c) $\text{R}' = \text{Me}$, $\text{R} = i\text{Pr}$
 d) $\text{R}' = \text{Me}$, $\text{R} = \text{allyl}$
 e) $\text{R}' = \text{H}$, $\text{R} = \text{Me}$
 f) $\text{R}' = \text{Ph}$, $\text{R} = \text{Me}$

Scheme 1. Addition of alcohols to unsubstituted alkynes in the presence of the catalyst prepared from methyl(triphenylphosphane)gold(I) and methanesulfonic acid.

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In the case of internal, symmetrical alkynes such as 3-hexyne (**1**), the only product formed in the presence of excess alcohol is 3,3-dimethoxyhexane (**2**).^[9] With unsymmetrical alkynes such as methylisopropylacetylene (**3**) only acetal **4** is formed as a result of addition to the less sterically hindered position, together with a small amount of enol ether **5**. The regioselectivity of the gold catalysts is thus higher than that of mercury catalysts.^[10] With diphenylacetylene (**6**) the main product is enol ether **7**, even in the presence of a large excess of methanol. At low conversions the *Z*:*E* ≈ 8:1, but in the course of the reaction it partially isomerizes (probably through the corresponding acetal), and at the end of the reaction the *Z*:*E* ratio is about 2:1, which is close to the equilibrium ratio.^[11]

Terminal alkynes such as **8a–e** are also suitable substrates. In this case addition occurs almost exclusively at the more highly substituted carbon atom to produce the expected acetals **9a–e**. Phenylacetylene yields a mixture of the enol ether **10f** and the acetal **9f** in a ratio of 2:1.

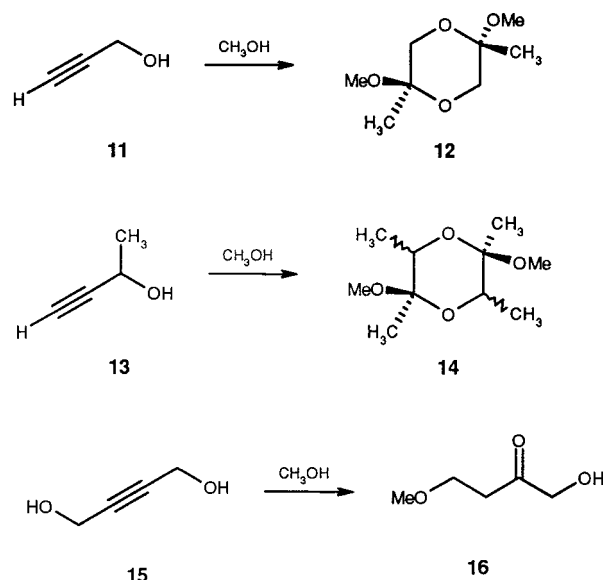
Propargyl alcohols also react smoothly. 2-Propynol (**11**), 1-butyne-3-ol (**13**), and 2-butyne-1,4-diol (**15**) react with excess methanol to give the expected products **12**,^[12] **14** (as a mixture of isomers), and **16**.^[2f, 13] However, 1,4-dichloro-2-butyne and propynoic acid methyl ester do not react at all (Scheme 2).

The reactivity of the alkynes increases with increasing electron density of the triple bond and decreases with increasing steric hindrance. The reactivity of the alcohols decreases by a factor of about ten when going from primary to secondary alcohols. Tertiary alcohols and phenols are unreactive.^[14]

The influence of catalyst structure on activity was also studied, with the addition of methanol to propyne as a model reaction (**8a** + 2 MeOH → **9a**). The nature of the ligand L in the cationic gold complex has a considerable influence upon catalytic activity. Initial turnover frequencies for the addition of methanol to propyne were measured with different [L–Au⁺] catalysts.^[15] The activity order for the ligands tested was as follows (initial turnover frequencies [h^{−1}] in parentheses): Ph₃As (430) < Et₃P (550) < Ph₃P (610) < (4-F-C₆H₄)₃P (640) < (MeO)₃P (1200) < (PhO)₃P (1500).^[16] As expected, electron-poor ligands lead to an increase in activity, but the stability of the complexes decreases. The catalyst with L = (PhO)₃P is more than twice as active as that with L = Ph₃P; however, the former is completely deactivated after only 2500 turnovers, whereas the latter is still active after 5000 turnovers.

As mentioned above, H⁺ is necessary as a cocatalyst,^[2b] but a Lewis acid such as boron trifluoride can also be utilized because it is rapidly hydrolyzed to trimethyl borate and HF under the reaction conditions.^[17] The turnover frequency increases in a roughly linear fashion with the concentration of H⁺.

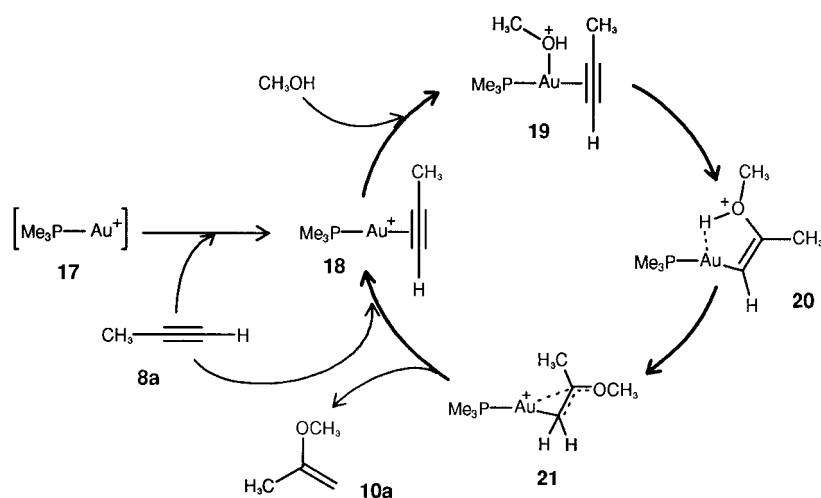
Anions present in the solution are also a very important factor with respect to catalytic activity. With the combination [Ph₃PAuX] and BF₃·OEt₂ the reactivity increases as one



Scheme 2. Gold(I)-catalyzed addition of methanol to propargyl alcohols.

progresses from soft to hard anions (initial turnover frequencies [h^{−1}] in parentheses): I[−] (**2**) < Cl[−] (**7**) < NO₃[−] ≈ CF₃COO[−] ≈ CH₃SO₃[−] (700).^[18] For very hard anions the turnover frequency levels off, probably because of the presence of excess fluoride from the hydrolysis of BF₃. This interpretation is supported by the fact that the catalyst generated from [Ph₃PAu(CH₃SO₃)] and BF₃·OEt₂ (TOF = 700 h^{−1}) is less active than that generated under halide-free conditions from [Ph₃PAuCH₃] and CH₃SO₃H (TOF = 1500 h^{−1}).

Based on these experimental results and ab initio calculations^[19] we propose the following mechanism for catalytic addition of alcohols to alkynes (illustrated in Scheme 3 for the addition of methanol to propyne). The cationic gold(I) complex **17**, generated for example by protonolysis of a methylgold complex, will not exist in free form but will instead coordinate with whatever donors are present in solution, as shown by ³¹P NMR spectroscopy. If [Ph₃PAuCH₃] is treated with one equivalent of CH₃SO₃H in [D₂]dichloro-



Scheme 3. Proposed mechanism for the addition of methanol to propyne catalyzed by the trimethylphosphane-gold(I) cation.

methane at -40°C and then cooled to -80°C , one observes in the ^{31}P NMR spectrum two broadened peaks at $\delta = 36$ and 28 , which we attribute to dichloromethane and methanesulfonate complexes of the triphenylphosphane-gold(I) cation.^[20] Addition of five equivalents of methanol at -80°C gives rise to a single broad peak at $\delta = 38$, tentatively assigned to the methanol complex. If five equivalents of 3-hexyne are instead added at -80°C a single broadened peak is observed at $\delta = 28$ (tentatively assigned to the alkyne complex), which remains almost unchanged up to 0°C . Ab initio calculations provide the following relative stabilities for complexes between the trimethylphosphane-gold(I) cation (**17**) and several neutral ligands (energies [kJ mol^{-1}] relative to the 2-butyne complex are given in parentheses): dichloromethane (+63) < water (+44) < acetylene (+38) < methanol $\approx$ 1,4-dioxane (+24) < propyne (+18) < tetrahydrofuran (+2) < 2-butyne (0) < dimethylsulfide (-18) < triphenylphosphane (-114). As expected, the soft bases triphenylphosphane and dimethylsulfide give the most stable complexes. Somewhat surprisingly, mono- and disubstituted alkynes are better ligands than methanol or dioxane, which favor the formation of **18**.

The gold(I) propyne complex (**18**) is then attacked by a molecule of methanol. Ab initio calculations predict this attack to occur by an associative mechanism that involves coordination of methanol to gold to give the intermediate complex **19**.^[21] This precoordination is computed to be exothermic by -24 kJ mol^{-1} . The calculated activation energy for rearrangement of **19** to **20** is only 43 kJ mol^{-1} , and the overall reaction is exothermic by -37 kJ mol^{-1} . Both **19** and the transition state between **19** and **20** are sterically quite crowded, and this may be the reason why secondary alcohols react almost ten times more slowly than primary alcohols. Interestingly, the isomer of **20** shown (the *Z* isomer) is stabilized by almost 10 kJ mol^{-1} with respect to the *E* isomer as a result of a close contact between gold and hydrogen ($2.26 \text{ \AA}$) within a planar five-membered chelating ring.

The rearrangement of **20** to **21** could in principle proceed along either of two pathways: deprotonation at oxygen with reprotonation at carbon, or a 1,3-hydrogen migration. The relative importance of these two pathways cannot easily be predicted with ab initio calculations. Nevertheless, we were able to locate the transition state for 1,3-hydrogen migration. This pathway, in which gold functions as a proton shuttle, has a computed activation energy of only 67 kJ mol^{-1} , and the migrating hydrogen atom is transferred to the position *cis* to the methoxyl group. However, rotation about the C–C double bond in **21** has a low activation energy (less than 70 kJ mol^{-1}). The catalytic cycle is then closed by a ligand exchange that again produces **18** (this ligand exchange is calculated to be endothermic by 41 kJ mol^{-1}). Another possibility is that intermediate **21**, whose structure resembles that of protonated 2-methoxypropene, adds a second mole of methanol and then undergoes protodeauration to give 2,2-dimethoxypropane directly. These pathways are indistinguishable, because under the reaction conditions there is very rapid equilibrium between methanol, 2-methoxypropene, and 2,2-dimethoxypropane.

Experimental Section

Typical procedure for the addition of methanol to propyne: A mixture of methanol (2.5 mol) and a Lewis or Brønsted acid (1.25 mmol) was heated to 40°C and saturated with propyne before the gold catalyst (0.125 mmol Au) was added.^[8] During the reaction a continuous stream of propyne was introduced at a constant rate. Aliquots were taken at regular intervals, and the reaction was quenched by addition of an excess of solid sodium methanolate. The concentrations of methanol, 2,2-dimethoxypropane, and 2-methoxypropene were determined by GC and used to calculate turnover numbers and frequencies.

trans-2,5-Dimethyl-2,5-dimethoxy-1,4-dioxane (**12**): Propargyl alcohol (15.1 mol, 848 g, freshly distilled), methanol (59.6 mol, 1908 g), and concentrated sulfuric acid (15 mmol, 1.47 g) were mixed and heated to 55°C . A solution of methyl(triphenylphosphane)gold(I)^[22] (148 μmol , 70.4 mg) in 125 mL of dioxane was then added within 10 h. The mixture was stirred for an additional 10 h, and then most of the remaining methanol was removed by distillation at reduced pressure. The residual solution was neutralized with 30% sodium methanolate in methanol and cooled in an ice bath. Precipitated product was collected by filtration and dried. A second batch of product can be obtained by further concentration of the mother liquor. Total yield of isolated product: 1238 g (93%). Colorless crystals, m.p. $127\text{--}129^{\circ}\text{C}$ (literature value: $126\text{--}128^{\circ}\text{C}$).^[12, 23]

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- [17] Amazingly, even HBF₄ is quickly hydrolyzed to trimethylborate under the reaction conditions.
- [18] The same turnover rate (700 h⁻¹) is observed when the catalyst is generated from the oxonium salt [(Ph₃PAu)₃O⁺BF₄⁻] and BF₃·OEt₂.
- [19] All ab initio calculations were performed with the TURBOMOLE program package. For an overview of TURBOMOLE, see R. Ahlrichs, M. von Arnim in *Methods and Techniques in Computational Chemistry: METECC-95* (Eds.: E. Clementi, G. Corongiu) STEF, Cagliari, **1995**, P. 509–554. Geometries were calculated at the RI-DFT level (K. Eichkorn, O. Treutler, H. Ihm, M. Häser, R. Ahlrichs; *Chem. Phys. Lett.* **1995**, *242*, 652) with the Becke–Perdew functional and the TURBOMOLE SV(P) basis sets (K. Eichkorn, F. Weigend, O. Treutler, R. Ahlrichs, *Theor. Chem. Acc.* **1997**, *97*, 119). For gold, the 60-mw relativistic pseudopotential was utilized (D. Andrae, U. Haeussermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, *77*, 123). Energies were calculated at the MP2 level with TZVP basis sets through the recently developed RI-MP2 implementation (F. Weigend, M. Häser, *Theor. Chem. Acc.* **1997**, *97*, 331).
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- [21] Coordination of methanol with **18** to form the T-shaped complex **19** disturbs the structure only slightly. The angle between phosphorus, gold, and the center of the triple bond changes from 179° in **18** to 175° in **19**. The Au–O bond in **19** is very long (3.7 Å compared to 2.1 Å for a Au–O single bond), and the P–Au–O angle is 83°.
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Synthesis and Biological Activity of Sarcodictyins**

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Isolated from certain species of soft corals, the sarcodictyins (**1**, **2**),^[1, 2] eleutherobin (**3**),^[3, 4] and the eleuthosides (**4**, **5**)^[5] have become important synthetic targets because of their novel molecular architectures, biological activities, and medicinal potential (Figure 1). Of special interest is their taxol-like mechanism^[6] of action, which involves tubulin polymeri-

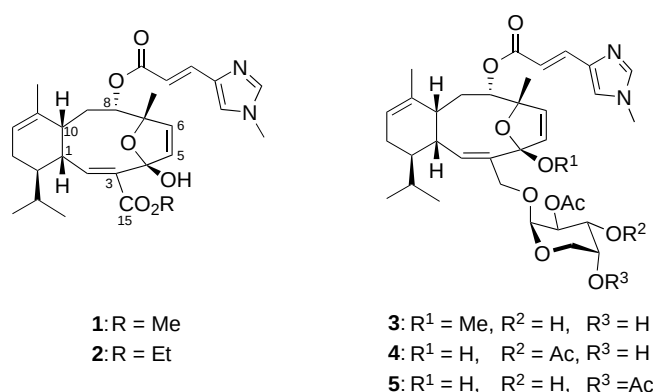


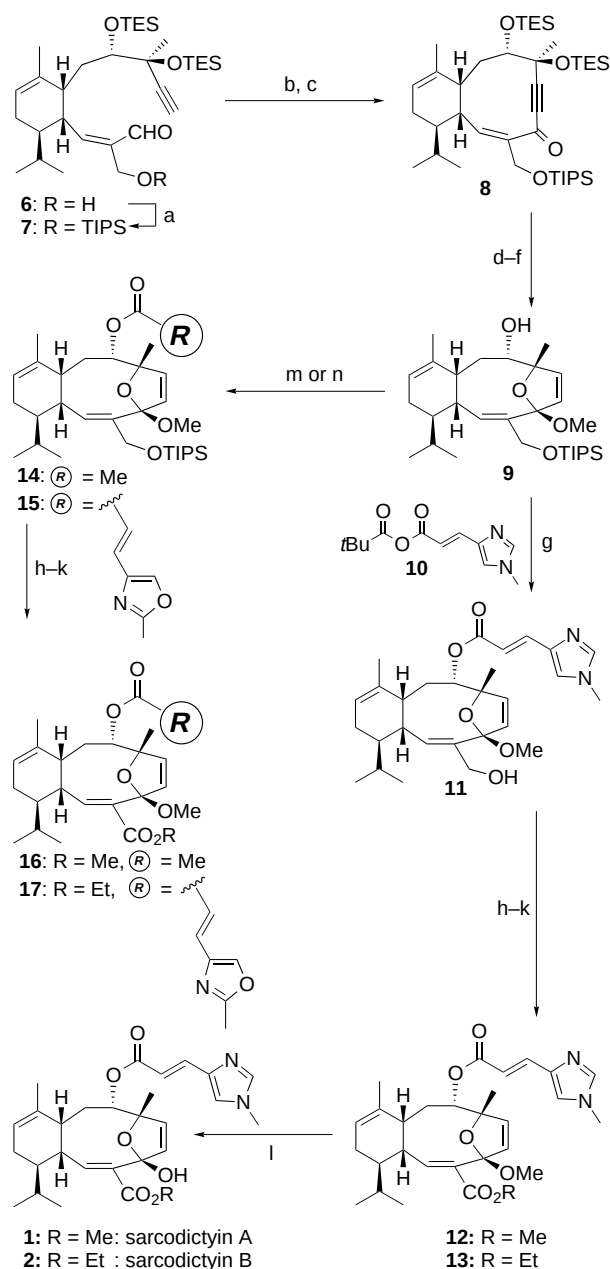
Figure 1. Structures of sarcodictyins A (**1**) and B (**2**), eleutherobin (**3**), and eleuthosides A (**4**) and B (**5**).

zation and microtubule stabilization and results in tumor-cell death. The combination of the scarcity and the appealing biological activity of these materials prompted us to initiate a program directed at their chemical synthesis. We recently disclosed the first total syntheses of sarcodictyins A (**1**)^[7] and eleutherobin (**3**).^[8] Here we report the first synthesis of sarcodictyins B (**2**), the construction of a sarcodictyins library, and the tubulin-polymerization and cytotoxic properties of members of that library, including their action against a number of taxol-resistant tumor-cell lines.

To conveniently access a sarcodictyins library, an improved method for their construction was devised (Scheme 1), which

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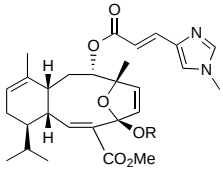
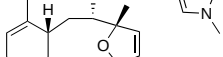
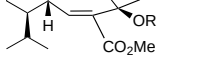
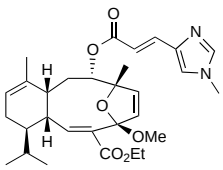
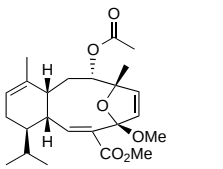
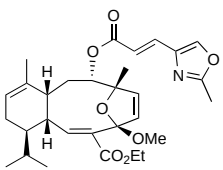
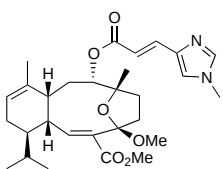
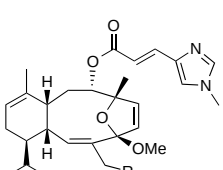
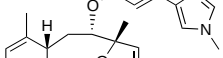
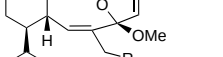
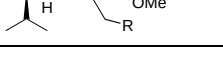
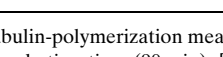
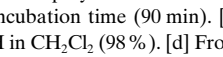
Scheme 1. Syntheses of sarcodictyins A (**1**) and B (**2**) and various analogues. a) TIPSOTf (5.0 equiv), *i*Pr₂NEt (10 equiv), CH₂Cl₂, –78 °C, 1 h, 79%; b) LiHMDS (2.0 equiv), THF, –20 °C, 20 min; c) Dess–Martin periodinane (2.0 equiv), pyridine (6.0 equiv), NaHCO₃ (6.0 equiv), CH₂Cl₂, 0 °C, 1 h, 89% over two steps; d) 3 HF · Et₃N (5.0 equiv), THF, 25 °C, 1.5 h, 78%; e) [Rh(nbd)(dppb)]BF₄ (0.05 equiv), H₂, acetone, 25 °C, 10 min; f) PPTS (0.5 equiv), MeOH, 25 °C, 10 min, 80% over two steps; g) **10** (5.0 equiv), Et₃N (20 equiv), DMAP (2.0 equiv), CH₂Cl₂, 25 °C, 48 h, 83%; h) TBAF (2.0 equiv), THF, 25 °C, 2 h, 100%; i) Dess–Martin periodinane (2.5 equiv), NaHCO₃ (10 equiv), CH₂Cl₂, 25 °C, 0.5 h; j) NaClO₂ (6.0 equiv), NaH₂PO₄ (3.0 equiv), 2-methyl-2-butene (50 equiv), THF, *i*BuOH, H₂O; k) CH₂N₂ or CH₃CHN₂, Et₂O, 88% (**12**) and 90% (**13**) over three steps; l) CSA (2.0 equiv), CH₂Cl₂:H₂O (10:1), 25 °C, 48 h, 80 (**1**) and 86% (**2**); m) Ac₂O (3.0 equiv), Et₃N (5.0 equiv), DMAP (1.0 equiv), CH₂Cl₂, 25 °C, 1 h, 95%; n) DCC (2.0 equiv), (*E*)-3-(2-methyloxazol-4-yl)propenoic acid (1.3 equiv), DMAP (0.5 equiv), CH₂Cl₂, 25 °C, 36 h, 86%. CSA = 10-camphorsulfonic acid, DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, dppb = 1,4-bis(diphenylphosphanyl)butane, LiHMDS = lithium hexamethyldisilazide, nbd = 2,5-norbornadiene, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetra-*n*-butylammonium fluoride, TIPSOTf = tris(isopropyl)silyl trifluoromethanesulfonate.

relies on the use of more effective protecting groups (**6**) and hydrogenation catalysts (**8**→**9**), and includes a number of alternative esterification protocols. Thus, the previously synthesized alcohol **6**^[8] was protected as a TIPS ether (**6**→**7**, 79%; for abbreviations, see the scheme legend) prior to ring closure (LiHMDS, –20 °C) and Dess–Martin^[9] oxidation to afford ten-membered ring enynone **8** (89% over two steps). Desilylation of **8** with 3 HF · Et₃N (78%) followed by selective hydrogenation^[10] in the presence of [Rh(nbd)(dppb)]BF₄ led through ring closure of a short-lived dihydroxydienone to the tricyclic skeleton. The resulting intermediate was converted to its methoxy acetal **9** (80% over two steps), which served as a common intermediate for the total synthesis of sarcodictyin B (**2**) and the construction of a sarcodictyin library. Three methods of esterification used in the generation of the library are exemplified in Scheme 1 by the syntheses of **11**, **14**, and **15**. Specifically, treatment of alcohol **9** with mixed anhydride **10** in the presence of DMAP resulted in the formation of urocanic ester derivative **11** in 83% yield. Subsequent cleavage of the silyl ether group with TBAF (100% yield) followed by a series of standard transformations (Dess–Martin and NaClO₂ oxidations and diazoalkane esterification) led to the isolation of methyl and ethyl esters **12** and **13** (88 and 90%, relatively, over three steps). The natural sarcodictyins A (**1**) and B (**2**) were obtained after acidic hydrolysis with 10-camphorsulfonic acid in CH₂Cl₂/H₂O (80 and 86%, respectively). In a second approach, treatment of **9** with acetic anhydride in the presence of DMAP provided acetate **14** (95% yield), which was in turn transformed into sarcodictyin A analogue **16** by the previously described sequence.^[7] Finally, reaction of **9** with (*E*)-3-(2-methyloxazol-4-yl)propenoic acid in the presence of DCC and DMAP gave a number of other side-chain analogues (Table 1).

The synthetic sarcodictyins were evaluated for tubulin-polymerization and cytotoxic properties, and were compared with taxol and epothilones A and B (Table 1). The colorimetric-filtration assay for tubulin polymerization^[11, 12] was utilized to determine the tubulin effects of sarcodictyins **1**, **2**, **11**–**13**, and **16**–**25**. They exhibited varying degrees of polymerizing properties ranging from 4.0 to 85% (for comparison: taxol, 65%; epothilone A, 72%; epothilone B, 97%). Cytotoxicity studies were conducted with the parental ovarian carcinoma cell line 1A9 and the taxol-resistant tumor-cell lines PTX10 and PTX22^[13] derived from 1A9. The observed activity of the synthetic compounds proved to be highly dependent upon their precise structures (Table 1).

A number of conclusions can be drawn from these studies with respect to structure–activity relationships (SARs). The C8 side chain is crucial for both tubulin-polymerization and cytotoxic properties, as shown by a comparison of compounds **13** and **16**. Reduction of the ester group at C15 to a primary alcohol (**11**) resulted in a decrease in activity. The sarcodictyin pharmacophore appears in fact to be rather sensitive to modification at C15 (reduction), as is apparent from the properties of compounds **21**–**25**. An increase in the size of the alkyl group on the C4 acetal seems to have only a small effect on the biological activity of the compounds (see **1**, **12**, **18**, and **19**).

Table 1. Tubulin-polymerizing and cytotoxic characteristics of the sarcodictyins.

Compound		Induction of tubulin polymerization [%]	Inhibition of cancer-cell growth (IC ₅₀ [nM])		
			1A9	1A9PTX10	1A9PTX22
	taxol	65.0	2.0	50	40
	epothilone A	72.7	2.0	1.9	4.0
	epothilone B	97.0	0.04	0.035	0.04
1	sarcodictyin A	67.0	340	140	360
2	sarcodictyin B	71.0	2.0	160	80
12		R = Me 72.0	70	3.6	84
18 ^[c]		R = Et 85.0	110	13	160
19 ^[d]		R = <i>n</i> Pr 79.0	170	> 2000	130
13		46.0	2.0	0.6	6.0
16		4.0	> 2000	1300	> 2000
17		4.0	> 2000	800	385
20 ^[e]		52.0	510	1700	1800
11		R = OH 37.5	800	> 2000	> 2000
21 ^[f]		R = F 27.4	1850	> 2000	> 2000
22 ^[g]		R = OAc 37.2	1050	> 2000	1620
23 ^[h]		R = OBz 34.1	> 2000	> 2000	> 2000
24 ^[i]		R = N ₃ 47.0	> 2000	> 2000	1800
25 ^[j]		R = OCONHPh 37.0	> 2000	> 2000	> 2000

[a] Tubulin-polymerization measurements were carried out at 37 °C as described,^[11, 12] apart from adjustments in the concentration of active agents (100 μM) and incubation time (90 min). [b] The cytotoxicity investigations were carried out as described.^[12, 13] [c] From sarcodictyin A (**1**) by treatment with CSA/EtOH in CH₂Cl₂ (98 %). [d] From sarcodictyin A (**1**) by treatment with CSA/*n*PrOH in CH₂Cl₂ (90 %). [e] By-product from overreduction of the triple bond and subsequent acetalization. [f] From **11** by treatment with DAST (99 %). [g] From **11** by treatment with Ac₂O, Et₃N, and DMAP (100 %). [h] From **11** by treatment with BzCl, Et₃N, and DMAP (95 %). [i] From **11** by treatment with (PhO)₂PON₃, DEAD, and Ph₃P (74 %). [j] From **11** by treatment with PhNCO and Et₃N (95 %). Bz = benzyl, CSA = 10-camphorsulfonic acid, DAST = (diethylamino)sulfur trifluoride, DEAD = diethyl azodicarboxylate, DMAP = 4-(dimethylamino)pyridine.

The apparent inconsistency between tubulin-polymerization activity and cytotoxicity for a number of these compounds (e.g., **13**, **17**, **20**) may be indicative of the availability of an additional mechanism of action in some cases. Indeed, inspection of the structures of sarcodictyins and

eleutherobins reveals their potential as alkylating agents under acidic conditions (Figure 2), so they may be capable of interacting with DNA and other cellular receptors. Experiments directed toward confirming this hypothesis are in progress.

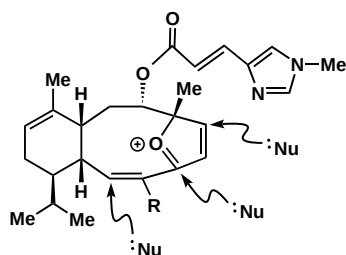


Figure 2. Alkylating properties of sarcodictyins and eleutherobins.

The chemistry and biological activity presented here shows the sarcodictyins to be a new class of potential anticancer agents. Access to additional derivatives and closer investigation are now possible through the use of molecular design and chemical synthesis. The first structure–activity information on sarcodictyins, reported here, should provide valuable guidelines for further chemical and biological studies.^[14]

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Cooperative Hairpin Dimers for Recognition of DNA by Pyrrole–Imidazole Polyamides**

John W. Trauger, Eldon E. Baird, and Peter B. Dervan*

Small molecules which permeate cells and bind to specific DNA sequences can potentially control the expression of specific genes.^[1, 2] Recently, a polyamide with eight heterocyclic units which binds to a target site consisting of six base pairs was shown to inhibit gene transcription in a cell culture.^[2] Polyamides that recognize longer DNA sequences should provide more specific biological activity,^[3] which could be achieved by synthesizing larger polyamides.^[4] However, the upper limit of polyamide size with regard to efficient cell permeation is not known.

Alternatively, a more biomimetic approach is to bind larger DNA sequences while maintaining the size of the polyamide. Natural transcription factors often bind large DNA sequences by formation of cooperative protein dimers at adjacent half-sites.^[5] In cooperatively binding extended pyrrole–imidazole (Py–Im) polyamide dimers, the two ligands can slip sideways with respect to one another to allow recognition of other sequences.^[6] Polyamides containing the turn-specific γ -aminobutyric acid linker^[7] adopt a hairpin conformation in which the DNA binding sites are fully overlapped and the slipped-motif option is precluded. Here we report a cooperative six-ring extended hairpin polyamide which dimerizes to specifically bind a predetermined sequence of ten base pairs.

As target site, we chose a sequence contained in the regulatory region of the HIV-1 genome.^[8] To design the ligand we considered the polyamide ring-pairing rules,^[9–13] the need to incorporate β -alanine (β) to relax the ligand curvature,^[6, 13] and the preference of γ -aminobutyric acid (γ) for a hairpin-turn conformation in polyamide–DNA complexes.^[6, 7a,e] This analysis suggested that the six-ring polyamide having the core sequence ImPy β ImPy γ ImPy might bind the target sequence 5'-AGCAGCTGCT-3' by formation of a cooperative hairpin dimer (Figure 1). To avoid a collision between the N-terminal end of one ligand and the C-terminal end of the other in the complex, the positively charged β -alaninedimethylaminopropylamide C terminus used in standard polyamides was replaced with the shorter, uncharged (CH₂)₂OH group (C₂–OH). The cationic turn residue (*R*)-2,4-diaminobutyric acid ((*R*)^{H₂N} γ)^[14] maintains the overall positive charge needed for optimal solubility in water.

Polyamide ImPy β ImPy(*R*)^{H₂N} γ ImPyC₂–OH (**1**) was synthesized by solid-phase methods^[15] on glycine–PAM resin,^[16] reductively cleaved from the solid support with LiBH₄,^[17]

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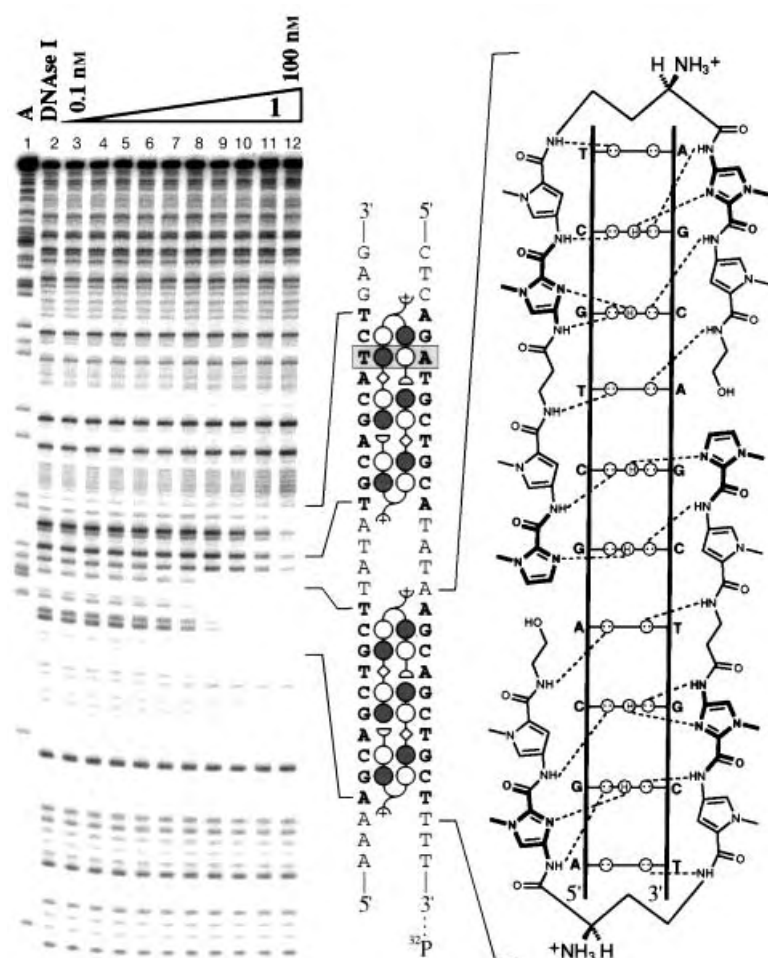
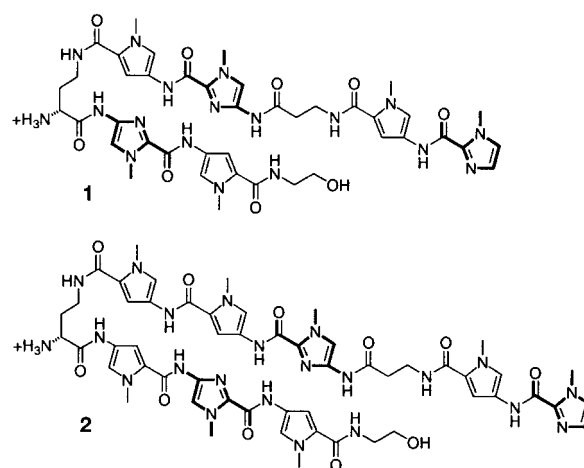


Figure 1. Right: Model of the $(1)_2 \cdot 5'\text{-AGCAGCTGCT-3'}$ complex. The symbol $\odot$ represents lone pairs on the N3 atoms of purine bases or on the O2 atoms of pyrimidine bases, and the symbol $\oplus$ represents the hydrogen atom bound to the N2 atom of guanine. Postulated hydrogen bonds are illustrated by dashed lines. Middle: Binding models for complexes of $(1)_2$ at a ten base pair match site and at a site with one mismatched base pair (the mismatched base pair is highlighted by shading). The shaded and open circles represent imidazole and pyrrole rings, respectively, diamonds represent β -alanine, half-circles represent $(\text{CH}_2)_2\text{OH}$ groups, and curved lines represent $(R)\text{-2,4-diaminobutyric acid}$. Left: Storage ^{32}P autoradiogram of the denaturing 8% polyacrylamide gel used to separate the fragments generated by DNase I digestion in a quantitative footprint titration experiment^[21] with polyamide 1: lane 1: A lane; lane 2: DNase I digestion products obtained in the absence of polyamide; lanes 3–12, DNase I digestion products obtained in the presence of 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 50, and 100 nM polyamide 1, respectively.

and purified by reverse-phase HPLC.^[18] Quantitative DNase I footprinting^[19] on a $3'\text{-}^{32}\text{P}$ -end-labeled restriction fragment with 245 base pairs showed that **1** binds its match site $5'\text{-AGCAGCTGCT-3'}$ at nanomolar concentrations (apparent monomeric association constant $K_a = (1.9 \pm 0.3) \times 10^8 \text{ M}^{-1}$) and also binds a site with one mismatched base pair ($5'\text{-AGATGCTGCA-3'}$) with ninefold lower affinity ($K_a = (2.2 \pm 0.5) \times 10^7 \text{ M}^{-1}$, Figure 1).^[20] The binding data for match and single base pair mismatch sites were well fit by cooperative binding isotherms, consistent with formation of cooperative 2:1 polyamide–DNA complexes.^[5] A site with two mismatched base pairs, $5'\text{-AGCTGCATCC-3'}$, was bound with 65-fold lower affinity. The fact that this mismatch site, which contains part of the target site ($5'\text{-AGCTGCA-3'}$), is not effectively bound indicates that recognition of the match site occurs

through cooperative dimerization and not by formation of 1:1 hairpin complexes.

Further study of the generality and sequence specificity of this binding motif is in progress. For example, we found that the eight-ring polyamide $\text{ImPy}\beta\text{ImPyPy}(R)^{\text{H}_2\text{N}}\gamma\text{PyImPyC}_2\text{-OH}$ (**2**) binds the twelve-base-pair match site $5'\text{-AAGCAGCTGCTT-3'}$ with tenfold higher affinity than **1**. The binding affinity of **2** to this sequence is approximately 100 times higher than to a site with two mismatched base pairs ($5'\text{-CAGATGCTGCAT-3'}$).



It is noteworthy that the DNA-binding affinity and specificity of the six-ring polyamide **1** for its ten base pair binding site are comparable to those of standard six-ring hairpins that recognize five base pairs.^[7] Thus, use of the cooperative hairpin dimer motif doubles the size of the binding site relative to the standard hairpin binding pattern without sacrificing affinity or specificity, and without increasing the molecular weight of the ligand. Our results show that by using a novel cooperative hairpin dimer motif, relatively low molecular weight pyrrole–imidazole polyamides ($M_r \approx 950\text{--}1200$) can specifically recognize 10–12 base pairs of DNA. Such polyamides will be useful in determining the optimal ligand size and optimal binding site size required for specific biological activity.

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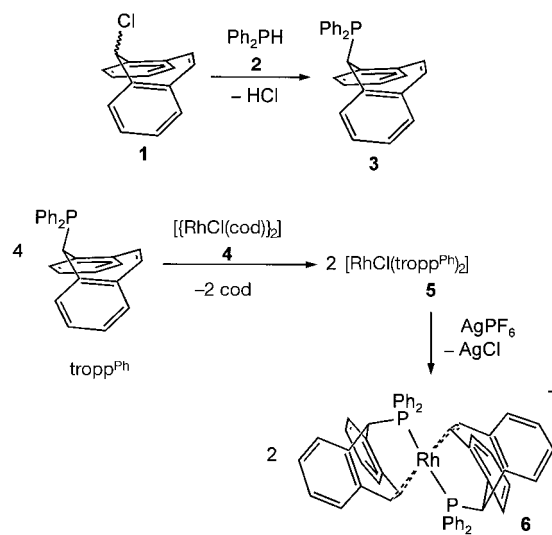
Keywords: cooperative effects • DNA recognition • polyamides

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A Monomeric d⁹-Rhodium(0) Complex**

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Complexes with rhodium centers in low formal oxidation states (0 or –1) are rare. They have been described as relatively short-lived intermediates in electrochemical reactions,^[1] as polynuclear clusters,^[2] or as complexes with strong π -acceptor ligands (such as $[\text{Rh}(\text{CO})_4]^-$,^[2] $[\text{Rh}(\text{PF}_3)_4]^-$).^[3] As far as we are aware, the isolation of a paramagnetic, monomeric d⁹-rhodium(0) compound has not yet been achieved. We report here a new ligand that allows the easy synthesis and reversible transformation of rhodium complexes with formal oxidation states +1, 0, and –1. 5-Chloro-5H-dibenzo[a,d]cycloheptene (**1**)^[5] reacts with diphenylphosphane (**2**) to form (5H-dibenzo[a,d]cycloheptene-5-yl)diphenylphosphane (**3**) (“dibenzo-tropylidenediphenylphosphane”, tropp^{Ph}) in good yield. In contrast to the synthesis of simple cycloheptatrienylphosphanes,^[6] only one isomer of **3** is obtained: the Ph₂P group is in the axial position of the seven-membered ring^[7] (Scheme 1).



Scheme 1. Synthesis of the rhodium(0) complexes **5** and **6**.

Reaction of four equivalents of **3** with $[(\text{RhCl}(\text{cod}))_2]$ (**4**) (cod = cyclooctadiene) leads in almost quantitative yield to the intense yellow rhodium(0) complex $[\text{RhCl}(\text{tropp}^{\text{Ph}})_2]$ (**5**).

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The chloride atom in **5** can be abstracted with AgPF_6 , and the complex salt $[\text{Rh}(\text{tropp}^{\text{ph}})_2]^+\text{PF}_6^-$ (**6**) is obtained. X-ray crystal structure analysis shows that the d⁸-rhodium(II) center lies on a center of inversion and has square-planar coordination geometry, as expected.^[8] Both **5** and **6** can be electrochemically reduced in a $\text{CH}_3\text{CN}/n\text{Bu}_4\text{NPF}_6$ electrolyte in reversible one-electron transfer steps, to generate, initially, the rhodium(0) complex **7** ($E_{1/2}^1 = -1.003 \text{ V}$), and subsequently the rhodium(–I) complex **8** ($E_{1/2}^2 = -1.189 \text{ V}$) (Figure 1). The

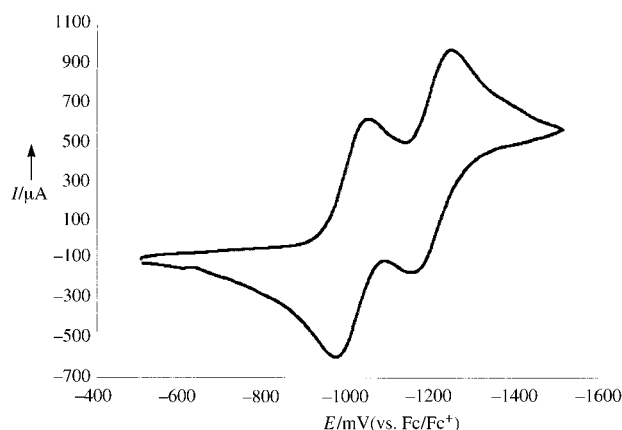
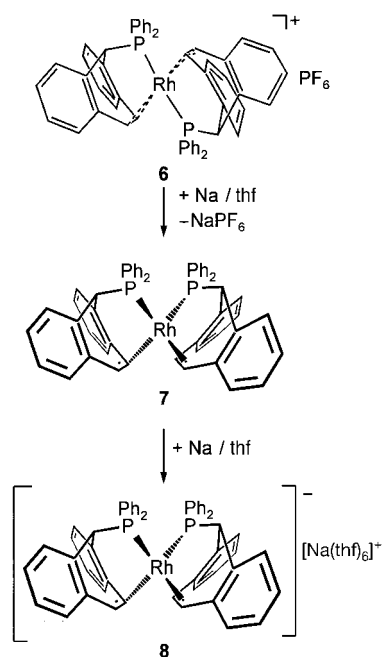


Figure 1. Cyclic voltammogram of **7**. Scan rate 30 mV s^{-1} , $\text{Pt}/n\text{Bu}_4\text{NPF}_6$, $\text{CH}_3\text{CN}/\text{Ag}$.

reduction potentials are significantly shifted to more anodic potentials when compared to previously reported values^[1b-g, 2] (-1.3 to -2.1 V vs. $\text{Ag}/0.1 \text{ M Ag}^+$). Reaction of **5** or **6** with sodium metal in THF also generates the deep green d⁹-complex $[\text{Rh}(\text{tropp}^{\text{ph}})_2]$ (**7**) or the red d¹⁰-complex $[\text{Na}(\text{thf})_6][\text{Rh}(\text{tropp}^{\text{ph}})_2]$ (**8**) (Scheme 2).



Scheme 2. Synthesis of the rhodium(0) complex **7** and the rhodium(–I) complex **8**.

The rhodium(0) complex **7** can also be prepared by a comproportionation reaction of the rhodium(II) complex **5** with **8**. The complex **7** is only slightly soluble in THF and hydrocarbons. Both complexes, **7** and **8**, are very air sensitive. Magnetic measurements of **7** gave an effective magnetic moment of $1.73 \mu_B$, as expected for one unpaired electron. The structures of **7** and **8** were determined by single-crystal X-ray structure analysis; the structure of **7** is shown in Figure 2.^[9]

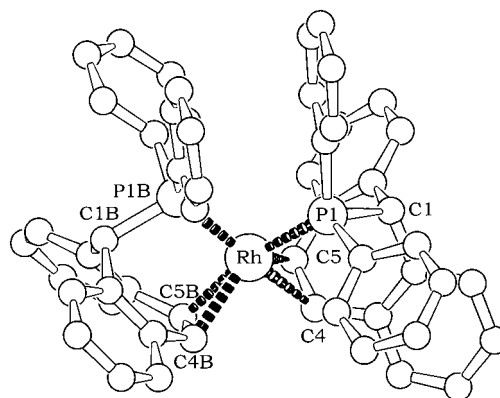


Figure 2. Structure of **7** in the crystal. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Rh1-P1 2.273(2), Rh-P1B 2.267(2), Rh1-C4 2.270(7), Rh1-C5 2.208(7), Rh1-C4B 2.216(7), Rh1-C5B 2.202(7), C4-C5 1.410(10), C4B-C5B 1.426(9), P1-C1 1.898(7), P1B-C1B 1.891(8); P1-Rh1-P1B 98.41(7), C4-Rh1-C4B 93.1(3), C5-Rh1-C5B 86.9(3), P1-Rh-C4 91.5(2), P1-Rh1-C5 91.1(2), P1B-Rh-C4B 87.1(2), P1B-Rh1-C5B 93.4(2).

The average Rh-P ($2.270(2) \text{ \AA}$) and Rh-C distances ($2.224(7) \text{ \AA}$) show no significant deviations from known values. The d⁹-rhodium(0) center in **7** has a nonplanar coordination in the crystal. The φ angle, defined by the planes running through the phosphorus and rhodium center as well as the middle of the coordinated $\text{C}=\text{C}$ bond, is about 43° . The phosphorus atoms have *cis* positions in this coordination sphere, which has an intermediate geometry between tetrahedral and square planar. The structure of the rhodanate anion in **8** (Rh-P 2.251(1) $\text{ \AA}$, Rh-C 2.159(4) $\text{ \AA}$, $\varphi = 52^\circ$) with formal d¹⁰ valence electron configuration at the metal center differs only slightly from the structure of the radical in **7**. The coordination polyhedron around the rhodium center in **8** is a little more distorted towards tetrahedral coordination ($\varphi = 52^\circ$). By means of EPR spectroscopy, a slightly distorted tetrahedral structure (D_{2d} symmetry) has been proposed for $[\text{Rh}(\text{CO})_4]$,^[1a] while a more square-planar structure was suggested for $[\text{Rh}\{\text{P}(\text{O}i\text{Pr})_3\}_4]$ ^[1b] and $[\text{Rh}(\text{cod})_2]$.^[1g]

Figure 3 shows the X-band CW-EPR spectrum of the Rh^0 complex **7** in THF at room temperature. The triplet structure is caused by isotropic coupling ($a_{\text{iso}} = 2.46 \text{ mT}$ (69.5 MHz)) with two equivalent phosphorus centers. Further magnetically relevant nuclei were detected by means of pulsed electron-nucleus-double-resonance spectroscopy (Davies-ENDOR)^[10] in a frozen solution at 30 K (Figure 4). In addition to the proton peaks between 11 and 18 MHz with hyperfine couplings (HFC) of up to 7 MHz, a doublet at 9 MHz with a splitting of 0.9 MHz is observed. This splitting is in agreement with the double Zeeman frequency of the rhodium nucleus. The assignment of this ENDOR line to rhodium with a HFC

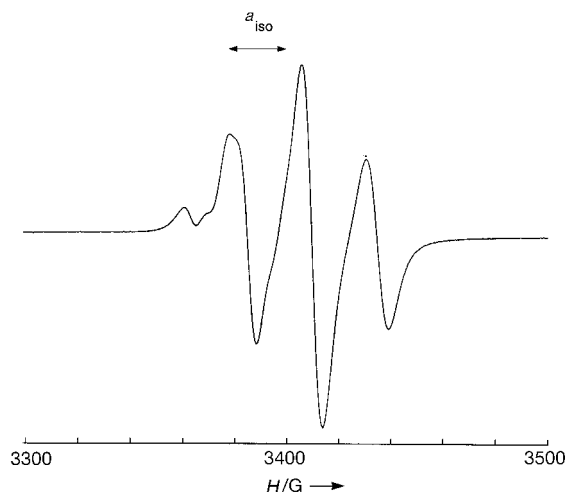


Figure 3. CW-ESR spectrum of **7** in THF at 295 K showing a hyperfine coupling constant a_{iso} of 69.5 MHz and an isotropic g factor of 2.0195.

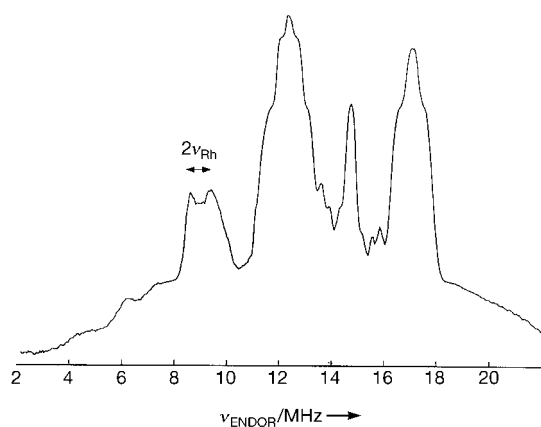


Figure 4. Davies-ENDOR spectrum of **7** at 30 K.

of 18 MHz was verified by two-dimensional pulse methods.^[11] A spin density of less than 1% in the s orbital of the phosphorus atom can be estimated from the isotropic ^{31}P HFC.^[12] The proton hyperfine couplings lie within the range expected for complexes in which the unpaired electron is localized at the transition metal center.^[13]

Experimental Section

3: A solution of **1** (5.5 g, 24.3 mmol) in toluene (50 mL) was slowly added to a solution of **2** (4.5 g, 24.3 mmol) in toluene (50 mL) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was refluxed for 15 h. The solvent was distilled off under vacuum, and the colorless residue was recrystallized from acetonitrile to afford 8.77 g (96%) **3** as colorless crystals. ^1H NMR (CDCl_3 , 300 MHz, 25°C , TMS): δ = 4.84 (d, $^3J_{\text{PH}}$ = 6.1 Hz, 1H, CHP), 7.07 (s, 2H, CH=CH); ^{31}P NMR (CDCl_3 , 81 MHz): δ = -14.9 (s).

5: **3** (3 g, 7.96 mmol) and **4** (0.98 g, 1.99 mmol) were dissolved in toluene (50 mL). The resulting deep red solution was stirred for 2 h at room temperature. After some time, **5** crystallized to give fine bright yellow needles 3.5 g (98.6%). ^1H NMR (CDCl_3 , 300 MHz, 25°C , TMS): δ = 5.19 (s, 1H, CHP), 4.68 (s, 2H, CH=CH); ^{31}P NMR (CDCl_3 , 81 MHz): δ = 79.9 (d, J_{PRh} = 75.5 Hz); ^{103}Rh NMR (CDCl_3 , 12.8 MHz): δ = 440 (br.); UV/Vis: λ_{max} = 277 nm (ϵ = $8.8 \times 10^3 \text{ m}^2 \text{ mol}^{-1}$).

7: Sodium (13 mg, 0.56 mmol) was added to a solution of **5** (500 mg, 0.56 mmol) in THF (10 mL), and the reaction mixture was stirred for 30 h at room temperature. A deep green solution and some precipitate were

formed. The residue was filtered off and washed several times with THF until only colorless NaCl remained. The combined THF extracts were concentrated to 5 mL and were layered with n -hexane (2 mL). Compound **7** crystallized as green black crystals (476 mg, 99%). ^{31}P NMR ($[\text{D}_8]\text{THF}$, 81 MHz): δ = 81.3 ($\Delta\nu_{1/2} \approx 3600 \text{ Hz}$); UV/Vis: λ_{max} = 645 nm (ϵ = $1.0 \times 10^3 \text{ m}^2 \text{ mol}^{-1}$).

8: Sodium (6 mg, 1.12 mmol) was added to a solution of **5** (500 mg, 0.56 mmol) in THF (10 mL), and the mixture was stirred for 48 h at room temperature. A deep red solution with some precipitate was formed. The residue was filtered off and extracted several times with THF until only colorless NaCl remained. The THF solution was reduced to 3 mL and layered with n -hexane (5 mL). Compound **8** crystallized as deep red crystals (larger crystals have a metallic golden luster) (727 mg, 99%). ^1H NMR ($[\text{D}_8]\text{THF}$, 300 MHz, 25°C , TMS): δ = 4.32 (d, J_{HP} = 9.48 Hz, 2H; CHP), 4.15 (m, 2H, CH=CH), 2.81 (m, 2H, CH=CH); ^{31}P NMR ($[\text{D}_8]\text{THF}$, 81 MHz): δ = 87.7 (d, J_{PRh} = 183 Hz); ^{103}Rh NMR ($[\text{D}_8]\text{THF}$, 12.8 MHz): δ = -496 (t, J_{RhP} = 179.6 Hz); UV/Vis: λ_{max} = 491 nm (ϵ = $16.0 \times 10^3 \text{ m}^2 \text{ mol}^{-1}$).

7 from reaction of **5** with **8:** Compounds **5** (500 mg, 0.561 mmol) and **8** (735 mg, 0.561 mmol) were dissolved in THF (15 mL) and stirred 2 h at room temperature. The resulting deep green solution was separated from the precipitate. The latter was treated as before and the combined THF extracts were reduced to 10 mL and layered with n -hexane (5 mL). Compound **7** crystallized as green-black crystals (950 mg, 99%).

Compounds **3**, **5** and **7** gave satisfactory elemental analyses after careful drying in vacuum. No correct elemental analysis, however, could be obtained for **8**, which rapidly loses solvent molecules.

Cyclovoltammetry and EPR measurements: The electrochemical investigations were performed on an apparatus designed by Heinze et al.^[14] Working electrode: planar platinum electrode (approx. surface area 0.785 mm^2); reference electrode: silver; counterelectrode: platinum wire; acetonitrile as solvent. At the end of each measurement, ferrocene was added as internal standard for calibration (+0.352 V vs. Ag/AgCl).

In order to determine the ^{103}Rh HFC, Davies-ENDOR experiments were performed on a frozen solution at various field positions. The measured ^{103}Rh HFC was found to be almost orientation independent.

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Novel Bonding of Iodine: Crystal Structure of $\text{HIS}_2\text{O}_8^{**}$

Martin Jansen* and Ralph Müller

Dedicated to Professor Achim Müller on the occasion of his 60th birthday

Ternary oxides of nonmetals are either ionic crystals with complex cations and anions or polymeric networks with oxygen as bridging atom, depending on the extent to which oxide ions are transferred from the acidic binary oxide to the more basic oxide. The polymeric networks are usually regarded as mixed anhydrides of oxoacids of the corresponding nonmetals, and their constitutions can be described in

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terms of known oxo anions as structural increments. The title compound contains the structural increment IO_2 , for which neither the corresponding free acid nor the corresponding free anion is known.

The system $\text{IO}_x/\text{SO}_3/\text{H}_2\text{O}$ is very complex and only rudimentarily understood.^[1] The difficulty in isolating pure crystalline phases is attributed to their polymeric nature and thermal instability. By carefully controlling the reaction conditions, especially the duration of crystallization, compounds of this system can be prepared reproducibly in amounts of up to one gram.^[2] The essential role of crystallization time is due mainly to changes in the composition of the reaction mixture during the crystallization of the product phases, and less to kinetic control of product formation. The title compound crystallizes from concentrated solutions of iodic acid in oleum under conditions similar to those described for the synthesis of $(\text{IO}_2)_2\text{S}_2\text{O}_7$ (see Experimental Section).

The composition of the title compound, including its hydrogen content, was confirmed by a single-crystal structure determination and by vibrational spectroscopy (Table 1).^[3]

Table 1. IR and Raman data for HIS_2O_8 [cm⁻¹].

IR	433(w)	455(w)	573(s)	613(w)	643(w)	738(w)	851(m)
	886(m)	1008(m)	1069(s)	1231(s)	1293(s)	2479(w)	2603(w)
	2895(m)						
Raman	102(s)	139(w)	162(w)	188(m)	205(m)	240(w)	278(s)
	305(s)	457(w)	513(m)	578(w)	639(vs)	744(m)	813(w)
	870(m)	899(m)	928(w)	1001(w)	1090(m)	1149(w)	1308(w)

The constitution of the trinuclear unit $\text{I}(\text{SO}_4)(\text{HSO}_4)$ can be understood as the condensation product of one unit of sulfuric acid and one unit of hydrogensulfate with the protonated form of the hypothetical iodic(III) acid H_2IO_2^+ . The result is a zwitterion with a positive formal charge on the iodine center and a negative charge on the nonprotonated sulfate group (Figure 1). The S–O distances and angles have a wide range of values, but their mean values lie in the range expected for sulfates and hydrogensulfates. Both intramolecular I–O distances correspond to single-bond lengths, and the environment of the iodine(III) center can be described as ψ^2 tetrahedral.^[4]

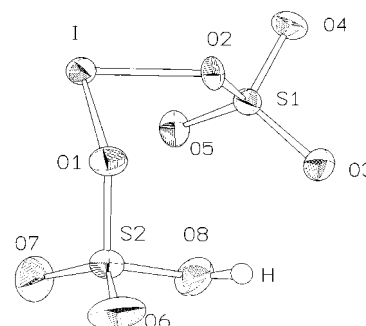


Figure 1. Structure of the trinuclear unit $\text{I}(\text{SO}_4)(\text{HSO}_4)$. Selected bond lengths [pm] (50% probability ellipsoids): I–O1 198.1(6), I–O2 197.0(6), S1–O2 158.5(6), S1–O3 145.3(7), S1–O4 147.2(7), S1–O5 140.7(7), S2–O1 157.9(6), S2–O6 140.9(9), S2–O7 139.2(8), S2–O8 151.9(8), O8–H 81.0(102).

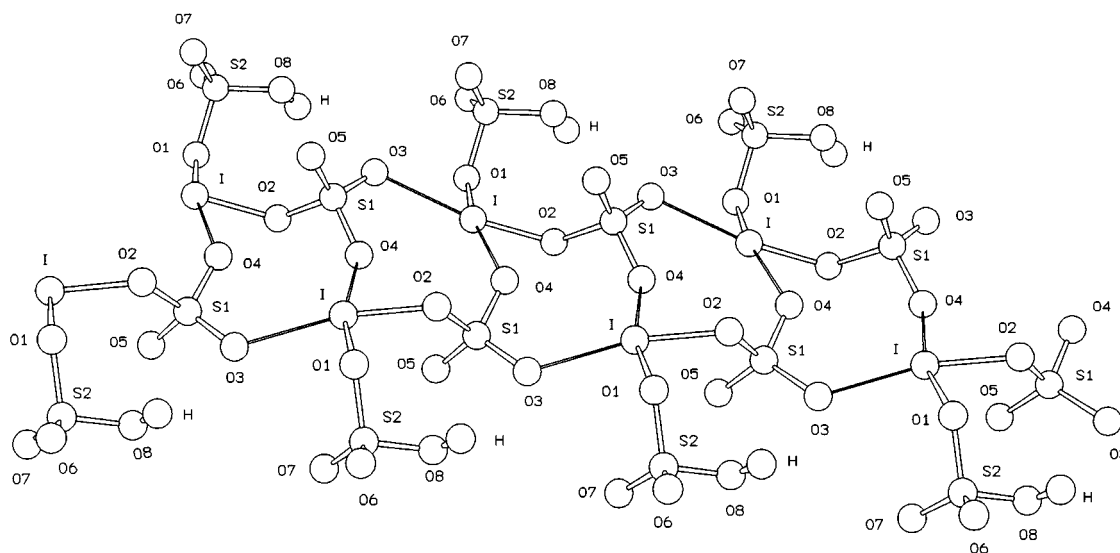


Figure 2. View of a polymeric ribbon in HIS_2O_8 . The ribbons are interconnected by hydrogen bonds to form layer packages. Selected bond lengths [pm] and angles [$^\circ$]: I–O3 242.4(7), I–O4 232.8(6); O1–O2 85.5(3), O1–O3 79.9(3), O1–I–O4 164.9(3), O2–I–O3 165.0(2), O2–I–O4 79.5(2), O3–I–O4 115.2(2).

The twofold coordination of the iodine center is supplemented by two oxygen atoms of two different neighboring sulfate groups to give a ψ^2 octahedrally distorted square-planar environment. However, these I–O bonds are considerably longer (233 and 242 pm) and lie between single bonds (202 pm) and van der Waals contacts (350 pm). These intermolecular interactions connect the primary units to form ribbons (Figure 2). The ribbons are interconnected by hydrogen bonds to give isolated layer packages. The variations in the I–O bond lengths can be easily understood in terms of the crystal chemical functions of the atoms involved. The shortest S–O bonds are those to the terminal oxygen atoms O5 and O7 and to O6, which acts as a hydrogen-bond acceptor. Bonds of intermediate length are formed with the O3 and O4, and the longest bonds with O8 (OH group) and with O1 and O2, which serve as bridges between iodine atoms. This gradation can be quantified by the partial valence sums.^[5] The contributions of the two oxygen atoms O3 and O4 in the second coordination shell of iodine to the valence sum of iodine are strikingly low (O3 0.34, O4 0.43; Table 2).

Table 2. Calculation of the valence sums for HIS_2O_8 .^[5]

v_{ij}	O1	O2	O3	O4	O5	O6	O7	O8	Σv_{ij}
I	1.11	1.14	0.34	0.43					3.02
S1		1.11	1.58	1.50	1.79				5.98
S2	1.12					1.78	1.87	1.32	6.09
H								0.90	
$\Sigma v_{ij(\text{O})}$	2.23	2.25	1.92	1.93	1.79	1.78	1.87	2.22	

$$R_{ij}(\text{I}) = 202.0, R_{ij}(\text{S}) = 162.4, R_{ij}(\text{H}) = 76.1.$$

Thus, the iodine atoms connecting two sulfate tetrahedra participate in novel bonding, which is best compared to that in IF_2^+ or in the monomeric S2.

Experimental Section

All preparations were performed under purified dry argon. Preparation of HIS_2O_8 : iodic acid (5 mmol, purum p.a. > 99%, Fluka) was added to oleum (100 mmol, purum p.a., Riedel-de Haën, ca. 20% SO_3) in a pear-shaped flask. The reaction mixture was heated to 210 $^\circ\text{C}$ over 30 min until oxygen was evolved, stirred at this temperature for a further 30 min, and then cooled to room temperature without stirring over 2 h to allow crystallization. The colorless crystals were collected by filtration, washed three times with trifluoroacetic acid (freshly distilled from P_4O_{10}), and dried in vacuo.

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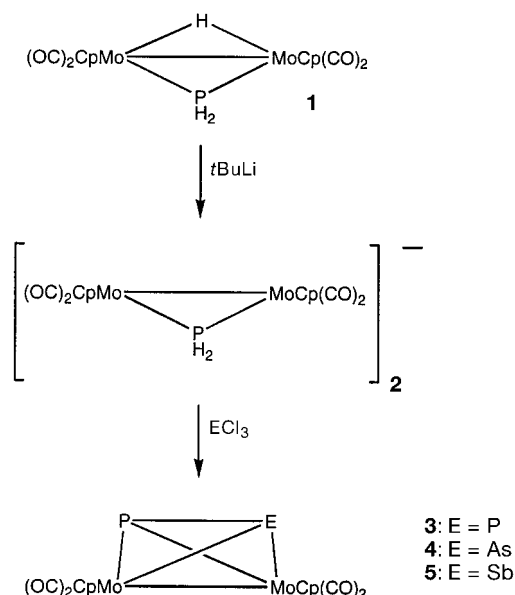
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Reaction of Group 15 Trichlorides ECl_3 with the Anion $[\text{Mo}_2\text{Cp}_2(\text{CO})_4(\mu\text{-PH}_2)]^-$; Synthesis and Characterization of the First Complexes Featuring a Hetero $\mu, \eta^2\text{-PE}$ ligand ($\text{E} = \text{As}, \text{Sb}$)**

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The synthesis of organometallics containing naked Group 15 ligands has been a fruitful area of research for a number of years. The E_2 ligand is particularly well known, having been observed in a wide range of complexes for both phosphorus and arsenic, and with rather fewer examples for antimony and bismuth.^[1] In contrast to this plethora of homocomplexes, to our knowledge there have been no reported examples of structurally characterized complexes featuring heteroligands such as PAs or PSb; indeed, there are very few reports of structural characterization of the P–Sb bond at all.^[2] We now report that the reaction of the anion $[\text{Mo}_2\text{Cp}_2(\text{CO})_4(\mu\text{-PH}_2)]^-$ (**2**) with ECl_3 ($\text{E} = \text{P}, \text{As}, \text{Sb}$) affords the tetrahedrane complexes $[\text{Mo}_2\text{Cp}_2(\text{CO})_2(\mu, \eta^2\text{-PE})]$ (**3**, $\text{E} = \text{P}$; **4**, $\text{E} = \text{As}$; **5**, $\text{E} = \text{Sb}$) in moderate yields, presumably with concomitant elimination of one equivalent of LiCl and two equivalents of HCl .

Reaction of a THF solution of $[\text{Mo}_2\text{Cp}_2(\text{CO})_4(\mu\text{-H})(\mu\text{-PH}_2)]$ (**1**), prepared by the literature method,^[3] with 1 equivalent of $t\text{BuLi}$ leads to an immediate color change from orange to purple and essentially quantitative formation of $[\text{Mo}_2\text{Cp}_2(\text{CO})_4(\mu\text{-PH}_2)]^-$ (**2**). Treatment of this solution with one equivalent of ECl_3 ($\text{E} = \text{P}, \text{As}, \text{Sb}$) results in a color change back to orange (Scheme 1). Chromatography on silica with 1:1 hexane:dichloromethane as eluent affords a small quantity of **1** and the air stable derivatives **3–5** as the only isolated products. Complex **3** was identified by comparison of its IR spectrum to that reported in the literature.^[4] The new complexes **4** and **5** were identified by IR and NMR spectroscopy, mass spectrometry, and microanalysis. Complexes **4** and **5** have been the subject of single-crystal X-ray diffraction analyses.^[5] The complexes crystallize in the space group $P2_1/c$ with two crystallographically distinct molecules in the unit cell, like the diarsenic analogue $[\text{Mo}_2\text{Cp}_2(\text{CO})_4(\mu, \eta^2\text{-As}_2)]$ (**6**)^[6] but unlike the diphosphorus complex $[\text{Mo}_2\text{Cp}_2(\text{CO})_4(\mu, \eta^2\text{-P}_2)]$ (**3**).^[4] The molecular structures of **4** and **5** are shown in Figures 1 and 2, respectively. Selected bond lengths and angles are given in Table 1. The PAs ligand of **4** shows a 50:50 disordering over the two sites; the interatomic separation of 2.2324(13) Å is intermediate between those observed for the diphosphorus and diarsenic complexes.^[4, 6] Similar behavior is



Scheme 1. Synthesis of **3–5**.

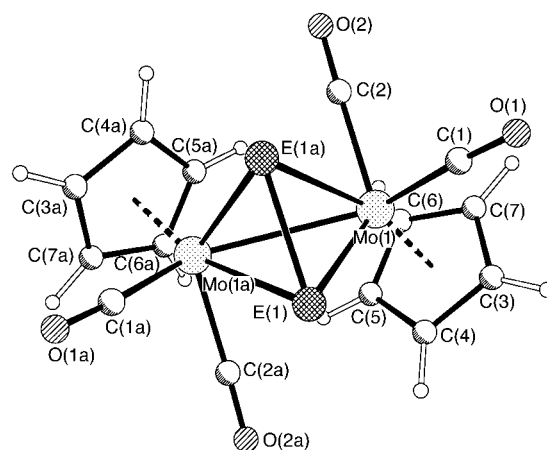


Figure 1. Molecular structure of **4**. E represents a P or an As atom.

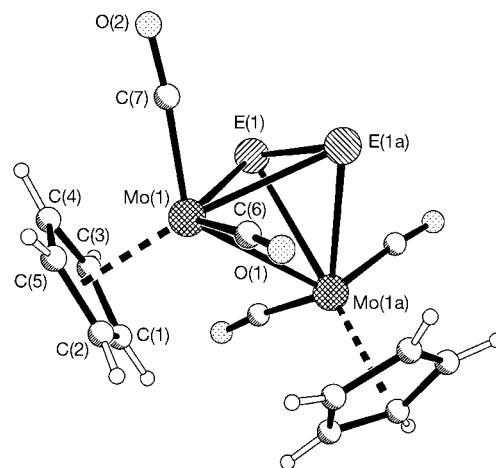


Figure 2. Molecular structure of **5**. E represents a P or an Sb atom.

observed for the PSb ligand in **5**, where the separation is observed to be 2.4699(14) Å. The Mo–Mo bond lengths of 3.0191(9) Å in **4** and 3.0563(11) Å in **5** are comparable with 3.038 Å in **6**^[6] and 3.021 Å in **3**^[4] and indicative of a single

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Table 1. Selected bond lengths [Å] and angles [°] for **4** and **5**.^[a]

	4	5
Mo(1)–Mo(1a)	3.0191(9)	3.0563(11)
E(1)–E(1a)	2.2324(13)	2.4699(14)
Mo(1)–E(1)	2.6428(9)	2.6942(9)
Mo(1a)–E(1a)	2.6428(9)	2.6942(9)
Mo(1a)–E(1)	2.5468(10)	2.7972(9)
Mo(1)–E(1a)	2.5468(10)	2.7972(9)
E(1)–Mo(1)–E(1a)	50.91(3)	53.42(3)
E(1)–Mo(1)–Mo(1a)	55.92(2)	57.80(2)
E(1a)–Mo(1)–Mo(1a)	52.96(2)	54.59(2)
E(1a)–E(1)–Mo(1)	66.67(3)	65.42(2)
E(1a)–E(1)–Mo(1a)	62.32(2)	61.16(2)
Mo(1)–E(1)–Mo(1a)	71.12(3)	65.42(2)

[a] Two independent, but not significantly different, molecules reside in the unit cell. Values given refer to one molecule only.

Mo–Mo bond, as required for agreement with the eighteen-electron rule.

Complexes featuring hetero-Group 15 ligands of this type have not previously been prepared. We are currently investigating the range of naked-ligand and related complexes preparable from the μ -PH₂ species in this manner and comparing their reactivity to the reactivity of the known homocomplexes with Group 15 ligands.

Experimental Section

All reactions were performed under an atmosphere of dry oxygen-free nitrogen with solvents freshly distilled from the appropriate drying agent. Synthesis of **5**: To a solution of **1** (0.497 g, 1.062 mmol) in THF (40 mL) was added *t*BuLi (0.63 mL of 1.7 M solution in pentane, 1.01 equiv.). The solution immediately became purple. SbCl₃ (0.244 g, 1.070 mmol) was added, and the mixture stirred for 2 min. The solution became deep orange. The solvent was removed under reduced pressure. The residue was redissolved in the minimum quantity of dichloromethane and applied to the base of TLC plates. Elution with hexane:dichloromethane (1:1) afforded orange **1** (0.096 g, 0.205 mmol, 19%) and red-orange **5** (0.241 g, 0.410 mmol, 39%). Similar treatment of **1** with PCl₃ or AsCl₃ result in the isolation of **3** and **4** in 29% and 33% yields, respectively. Selected spectroscopic data: [IR ($\bar{\nu}_{\text{CO}}$ cm^{−1}) recorded in dichloromethane solution; ¹H NMR and ³¹P NMR recorded in CDCl₃ solution; ³¹P NMR chemical shifts recorded relative to P(OMe)₃ at δ = 0.0 with positive shifts downfield. For conversion to 85% H₃PO₄ as a reference, δ = 146.2 should be added to the values given; calculated microanalytical values in parentheses]. **3**: $\bar{\nu}_{\text{CO}}$ 1965 vs, 1913 vs; ³¹P NMR δ = −188.5, s. **4**: $\bar{\nu}_{\text{CO}}$ 1959 vs, 1908 vs; ¹H NMR δ = 5.17, s; ³¹P NMR δ = −111.5, s; FAB MS 541 [*M*⁺+1], 484, 457, 428 [*M*⁺ − *n*CO, *n* = 2–4]; microanalysis C 30.96 (31.08), H 1.76 (1.85). **5**: $\bar{\nu}_{\text{CO}}$ 1949 vs, 1900 vs; ¹H NMR δ = 5.14, s; ³¹P NMR δ = −50.6, s; FAB MS 588 [*M*⁺+2], 532, 504 [*M*⁺ − *n*CO, *n* = 2, 3]; microanalysis C 28.45 (28.65), H 1.64 (1.72), P 5.31 (5.28).

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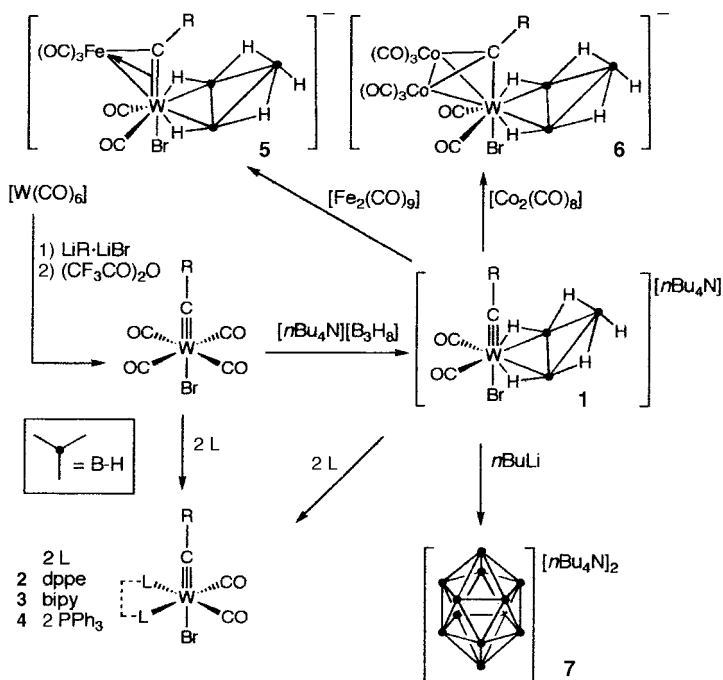
Alkylidyne – Metal Templated Triboronate Condensation**

Paul J. Dyson,* Anthony F. Hill,* Alexander G. Hulkes, Andrew J. P. White, and David J. Williams

Dedicated to Professor Warren R. Roper, on the occasion of his 60th birthday

From the earliest reports of high nuclearity boronates,^[1] their syntheses have typically involved elevated temperatures, with an attendant loss of selectivity. An attractive alternative would be the condensation of small borohydride-based ligands on a metal template. This has been achieved in a few cases with the preparation of $[L_nMB_2H_5]$ ^[2] and $[L_nMB_3H_8]$ ^[3] ensembles from suitably nucleophilic metal complexes and monoborane precursors. As the oxidation state of boron typically increases with increasing nuclearity, deployment of such a strategy for the preparation of high-nuclearity boranes would require the incorporation of a "hydrogen sink". Stone and co-workers have documented two features of alkylidyne ligands that might predispose them to such a role: Firstly, hydroboration of the metal–carbon multiple bond can be facile, providing access to novel α -boraalkyl and boraalkyne complexes.^[4] Secondly, in numerous instances high-nuclearity carbaborane cages couple with alkylidyne coligands, often by complete reduction of the alkylidyne to an alkyl group, which ultimately resides on the carbaborane cage.^[5] Furthermore, we have recently shown that dihydrobis(pyrazolyl)borate coligands can also effect such a reduction.^[6] We report here the synthesis and structural characterization of the first example of an alkylidyne metal-latetriborane and its remarkably facile conversion to $[Bu_4N]_2[B_{12}H_{12}]$ in good yield under exceptionally mild conditions.

Successive treatment of $[W(CO)_6]$ with $Li[2,6-C_6H_3Me_2] \cdot LiBr$, $(CF_3CO)_2O$ and $[Bu_4N][B_3H_8]$ results in good yields of the somewhat thermolabile salt $[Bu_4N][W(B_3H_8)(\equiv CC_6H_3Me_2)Br(CO)_2]$ (**1**) (Scheme 1). The formulation of the orange, air-sensitive compound follows from spectroscopic data and was confirmed by a crystallographic study.^[7] The alkylidyne ligand is manifest in the $^{13}C\{^1H\}$ NMR spectrum as a doublet at $\delta = 252.4$ showing coupling to tungsten [$J(WC) = 193$ Hz], accompanied by a single resonance for the two equivalent carbonyl coligands at $\delta = 217.7$. The molecular symmetry plane results in only two ^{11}B resonances being observed for the triboronate ligand at $\delta = 0.00$ (WB_2) and $\delta = -40.0$ ("wingtip"). The gross composition is reflected in the negative ion FAB-mass spectrum, which includes a



Scheme 1. Synthesis and reactions of **1**. R = 2,6- $C_6H_3Me_2$.

molecular ion and fragmentations arising from loss of the carbonyl and triboronate ligands.

Two tungstatetriborane compounds have been previously isolated.^[8,9] One of these, $[WH_3(B_3H_8)(PMe_3)_3]$, has been structurally characterized^[9] revealing bond W–B lengths of 2.519 and 2.495 Å within a disordered butterfly unit. The structure of the complex anion of **1** is shown in Figure 1. The

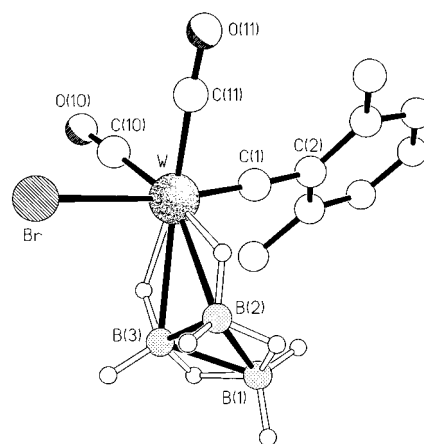


Figure 1. Molecular structure of the anion of **1**. Hydrogen atoms placed in idealized positions.

" $W(\equiv CC_6H_3Me_2)Br(CO)_2$ " component of the anion assumes essentially octahedral geometry with interligand angles in the range 85.5(4)–90.0(5)°. The $W\equiv C(1)$ bond at 1.805(13) Å is typical of low-valent tungsten alkylidynes, which are typically in the range 1.76–2.02 Å. The angle at C(1) is essentially linear $[W-C(1)-C(2) 175(1)^\circ]$. The principal structural feature of interest is the tungstatetriborane unit which has W–B separations of 2.53(2) and 2.55(2) Å and a butterfly hinge

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angle of 121(1)°. The B(2)–B(3) length of 1.78(3) Å is comparable to the remaining B–B bonds [1.77(3), 1.80(3) Å] in the essentially equilateral triboronate triangle, perhaps reflecting the weak coordination. There are no significant intermolecular interactions between the complex and the [Bu₄N] counterion.

The thermolability of **1** has been noted above, and the comparatively high values for the $\tilde{\nu}_{(\text{CO})}$ IR absorptions suggest that despite the negative charge on the complex, this is not strongly felt at the metal center but presumably resides substantially on the triboronate ligand. Anionic alkylidyne complexes remain rare, the most celebrated being the carbaborane derivatives [W(≡CR)(CO)₂(Cb)][−] (R = alkyl, aryl; Cb = C₂B₉H₉Me₂, C₂B₁₀H₁₀Me₂), which have been systematically investigated by Stone and co-workers,^[5] and it may be argued that for this class of complex, once again much of the negative charge is located within the carbaborane cage. The reactivity of **1** was investigated with respect to both ligand exchange and bridge-assisted metal–metal bond-forming processes. Thus, the reactions of **1** with 2,2′-bipyridyl (bipy) or 1,2-bis(diphenylphosphino)ethane (dppe) lead, unfortunately, to replacement of the triboronate anion and formation of the complexes [W(≡CC₆H₃Me₂-2,6)Br(CO)₂(bipy)] (**2**) and [W(≡CC₆H₃Me₂-2,6)Br(CO)₂(dppe)] (**3**), which are more easily prepared directly from *trans*-[W(≡CC₆H₃Me₂)-Br(CO)₄].^[10] Treating **1** with one equivalent of triphenylphosphane led to a mixture of **1** and *trans,cis,cis*-[W(≡CC₆H₃Me₂)Br(CO)₂(PPh₃)₂] (**4**), whilst two equivalents of PPh₃ provided high yields of **4**. The reactions of **1** with [Co₂(CO)₈] and [Fe₂(CO)₉] appeared (color, solution IR) to provide compounds formulated as [Bu₄N]-[WFe(μ-CC₆H₃Me₂)(B₃H₈)Br(CO)₅] (**5**) and [Bu₄N]-[WCo₂(μ₃-CC₆H₃Me₂)(B₃H₈)Br(CO)₈] (**6**). However, these salts were exceedingly air- and temperature-sensitive and decomposed on attempted chromatographic purification, even on silica gel at −40°C. Accordingly, their formulations rest tenuously on limited data and by analogy with related reactions of [W(≡CC₆H₃Me₂)(CO)₂(η-C₅H₅)].^[10]

The above results taken together would appear to suggest that the coordination of the triboronate ligand in **1** is somewhat fragile. The most intriguing indication of this comes from the reaction of **1** with *n*BuLi and iodomethane. When the reaction is carried out in a dry ice/propanone bath, after 15 minutes a white precipitate forms, which was characterized as [Bu₄N]₂[B₁₂H₁₂] (**7**) and isolated in 70% yield based on incorporated boron. The use of iodomethane in this process is serendipitous, having initially been employed (unsuccessfully) to trap any intermediates. However, whilst not essential to the boronate aggregation, it does serve to solubilize whatever low-valent tungsten side products are formed, thereby expediting work-up. The identity of **7** follows from spectroscopic data and a crystallographic study of the dichloromethane bis(solvate),^[7] which shows the [B₁₂H₁₂]^{2−} anion to have crystallographically imposed C_i symmetry and near ideal molecular I_h symmetry. Within the crystal lattice, each dodecaborate cage is “cupped” between two pairs of cationic “hands” as illustrated in Figure 2.

Previously, the extended pyrolysis (200°C, 10 h) of Na[B₃H₈] has been shown to provide (after Na/Cs exchange)



Figure 2. Crystal structure of **7**. Dichloromethane solvate omitted.

Cs₂[B₁₁H₁₄][BH₄].^[11] That **7** should form at such a low temperature and in such respectable yields is truly remarkable and clearly implicates the noninnocence of the alkylidyne ligand, presumably as a hydrogen sink by successive hydride transfers, ultimately to afford mesitylene. The closest known relative of **1** is the salt Cs[W(B₃H₈)(CO)₄], which is obtained from the reaction of [W(CO)₆] with Cs[B₃H₈] in 2,2′-dimethoxyethyl ether at reflux,^[8] these stringent conditions attest to the stability of the “WB₃H₈” core in the absence of an alkylidyne ligand. The formation of **7** under our exceptionally mild conditions calls to mind the recent discussion by Curl of the assembly of C₆₀ from low nuclearity C_x fragments in supersonic jets,^[12] although the genesis of the B₁₂ skeleton is perhaps more physically tangible than that of the carbon cluster.

Experimental Section

1: [W(CO)₆] (1.00 g, 2.84 mmol) in Et₂O (20 cm³) was treated with a solution of Li[2,6-C₆H₃Me₂]-LiBr (1.0 mol dm^{−3}, 2.9 cm³, from Li and Br[2,6-C₆H₃Me₂]). The resulting yellow solution was cooled (dry ice/propanone), and (CF₃CO)₂O (0.40 cm³) added. The mixture was then allowed to warm to 0°C at which point [*n*Bu₄N][B₃H₈] (0.80 g)^[13] was added. The mixture was stirred for 30 min (0°C) to provide a fine yellow precipitate, which was isolated by decantation and dried in vacuo. Yield 0.98 g (49%). IR (Nujol) 2493w, 2437w, 2385w [$\tilde{\nu}(\text{BH})$], 2001vs, 1913vs [$\tilde{\nu}(\text{CO})$] cm^{−1}; ¹H NMR (CDCl₃, 25°C, 270 MHz, Bu resonances omitted): −11.0 [s(br), 2H, WHB], 0.85 [m, 2H, BH], 1.23 [m, 2H, BH], 2.44 [m, 2H, BH], 2.51 [s, 6H, C₆H₃CH₃], 6.8–7.7 [m, 3H, C₆H₃]. ¹³C{¹H} NMR: 252.4 [W=C, J(WC)=193.3 Hz], 217.7 [WCO], 140–126 (C₆H₃), 20.8 (C₆H₃CH₃); ¹¹B NMR: 0.00 [2 B, WB], −40.0 [1 B, wingtip B]; negative ion FAB-MS *m/z* = 477 [*M*[−]], 449 [*M*[−]-CO], 437 [*M*[−]-B₃H₈]. Elemental analysis calcd for C₂₇H₅₃B₃BrNO₂W: C 45.1, H 7.4, N 2.0%; found: C 44.4, H 7.4, N 1.9%. The salt was also characterized crystallographically.^[7]

7: A suspension of **1** (0.200 g, 0.28 mmol) in THF (10 cm³) and benzene (5 cm³) at −78°C was treated with *n*BuLi (0.27 cm³, 2.0 mol dm^{−3} in cyclohexane), and the mixture stirred for 15 min resulting in the formation of a white precipitate. Iodomethane (0.3 cm³) was then added, and the mixture allowed to warm to room temperature. The white precipitate was isolated by decantation and recrystallized from a mixture of CH₂Cl₂ and petroleum ether (40/60). Yield 0.031 g (69% based on incorporated boron); IR (Nujol) 2470 vs [$\tilde{\nu}(\text{BH})$] cm^{−1}; negative ion FAB-MS *m/z* = 141 [*M*[−]]. The salt was also characterized crystallographically.^[7]

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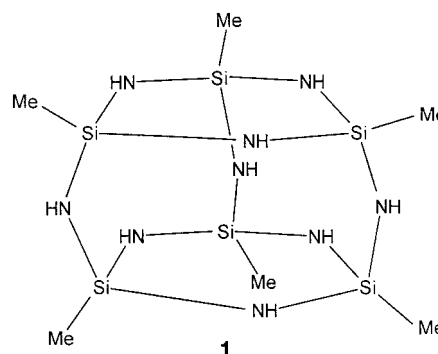
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Synthesis and Structure of $(CH_3Si)_6(NH)_9$: A Si–N Cage Made from Methyltrichlorosilane and Ammonia

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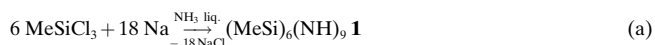
Dedicated to Professor Hans Bock on the occasion of his 70th birthday

Silicon–nitrogen compounds are being increasingly used for industrial purposes. Silicon nitride, for example, forms an integral part of many materials due to its high mechanical stability.^[1] In recent years there has been an increasing effort to study nitridosilicates. These compounds consist of a highly polymeric three-dimensional silicon–nitrogen framework with incorporated cations.^[2] We recently reported on cagelike silicon–nitrogen compounds with covalently bonded heteroatoms.^[3, 4] Cyclopolyalkylsilazanes and alkylsilsesquiazanes have been known for a long time,^[5] however these compounds have not been structurally characterized. Single crystals of $(MeSi)_6(NH)_9$ (**1**)^[6] have now been investigated by X-ray



structure analysis for the first time. They were obtained by developing a synthetic route in which no ammonium chloride is formed; our experience has shown that NH_4Cl hinders the growth of single crystals and is difficult to remove.

Ammonia was condensed onto elemental sodium at $-78^\circ C$, and methyltrichlorosilane was added. This led to $NaCl$ (which can be easily removed) and **1**, which was characterized by NMR and IR spectroscopy, mass spectrometry, and elemental analysis [Eq. (a)]. We assume that in the



course of the reaction sodium amide is initially formed, which then reacts with methyltrichlorosilane under formation of sodium chloride. According to the single-crystal X-ray structure analysis, **1** consists of two six-membered Si_3N_3 rings in the chair conformation with alternating silicon and nitrogen atoms. The rings are linked to one another by bridging NH groups connected to the Si centers, resulting in a prismatic

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cagelike structure (Figure 1). One methyl group is bonded to each of the silicon centers. Two groups of nitrogen centers can be differentiated: six are part of the two six-membered rings

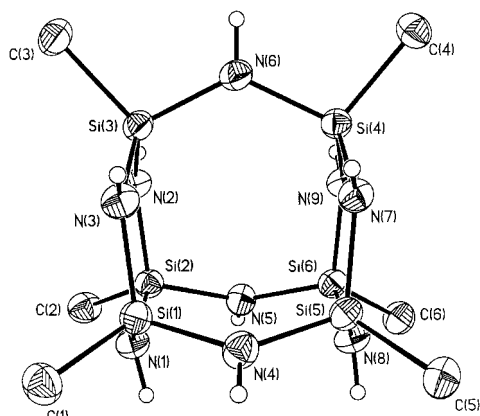


Figure 1. Structure of **1** in the crystal. Selected bond lengths [Å] and angles [°]: Si(1)–N(1) 1.729, Si(1)–N(3) 1.718, Si(1)–N(4) 1.733, Si(1)–C(1) 1.870; N(3)–Si(1)–N(1) 106, N(4)–Si(1)–N(1) 111, N(4)–Si(1)–N(3) 111, C(1)–Si(1)–N(1) 112, C(1)–Si(1)–N(3) 112, C(1)–Si(1)–N(4) 106.

(av Si–N distance: 1.720(3) Å) and three bridge the rings (av Si–N distance: 1.736(3) Å). The differences in bond length can be explained by the ring strain that is present in this cage.

The silicon centers all have slightly distorted tetrahedral coordination, and four groups of angles can be distinguished: the N–Si–N angle within the six-membered rings (av 111.1(2)°); the somewhat smaller angle between a nitrogen center of one of the six-membered rings and a bridging nitrogen atom (av 105.5(2)°); the N–Si–N angle between carbon centers and one nitrogen of a six-membered ring (av 111.8(2)°); and the somewhat smaller angle between carbon and bridging nitrogen centers (av 105.7(2)°). The nitrogen centers in the six-membered rings exhibit almost planar coordination (average sum of angles = 356.9(2)°), as do the bridging nitrogen centers—within the limits of experimental precision—with an average sum of angles of 359.8(2)°. The average Si–C bond length of 1.864(3) Å lies in the range typical for Si–C single bonds. A comparison of this structure with the isoelectronic oxygen compound was not possible as its structure is still unknown according to a search of the literature.

The ¹H NMR spectrum shows a signal for the methyl protons (δ = 0.04) and a very broad singlet from the NH protons (δ = 0.20–1.20), and the ²⁹Si NMR spectrum contains as expected just one signal (δ = –21.98). The molecular ion (m/z = 393) is clearly apparent in the mass spectrum. Signals from other fragments resulting from the cleavage of methyl groups are also present. The results of the elemental analysis for carbon and silicon deviate somewhat from the calculated values because small amounts of silicon carbide are formed on decomposition of the compound. The bands of the N–H vibration (3393 cm^{–1}) and the Si–N vibrations (949, 1166, 1196 cm^{–1}) in the IR spectrum were assigned by experiment.

The unproblematic workup of the methyl derivative illustrates that the use of metallic sodium in liquid ammonia provides a facile route to cagelike Si–NH compounds without

the need for bulky ligands bonded to the silicon centers. It should also be possible to use this synthetic route with other element halides.

Experimental Section

An excess of ammonia was condensed onto sodium (1.38 g, 60 mmol) at –78 °C. A solution of methyltrichlorosilane (2.99 g, 2.35 mL, 20 mmol) and *n*-hexane (60 mL) cooled to –78 °C was carefully added dropwise over a period of 1 h. The residue was filtered off and the volatile components were removed under vacuum. The residue was then taken up in diethyl ether. The solution was stored at –25 °C whereupon single crystals of **1** (0.3 g, 23%) suitable for X-ray structure analysis were formed.

Decomposition temperature: 60 °C; ¹H NMR (200 MHz, C₆D₆, TMS): δ = 0.04 (s, 18 H; CH₃), 0.2–1.2 (s, 9 H; NH); ²⁹Si NMR (79 MHz, C₆D₆, TMS): δ = –21.98 (s); IR (KBr, Nujol): $\tilde{\nu}$ = 3462, 3393, 3314, 2980, 1546, 1410, 1257, 1196, 1166, 1095, 1020, 949, 801, 723, 625 cm^{–1}; MS (EI): m/z (%): 393 (42, *M*⁺), 378 (100, *M*⁺ – CH₃). Satisfactory elemental analysis for C₆H₂₇N₆Si₆.

Structure analysis of **1**: *M*_r = 393.91, crystal dimensions 0.40 × 0.30 × 0.20 mm³, triclinic space group, *P* $\bar{1}$, *a* = 8.722(2), *b* = 9.876(2), *c* = 11.411(2) Å, α = 76.25(3), β = 83.14(3), γ = 87.50(3)°, *V* = 947.8(3) Å³, ρ_{calc} = 1.380 g cm^{–3}, *Z* = 2, absorption coefficient: μ = 0.448 mm^{–1}, max. resolution: $2\theta = 55^\circ$, 18769 reflections measured of which 4330 (*R*_{int} = 0.0391) independent. Data/restraints/parameter ratio: 4330/9/223, *R*₁ = 0.0545, *wR*₂ = 0.1420 (*I* > 2σ(*I*)), *R*₁ = 0.0786, *wR*₂ = 0.1628 (all data), GOF = 1.163; (*R*₁ = $\sum ||F_o| - |F_c|| / \sum |F_o|$, *wR*₂ = $[\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)]^{1/2}$, *S* = $[\sum w(F_o^2 - F_c^2)^2 / \sum (n - p)]^{1/2}$); weighting scheme: $w^{-1} = \sigma^2(F_o)^2 + (0.085P)^2 + 0.815P$; $P = [F_o^2 + 2F_c^2]/3$; max./min. residual electron density 0.840/–0.550 e Å^{–3}.

The crystal was removed from the Schlenk tube under inert gas, mounted onto a glass fiber with perfluoropolyether and shock frozen.^[7] The data collection was performed at 133 K on a Stoe-Siemens-Huber four-circle diffractometer connected with a Siemens CCD surface detector with graphite-monochromated MoK α radiation (λ = 0.71073 Å) performing φ and ω scans. The structure was solved by direct methods using SHELXS-97^[8] and refined by using SHELXL-97^[9] by the full-matrix least-squares method against *F*². All non-hydrogen atoms were refined anisotropically. All hydrogen atoms bonded to nitrogen were localized in the difference Fourier synthesis and refined freely with the aid of distance restraints. The methyl hydrogen atoms were added to geometrically calculated positions and refined with a 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-100995. 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).

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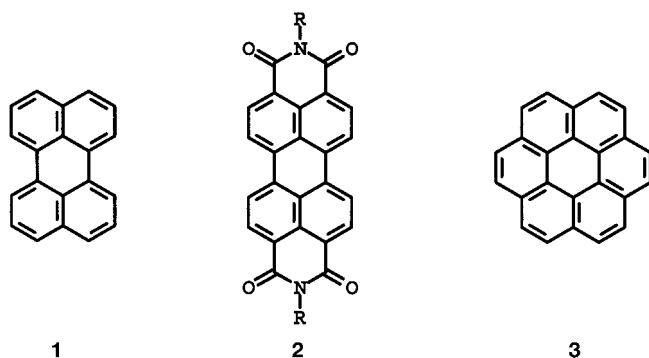
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Liquid Crystalline Coronene Derivatives with Extraordinary Fluorescence Properties**

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Dedicated to Professor Emanuel Vogel on the occasion of his 70th birthday

Perylene (1) and perylene-3,4:9,10-bis(dicarboximide)s 2 are among the most intensively investigated chromophores in dye chemistry.^[1] Coronene (3), which is similar to perylene,



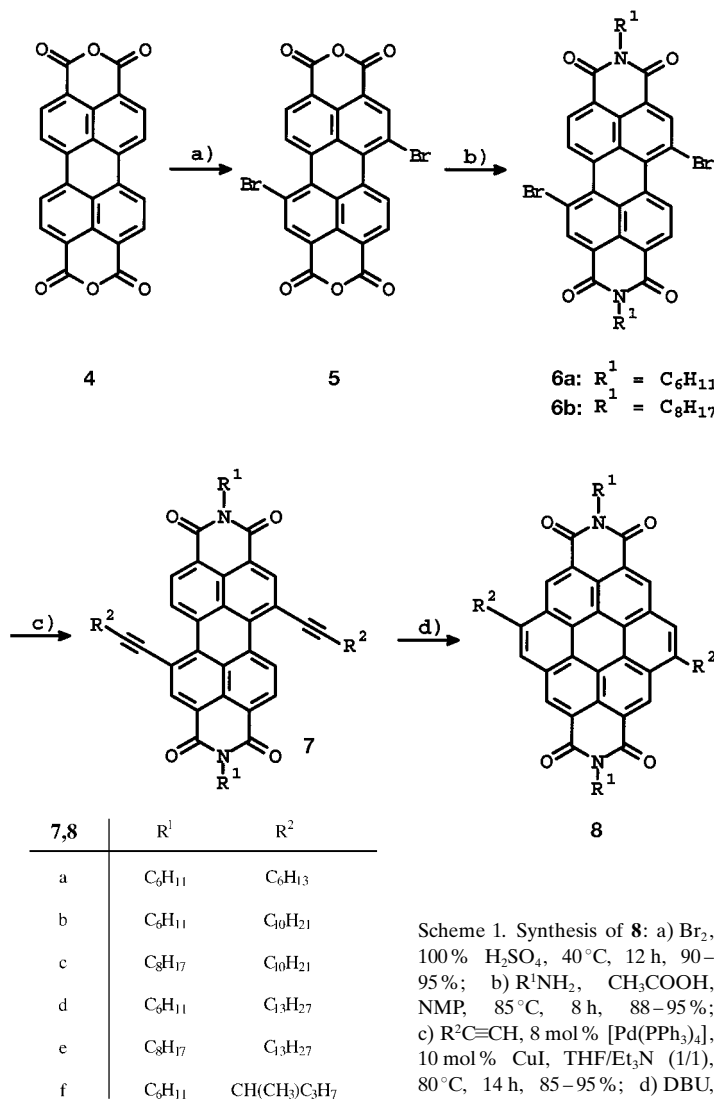
constitutes a classical aromatic hydrocarbon; however, owing to its limited preparative accessibility, there have been only few attempts to modify it chemically.^[2] We present here the coronene-3,4:9,10-bis(dicarboximide)s 8, which as a combination of 2 and 3 represent a novel type of dye.

The photostable yellow title compounds 8

- are obtained by a surprisingly simple procedure from readily available derivatives of 2, and provide access to additional chromophores.
- are active in an interesting wavelength range between that of 1 and 2 in both absorption and emission spectra,
- form, when they contain suitable alkyl substituents R¹ and R², discotic mesophases and combine the properties of both dyes and liquid crystals,^[3] and
- form aggregates in a solid matrix whose photoluminescence wavelength varies depending on the respective tempering process. Therefore, 8 is a promising compound for the preparation of multicolored displays on the basis of organic luminescent diodes.

The functionalization and alkylation of perylene (1) was achieved by coupling 3,9(10)-dibromoperylene with various

terminal alkynes and subsequent catalytic hydrogenation of the triple bonds.^[4] It appeared logical to apply this aryl-ethynyl coupling to the functionalization of the *N,N'*-dialkyl-1,7-dibromo-3,4:9,10-bis(dicarboximide)s 6. However, a very surprising reaction sequence was observed which led to the novel compounds 8 (Scheme 1). The derivatives 6a and 6b



Scheme 1. Synthesis of 8: a) Br₂, 100% H₂SO₄, 40 °C, 12 h, 90–95%; b) R¹NH₂, CH₃COOH, NMP, 85 °C, 8 h, 88–95%; c) R²C≡CH, 8 mol% [Pd(PPh₃)₄], 10 mol% CuI, THF/Et₃N (1/1), 80 °C, 14 h, 85–95%; d) DBU, toluene, 100 °C, 12 h, 95–100%. NMP = *N*-methylpyrrolidone.

required in the first step of the alkyne coupling can be obtained in a two-step synthesis. The commercially available perylene-3,4:9,10-tetracarboxylic dianhydride (4) is subjected to a twofold bromination with elemental bromine in 100% sulfuric acid to provide 5 (90–95%), which is then converted into 6a and 6b (88–95%) with cyclohexylamine or *n*-octylamine, respectively.^[5] The palladium(0)-catalyzed^[4] reactions of 6 with 1-alkynes in the presence of bases such as triethylamine afforded the expected bis(alkynyl)-substituted perylene-3,4:9,10-bis(dicarboximide)s 7a–e in high yields (85–95%). Treatment of 7 with strong, nonnucleophilic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) triggers a cyclization reaction of unknown mechanism to yield almost

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quantitatively the yellow title compounds **8** with various substituents at the resulting phenyl rings.^[6] The structures of the coronenebis(dicarboximide)s **8** could be verified by ¹H and ¹³C NMR spectroscopy, UV/Vis spectroscopy, and FD mass spectrometry (Table 1). Saponification of the imide functionalities in **8b** under standard conditions (KOH in *tert*-

Table 1. Spectroscopic data of **8b**.

M.p. (DSC): $T_m = 245^\circ\text{C}$ (Col _{ho}); ¹ H NMR (500 MHz, CDCl ₃): $\delta = 9.31$ (s, 2H; ArH), 9.06 (s, 2H; ArH), 8.13 (s, 2H; ArH), 5.37–5.31 (m, 2H; NCH), 3.46–3.42 (t, 4H, ³ J = 7.8 Hz; CH ₂ C≡C), 2.91–2.85 (m, 4H; cHex), 2.18–2.12 (m, 8H; cHex and CH ₂), 2.01–1.90 (m, 6H; cHex), 1.74–1.23 (m, 34H; cHex and CH ₂), 0.89–0.86 (t, 6H, ³ J = 7 Hz; CH ₃); ¹³ C NMR (125 MHz, CDCl ₃ , spin-echo experiment): $\delta = 164.86$ (q; C=O), 164.6 (q; C=O), 140.72 (q; arom. C), 128.97 (arom. CH), 128.43 (q; arom. C), 127.79 (q; arom. C), 127.12 (arom. CH), 125.00 (arom. CH), 121.84 (q; arom. C), 121.35 (q; arom. C), 121.27 (q; arom. C), 121.08 (q; arom. C), 120.59 (q; arom. C), 119.19 (q; arom. C), 54.58 (CHN), 33.70 (CH ₂), 31.78 (CH ₂), 31.37 (CH ₂), 31.22 (CH ₂), 29.64 (CH ₂), 29.53 (CH ₂), 26.85 (CH ₂), 25.71 (CH ₂), 22.74 (CH ₂), 14.10 (CH ₃); UV/Vis (CH ₂ Cl ₂): λ_{max} (ϵ) = 477 (9400), 511 (19700), 428 (62100), 404 (30500), 382 (7900), 338 (73200), 334 nm (72800); FD-MS (8 kV, FD = field desorption): $m/z = 882.5$ (100%) [M^+]

butyl alcohol/water) afforded the dianhydride **9** in high yields (85–90 %, Scheme 2).^[7] Reaction of the latter with diamines can be used to build up coronene-based polyimides, analogous to the well-known polyperylenebis(dicarboximide)s.^[8] Compound **9** can be decarboxylated with Cu/Cu₂O^[9] to the previously unknown dialkylcoronene **10**.

The absorption bands of **8** show a hypsochromic shift with respect to those of **2** and a bathochromic shift with respect to those of **3**. Coronenebis(dicarboximide)s **8** fluoresce with an intensive green-yellow color with the maxima at 517 nm (in CHCl₃).^[10] With suitable substituents R¹ and R², compounds **8** form mesophases with transition temperatures between 177 and 266 °C; this could be proven by differential scanning calorimetry (DSC) as well as by polarization microscopy and X-ray diffractometry (for the transition temperatures see Table 2; isotropization could not be observed, and decomposition occurred at approximately 450 °C). A comparison of the transition temperatures for the derivatives prepared to date does not allow a correlation between the melting points and the type of alkyl side chains at the imide groups and the

Table 2. Melting points of **8**.

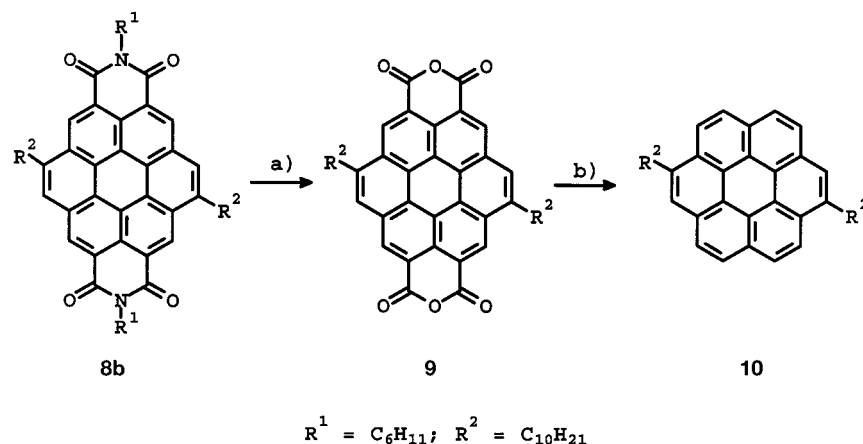
R ²	R ¹ = C ₆ H ₁₁		R ¹ = C ₈ H ₁₇	
	8	T_m [°C]	8	T_m [°C]
C ₆ H ₁₃	a	> 300	–	–
C ₁₀ H ₂₁	b	245 ^[a]	c	192 ^[a]
C ₁₃ H ₂₇	d	266 ^[a]	e	177 ^[a]
CH(CH ₃)C ₃ H ₇	f	> 300	–	–

[a] These derivatives form a mesophase at $T > T_m$.

coronene skeleton. However, hexyl substituents at the aromatic moiety do not suffice to form a mesophase (Table 2: derivative **8a**; R¹ = C₆H₁₁, R² = C₆H₁₃). X-ray diffractometry investigations suggest the presence of a columnar discotic mesophase with a hexagonal superstructure (Col_{ho}) at temperatures above the melting point.^[11] For the use of the coronene derivatives **8** as photoconductors, the order in the mesophase is important for a high charge-carrier mobility;^[12] however, lower transition temperatures are required for application purposes.

The formation of columnar mesophases with stacks of disclike chromophores leads to the question of whether aggregates are formed in solution, in amorphous films of the pure substance, or in mixtures with host polymers, and furthermore to what extent the absorption and emission behavior can be controlled by the type of aggregate formation. UV/Vis spectra of solutions of **8b** in chloroform are concentration-independent in a range from 4×10^{-7} to 1×10^{-3} mol L⁻¹.^[14] At the same concentration (10^{-3} mol L⁻¹ ~ 0.1 mass %) of **8b** in a polystyrene (PS) matrix the absorption spectrum of the film matches that of dissolved **8b**, except for the strong broadening of the band. Only at concentrations above 1–2 mass % does a new absorption band develop in the long-wave range which suggests the formation of an aggregate (Figure 1). PS films doped with 1–40 mass % of **8b** and amorphous layers of the pure compound fluoresce orange, and the spectra exhibit only a slight concentration dependence (Figure 2a).

Entirely different spectra are obtained (Figure 2) when these PS films and the film consisting of pure **8b** are tempered under an atmosphere of inert gas for 5 min at 280 °C (i.e., above the melting point of 245 °C in the mesophase): The broad fluorescence band (590 nm) of films containing small amounts of **8b** (1–2 mass %) is shifted towards blue, whereas the band at 510 nm becomes more intense. The emission spectrum of the tempered film containing 1 % of **8b** exactly matches the existence of isolated coronenebis(dicarboximide) molecules. Whereas tempering films with intermediate concentrations of **8b** (5–10 mass %) has a negligible effect on the fluorescence spectrum, a shift towards red can be observed after tempering films containing more than 20 mass % of **8b**. The transition from PS films containing 40 mass % of **8b** to a film of the pure compound is abrupt, with the band



Scheme 2. Synthesis of **10**: a) KOH, H₂O, *t*BuOH, 100 °C, 4 h, 90%; b) decarboxylation with Cu and Cu₂O in quinoline at 220 °C.

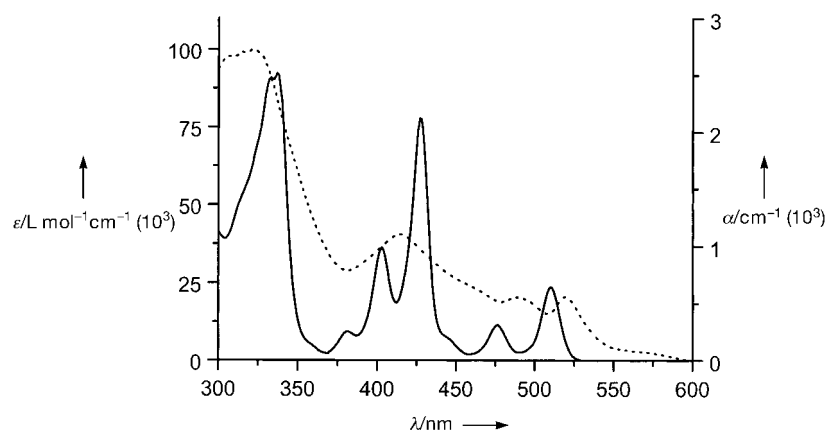


Figure 1. Absorption spectra of **8b** in solution (solid line) and in a PS matrix (10 mass %, dotted line). ϵ = extinction coefficient, α = absorption coefficient.

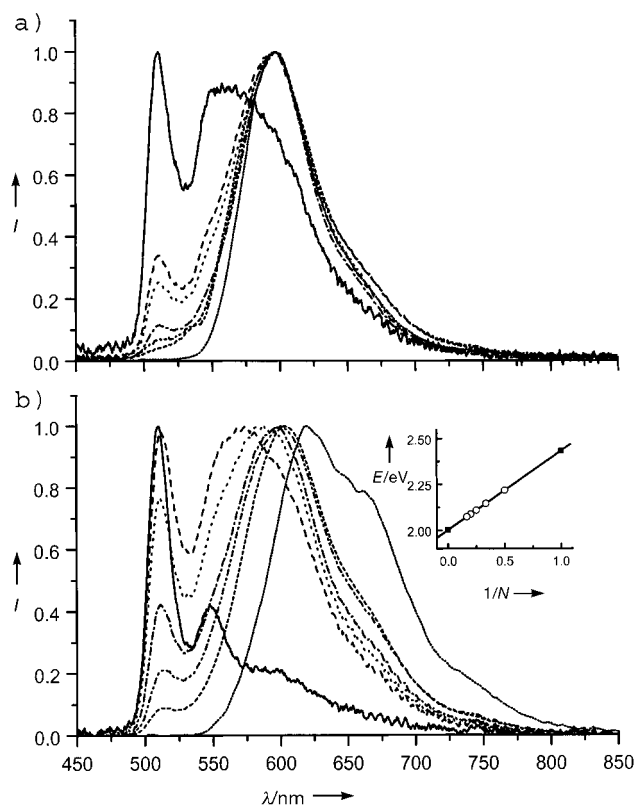


Figure 2. Normalized fluorescence intensities of PS films doped with various concentrations of **8b** [1 % (—), 2 % (---), 5 % (····), 10 % (— · —), 20 % (— — — —), 40 % (— · — · —), 100 % (····)]: a) freshly prepared films, b) films tempered at 280 °C. Inset: plot of E_0 versus $1/N$ (N = number of coronenebis(dicarboximide) mesogens in an aggregate). For $N=1$, the energy of the fluorescence band of shortest wavelength of the smallest concentration (0–0 vibrational transition; 510 nm $\equiv$ 2.43 eV) was used, and for $N=\infty$, the transition energy of the pure **8b** films (620 nm $\equiv$ 2.00 eV) was assumed. The following values were calculated from the linear transformation: $N=2$: 560 nm; $N=3$: 578 nm; $N=4$: 588 nm; $N=5$: 594 nm.

being shifted 25 nm towards red (Figure 2b). The film of pure **8b** fluoresces red.

In the case of the films doped with small concentrations of **8b**, similar observations were also made at lower temperatures; however, much longer tempering times are required

(several hours at 120 °C). In contrast, pure **8b** has to be tempered at temperatures above the transition point in order to obtain a color change. Time-dependent experiments show that the process occurring during tempering at 175 °C advances in a few seconds to such a degree that could be utilized for the fabrication of multicolor pixelated displays. Particularly noteworthy in this context is that, in contrast to other known fluorophores that tend to form aggregates (e.g. quinacridone^[15]), no complete quenching of fluorescence takes place for our compounds; instead, the light output reaches a maximum for the films with 40% **8b**. However, the fluorescence quantum efficiency decreases with increasing concentration (factor of 4 upon going from films with 1% to 4% of **8b**).

For the color shift caused by the tempering process we offer the following interpretation: Spin-coating leads to inhomogeneous polymer films with microdomains in which aggregates of various size (stacks) have formed due to the discotic shape of **8b**. These microdomains cause the broad excimer fluorescence at approximately 590 nm (overlap of various transitions!). Assuming a linear relationship between the energy of the fluorescence transition and $1/N$,^[16] N (the number of molecules in an aggregate) can be estimated from the fluorescence spectrum of the films (details are given in the inset of Figure 2b). Accordingly, the untempered films consist mainly of tetramers. Upon tempering of films with low concentrations (1–2 mass %), the material is better homogenized by additional dissolving of the **8b** molecules in the PS matrix; the number of the aggregates decreases in favor of isolated molecules, and their size also decreases (monomers to trimers are present). In contrast, for higher concentrations larger stacks are formed between the discotic molecules, which emit light of longer wavelengths. The overall largest bathochromic shift occurs upon tempering of the pure coronenebis(dicarboximide) layers, as they are capable of forming very long stacks.

Since the photo- and electroluminescence properties of the title compounds match qualitatively—this will be discussed in detail in a separate publication—the emissions of these aggregates could be utilized for a variety of applications: Selective heating allows the emission color to be controlled locally, so that large areas can easily be colored dot by dot. To create multicolored displays, current investigations focus on the long-term stability of aggregate formation as well as how the choice of substituents R^1 and R^2 can possibly lead to large color changes upon aggregate formation, resulting in a drastic increase in the slope of the $E_{\text{max}} - 1/N$ curve.

Experimental Section

7b: In a carefully dried and argon-purged 500-mL Schlenk flask, **6a** (500 mg, 0.7 mmol) was dissolved in a 1:1 mixture (300 mL) of anhydrous THF and anhydrous Et_3N . To this solution was added 4 mol % $[\text{Pd}(\text{PPh}_3)_4]$ (32 mg, 26 μmol) and 5 mol % CuI (6.5 mg, 34 μmol). After two additional cycles of evacuation and purging with argon, 1-dodecyne (466 mg, 2.80 mmol) was added with a syringe through a septum. This mixture was

stirred for 10–14 h at 80 °C. After the starting material had been consumed (TLC), the mixture was added to an ice/HCl mixture (3/1, three times the reaction volume). The mixture was then extracted several times with CH₂Cl₂. The combined CH₂Cl₂ fractions were dried over MgSO₄, and the solvent was removed by distillation. The residue was purified by chromatography on silica gel with CH₂Cl₂ to yield red **7b** (555 mg, 91 %).

8b: Bis(dicarboximide) **7b** (500 mg) was dissolved in 250 mL of toluene. The mixture was heated to 100 °C and 0.5 mL of DBU added with a syringe through a septum. The reaction mixture was stirred for 8–12 h at 100 °C. For the workup, the mixture was added to ice-cooled, dilute HCl and extracted with CHCl₃. The organic layer was dried over MgSO₄, and the product precipitated from CH₃OH to afford orange **8b** in quantitative yield (500 mg).

Spectroscopic investigations: For the film experiments defined amounts of **8b** along with PS (Aldrich, M_w = 280 000, T_g = 100 °C) were dissolved in CHCl₃ and films prepared from these by spin-coating.

For the fluorescence experiments the samples were excited at 413 nm (ca. 10 mW on an irradiation area of 2 mm in diameter) with a krypton-ion laser. The fluorescence spectra were recorded with a computer-integrated spectrometer card (Ocean Optics, model PC1000) under an angle of 30°. A cut-off filter was used to suppress any scattered light of the excitation laser.

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The Thioesterase of the Erythromycin-Producing Polyketide Synthase: Influence of Acyl Chain Structure on the Mode of Release of Substrate Analogues from the Acyl Enzyme Intermediates**

Kira J. Weissman, Cameron J. Smith, Ulf Hanefeld, Ranjana Aggarwal, Matthew Bycroft, James Staunton,* and Peter F. Leadlay

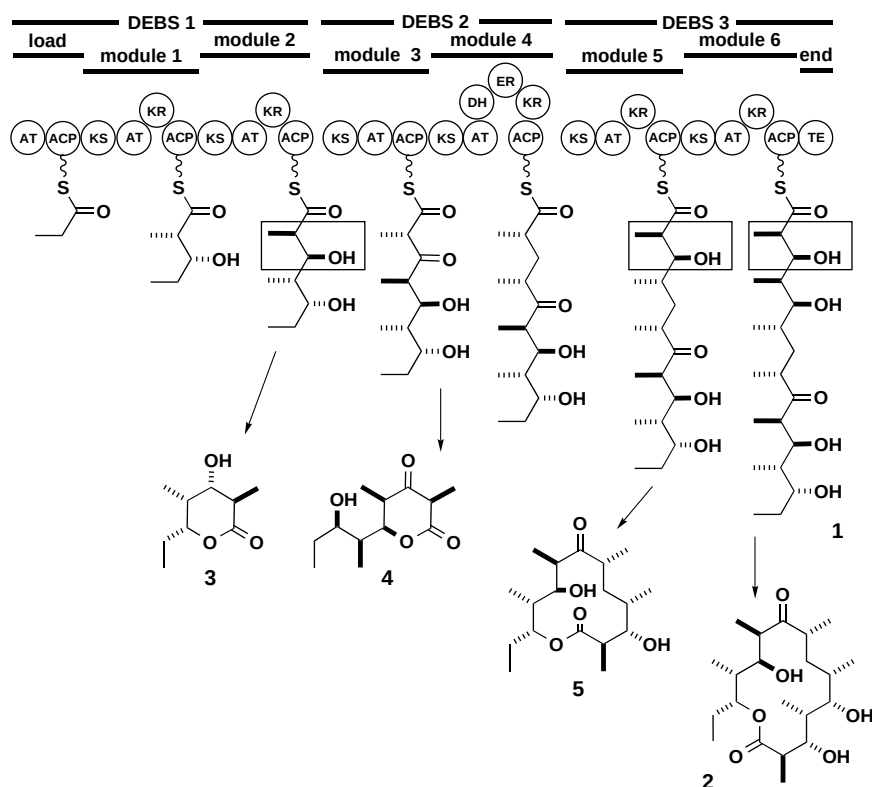
The polyketide core of the antibiotic erythromycin A is assembled by a polyketide synthase (PKS) from seven C₃ units.^[1] The units are condensed to form a putative enzyme-bound heptaketide product **1**, which is then released through cyclization to the macrolactone, 6-deoxyerythronolide B (**2**) (Scheme 1). The PKS contains a separate catalytic domain for each step in the formation of **2**, housed in three gigantic multifunctional proteins, DEBS 1–3. The ordering of the domains can be analyzed in terms of six chain-extension modules, fronted by a loading domain for the starter acyl group, and terminated by an off-loading thioesterase (TE) responsible for release of the completed product.^[2]

A pivotal step in this biosynthetic scheme is the thioesterase-catalyzed cyclization of the heptaketide **1** to form the macrolide ring **2**. Early in vitro studies with simple substrate

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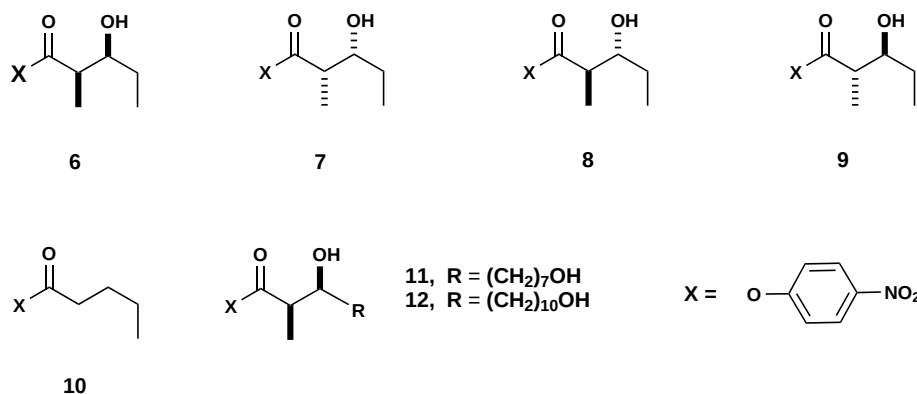
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Scheme 1. Genetic engineering of the erythromycin PKS.

analogues and a purified extract of the bidomain ACP-TE derived from the end of DEBS 3 demonstrated that the first step in acyl ester cleavage involves transfer of the acyl chain to the active-site serine hydroxyl of the TE domain to form an acyl enzyme intermediate.^[3] In the natural system this intermediate is then cleaved by nucleophilic attack of the C-13 hydroxyl group to release the macrocyclic lactone. For this reaction to occur, not only must the thioesterase recognize and position the C-13 hydroxyl for attack on the acyl enzyme intermediate, but the alternative hydrolytic mechanisms of release characteristic of many esterases must also be suppressed.

The TE domain has been repositioned by genetic engineering to cause premature release of the ketide chain at the triketide **3**, tetraketide **4**, and hexaketide stages **5** (Scheme 1).^[4] Structurally modified versions of these products have also been produced by further genetic engineering of the PKS.^[5] The success of this approach for the production of polyketides critically depends on the availability of a thioesterase capable of off-loading and/or cyclizing each novel substrate with nucleophiles that are present in vivo. Knowledge of which structural features facilitate or prevent product release by the erythromycin TE would increase the success rate of future genetic engineering by allowing designers to avoid negative results caused by the inability of the thioesterase to release a target product from the PKS.



With the exception of tetraketide **4**, all of the published novel products whose release has been catalyzed in vivo by the erythromycin TE have the natural (2*R*,3*S*)-2-methyl-3-hydroxyl substitution pattern adjacent to the acyl terminus. No conclusions can therefore be drawn concerning the importance of structure and stereochemistry at these two potentially crucial positions.^[4] The most direct way to gain information on these key questions of substrate specificity is to carry out experiments with synthetic analogues in vitro. In this study we selected the four diastereoisomers **6–9** of the putative diketide intermediate to investigate whether stereochemical variation at the C-2 and C-3 positions might be a barrier to the release of novel substrates from the DEBS in vivo. To determine the effect of functionality at these key positions, turnover results with compounds **6–9** were compared to those of **10**, an unfunctionalized diketide analogue of the same chain length. Other structural analogues (**11** and

12) with longer chains and distal hydroxyl groups capable of participating in the formation of lactone rings were also tested.

As before, the experiments were conducted in vitro with a truncated version of the DEBS 3 protein, consisting of the C-terminal bidomain, an acyl-carrier protein plus the thioesterase (ACP-TE), or the thioesterase alone, which were over-expressed in *Escherichia coli*.^[3, 6] In this host, the acyl-carrier protein was not modified by post-translational addition of a phosphopantetheine residue, but the ability of the neighboring TE domain to function independently as a thioesterase in vitro was not affected by this deficiency. The substrates were derivatized as their *p*-nitrophenyl esters to allow convenient UV monitoring of reaction rates. Although *N*-acetylcysteamine thioesters are formally a better mimic of the natural derivative on the acyl carrier protein,^[7] *p*-nitrophenyl derivatives were found in initial experiments to react more quickly,

without significantly altering the observed trends of relative reactivity for different acyl chains.^[3]

Initially the substrates **6–10** were incubated under standard conditions with ACP-TE at pH 7.4 in an aqueous phosphate buffer containing 1% (v/v) of acetonitrile to aid substrate solubility (Table 1). The rates of ester cleavage were monitored at 400 nm (λ_{max} for the phenolate anion) and calculated

Table 1. Rate of release of *p*-nitrophenolate anion catalyzed by the erythromycin thioesterase.^[a]

Substrate	ν [nmol min ⁻¹]		Increase with EtOH [%]	Normalized increase [%] ^[b]
	with MeCN	with EtOH		
6	1.05	3.50	233	75.4×10^3
7	1.75	4.55	160	51.8×10^3
8	1.40	2.10	50	16.2×10^3
9	1.75	9.45	440	14.2×10^4
10	6.88	15.1	119	38.5×10^3

[a] Measured at 37°C for the appearance of *p*-nitrophenolate anion (λ_{max} 400 nm) after the reaction had reached the initial linear phase; substrate concentration, 800 μM ; enzyme concentration 1.31 μM ; potassium phosphate (200 mM) and Tris (2.5 mM) buffer containing EDTA (50 μM) at pH 7.4. [b] With allowance for relative molarities of water and ethanol.

from the initial linear portion of the curves. In all cases, the rates were corrected for the background rate of chemical hydrolysis in the absence of enzyme.

Although the TE released all four C-2, C-3 functionalized diketides by hydrolysis, the rates of reaction were markedly reduced relative to the unfunctionalized substrate **10** (Table 1); analogue **6**, which has the same relative configuration at the acyl terminus as the natural substrate **1**, had the lowest rate of hydrolysis. These results indicate that the erythromycin TE is optimized, through the recognition of functionality and stereochemistry at the acyl terminus of its substrates, to avoid wasteful hydrolytic release of acyl enzyme intermediates. This optimization is greatest when the C-2 methyl, C-3 hydroxyl stereochemistry of a substrate is in the natural 2*R*,3*S* configuration. However, hydrolytic release was also significantly suppressed for compounds incorporating the three unnatural configurations at these positions. It is therefore likely that macrolactones with altered stereochemistry at C-2 and C-3 can be obtained by genetic engineering.

Macrolactonization depends not only on the suppression of hydrolytic release, but on the formation of an ester bond. As the TE has been shown to favor ethanol over water as the nucleophile for the deacylation step,^[3] it was of interest to see whether this preference could be used to increase the turnover of the C-2, C-3 functionalized substrates. Evidence for the formation of esters over free carboxylic acids would further support the case that the TE is optimized for macrolactonization. The substrates **6–10** were therefore incubated as above, but with 1% (v/v) ethanol, and again the reaction rates were monitored by UV and corrected for background chemical turnover. Addition of only 1% (ca. 1:300 molar) ethanol greatly enhanced the rates of enzyme-catalyzed turnover of three of the four functionalized diketides relative to the unfunctionalized analogue (Table 1). This preference is particularly evident when the rates of

reaction are calculated in terms of moles of nucleophile (water or ethanol) present in the medium. Interestingly, the best substrate was not **6**, the stereochemical mimic of the natural substrate **1**, but **9** (7.70 nmol min⁻¹), which has the same configuration at C-3 but the opposite at C-2. Compound **6** reacted at a medium rate (2.45 nmol min⁻¹), as did its enantiomer **7** (2.80 nmol min⁻¹). The substrate with the lowest turnover (**8**, 0.70 nmol min⁻¹) is the enantiomer of **9**, the best substrate. The important conclusion is that all four stereoisomers are effective substrates and stereochemical variation of the methyl group at C-2, or the hydroxyl group at C-3, is no barrier to product release in vivo as a macrolactone given a suitable distal carbinol center.

In order to confirm that ethanol was being used by the TE in preference to water, the assays with ethanol were performed on a larger scale, and the products analyzed by ¹H NMR (for turnover), and by methylation followed by gas chromatography (for partitioning between diketide acid and ethyl ester). By GC analysis, the ethyl ester analogues were formed in all four enzyme reactions with the diketide stereoisomers, but no such products were generated in the control reactions in the absence of the TE. When allowance was made for the amount of hydrolysis in control reactions, it was again clear that ethanolysis was the preferred mechanism of release in all cases. As in the UV assays, the highest turnover was observed for substrate **9** ($51.6 \pm 0.6\%$ in 1 h under standard conditions), medium rates for compounds **6** and **7** ($22 \pm 1\%$ and $19 \pm 1\%$ respectively), and a low turnover for analogue **8** ($5 \pm 2\%$).

To address the esterase's preference for ethanol on a mechanistic level, we monitored the thioesterase by electrospray mass spectrometry (ESMS) during its reaction with analogue **9** in the presence of added ethanol or acetonitrile (9% v/v). Although it was not possible to analyze the protein under the original assay conditions, the relative substrate and enzyme concentrations were maintained in order to permit comparison. Spectra were transformed to produce single peaks with *m/z* values corresponding to singly charged ions. After five minutes of incubation, only a single peak consistent with the ACP-TE acylated by the acyl group of the substrate was observed, with or without ethanol present. As formation of the acyl enzyme intermediate is obviously not a barrier to turnover in the case of C-2, C-3 functionalized substrates, deacylation must be the rate-limiting step. It seems likely that recognition of functionality and/or stereochemistry at the C-2 and C-3 positions causes the TE enzyme to contract around the acylated substrates, excluding water from the active site and preventing the hydrolytic release seen in earlier work with simpler substrates.^[3] Presumably ethanol occupies the site normally filled by the carbinol alcohol, and is not similarly excluded.

It was also of interest to see if macrolactonization might be the favored method of release over ethanolysis given a suitable distal hydroxyl group in the substrate. We therefore investigated two compounds (**11** and **12**) with the natural (2*R*,3*S*)-2-methyl-3-hydroxyl substitution pattern and an additional ω -hydroxyl functionality to enable lactonization. By ¹H NMR spectroscopy, the longer chain compound **12** was not converted into product at a measurable rate. The shorter

analogue **11** did react satisfactorily under standard conditions. The principal mechanism of release was again ethanolysis (>95%), while hydrolysis accounted for the remainder of product turnover. A further attempt to encourage lactonization by substituting acetonitrile for ethanol gave less than 0.1% lactone or free acid; as the acyl enzyme intermediate was detected by ESMS for both substrates **11** and **12** under these conditions, the barrier to release of the products must lie in the deacylation step. The absence of lactone in these experiments shows that in vivo suppression of hydrolysis is not sufficient to ensure macrolactonization, and that additional structural features of the chain in the natural substrate **1** are required to ensure that the TE domain folds correctly.

The results imply that intermediates with 2-methyl, 3-hydroxyl functionality in any stereochemical configuration may be released by lactonization given an appropriately placed and structurally suitable distal hydroxyl group. However, if lactonization is prevented by the absence of a suitable hydroxyl group or other cause, such acyl enzyme intermediates would not be rapidly cleaved by the alternative in vivo mechanism of hydrolysis. The relative inefficiency of hydrolytic release with these substituted analogues is a potentially serious limitation to the range of novel products that are expected to be released in vivo by the erythromycin thioesterase.

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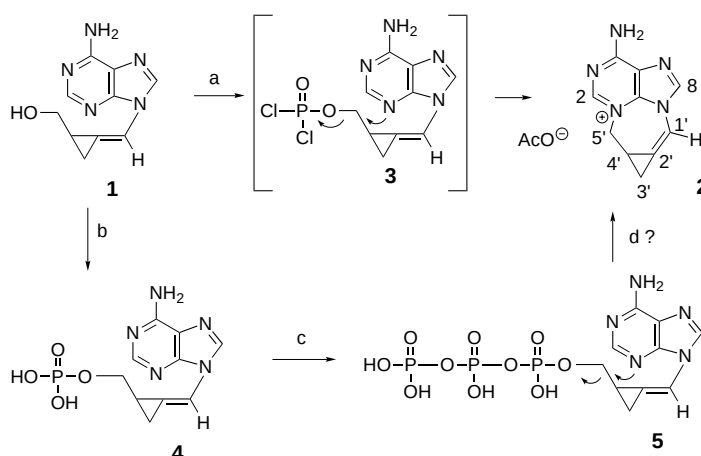
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3,5'-Anhydrosynadenol: A Polycyclic Anhydronucleoside Analogue**

Yao-Ling Qiu and Jiri Zemlicka*

Recently we reported new nucleoside analogues that exhibit broad-spectrum antiviral activity and contain a methylenecyclopropane unit.^[1–2] Of these compounds, (Z)-9-[(2-hydroxymethyl)cyclopropylidenemethyl]adenine (synadenol; **1**) exhibits potent activity^[1] against human and murine cytomegalovirus (HCMV and MCMV), Epstein–Barr virus (EBV), human herpes virus 6 (HHV 6), and hepatitis B virus (HBV), and a moderate effect against human immunodeficiency virus 1 (HIV-1). The ¹H NMR spectra and biological activity indicated that **1** and related compounds can be regarded as analogues of nucleosides. Like nucleosides, the base (adenine) can exist in two conformations, *anti* and *syn*.^[3] The ¹H NMR spectra indicated that the adenine component of **1** has mainly the *anti* conformation in solution, as in nucleosides.^[1]

Here we report that the *syn* form of **1** can be converted into the anhydronucleoside analogue **2**; this strengthens the analogy to nucleosides.^[4] Reaction of **1** with POCl₃/PO(OMe)₃ led to a smooth cyclization and gave anhydrosynadenol (**2**), which was isolated as the acetate in 87% yield (Scheme 1). The dichlorophosphate **3** is a likely intermediate in this transformation. In nucleosides this reaction leads only to 5'-O-phosphorylation without formation of anhydronucleoside.^[5,6] Trisimidazolylphosphine oxide^[7] in pyridine also gave **2** as the sole product. The ease of cyclization is surprising given that methylenecyclopropanes are generally assumed to be destabilized by substantial ring strain.^[8] However, according to recent ab initio calculations,^[9] the loss of strong



Scheme 1. a) POCl₃, PO(OMe)₃; b) Dowex 2 (AcO⁻); c) intracellular phosphorylation; d) intracellular inactivation.

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cyclopropane C–H bonds associated with the introduction of a trigonal center is largely responsible for destabilization of the molecule. The formation of **2** may be facilitated by an entropic factor (juxtaposition of the 5'-CH₂ group with the heterocyclic base in **1** owing to the presence of a rigid methylenecyclopropane system) and by incorporation of the methylenecyclopropane moiety into a multiring system.

The reaction of **1** with less reactive phosphorylating agents, such as chlorophosphoramidates,^[10] leads to 5'-*O*-phosphorylation products without formation of **2**. There is also evidence^[11] that intracellular phosphorylation of **1** forms the phosphates **4** and **5** necessary for antiviral activity (Scheme 1). Like other nucleoside analogues, **1** is thus a prodrug of the corresponding triphosphate **5**, which is the final product of the phosphorylation cascade. Anhydrosynadenol (**2**) lacks two features important for the biological activity per se: 1) the 5'-hydroxyl group necessary for phosphorylation and 2) the *anti* conformation of the base as in **1**. The triphosphate group of **5** is a better leaving group than the monophosphate residue of **4**. Nucleophilic displacement of this functional group in ATP is an important feature of some enzyme-catalyzed transformations.^[12] Whether a similar intramolecular reaction (Scheme 1) can play a role in the inactivation of **5** remains to be established.

The ¹H NMR spectrum of **2** exhibits a strong downfield shift of the signals of all cyclopropane protons. The H-5' protons are nonequivalent; one of them is strongly shielded. Models indicate that this shielding is possibly due to the double bond of the methylenecyclopropane unit in an *exo* conformer^[13] of **2**. The formation of **2** is unambiguous proof of the *Z* configuration of **1**. This configuration is important for the antiviral activity of **1** and its analogues.^[1, 2] In addition, the structure of **2** is a novel polycyclic system containing a methylenecyclopropane moiety.

Experimental Section

2: POCl₃ (86 µL, 0.92 mmol) was added to a suspension of **1** (100 mg, 0.46 mmol) in PO(OMe)₃ (16 mL) with stirring at 0°C. The clear solution was allowed to stand for 19 h at room temperature, and the solvent was then removed in vacuo (bath temperature <47°C). The sirupy residue solidified after addition of THF (20 mL) and sonication. The solvent was decanted to leave a hygroscopic solid, which was washed with THF (5 mL) and dissolved in water (50 mL). The aqueous phase was washed with CH₂Cl₂ (5 × 20 mL) and then lyophilized. The residue was stirred with Dowex 2 (X-8, 100–200 mesh, acetate, 7 g) in water (20 mL) for 0.5 h. Filtration and lyophilization of the filtrate gave **2** (112 mg, 87 %), m.p. > 300°C. Paper electrophoresis (Whatman No. 1 paper, 0.02 M Na₂HPO₄, pH 7.0, 40 V cm⁻¹, 1 h): Mobility –1.33 of AMP, identical with that of 2',3'-*O*-isopropylidene-3,5'-anhydroadenosine.^[14] UV (ethanol): λ_{max} (ε) = 274 (16700), 238 (14100); (H₂O, pH 7): 272 (16400), 240 (13400). ¹H NMR (D₂O): δ = 8.47, 8.37 (2s, 2H, H-2, H-8), 7.47 (s, 1H, H-1'), 5.05 (dd, 1H) and 3.60 (dd, 1H, H-5'), 2.50 (q, 1H), 2.38–2.50 (m, 1H) and 1.82 (dd, 1H, H-3', H-4'); ¹³C NMR: δ = 181.05 (CO), 157.16, 148.88, 141.86, 138.74, 124.30, 120.22, 115.22 (adenine, C-1' and C-2'), 58.05 (C-5'), 23.16 (CH₃), 15.89 (C-4'), 14.24 (C-3'). FAB-MS (thioglycerol matrix): *m/z* (%): 308 [M+H – AcOH+thioglycerol] (100), 260 [M+H] (22), 200 [M+H – AcOH] (41.0), 136 [adenine+H] (59.5); elemental analysis calcd for C₁₀H₉N₅·0.95CH₃CO₂H·1.35H₂O: C 50.94, H 5.57, N 24.96; found: C 50.67, H 5.37, N 25.24.

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Perchloropolysilane: X-Ray Structure, Solid-State ²⁹Si NMR Spectroscopy, and Reactions of [SiCl₂]_n**

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We have succeeded in the preparation of perchloropolysilane, [SiCl₂]_n (**1**) as very pale yellow, highly moisture-sensitive single crystals and obtained the X-ray structure. This is the first example of a single crystal X-ray structure analysis of a polysilane. We also report solid-state ²⁹Si NMR data.^[1]

Since the investigations by Schwarz and co-workers^[2a, b] of the higher silicon halides (described as viscous liquids or

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glassy solids), there have been few reports in this area, save for discussions^[2c, 3, 4] on the small cyclic species $[\text{SiCl}_2]_n$ where $n = 4, 5$, and 6. Continuing our investigations^[5] of cyclic and linear polysilanes, we sublimed Si_4Cl_8 ^[2c] and obtained crystals of **1** in yields of about 27% upon condensation onto a cold finger (-10°C). This phenomenon was apparently not observed during the purification of Si_4Cl_8 by sublimation described in earlier reports.^[2c] We postulate that **1** is formed by the ring-opening of Si_4Cl_8 molecules after sublimation to give diradical species which could couple by radical recombination to yield the observed linear perchloropolysilane.

The X-ray data for the structure analysis of **1** was collected at -140°C with a charge-coupled device (CCD) area detector, which enabled rapid analysis (ca. 12 h); speed is important because of the great sensitivity of **1** towards moisture (many attempts were required to find a crystal that diffracted satisfactorily). The final R value (18%) is high and reflects the poor sample quality by crystallographic standards. This poor crystallinity, which may be due to hydrolysis, chain length inhomogeneity, or the presence of terminal groups, is revealed by very broad peak profiles of 3–8 degrees. Such broad peaks could not have been measured on routine instruments with point detectors, but required an area detector to collect the intensity data. Nevertheless, a chemically reasonable structure solution could be refined and produced the arrangement of atoms shown in Figure 1.^[6]

The polysilane **1** consists of infinite parallel-aligned all-*trans* chains of SiCl_2 repeat units. It is interesting that the Si–Si bond length (2.414(8) Å) is unusually long (typical value 2.34 Å) and even longer than that in the strained precursor to **1**, Si_4Cl_8 (2.372(2) Å).^[5] The Si–Si–Si and Cl–Si–Cl angles (114.4(6) and 111.0(4)°, respectively) are both slightly larger than the ideal tetrahedral angle.

The polymer is virtually insoluble in all solvents, but is nevertheless chemically reactive, and substitution of the Cl atoms by nucleophiles is possible. In the presence of excess 2-propanol, the diisopropoxypolysilane (**2**)^[7] is formed as a

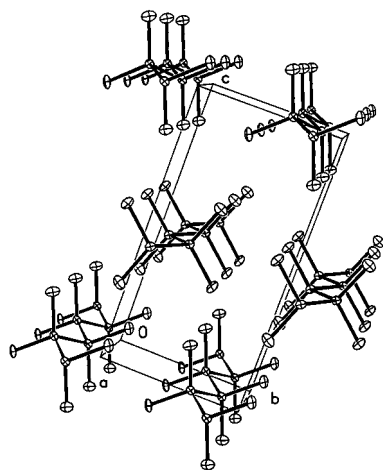


Figure 1. Unit cell and molecular structure of $[\text{SiCl}_2]_n$ **1** in the crystal (50% probability displacement ellipsoids). Selected interatomic distances (Å) and angles (°): Si(1)–Cl(1) 2.120(9), Si(1)–Cl(2) 2.088(9), Si(1)–Si(1)^a 2.414(8), Si(1)–Si(1)^b 2.414(7), Si(1)^a–Si(1)–Si(1)^b 114.4(6), Cl(1)–Si(1)–Cl(2) 111.0(4). a and b indicate symmetrically equivalent atoms generated by the symmetry transformations $x - 0.5$, $-y + 0.5$, $-z + 1$, and $x + 0.5$, $-y + 0.5$, $-z + 1$.

white powder. Size exclusion chromatography indicated a degree of polymerization (DP) for **2** of about 35. This may be taken as an approximate guide to the DP of **1**, and hence the average molecular weight of **1** may be estimated as approximately 3500. Exposure of **1** to moist air resulted in the evolution of HCl gas and a color change of the solid from off-white to bright yellow. Infrared analysis of this material indicated both Si–OH (3400 cm^{-1}) and Si–OSi (1016 cm^{-1}) moieties. Exposure for a further 24 h afforded a very pale yellow material, analysis of which showed a decrease in the Si–OH absorption and an increase in the Si–OSi peak. This indicates the formation, initially, of a partially hydroxy-substituted polysilane (bright yellow), which becomes gradually cross-linked to give a network-type, polysiloxy-cross-linked polysilane (pale yellow). The polysilane **1** also reacts with dialkylamines and amide salts to yield low molecular weight aminopolysilanes.

It seems evident that **1** will prove to be a valuable synthon for the preparation of new kinds of polysilanes that cannot be synthesized by current methods. Further work to clarify the mechanism of formation and chemistry of this unique compound is underway.

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