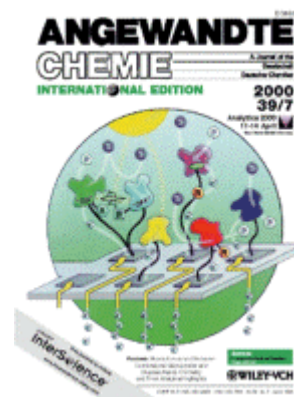


Cover Picture

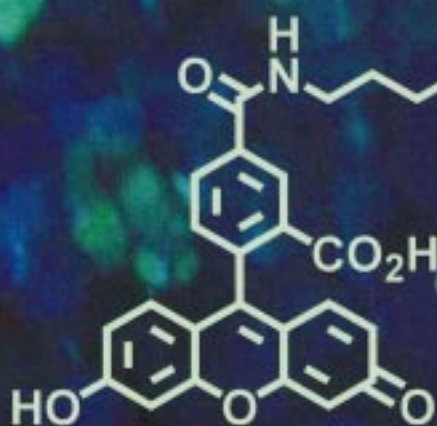
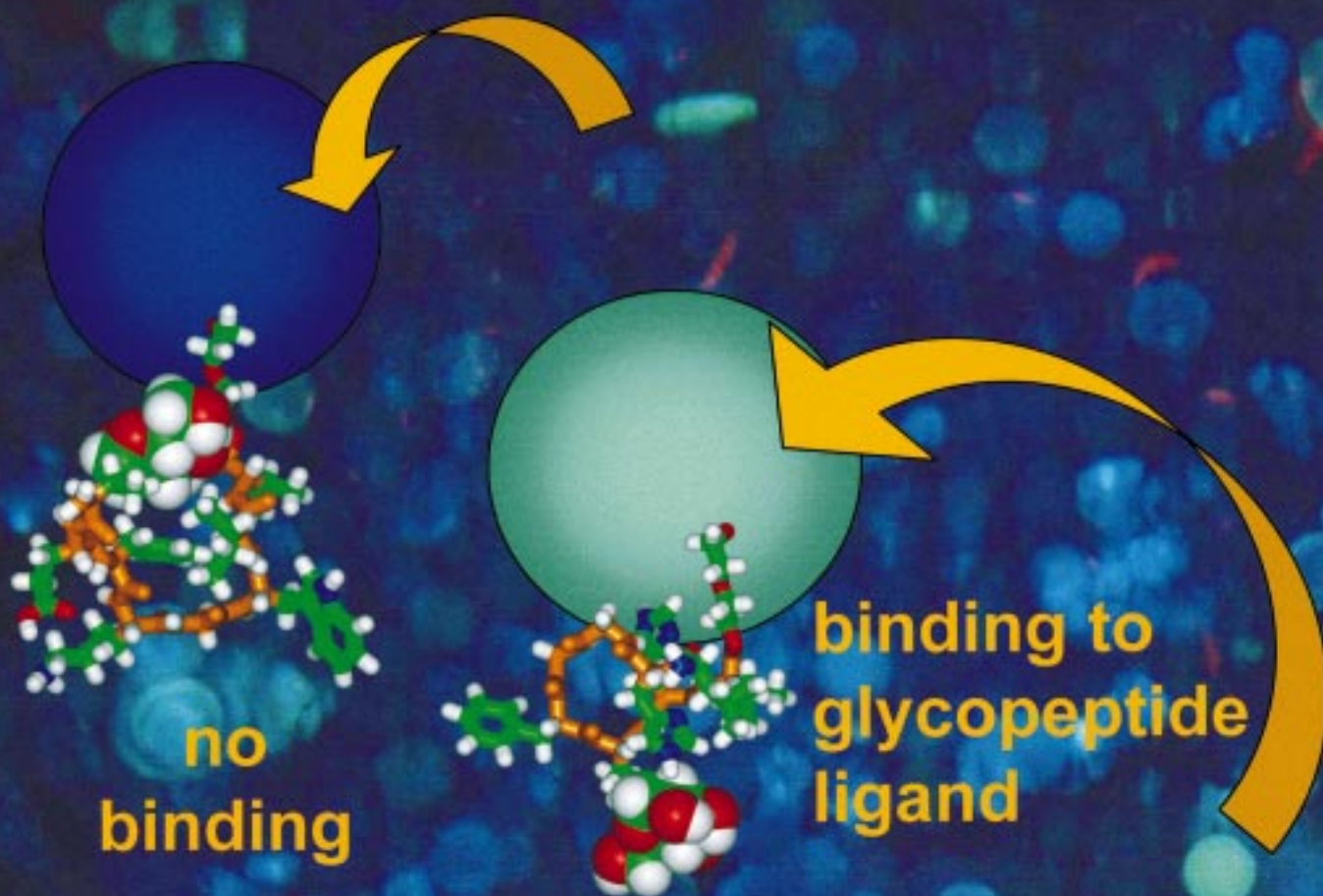
Itamar Willner, Dr. Eugenii Katz

The cover picture shows schematically the elements of the rapidly developing research fields of bioelectronics and optobioelectronics. Immobilization of redox enzymes as monolayers or thin films on conductive supports yields functionalized biocatalytic electrodes. The formation of electrical contact between the redox center of the enzyme and the electrode surface, which is possible in various ways, provides a means of assembling integrated enzyme electrodes for bioelectronic applications. Photoswitchable redox proteins assembled on electrode surfaces form the basis of optobioelectronic devices. A further element of bioelectronic and optobioelectronic systems is the possibility for the microscale patterning of biomaterials onto the solid supports—through photolithography, micromachining, and stamping. More on the different aspects of bioelectronics and optobioelectronics can be found in the review by I. Willner and E. Katz on page 14;1180 14;ff.



Oligosaccharide Mimetic Libraries

ANGEWANDTE
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Fluorescein-
labeled lectin

Glycopeptide and Oligosaccharide Libraries

Phaedria M. St. Hilaire and Morten Meldal*

Despite the burgeoning interest in the various biological functions and consequent therapeutic potential of the vast number of oligosaccharides found in nature on glycoproteins and cell surfaces, the development of combinatorial carbohydrate chemistry has not progressed as rapidly as expected. The reason for this imbalance is rooted in the difficulty of oligosaccharide assembly and analysis that renders synthesis a rather cumbersome endeavor. Parallel approaches that generate series of analogous compounds rather than real libraries have therefore typically been used. Since generally low affinity is obtained for interactions between carbohydrate receptors and modified oli-

gosaccharides designed as mimetics of natural carbohydrate ligands, glycopeptides have been explored as alternative mimics. Glycopeptides have been proven in many cases to be superior ligands with higher affinity for a receptor than the natural carbohydrate ligand. High-affinity glycopeptide ligands have been found for several types of receptors including the E-, P-, and L-selectins, toxins, glycohydrolases, bacterial adhesins, and the mannose-6-phosphate receptor. Furthermore, the assembly of glycopeptides is considerably more facile than that of oligosaccharides and the process can be adapted to combinatorial synthesis with either glycosylated amino acid

building blocks or by direct glycosylation of peptide templates. The application of the split and combine approach using ladder synthesis has allowed the generation of very large numbers of compounds which could be analyzed and screened for binding of receptors on solid phase. This powerful technique can be used generally for the identification and analysis of the complex interaction between the carbohydrates and their receptors.

Keywords: Combinatorial chemistry • Oligosaccharides • Carbohydrates • Glycopeptides • Receptors

1. Parallel Arrays versus Libraries of Compounds

Combinatorial methodology has been a driving impetus in many areas of research and has gained considerable ground since its introduction at the turn of last decade. This progress, however, has not been reflected in the field of oligosaccharides, primarily due to difficulty in their synthesis and analysis. As an alternative, the readily available glycopeptide libraries have been exploited as potential functional mimics of oligosaccharides. These libraries can be essential tools in the development of carbohydrate-based therapeutics such as tumor vaccines,^[1] xenotransplantation aids, and anti-infectives. A few reviews have recently briefly described carbohydrate-based combinatorial libraries and parallel syntheses.^[2–9]

Here, we present a comprehensive overview of the many aspects required for the design, synthesis, analysis, and screening of solution and solid-phase carbohydrate-based

libraries. In this review, combinatorial libraries have been defined as assemblies of compounds, which are derived through a real combinatorial step leading to exponentially increasing numbers of products relative to the number of reagents used (Figure 1a). This staggering increase in products may be achieved either by mixing reagents to form product mixtures or by introducing mixing of intermediates in solution or compartmentalized on solid phase, for example, by the split and combine approach. Due to the ease with which this process is carried out on solid phase, the potential of solid-phase libraries by far exceeds solution libraries and thus, emphasis is placed on solid-phase libraries in the present review. Combinatorial methods which have only been demonstrated by synthesis of libraries containing a few compounds, but with the potential of generating large numbers of structures are considered. Indeed, the very fact that there are few examples of truly combinatorial oligosaccharide libraries, underscores the great challenge faced by researchers in this field.

Parallel syntheses are also described, particularly in cases where the strategy employed can be extrapolated to create a true library or where interesting biological results have been obtained. It must be noted however, that these are considered to be extensions of conventional synthesis of analogues and

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not libraries since they do not easily give rise to a very large number of compounds, that is, they do not take advantage of combinatorial exponential increase in numbers of products (Figure 1 b).

2. Carbohydrate-Binding Proteins

Carbohydrate-binding proteins (CBP's) located in cellular membranes or recirculating in the cytosol or serum are involved in a variety of important biological functions including communication and intercellular adhesion, adhesion of bacteria or viruses, activation of the innate immune system, leukocyte rolling, hepatic clearing of aged serum proteins, and sorting of newly synthesized glycoproteins.^[10, 11] Based on their mode of binding, mammalian CBP's have been divided into three major groups: the C-type, the S-type, and the P-type lectins.^[12]

The calcium-dependent C-type lectins include the E-, L-, and P-selectins while the galectins are calcium-independent S-type lectins. The latter have a binding site sized for tight interaction with di- or trisaccharides. The former bind their ligands mainly through coordination of two vicinal hydroxyl groups of a single sugar moiety to a bound calcium ion in the carbohydrate recognition domain (CRD) and the surrounding sugars of the oligosaccharide ligand add to the binding specificity through relatively weak additional interactions. Due to the simple nature of this interaction, the specificity of selectin binding is quite broad and can be mimicked by simple

monosaccharide-bearing compounds.^[13, 14] However, the biological activity of ligands is structure dependent and complicated by a range of factors such as multivalency and clustering.^[15, 16]

The calcium-independent receptors of the P-type involved in the clearing and sorting of glycoproteins include the mannose 6-phosphate receptors,^[17] the hepatic Gal/GalNAc receptors,^[18] and the Man/GlcNAc receptors isolated from liver extracts.^[19] These receptors are truly multivalent and bind to the termini of bi-, tri- or tetraantennary N-linked oligosaccharides. Although most known receptors recognize Gal/GalNAc or Man/GlcNAc, there are also receptors, such as the macrophage sialic acid receptor, for the recognition of sialylated complex glycans.^[20]

The collectins, mostly involved in the innate immune system,^[21] are large surface or serum proteins composed of bundles of structural collagen stalks with trimer heads containing a calcium-dependent CRD's and may be considered C-type by structural similarity. Their binding to simple mannose oligosaccharides is relatively weak and activation of the complement cascade is only effected when the protein interacts multivalently with large polymannans on foreign cell surfaces creating an activation template for complement-processing enzymes.^[22] Due to the unspecific nature of this multivalent interaction and the long distance between the sites of interaction (53 Å),^[23] multivalent synthetic ligands for these proteins are difficult to design and prepare. However, each CRD may be targeted with high-affinity monovalent ligands.

Phaedria M. St. Hilaire was born in Dominica in the Eastern Caribbean and received her B.Sc. in Chemistry from the University of South Carolina where she was a Presidential Scholar. As a Fellow of the Integrated Toxicology Program she obtained her Ph.D. in Organic Chemistry from Duke University in 1995 where, under the supervision of Dr. Eric Toone, she characterized the interaction of the Shiga-like toxin with its carbohydrate receptor. An interest in carbohydrate-mediated interactions led to a postdoctoral position at the Carlsberg Laboratory where she has developed methods for the synthesis and analysis of glycopeptide libraries. In 1997, she became a Research Associate and her current research interests include the use of combinatorial libraries to study protein-carbohydrate interactions and to develop novel, specific, protease inhibitors. She also examines fundamental processes related to the solid-phase screening process.



P. M. St. Hilaire



M. Meldal

Morten Meldal was born in Denmark in 1954 and is a Senior Scientist heading the Synthesis Group at the Carlsberg Laboratory and also an Adjunct Professor at the Danish Technical University. He directs the combinatorial chemistry research at the SPOCC Center, hosted at the Carlsberg Laboratory. He received the 1990 Danish Chemistry Award, the 1996 NKT Research Award for Chemistry, the 1996 Leonidas Zervas Award, and the 1997 Ellen and Niels Bjerrum Gold Medal in Chemistry. He has over 190 publications and reviews in international journals and has filed 10 patents. His research interests include: solid-phase organic combinatorial chemistry, polymer chemistry, peptide and glycopeptide synthesis, glycobiology and molecular immunology, methodology and automation, and enzymology and enzyme inhibition. He is well-known for the development of novel PEG-based supports suitable for both solid-phase synthesis and screening, and for novel solid-phase assays based on FRET which are used for the determination of enzyme activity and inhibition.

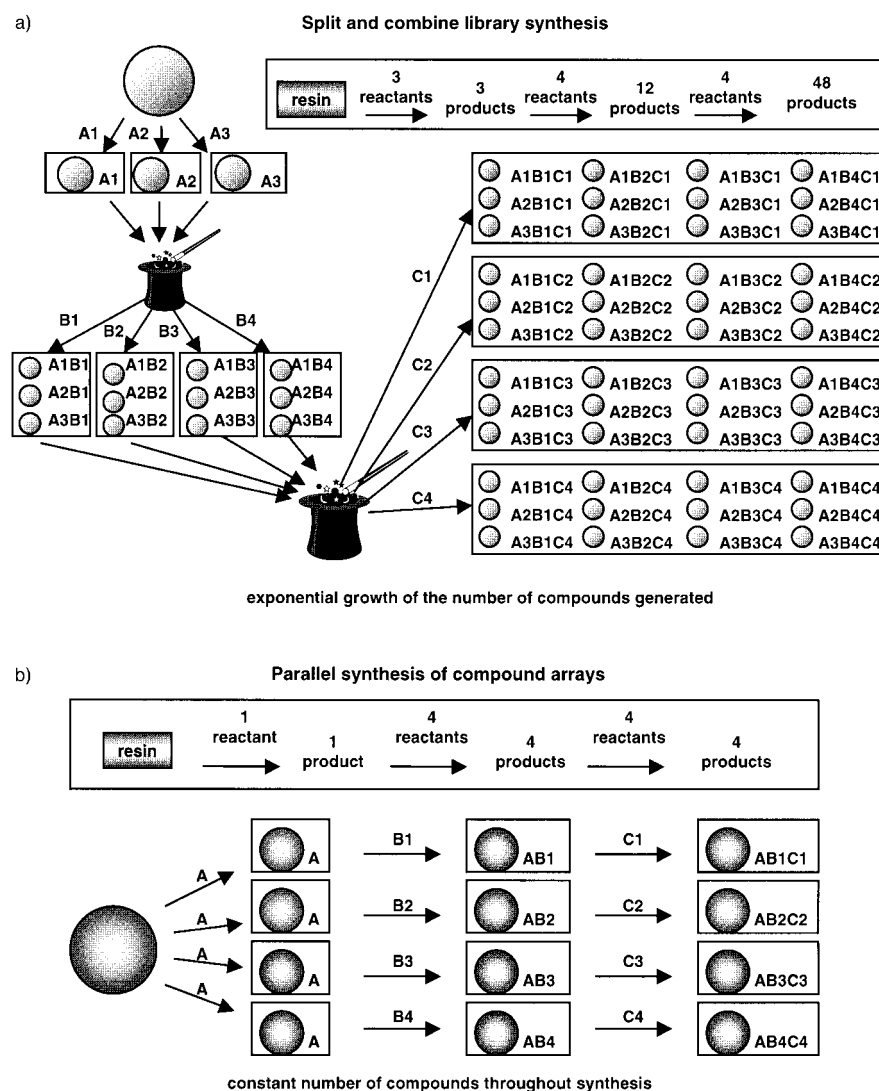


Figure 1. The conceptual difference between the synthesis of a combinatorial library with exponential increase in number of compounds (a) and the syntheses of parallel arrays of discrete compounds (b).

3. The Carbohydrate Ligands

Mammalian glycoproteins consist of 5–90% of glycan structures and these fall in several major groups. There are the N-glycosylations including high-mannose, complex, and hybrid oligosaccharides, and O-glycosylations including the mucins, the blood group determinants, and the proteoglycans (Figure 2).

Glycolipids comprise another group of oligosaccharide-signaling molecules. The high-mannose oligosaccharides are based on 1→2- α -mannosylation of the mannose pentasaccharide core, α -D-Man-(1→3)-[α -D-Man-(1→3)-[α -D-Man-(1→6)-] α -D-Man-(1→6)-] β -D-Man-(1→4)- β -D-GlcNAc-(1→4)- β -D-GlcNAc-(1→N), and these oligosaccharides exist as a mixture of conformational populations around the 1→6 bonds (Figure 3). Any of these conformers may be the active one in contact with a receptor.

The complex antennary glycans are structures obtained by attachment of β -(1→4)-linked lactosamine units to the 2, 4, and 6 positions of terminal mannoses in a α -D-Man-(1→3)-[α -D-Man-(1→6)-] β -D-Man-(1→4)- β -D-GlcNAc-(1→4)- β -D-

GlcNAc-(1→N) core. The terminal galactoses are often sialylated at the 3 or 6 position.

The tetraantennary oligosaccharide shown in Figure 2 has been shown to present an umbrellalike structure as one of the major conformational populations.^[24, 25] The distance between terminal sugar residues interacting with receptors may vary from approximately 8–30 Å. In the case of the phosphorylated high-mannose ligands for the mannose 6-phosphate receptor (MPR) the distance between phosphates is about 15 Å.^[26]

The mucin oligosaccharides do not appear to have many mammalian receptors. However, bacteria in the gastrointestinal tracts often display receptors that adhere to the mucin-coated epithelia.^[27] Recognition of the aberrantly glycosylated forms present in malignant tissue is essential for the rejection of tumors by the immune system.^[28–30] The most thoroughly investigated ligands are analogues of the SLe^x antigen^[13, 31] involved in leukocyte rolling, adhesion, and shedding by interaction with the E-, P-, or L-selectins for which the optimal ligands and mode of recognition for biological activity are still sought. The fucose residue, one hydroxyl group from the central galactose unit, and the carboxyl group of the sialic acid are essential for the interaction (Figure 4).

The structural investigations of receptors and their carbohydrate ligands indicate that binding of the ligand to the receptor often involves only a few terminal residues. It is therefore anticipated that these receptors will bind to carbohydrate mimetics that present these essential functional groups in the optimal binding orientation. The use of carbohydrate-based combinatorial libraries that are either randomly generated or carefully designed based on knowledge of the receptor and/or ligand will greatly facilitate the discovery of mimetics of complex oligosaccharide ligands.

4. Supports for Solid-Phase Libraries

Parallel arrays as well as libraries of glycopeptides and oligosaccharides can be synthesized in solution or solid phase. The advantages of using solid-phase methods^[32] are well documented and detailed descriptions have recently been published.^[5, 33] The choice of solid support is crucial and depends on the types of reactions to be carried out as well as the screening methods to be employed. The two most

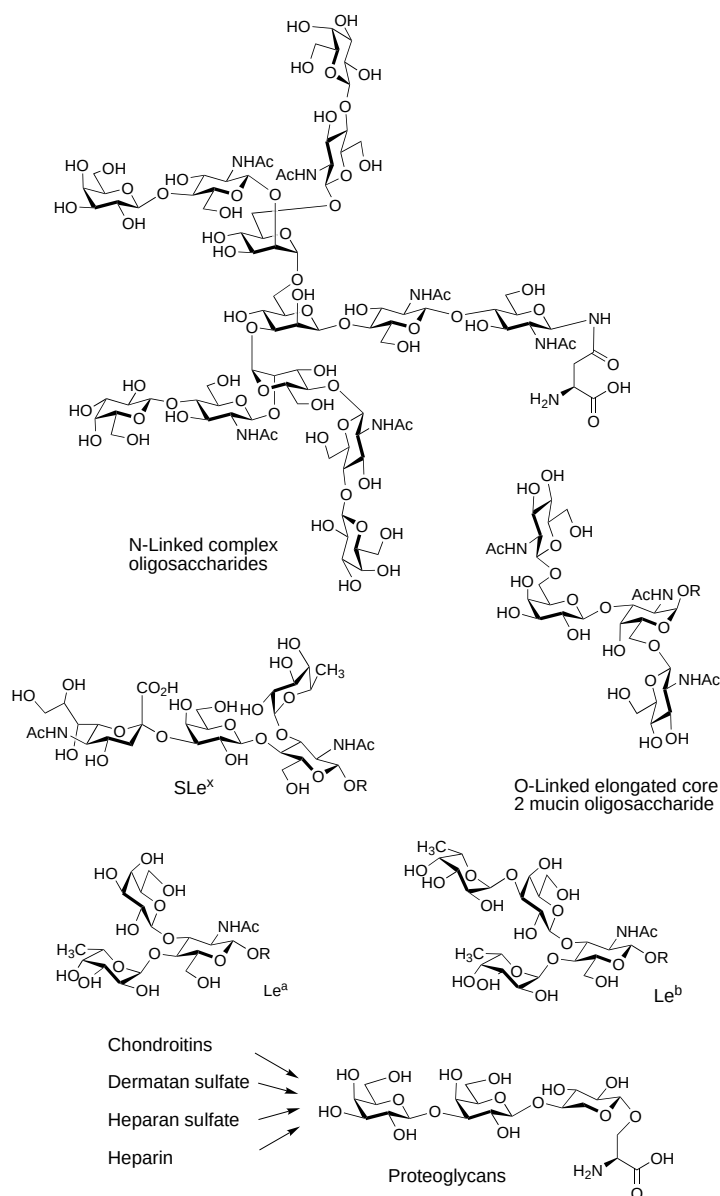


Figure 2. Representative oligosaccharide structures found on mammalian glycoproteins and glycolipids. The complex oligosaccharides may be bi-, tri-, or tetraantennary while the branches may be more or less elongated with 1→4 linked lactosamine units and they may or may not be sialylated. The SLe^x, Le^a, and Le^b structures represent the different blood group determinants often present on lipids and the elongated core 2 structure is a mucin-type glycosylation. Proteoglycans have a common core to which a variety of linear acidic polysaccharides are attached.

commonly used types of solid supports are polystyrene (PS) based (for example, Merrifield supports^[32] including the commonly used Wang resin^[34] and TentaGel^[35]) or polyethylene glycol (PEG)-based (such as PEGA,^[36] POEPOP,^[37] POEPS-3,^[38] and SPOCC^[39]); examples are shown in Figure 5.

Polystyrene resins are comprised of mainly 1–2% divinylbenzene cross-linked backbones with short linkers (Figure 5a). Polystyrene based gels are generally unsuitable for direct on-bead screening, either due to loss of enzyme activity in the polymer or due to their poor swelling in polar media

and consequent exclusion of biomolecules from the hydrophobic core of the polymer. This is also true for PS-resins grafted with long PEG chains such as ArgoGel or TentaGel (Figure 5b),^[40] although swelling in water is improved and some access to the interior has been achieved.^[41, 42] Furthermore, the polystyrene material absorbs light, thus interfering with some fluorescence assays and the hydrophobic core may result in nonspecific protein binding.

PEG-based resins, on the other hand, are cross-linked with long chain PEG macromonomers which also present the amino or hydroxyl functional groups. Therefore, the mechanical and chemical properties of the resins are strongly influenced by the nature of the PEG chains.^[33] Additionally, PEG chains are highly miscible with most solvents creating a quasi-homogenous reaction medium. PEG-based resins swell tremendously in aqueous media, thus allowing biomolecules access to the entire bead.^[43, 44] These resins are, therefore, suitable for protein ligation,^[45] enzymatic reactions, and screening for enzyme activity and inhibition.^[42, 46–51]

Since PEG-based polymers confer the advantage of a support that is amenable to both synthesis as well as screening of enzyme activity and protein binding, efforts have been made to generate such polymers with superior properties in both areas. They may be obtained by radical polymerization of long-chain PEG macromonomers to give PEG–polyacrylamide (PEGA, Figure 5c) copolymer^[36, 43] or PEG–cross-linked oligostyrene (POEPS-3, Figure 5d).^[38] Recently, two novel types of gel supports obtained by anion-catalyzed bulk polymerization of PEG, derivatized with epichlorohydrin (POEPOP, Figure 5e)^[37] or by cation-catalyzed bulk polymerization of PEG, derivatized with oxetane (SPOCC, Figure 5f)^[39] were introduced. The inert character of the polymers allows the application of harsh organic reactions. The excellent swelling in aqueous buffers has allowed all the above resins to be used in bioassays for enzymes, and PEGA resin was further investigated and showed no nonspecific binding in protein-binding studies.^[52]

For the solid-phase synthesis of glycopeptides and oligosaccharides, both polystyrene and PEG-based resins have been successfully used. Experiments that compare the rates of reactions on various resins have revealed that the rate of reaction completely depends on the nature of the reaction itself.^[53] Some reactions perform better on hydrophobic resins while others are better on hydrophilic resins. Another issue of particular importance for the synthesis of oligosaccharides on solid phase is the influence of the solid support on the stereochemical outcome of the glycosylation reaction. There are few detailed studies that address this issue, however, preliminary results are contradictory, and some suggest that the anomeric ratio is strongly influenced by the nature of the resin as well as solvent, C-2 group on the donor, and temperature.^[54–56] In some cases there seem to be an enhancement of anomeric selectivity on the solid phase.^[55] There are presently four examples of successful synthesis of oligosaccharide and glycopeptide libraries in the literature and these have been generated using either TentaGel or a PEG-based resin (PEGA and POEPOP), thus enabling rapid solid-phase screening of the library (see Sections 6.3 and 8.2).

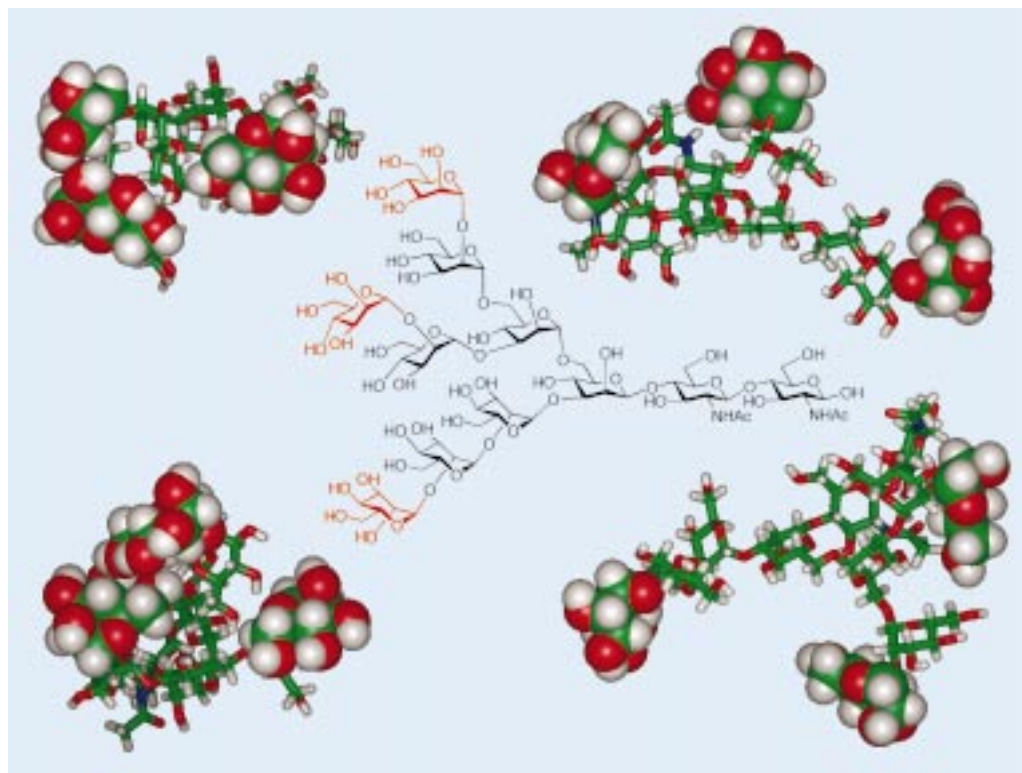


Figure 3. Structural models of four different conformer populations (2 for each 1 → 6 link) of a triantennary high-mannose undecasaccharide M9. Terminal mannoses are highlighted as CPK-models.^[22]

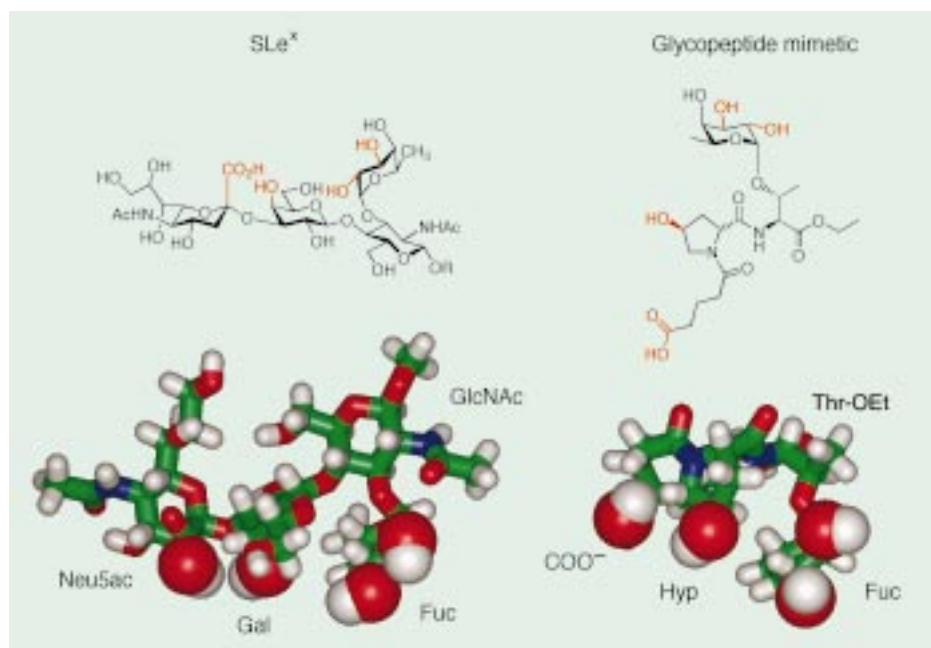


Figure 4. Bound conformation of the SLe^x tetrasaccharide relative to that of an efficient fucosyl glycopeptide mimetic compound.^[118] Tightly bound hydroxyl groups are shown as spheres.

5. Analytical Tools for Oligosaccharide and Glycopeptide Libraries

For solution-phase libraries which are composed of mixtures of compounds, the difficulty of analysis escalates with increasing numbers of compounds. Typically, large mixtures of compounds are not analyzed before screening while small

ones may be analyzed for reaction completeness using mass spectrometry, HPLC, NMR, or combinations thereof. The identification and analysis of active compounds from these mixtures is painstakingly tedious and complete characterization is only possible after deconvolution procedures and resynthesis of the active compound.^[57] For solid-phase libraries, the methods currently developed are discussed below.

5.1. Tagging Techniques in Oligosaccharide Libraries

The number of methods for analyzing non-peptide libraries are increasing and generally fall into two categories: direct methods, usually based on mass spectrometry and NMR spectroscopy, or indirect methods employing encoding—chemical,^[58–60] chemoluminescent,^[61] or otherwise.^[62–64] Many of the methods of chemical encoding are restricted by the additional synthetic effort required and the need to design orthogonal reaction conditions required for the two sets of syntheses. However, chemical coding is the only method that has so far been successfully used for identifying components in an oligosaccharide library.^[59] This study utilizes a carbene insertion reaction to attach polyhalogenated aromatic tags that are photochemically released and then analyzed by GC-MS.^[60]

5.2. Analysis by Mass Spectrometry

The development of oligosaccharide and glycopeptide libraries obtained by the split and mix method is severely hampered by the lack of concurrent development of general, facile separation and characterization technology. Some headway has been made with chemical coding of the libraries but very few direct methods of analysis exist. One of the promising methods that could be applied to the direct

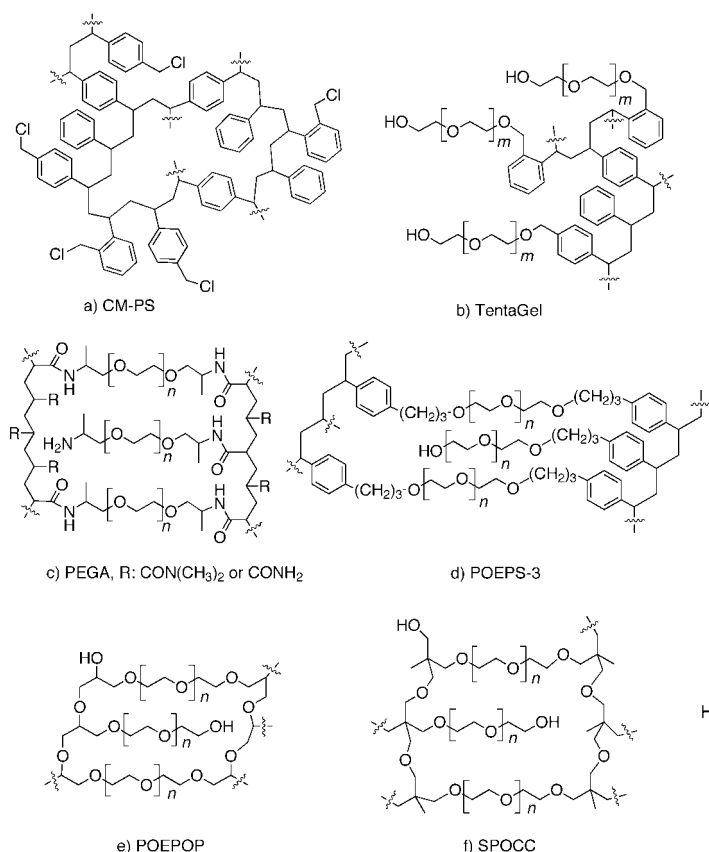


Figure 5. The chemical structure of TentaGel and PEG-based resins. The open structure and inert nature of PEG in biological systems confer ideal properties to the PEG-based resins for bioassays.^[33]

characterization of both types of libraries is mass spectrometry, more specifically Matrix Assisted Laser Desorption/Ionisation-Time of Flight mass spectrometry (MALDI-TOF-MS), Electrospray Tandem mass spectrometry (ES-MS-MS), or Fourier Transform-Ion Cyclotron Resonance mass spectrometry (FT-ICR-MS). MALDI-TOF-MS and ES-MS-MS have been used to characterize glycopeptides^[65–67] and complex oligosaccharides.^[68–72]

The analysis of carbohydrates by mass spectrometry presents special challenges in distinguishing between the branch points, isobaric monosaccharides, and the anomeric configuration of the glycosidic bond. Several methods have emerged using MALDI-TOF-MS. In one strategy, the oligosaccharide is treated sequentially with glycosidases, the mass of the resulting fragments recorded and the identity of the original oligosaccharide determined by a process of deduction.^[71, 73] Alternatively, the oligosaccharide fragments are generated during the ionization process in several ways: by postsource decay (PSD), delayed extraction with high-energy collision-induced decomposition (CID), in-source fragmentation or tandem MALDI-MS.^[68, 69] In all cases, fragmentation occurs across the glycosidic bond in a manner that is dependent in part on the type of linkage (such as 1→6 or 1→3), the anomeric configuration, and the nature of the monosaccharide.^[72, 74] Interpretation of PSD spectra can be somewhat difficult and challenging for complex saccharides

but should be much simpler if the oligosaccharide libraries are restricted to three to four monosaccharides.

Similarly, the analysis of glycopeptides has been carried out using primarily MALDI-PSD-MS. Two strategies are employed: the glycan portion is first cleaved enzymatically or by base-catalyzed β -elimination^[66, 75] and separately characterized by other means (MS or NMR) while the peptide is sequenced using PSD, or the entire glycopeptide is fragmented by PSD and the spectra analyzed.^[65, 67] Again, all these spectral analyses are time consuming and not suited for high-throughput screening. The only example to date of a facile, direct method of characterizing glycopeptide libraries generated using the building-block approach is one that combines chemical coding (to determine the glycan portion) with capping steps to generate fragments for the mass analysis (ladder synthesis).^[52] An example of the mass spectrum of a bisglycosylated peptide from such a library is shown in Figure 6. The principle of this method and its application in the synthesis of a glycopeptide library are detailed in Section 8.2.

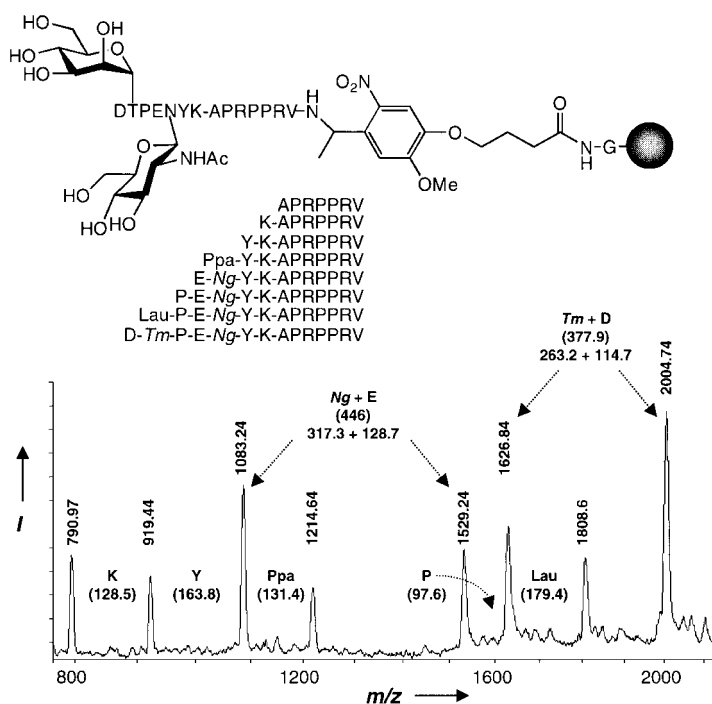


Figure 6. Representative mass spectrum showing the "ladder" of a bisglycosylated glycopeptide obtained from screening of a glycopeptide library. The phenylpropionic acid (Ppa) and lauric acid (Lau) encode for Asn(GlcNAc) and Thr(Man), respectively.^[52]

5.3. Structural Analysis by MAS NMR Spectroscopy of Compounds Linked to Single Beads

In the absence of highly-efficient and effective tagging methods, nanoprobe Magic-Angle Spinning (MAS) NMR spectroscopy is the analytical technique which holds most promise for direct identification of single compounds bound to one polymer particle. Furthermore, the completeness of each synthetic step can be assessed in a nondestructive

manner. Gel-phase NMR spectroscopy can give respectable ^{13}C NMR spectra of large amounts of resin bound compounds, but for single beads such analysis is not possible and proton spectra do not show useful resolution. The properties of the polymer have a major influence on the quality of the spectra recorded and, in general, the more mobile and liquidlike the backbone of the polymer, the better the resolution of the ^1H NMR spectra. This also holds true for MAS NMR spectroscopy at intermediate spinning rates of 2000–4000 Hz where compounds on the PEG-based resins are much better resolved than on polystyrene or even TentaGel.^[76] In fact, solid-phase spectra displaying a resolution indistinguishable from that of solution spectra may be obtained with these resins.^[77]

Complete structural elucidation of unknown compounds on single beads remains challenging and most other routine analyses require substantial amounts of resin beads, except in one case where macrobeads of the TentaGel type were used.^[78] Typically, analysis has been performed using polystyrene beads and, although generally the 1D ^1H MAS NMR spectra showed little or no resolution of coupled resonances, useful 2D MAS NMR spectra could be obtained.^[79] Only known reaction products and known compounds on polystyrene or TentaGel have been analyzed so far.^[80–83] Recently, the only complete structural elucidation of an unknown peptide of eight residues on a single POEPOP bead (10 nmol) has been achieved.^[77] The minimum amount of resin-bound material required for a complete structural elucidation on PEG-based resins at 500 MHz is 2–7 nmol of compound, depending of the complexity of the structure and the resin.^[77] The time-consuming nature of NMR structural analysis also demands a more robust (no false positives) and quantitative biological assay in which the rank of the compound activities may be directly quantified in order to limit the number of structural analyses necessary.^[84] MAS NMR spectroscopy has been used for the monitoring of solid-phase glycosylation reactions of peptide templates with the aim of analyzing single-bead glycopeptides from consecutive glycosylations of peptide template libraries.^[85, 86]

6. Parallel and Library Synthesis of Oligosaccharides

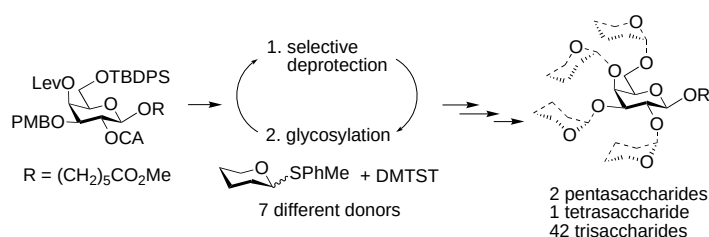
6.1. Introductory Considerations

While tremendous progress has been achieved in the generation of libraries comprised of small molecules, peptides, or nucleotides, the synthesis and characterization of carbohydrate-based libraries has remained elusive. The assembly of carbohydrate libraries is complicated by the chemical complexity of the carbohydrate itself and the reactions involved. A well-planned orthogonal protecting group strategy must be implemented in order to selectively mask and unmask the relevant hydroxyl groups for glycosylation, which must be achieved stereoselectively and in high yields. Three types of glycosyl donors, the thioglycosides^[87] the glycosyl sulfoxides,^[88] and trichloroacetimidates,^[89] have precipitated as being generally effective in coupling reactions providing high

yield and reasonable stereoselectivity. Furthermore, the methods offer homogeneous reaction conditions and may therefore be used for solid-phase glycosylation reactions. It must be noted however, that it is still difficult, even in solution, to generate important oligosaccharide linkages such as the β -Man, α -Neu5Ac, and α -Kdo in greater than 50 % yield. In solid-phase libraries, the adaptation of glycosylation reactions which perform well in solution to the solid phase is often problematic. These challenges notwithstanding, there have been significant breakthroughs in the generation of oligosaccharide libraries of small to medium size.

6.2. Parallel Synthesis of Oligosaccharide Arrays

The structural diversity of oligosaccharides may be generated through parallel solution synthesis based on a common core entered at the first synthetic step. A recent, elegant solution-phase approach^[90] employs four orthogonal protecting groups for the monosaccharide hydroxyl groups and has been used to produce a 45-member array of compounds (42 trisaccharides, one tetrasaccharide, and two pentasaccharides) synthesized by parallel glycosylation of the common acceptor with seven different glycosyl donors (Scheme 1). The key



Scheme 1. Solution-phase parallel synthesis of oligosaccharide arrays. Yields of oligosaccharides varied widely, ranging from 5–85 % for two glycosylation/deprotection cycles.^[90] DMTST = (dimethylthio)methylsulfoniumtrifluoromethanesulfonate, CA = chloroacetyl.

monosaccharide acceptor contained the chloroacetyl (CA), levulinoyl (Lev), *p*-methoxybenzyl (PMBO), and *tert*-butyldiphenylsilyl (TBDPS) protecting groups. The various hydroxyl groups were sequentially unmasked and coupled with thiocresyl donors yielding the products in widely varying yields and stereoselectivity. As the size of the oligosaccharide increased, a decrease in selectivity and yield was observed and overall yields for two deprotection and coupling cycles ranged from 5–85 %. Compounds synthesized were completely deprotected and characterized by mass spectrometry and NMR spectroscopy. This strategy as described in solution phase is extremely labor intensive and limited by the requirement of an orthogonal protection scheme.

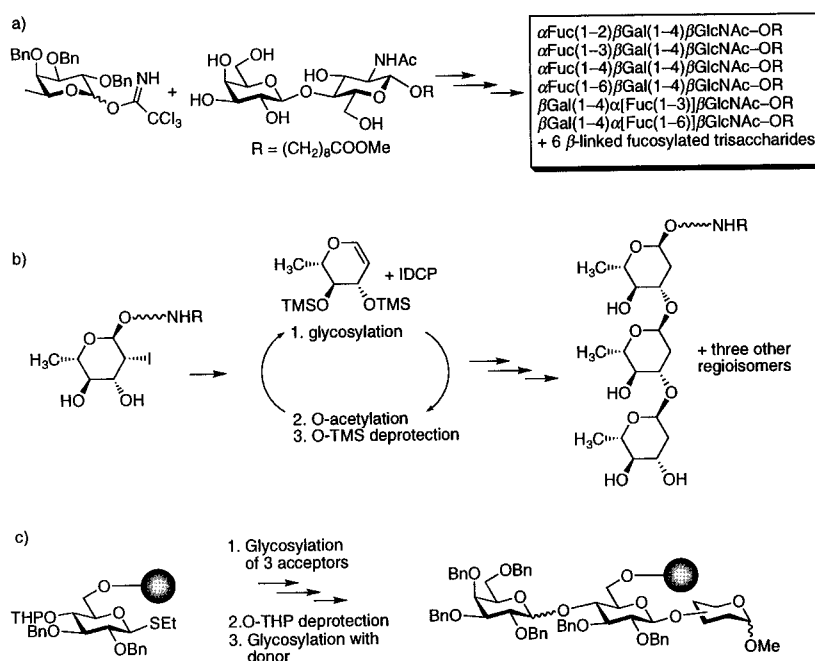
This highly orthogonal protection scheme can be avoided by use of a variety of enzymes with the desired glycosylation specificity. In particular, inversion of the reaction of glycosyl hydrolases has been found to be useful and small arrays of oligosaccharides including the mucin core 1 and 2 structures have been synthesized by this procedure, albeit in low yields.^[91] Yields of the products may be improved by the use of thermostable glycosidases at elevated temperatures.^[92]

Alternatively, glycosyl transferases may be used for anomeric and regioselective synthesis of glycosidic bonds. Small arrays of nonnatural SLe^x (11 compounds) and SLe^a (16 compounds) analogues were synthesized by sequential incubation of nonnatural *N*-acyl disaccharides with α (2-3) sialyl transferase and either Fucose III or IV transferases.^[93]

Solid phase methodology for parallel synthesis of oligosaccharides has also been developed.^[55, 56, 88, 94–97] The orthogonal linkers used include those based on the TMSET (trimethylsilylethyl) protective group cleaved with $\text{BF}_3 \cdot \text{Et}_2\text{O}$,^[96] the *p*-alkoxybenzyl group cleaved with cerium ammonium nitrate,^[95] the hydroxymethylbenzoic acid linker cleaved with dilute base, and photolabile linkers. Acid-labile linkers are sometimes problematic under acidic glycosylation conditions. The glycosylations must be carried out under homogeneous conditions and the ones which have been used are the trichloroacetimidate procedure,^[55, 89] the sulfoxide/ Tf_2O procedure,^[88] pentenylglycoside procedure with iodonium activation (N-iodosuccinimide/triethylsilyl trifluoromethanesulfonate, NIS/TES-OTf),^[56] and the glycal procedures using either iodonium intermediates or epoxide^[94] with Lewis acid activation. Since these methods are performed on solid phase they would be particularly suited for oligosaccharide library synthesis.

6.3. Synthesis of Oligosaccharide Libraries

Oligosaccharide libraries have been successfully generated either in solution or on solid phase using primarily chemical synthesis. Solution-phase synthesis of carbohydrate libraries is carried out employing two main strategies: reacting protected glycosyl donors either with unprotected acceptors^[98–100] or protected acceptors.^[101] The former strategy is designed to eliminate the need for major synthetic efforts required to synthesize the orthogonally protected saccharide building blocks that ensure regioselectivity, thereby reducing the time and cost involved in the synthesis of oligosaccharide libraries. In the seminal work (Scheme 2a),^[98] a library of all six possible α -linked trisaccharides was synthesized by coupling of the perbenzylated fucosyl trichloroacetimidate to the unprotected LacNAc acceptor. Key features for the success of this methodology are the incorporation of a UV active grease “tail” in the acceptor to aid separation and detection of the products in the mixture, the use of polar solvents (DMF) for the glycosylation, and the termination of the reaction after 30% completion to prevent multiple glycosylation. Interestingly, the regioisomers were obtained in near-equimolar quantities despite previous evidence suggesting that the different hydroxyl groups have highly differing reactivities toward glycosylation in nonpolar solvents. The mixtures were used to screen for the activity of glycosyl transferases.^[100] The



Scheme 2. Examples of oligosaccharide library synthesis. a) Solution-phase synthesis with unprotected acceptors.^[98] b) Solution-phase synthesis with protected acceptors.^[102] c) Solid-phase synthesis.^[103] In all cases, libraries were obtained as mixtures of compounds. Ac = acetyl, Bn = benzyl, IDCP = iodonium dicollidine perchlorate, THP = tetrahydropyranyl, TMS = trimethylsilyl.

main problems of this strategy are separation and identification of the products; despite the use of the hydrophobic tail, separation of the isomers was quite difficult. The scope of the method was limited by difficulty in the identification of the products, possible only after comparison of the mixture NMR spectra with those of the individual products separately synthesized as single compounds.

While glycosylation using unprotected acceptors can be truly random, caution must be exercised in order to prevent multiple glycosylation, which would make deconvolution and separation of the library components even more difficult. Therefore, others have opted to use the approach wherein both donor and acceptor are protected, thus enabling one to drive the reaction to completion without fear of multiple glycosylation. For example, a small library of 20 (including α/β anomers) trisaccharides was generated using the vinyl latent-active strategy.^[101] The 3-methyl allyl glycoside with benzyl protecting groups and one acetyl group was used as the common building block and was converted into the glycosyl donor by isomerization to the vinyl glycoside or to the acceptor by removal of the acetyl group. TMSOTf-promoted glycosylation reactions proceeded in greater than 70% yield to give a 1:1 mixture of α/β anomers. This procedure is in fact a combination of parallel synthesis and the split and mix methodology. A common monosaccharide building block with only two different protecting groups was used so very limited diversity was introduced by the split and mix step. At the end of the synthesis of the trisaccharide library, the individual compounds were not separated but analyzed simply on the basis of the trisaccharide mass and monosaccharide composition. Mass spectrometry was also used to analyze the completion of the glycosylation reactions.

In another example utilizing only the split and mix methodology, a small, four-membered library of 2,6-dideoxy-trisaccharides was generated also using a common protected glycal building block (Scheme 2b).^[102] Thus, the glycal was first converted to the 2-iodoglycoside by iodonium dicollidine perchlorate (IDCP) activation. The protecting groups in the 3 and 4 positions were removed and then simultaneously glycosylated stereoselectively at low temperature with an equimolar amount of donor to yield a mixture of the two α -linked regio-disaccharides in equal amounts. Although reactions were allowed to proceed for as long as possible, surprisingly, there was no mention of the formation of trisaccharides, resulting from glycosylation of both the available positions, or of unreacted starting material. The remaining hydroxyl groups were then acetylated and the TMS groups removed. The new hydroxyl groups were glycosylated as previously to yield a mixture of four 2-iodotrisaccharides which were reduced by treatment with tributyltin hydride. Again, the products were not separated but analyzed as a mixture using mass spectrometry and NMR spectroscopy.

Although most oligosaccharide libraries have been synthesized in solution, there are two examples of solid-phase synthesis of such libraries. In the first example, a small library of 12 different trisaccharides (including α/β anomers) was synthesized on TentaGel resin using the split and mix method with thioethyl glycoside as the donor (Scheme 2c).^[103] This library was very limited in its diversity since only one hydroxyl group was used as the acceptor. The starting thioethyl glycoside was attached to the solid support by a succinic ester linker at C6 thus allowing it to be used both as the donor and acceptor in glycosylation reactions.

In a more extensive effort, the split and mix method was used for the synthesis of approximately 1300 di- and trisaccharides as a “one bead–one compound” library (Figure 7).^[59] Six suitably protected azide-containing monosaccharides attached to TentaGel were glycosylated with 12 different mono- and disaccharide sulfoxide donors to yield 72 different compounds. Additional diversity was achieved by reduction of the azide and acylation of the oligosaccharide amine with 20 different carboxylic acids. The identity of

compounds attached to the beads was established using a haloaromatic tagging technique employing carbene coupling reactions.^[60] While this technique provided a way of decoding which carbohydrates were coupled to each other on a bead, the precise nature of the glycosidic linkage could not be conclusively determined. It was assumed, based on previous experience, that the glycosylation reactions were completely stereoselective under the conditions used. The library was screened for active ligands for *Burhinia purpurea* lectin using a solid-phase enzyme-linked assay.

Synthesis of oligosaccharide libraries both in solution and on solid phase is by no means trivial. The main impediment to progress in the synthesis of carbohydrate libraries has been the yields and selectivities of the glycosylation reactions and the technology for separation and analysis. Recently, a novel solid-phase approach to S-linked oligosaccharides based on nucleophilic substitution of sugar triflates with thioglycosides was introduced.^[104] This approach has not yet been used for libraries, but could alleviate the inherent difficulty in selective glycoside bond formation on solid phase, thereby facilitating the preparation and analysis of split and combine oligosaccharide libraries. In all the examples described above, apart from one instance, the library of oligosaccharide compounds was never separated nor were the individual products precisely identified and characterized. The recent method using orthogonal protecting groups for parallel synthesis in solution (Scheme 1)^[105] has great potential for library synthesis on solid phase provided the required analytical methods can be developed. It should also be noted that only in one case of oligosaccharide libraries described^[59] has the exponential increase of compound numbers by consecutive reactions been exploited to any significant extent.

7. Glycopeptides as Oligosaccharide Mimetics

In the quest for carbohydrate-based therapeutics, the synthesis of large numbers of diverse oligosaccharides is an expensive, synthetically challenging and time-consuming process. Whereas the use of oligosaccharide libraries would save time during synthetic operations and screening, the expense and the difficulties of the synthesis and analysis of active compounds from the library would still be problematic. Furthermore, it has been shown that small modifications of the natural oligosaccharide ligand rarely confer any increase in binding efficacy.^[106–108] This has been attributed to the enthalpy–entropy compensation often found for analogous structures in the interaction with their receptors in aqueous media.^[109–111] The free energy of binding of a receptor with any ligand of similar structure has been correlated to the preorganization of water molecules in the media close to the binding site.^[112] If this is the case, only ligand structures, which allow significantly different interactions with both the receptor and the aqueous environment, are expected to have affinities significantly different from that of the natural ligand.

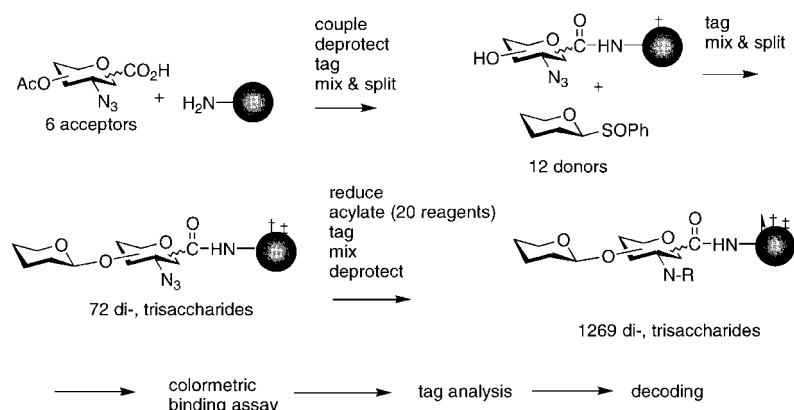


Figure 7. A solid-phase oligosaccharide library synthesized with exponential increase in the number of compounds with each reaction step. The library was screened for active compounds using a solid-phase enzyme-linked assay and the components were identified using chemical coding. The new ligands identified had activity comparable with that of the natural ligand.^[59]

When glycopeptides were first introduced as mimetics of oligosaccharides,^[113] it was envisaged that the saccharide moiety would provide the specificity of the binding by directing the ligand to the oligosaccharide binding site, while the peptide would function as a scaffold for optimal orientation of the glycan portion. However, since peptide ligands generally bind with high affinity to peptide receptors, it is also expected that the glycopeptide could furthermore interact favorably with the carbohydrate-binding receptor through the peptide scaffold, thus leading to increased binding affinity.^[26] The source of this enhanced affinity of peptides may lie in their ability to perform an induced fit because the relatively limited flexibility around peptide bonds leads to fast on-rates for the binding. In the peptide architecture, this flexibility is obtained with the minimum entropic penalty. Conversely, the carbohydrates generally display conformational assemblies located closely around one global energy-minimum conformation (or a multiple of two for each 1 → 6 linkage included, see Figure 3). In contrast to glycopeptides, highly flexible neoglycoconjugates^[114] do not show high affinity due to the large entropic penalty.^[115, 116]

The principle of glycopeptides mimicking oligosaccharides was consolidated through binding studies with an array of phosphorylated glycopeptides and the divalent mannose 6-phosphate receptor.^[26] The structural similarity between the oligosaccharide and the most active glycopeptide ligand was supported by molecular dynamics (Figure 8).

Similar results were later obtained with glycopeptides designed for binding to the selectins.^[14] A glycopeptide mimic

of the SLe^x tetrasaccharide containing fucose on a peptide scaffold had a greater than tenfold increased binding affinity for E-selectin.^[117] There was no further significant increase in affinity when the ligands were immobilized in a polymeric multivalent arrangement in liposomes.^[118] In another example, a high-affinity divalent adhesin ligand which contained α Gal(1 → 4) α Gal linked by peptide bonds to an aromatic nucleus was prepared for *Streptococcus suis*. The assay with structurally similar tetravalent ligands showed no significant increase in binding indicating the interaction to be truly divalent.^[27] Glycopeptide mimics of galactose or GlcNAc containing oligosaccharides afforded inhibitors ($K_d = 1.7 \mu\text{M}$) of galactosidase,^[119] and GlcNAc-transferase inhibitors,^[120] respectively. In another approach, glycopeptide-like azasugar inhibitors were prepared; however, reduction of inhibitory activity was found when compared with the parent azasugar without the peptide moiety.^[121]

Glycopeptides are excellent mimics of the complex oligosaccharides and may be utilized in a library format to identify high-affinity ligands.^[122] The ease with which glycopeptides are synthesized using preactivated amino acids and glycosylated amino acid building blocks can, by careful assembly of a library, ensure the generation of a single compound in each bead. For the preparation of glycosyl amino acid building blocks, the glycosylation of Fmoc-amino acid-OPfp esters or free Fmoc-amino acids have proved a general and versatile method useful for the preparation of complex compounds for direct incorporation into the glycopeptide libraries (Fmoc = fluoren-9-ylmethoxycarbonyl, Pfp = penta-

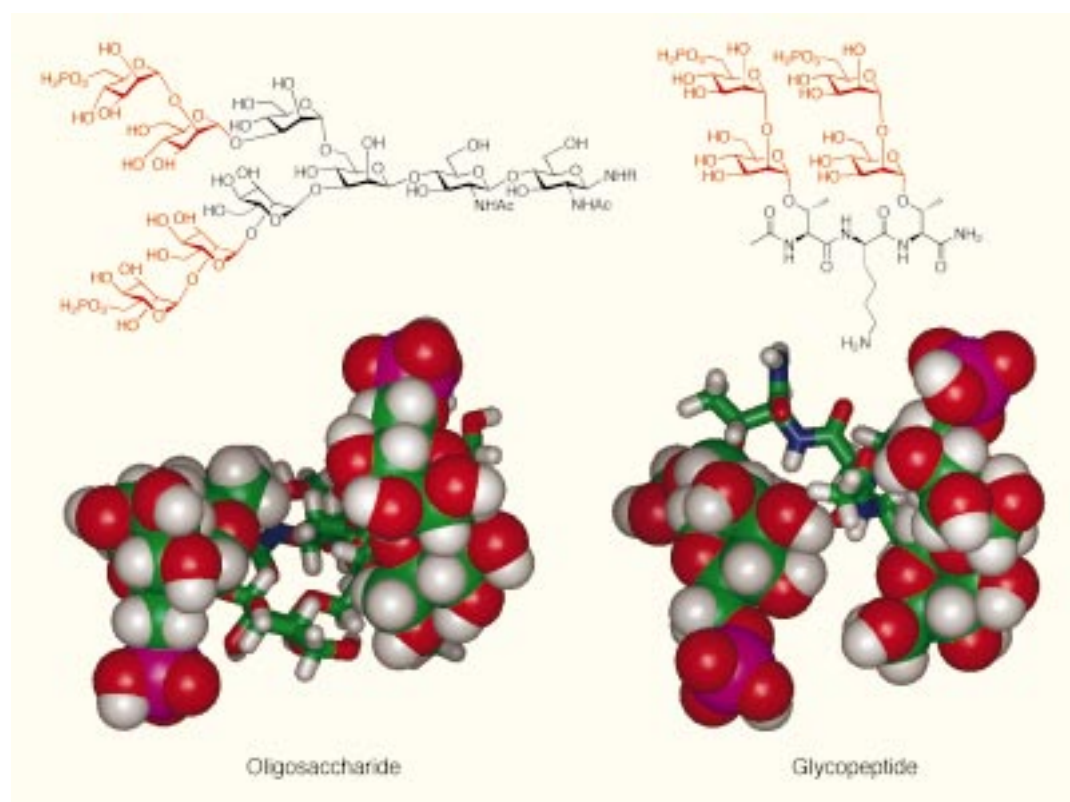


Figure 8. Models of a phosphorylated high-mannose M7 and a glycopeptide mimic which show similar conformations. They are seen from the point of interaction with the mannose-6-phosphate receptor. Disaccharide phosphates are emphasized as spheres.^[26]

fluorophenyl).^[123–127] Many other strategies have also been successfully employed for glycopeptide synthesis. However, these all require further manipulations of the glycosylated building blocks before use in peptide synthesis.^[128] In addition to the relative ease of synthesis, facile characterization of active compounds makes libraries of glycopeptides very attractive alternatives to oligosaccharide libraries.

8. Parallel and Library Synthesis of Glycopeptides

8.1. Parallel Synthesis of Glycopeptide Arrays

When considerable a priori structural knowledge of a protein carbohydrate interaction is available, it is possible to synthesize a range of active glycopeptide analogues by biased design using a parallel synthetic approach. The requisite knowledge is the nature of the dominant sugars involved in the interaction and their spatial orientation in the receptor interaction. With such information available from X-ray crystal data or from transfer NOE NMR spectroscopic experiments, a range of high-affinity ligands of the glycopeptide type have been developed for several receptors by parallel synthesis.

Twenty bidentate glycopeptide ligands for the mannose 6-phosphate receptor (MPR) were synthesized by parallel synthesis and high-affinity ligands with approximately 20-fold increased affinity for the receptor were obtained.^[26] The array of analogues contained glycosylated linear tri- to pentapeptides and cyclic hexa- to octapeptides. The glycans were phosphorylated 1→2 and 1→6 linked mannodisaccharides and phosphorylated mannosides. Glycopeptides were synthesized by solid-phase multiple-column peptide synthesis (MCPS)^[129, 130] using Fmoc-amino acid-OPfp esters and PEGA resin. The glycosylated building blocks were protected as acetates or benzoates and the phosphate with trichloroethyl groups. Deprotected glycopeptides were obtained in high yield and purity. Assays of the compounds demonstrated that a minimum of two disaccharides on a scaffold was required for the specific interaction with the receptor and clearly showed the necessity to have sufficient but not excessive flexibility in the scaffold. Two 6-P- α -Man-(1→2)- α -Man disaccharides on a linear tripeptide had the highest affinities for the receptor. Attempts to increase the affinity through cyclization of the peptide were unsuccessful.^[131]

An array of 120 galactose-containing compounds (30 mixtures of four diastereomers) was prepared in parallel by base-catalyzed Michael addition of β -D-(C₁₂H₂₅CO)₄Gal-Sac to four different unsaturated ketones and an α -chloro ketone, followed by reductive amination with six amino acids. The thirty products were purified by solid phase extraction and tested as inhibitors of galactosidase. Galactose provided the specificity for the enzyme, while the affinity was obtained through interaction with the aglyconic scaffold. In this way, inhibitors of the enzyme activity ($K_d = 1.7 \mu\text{M}$) were obtained.^[119]

An array of glycopeptide ligands, which bind to MHC class II E^k and interact with the T-cell receptor (Figure 9a) in which the glycan part was varied, were synthesized by MCPS.^[132, 133]

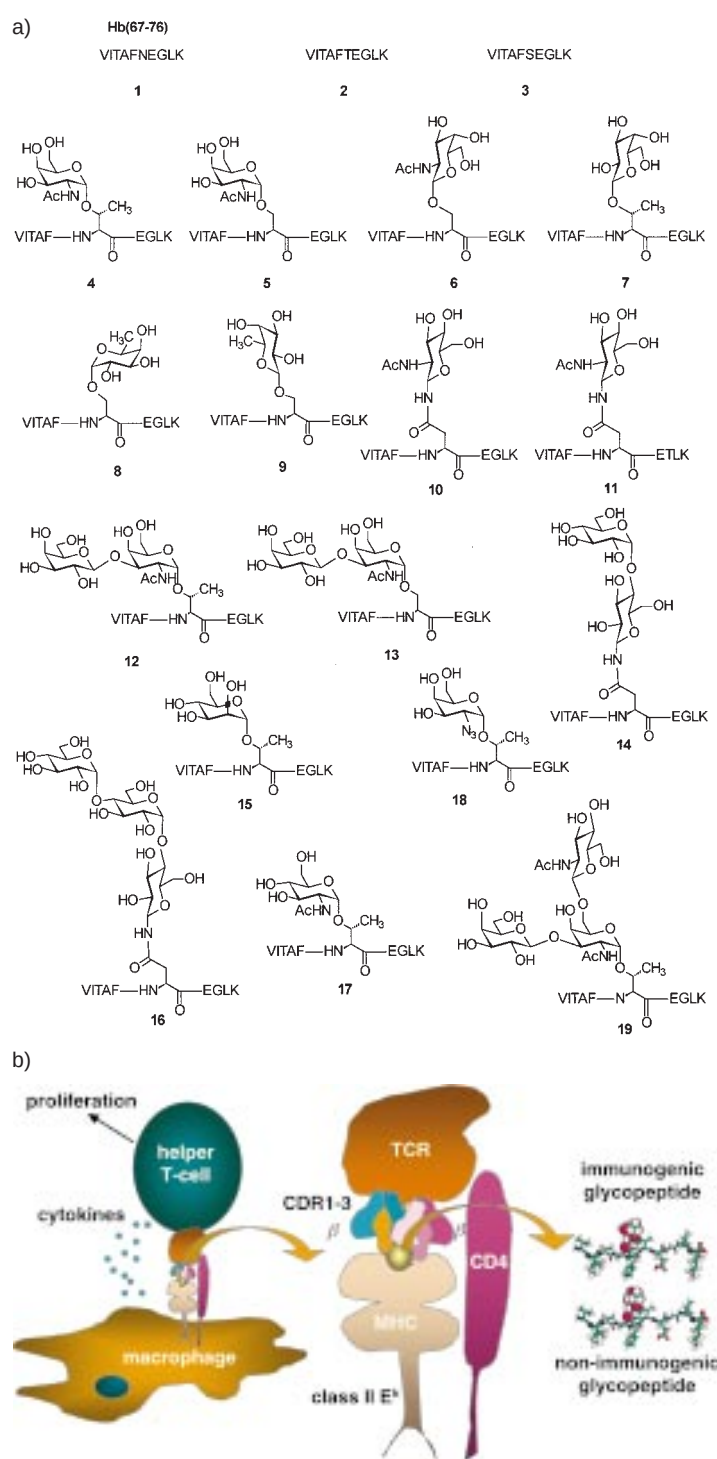


Figure 9. a) An array of glycopeptides for the study of glycan specificity of the MHC/TCR recognition. When mice were injected with the glycopeptides and the proliferation index of T-cells isolated from lymph nodes was measured, only the Tn and T antigens were strong immunogens.^[28] b) Glycopeptide/MHC/TCR-interaction. The minor modification of substitution of α -GalNAc with α -GlcNAc, namely change of an axial 4-hydroxyl group to an equatorial one (as illustrated in the two glycopeptides), completely abolished immunogenicity.^[28]

The glycosylated building blocks were synthesized by glycosylation of Fmoc-amino acid-OPfp esters and these were directly used for coupling reactions. The glycans included the mucin Tn (α -D-GalNAc) antigen core 1–4 structures, as well

as a large array of mucin-unrelated saccharides. Using the panel of glycopeptides shown in Figure 9a, it was found that mainly the T and Tn antigens were recognized and they were considerably more immunogenic (yielding much higher T-cell titers in mice) than other glycans (Figure 9b).^[28] The results indicated that there is a repertoire of TCR's specifically directed towards tumor-associated antigens and elongation with GlcNAc (such as cores 2 and 4) gave nonimmunogenic compounds.

Parallel synthesis of 62 different fucosylated tripeptides resulted in two ligands with submicromolar affinity for the P-selectin, however, the desired activity for the E-selectin was not observed.^[134] For the E-selectin selectivity it was necessary to incorporate a hydroxyl group, which mimics the 4-hydroxyl group of the central Gal in SLe^x, in addition to a Fuc-residue, and a carboxylate, to obtain ligands with greater than 10-fold increased activity over that of the SLe^x tetrasaccharide.^[117] One of the best ligands was obtained from Thr(α -Fuc)-OEt, which was first N-acylated with a hydroxyamino acid and then elongated with a diacid to furnish the acid mimic of the sialic acid carboxylate (Figure 10). This approach was further developed as a solid-phase method where the molecule was linked to a solid support through the invariable fucosyl moiety.^[135]

In an elegant and different approach, an array of C-linked glycopeptide-like mimics of SLe^x were synthesized in parallel by an Ugi four-component reaction.^[136] Reaction of different anomeric two or three carbon extended C-glycosyl aldehydes or acids with resin-bound amines, isonitriles, and other acids or aldehydes yielded an array of C-linked analogues. The method is easy to perform in good yield on solid phase. However, this strategy can only be used for a mixed library and not for a one bead–one compound library. It is derived through a multicomponent reaction where all components are introduced in a single step and deconvolution strategies such as positional scanning or iterative synthesis are required for identification of the components of the library. On the other hand, deconvolution is feasible with fast screening because the products are generated rapidly.

8.2. Preparation and Analysis of Solid-Phase Glycopeptide Libraries

While parallel synthesis of arrays of glycopeptides is readily achieved by implementation of the building-block approach (Scheme 3a),^[125] glycopeptide library synthesis in a combinatorial manner by the split and mix method has yet to prove

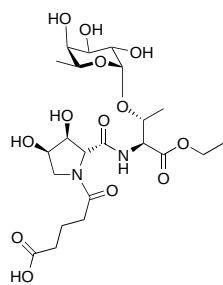
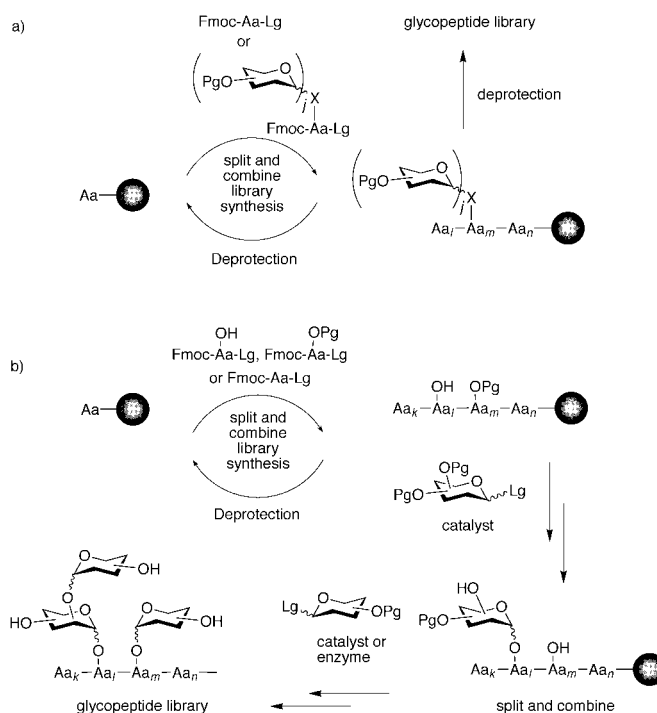


Figure 10. A ligand with high affinity for E-selectin. The receptor interacts with the 2- and 3-hydroxyl groups of Fuc, probably the hydroxyl groups of the dihydroxyproline ring, and the carboxylate moiety. A similar high-affinity ligand is compared with the SLe^x structure in Figure 4.^[118]



Scheme 3. Strategies for glycopeptide library synthesis. a) The building block approach (X = O, C, S, N). b) Chemical or enzymatic glycosylation of peptide or glycopeptide. While enzymes have not yet been used in the solid-phase synthesis of glycopeptide libraries, several resin-bound glycopeptides have been glycosylated enzymatically.^[44, 148] Lg = leaving group, Pg = protecting group.

routine. The difficulty lies in the structural analysis of the vast number of compounds generated in picomolar quantities on a single bead. Whereas peptides on beads can be conveniently analyzed by solid-phase ladder sequencing^[137] or Edman degradation, neither of these methods are suitable for glycopeptides because of the instability of the glycosidic bond under the acidic and basic conditions employed.

An early report described a pentaglycopeptide library containing three randomized positions and an Asn(GlcNAc) building block fixed at position 4.^[138] However the library members were not characterized and screening results were not described. Presently, only one example of a combinatorially generated glycopeptide library suitable for screening and structural analysis has been reported.^[52] Generation of a 300 000 member library and analysis of its components was made possible in part by the development of a technique based on mass spectrometry for identification of the sequence of individual glycopeptides in the library. In this method, the synthetic history of the glycopeptide is captured on the beads by capping a small percentage of the growing oligomer chain in each synthetic step.^[139] Thus, a series of related fragments is generated on the bead rather than a single compound (Figure 6). The difficulty arises when this technique is applied for a glycopeptide library in which the amino nucleophiles present significant reactivity differences. To account for amine reactivity differences, an in situ capping method based on Fmoc amino acids mixed with 10% of the Boc analogue was developed (Boc = *tert*-butoxycarbonyl).^[122] The glycosylated Fmoc-amino acid-OPfp esters were encoded by capping

with selected carboxylic acid–OPfp esters. The library was linked to the solid support by a photolabile linker (Figure 6) which facilitated the immediate MALDI-TOF mass spectrometry analysis of compounds released from the resin beads by 20 minutes of irradiation with an Hg lamp. The purity of the library was assessed by MALDI-TOF mass spectrometry through collection and analysis of a few beads. Most of the beads afforded spectra of the ladders, which could easily be deciphered using mass-difference assignment software.

In a departure from the building-block approach, glycopeptide libraries were also obtained by glycosylation of a preattached glycan or the hydroxyl group of an amino acid side chain from a peptide library (Scheme 3b). In preliminary studies,^[55, 140] good yields of (approximately 35 % of the initial resin loading) of glycopeptides containing di- and trisaccharides were obtained using 5–8 equivalents of the perbenzoylated glycosyl trichloroacetimidate donor to glycosylate a known glycopeptide. Glycosylation was attempted on four resins: Polyhipe, TentaGel, PEGA1900, and Macrosorb-SPR250 but was successful only on PEGA and Polyhipe.

Early attempts of direct solid-phase glycosylation of a longer peptide were not very successful although the presence of glycopeptide product could be demonstrated.^[128, 141] Direct glycosylation of the amino acid side chain hydroxyl groups was partially successful albeit in low yield.^[55, 142] The failure of polar resins such as PEGA may be due to the many primary amides in the backbone, which interfere with the carbocation intermediate. Peptide amide bonds seem to show less interference. However, since polar resins are required for solid-phase bioassays, new types of polar resin containing only ether bonds were developed for the solid-phase glycosylation of peptides. Quantitative glycosylation of a known peptide was achieved on a PEG-based resin (POEPOP) containing only ether bonds^[37] using 5–8 equivalents of the peracetylated or benzoylated trichloroacetimidate. In a one bead–one compound approach, two resin-bound peptides bearing protected and unprotected hydroxyl groups were first glycosylated with galactose and then with fucose after deprotection of the second hydroxyl group, affording a small library of four glycopeptides. The glycopeptides were cleaved off, separated, and characterized by mass spectrometry.

While solid phase glycosylation is undoubtedly a feasible alternative for the generation of truly random glycopeptide libraries with diversity in both the peptide and glycan portions, analysis of such libraries will present quite a challenge. One possibility is the use of fragmentation of the compounds by mass spectrometry or, alternatively, MAS NMR as discussed in Section 5.

9. Screening of Oligosaccharide and Glycopeptide Libraries

An important requirement for the successful application of the combinatorial library approach to the drug discovery process, is the ability to utilize the library in high-throughput screening (HTS) procedures. HTS screening of oligosaccharide and glycopeptide libraries is dependent on the mode of library synthesis and can be achieved by screening mixtures of

compounds in solution, discrete compounds in solution, or discrete resin-bound compounds. Screening mixtures of compounds is nontrivial and the various methodologies that can be used for this purpose have been recently reviewed.^[57] One method that has been used for screening an oligosaccharide “library” is based on NMR transfer nuclear Overhauser effects (tr-NOE’s).^[143, 144] In one demonstration, the *Aleuria aurantia* agglutinin was bound to α -L-Fuc(1→6)- β -D-GlcNAc-OMe in the presence of 5 or 14 other nonbinding oligosaccharides.^[143] This methodology is limited by the number of compounds in the mixture that can be screened simultaneously, the difficulty in detecting low or very high-affinity ligands and the time required for analysis of spectra.

In another approach, the mixture of 12 trisaccharides obtained by a solution-phase random glycosylation strategy (Section 6.3) was used to screen for the activity of fucosyl transferases by measurement of incorporated radio-labeled GDP-Fuc.^[98] This transfer was successfully detected even on acceptors that made up 5 % of the mixtures. Recently, a library of 640 carbohydrate triazine derivatives obtained by the reaction between *p*-aminophenyl pyranoside with cyanuric chloride was rapidly screened as inhibitors of the proteases Factor Xa and plasmin.^[145] The synthesis of the libraries as parallel arrays of discrete compounds in 96-well plates facilitated the high-throughput screening of protease activity in the same plates using spectrophotometric measurement of the *p*-nitroaniline derivative released during substrate hydrolysis. No carbohydrate-based inhibitors were found.

As discussed earlier in this review, the split and mix methodology facilitates the rapid production of large number of compounds. Traditionally, the compounds were subsequently cleaved then screened and analyzed in solution. More recently, the development of solid supports that are compatible with both organic and aqueous media has allowed screening of the library to take place on the solid support itself. Active ligands are detected using immunostaining or colorimetric methods or, more directly, by use of fluorescent-labelled receptors. For example, carbohydrate ligands bound to TentaGel resin were screened in parallel arrays using digoxigenin-labelled *Maackia amurensis* agglutinin (a sialic acid specific lectin).^[146] Beads binding fluorescent-labeled lectin were detected using flow cytometry.^[146] The solid-phase screening of the 1300-compound carbohydrate library (Section 6.3) was carried out on the entire library utilizing a colorimetric assay.^[59] Beads were incubated with biotin-labeled *Burhinia purpurea* lectin and bound lectin was detected by secondary incubation with alkaline phosphatase conjugated streptavidin. The screening yielded several non-natural oligosaccharide ligands for the lectin but, surprisingly, the known natural ligand that should have been present in the library was not detected. The reason for the lack of detection is either that binding of the lectin to the ligand was somehow hindered or this particular oligosaccharide was never synthesized. When using tagging methods, the failure of a synthetic step is not detected whereas analysis of the resin-bound compounds using methods such as MS or NMR readily indicates any problems in the synthesis. In subsequent

solution-phase assays, the natural ligand and the mimics showed comparable binding affinity.

Glycopeptide libraries have also been screened in solid-phase assays using soluble receptors. For example, the library generated by ladder synthesis on PEGA resin (Section 8.2) was incubated with the fluorescent-labeled lectin from *Lathyrus odoratus* (Figure 11 a). The most fluorescent beads were collected and ligands identified by MALDI-TOF mass spectrometry. The most active compounds were glycopeptides which contained only mannose (T(α -D-Man)ALKPTHV, LHGGFT(α -D-Man)HV, T(α -D-Man)EHKGSKV, GT(α -D-Man)-FPGLAV, and T(α -D-Man)-LFKGFHV) and these displayed up to a 25-fold increase in fluorescence compared to lectin binding with resin-bound mannose. Binding of the lectin to resin-bound mannose was inhibited by the active

glycopeptides synthesized (Figure 11 b) which suggests that the glycopeptides and the natural carbohydrate ligand bind the same or closely related binding sites of the lectin.

Parallel arrays of resin-bound glycopeptides and resin-bound glycopeptide libraries have also been used in high-throughput screening of whole cells. A GlcNAc containing pentapeptide library attached to polystyrene resin was incubated with erythrocytes and adherence was observed but not further investigated.^[138] More recently, Tn-antigen containing glycopeptide dendrimers bound to TentaGel resin were used in rosetting tests and showed positive reaction with anti-Tn antibodies and Tn+ erythrocytes.^[147] Immunization of animals with one of the most active glycopeptide dendrimers led to an amazing increase in the level of anti-Tn.

10. Conclusions

It is clear that protein-carbohydrate interactions are essential in numerous biological processes and that the development of carbohydrate mimetics that interfere with these processes would provide a powerful methodology for both modulation and amelioration of specific biological activity. In recent years, novel methodologies have been presented for the synthesis of oligosaccharide and glycopeptide libraries that should provide rapid access to such carbohydrate mimics. The technology for the identification of active oligosaccharide or glycopeptide ligands isolated from solid phase libraries for these carbohydrate-binding proteins has also been developed to a certain extent. In spite of its conceptual appeal however, there are major limitations that hamper the progress of carbohydrate-based library synthesis, characterization, and screening. These limitations are related in part to the lack of proper methods for miniaturization and analysis of compounds on solid phase. Additionally, the effect of the solid support on the outcome of the screening results needs to be thoroughly investigated. Although the synthesis and analysis of oligosaccharide libraries remains challenging, alternative use of larger solution-phase libraries requires difficult deconvolution synthesis, which is not practical with oligosaccharide synthesis due to its complexity and lengthy nature. Alternatively, glyco-

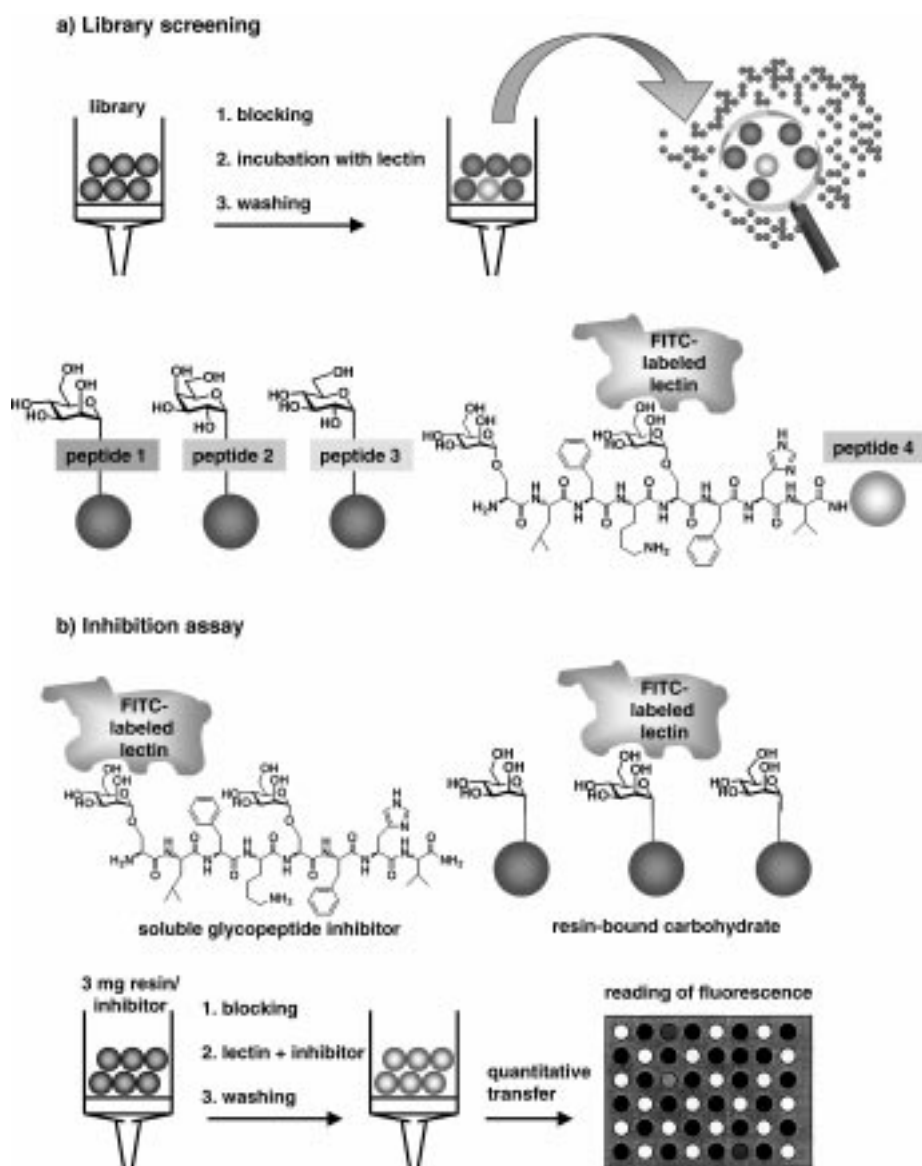


Figure 11. a) Screening of a glycopeptide library using a fluorescent-labeled lectin and ligands bound to PEGA-beads. The active compounds are analysed by mass spectrometry. b) FITC-labeled lectin binding to resin-bound mannose could be inhibited by soluble glycopeptides obtained from a library screen. Percentage inhibition was quantified by recording lectin fluorescence. Only every second well of the microtiter plate was used and nonfluorescent beads indicated good inhibitors.^[52] FITC = fluorescein isothiocyanate

peptides, in which the peptide portion confers additional favorable binding affinity and which may easily be formed on solid phase and are less difficult to prepare in high purity, hold a lot of promise. Currently, the most versatile method for glycopeptide library synthesis utilizes an in situ capping procedure with a mixture of Boc and Fmoc amino acids while glycosylated amino acids are separately encoded by capping with carboxylic acids. The analysis of structures is facilitated by direct photolytic release from PEG-based supports for MALDI-TOF-MS analysis. Application of this technique yields high affinity ligands for carbohydrate-binding proteins.

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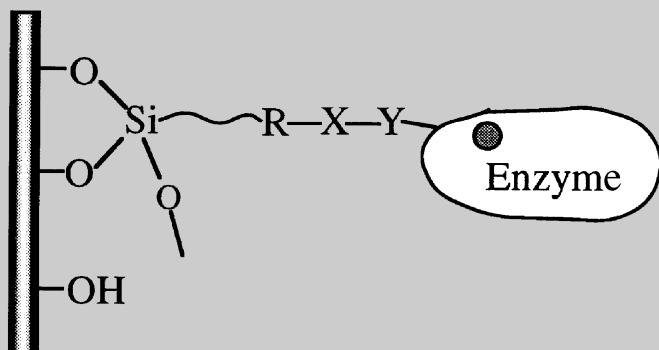
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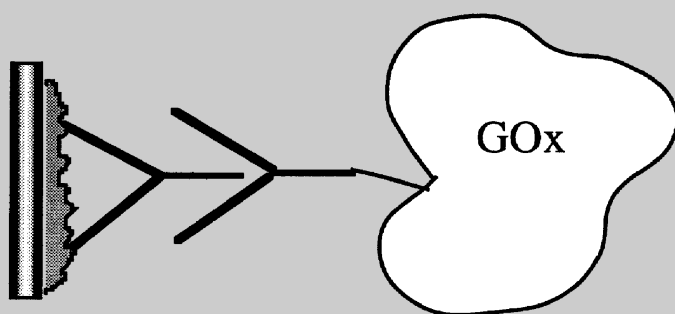
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Enzyme electrodes allow the production of more types of products:

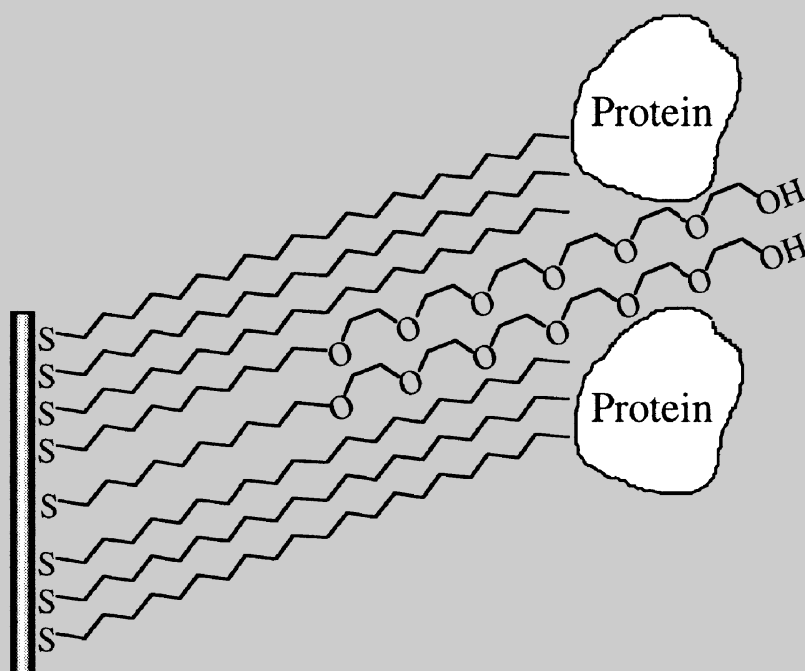


through building covalent bonds



with help from affinity interactions

through the use of hydrophilic-/hydrophobic-type interactions



Integration of Layered Redox Proteins and Conductive Supports for Bioelectronic Applications

Itamar Willner* and Eugenio Katz

Integration of redox enzymes with an electrode support and formation of an electrical contact between the biocatalysts and the electrode is the fundamental subject of bioelectronics and optobioelectronics. This review addresses the recent advances and the scientific progress in electrically contacted, layered enzyme electrodes, and discusses the future applications of the systems in various bioelectronic devices, for example, amperometric biosensors, sensoric arrays, logic gates, and optical memories. This review presents the methods for the immobilization of redox enzymes on electrodes and discusses the covalent linkage of proteins, the use of supramolecular affinity complexes, and the reconstitution of apo-redox enzymes for the nanoengineering of electrodes with protein monolayers of electrodes with protein monolayers and multilayers. Electrical contact in the layered enzyme electrode is achieved by the application of diffusional electron mediators, such as ferrocene derivatives, ferricyanide, quinones, and bipyridinium salts. Covalent tethering of elec-

tron relay units to layered enzyme electrodes, the cross-linking of affinity complexes formed between redox proteins and electrodes functionalized with relay-cofactor units, or surface reconstitution of apo-enzymes on relay-cofactor-functionalized electrodes yield bioelectrocatalytic electrodes. The application of the functionalized electrodes as biosensor devices is addressed and further application of electrically "wired" enzymes as catalytic interfaces in biofuel cells is discussed. The organization of sensor arrays, self-calibrated biosensors, or gated bioelectronic devices requires the microstructuring of biomaterials on solid supports in the form of ordered micro-patterns. For example, light-sensitive layers composed of azides, benzophenone, or diazine derivatives associated with solid supports can be irradiated through masks to enable the patterned covalent linkage of biomaterials to surfaces. Alternatively, patterning of biomaterials can be accomplished by noncovalent interactions (such as in affinity complexes between avidin and a photolabeled

biotin, or between an antibody and a photoisomerizable antigen layer) to provide a means of organizing protein microstructures on surfaces. The organization of patterned hydrophilic/hydrophobic domains on surfaces, by using photolithography, stamping, or micromachining methods, allows the selective patterning of surfaces by hydrophobic, noncovalent interactions. Photoactivated layered enzyme electrodes act as light-switchable optobioelectronic systems for the amperometric transduction of recorded photonic information. These systems can act as optical memories, biomolecular amplifiers, or logic gates. The photoswitchable enzyme electrodes are generated by the tethering of photoisomerizable groups to the protein, the reconstitution of apo-enzymes with semisynthetic photoisomerizable cofactor units, or the coupling of photoisomerizable electron relay units.

Keywords: bioelectronics • biosensors • electron transfer • enzyme electrodes • monolayers

1. Introduction

Bioelectronics is a rapidly progressing field at the junction of chemistry, biochemistry, and physics.^[1] The basic feature of a bioelectronic device is the immobilization of a biomaterial

onto a conductive or semi-conductive support, and the electronic transduction of the biological functions associated with the biological matrices. Biomaterials that can be thus assembled include proteins, that is, enzymes,^[2] receptors,^[2a, 3] antibodies or antigens,^[4] oligonucleotides or DNA fragments,^[5] or low molecular weight molecules exhibiting affinity interactions with other biomaterials such as cofactors, namely, NAD(P)⁺,^[6] biotin,^[7] or, for example, saccharides exhibiting affinity interactions with lectins.^[8] Different electronic signals were employed to transduce the biological functions occurring at the support element.^[9a] These include electrical

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transduction, namely, current,^[9] potential changes,^[9a, 10] capacitance,^[11] and impedance,^[12] piezoelectric transduction,^[9a, 13] and field effect transistor (FET) transduction^[14] and others.^[9a, 15]

Systems that employ enzymes as bioactive interfaces represent the most extensively studied assemblies in bioelectronics. Electronic transduction of the enzyme–substrate interactions provides a general analytical means to detect the respective substrate. The high specificity of enzyme–substrate interactions, and the usually high turnover rates of biocatalysts, open the way to tailor sensitive and specific enzyme-based biosensor devices.^[16] Activation of enzymes at conductive surfaces allows the application of biocatalysts in electrically driven biotransformations (electrobiosynthesis).^[17] Recently, photosensitive enzymes^[18] and proteins^[19] assembled on electrode surfaces were activated by light, and the recorded optical signals were electronically transduced by the support. The high turnover rates of the enzymes allowed the amplified electronic transduction of weak optical signals.^[18b] The potential application of such systems in optical memories, optical bioswitches, electronic gates, and biological actinometers has been addressed.^[20]

Bioelectronic systems based on other biointerfaces, for example, DNA sensors or immunosensors, often make use of enzymes as biological probes of the recognition elements for biological affinity.^[21] The high turnover rates of enzymes provide a sensitive means for the amplified transduction of biointeractions between the affinity recognition pairs that control the enzyme functions and their electrical contact with electrode supports.

The organization of an enzyme-based bioelectronic system requires the integration of the biocatalyst with the conductive supports to the extent that the biocatalytic transformation is electronically transduced (Figure 1 A). Any electrical changes at the support element as a result of the biocatalytic process, that is, depletion of the reactant or formation of the product,

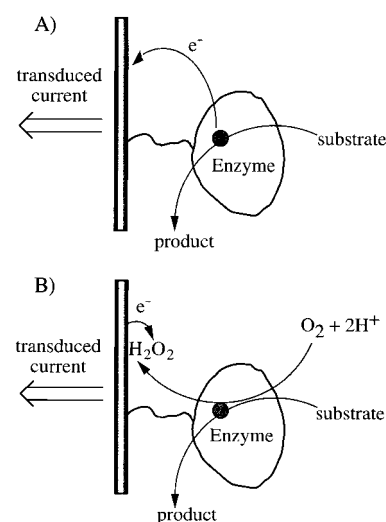


Figure 1. Integrated enzyme electrodes for bioelectronic applications: A) bioelectrocatalyzed oxidation of a substrate, B) electrochemical reduction of H₂O₂, which is formed upon the O₂-biocatalyzed oxidation of the substrate.

provide routes for the electronic transduction of the biological processes occurring at the electrode surface. For example, the changes in potential at conductive supports as a result of biocatalyzed O₂ depletion,^[22] NH₃ formation, or CO₂ evolution,^[23] represent electronic signals responding to the respective biocatalyzed transformations. Amperometric detection of enzyme-generated products, such as H₂O₂, was often used in the development of biosensor devices (Figure 1 B).^[24]

Direct electrical activation of enzymes, and particularly redox enzymes, represents a general approach to stimulate the bioelectrocatalyzed oxidation (or reduction) of the enzyme substrates.^[25] Provided electron transfer between the electrode and the redox enzyme is fast, the resulting current

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corresponds to the turnover rate of the electron exchange between the substrate and the biocatalyst. Hence, the transduced current reflects the substrate concentration in the system. Direct electrical communication between redox proteins, and specifically redox enzymes, and electrodes is, however, usually prohibited.^[9] Electron-transfer theory^[26] defines the rate of electron transfer between a donor–acceptor pair by Equation (1), where ΔG° is the change in free

$$k_{\text{et}} \propto e^{-\beta(d-d_0)} e^{-\frac{(\Delta G^\circ + \lambda)^2}{4RT\lambda}} \quad (1)$$

energy associated with electron transfer and the generation of the redox products; λ is the reorganization energy; d_0 is the van-der-Waals distance and d the actual distance separating the donor and acceptor; and β is the electronic coupling coefficient. This relation emphasizes that the donor–acceptor separation distance is a major factor that controls the electron transfer rates. In fact, for most redox proteins (diameter 80–150 Å) the redox centers are deeply embedded in the protein and therefore electrically insulated. That is, redox enzymes (or proteins) that form a donor–acceptor pair with an electrode support lack electrical contact with this support.

The topic of bioelectronics relies on this basic feature of electrical contact between biomaterials and electrode surfaces. Various bioelectronic devices are based on the design of an artificial electrical contact between redox proteins and the electrode interfaces. In these systems the biofunctions of the proteins are electrochemically driven and stimulated by electron transfer.^[25] In other bioelectronic systems the perturbation of the electrical contact between redox proteins and the conductive support is used as a transduction signal of biochemical events.^[2, 16]

The tailoring of bioelectronic systems requires the assembly of biomaterials on solid conductive supports and the design of the appropriate electronic communication between the biological matrices and the support element. The chemical means to support the biomaterials include the immobilization of proteins and redox enzymes on electrodes by means of polymers,^[27] membranes,^[28] carbon paste,^[29] and sol–gel materials.^[30] The electrical contact with conductive supports was accomplished by the application of redox polymers^[31] or conductive polymers.^[32] Functionalization of solid surfaces with monolayers of organic compounds and biomaterials has been a subject of extensive research for more than two decades.^[33] It is the aim of this review article to address the chemical methods for integrating biomaterials and electronic transducing elements. We discuss in particular the assembly of redox enzymes, redox proteins, and semisynthetic redox biocatalysts of natural origin as monolayers or multilayers on solid supports. We address recent advances involved in the integration and electronic coupling of redox proteins with conductive surfaces. Special emphasis is given to summarize the state-of-the-art methods of spatially patterning surfaces with biomaterials, and of generating ordered nanostructures of proteins on solid supports. Finally, we discuss the organization of optobioelectronic systems, and present the activation of redox proteins associated as layers on electrode supports by external light stimuli. We have tried to emphasize the present and future applications of such integrated

assemblies consisting of proteins and electronic transducer elements within the broad context of bioelectronics and optobioelectronics. It is anticipated that the rapid progress in the area will lead to novel biosensor devices, biofuel cell elements, and biomaterial-based computing systems and logic gates.

2. Surface Functionalization of Electrodes for Covalent Linkage of Enzymes

Covalent linkage of proteins to conductive or semiconductive supports often utilizes the availability of functional groups on the surface of the solid support. For example, metal-oxide materials such as TiO₂, SnO₂, contain surface hydroxyl groups that are synthetically useful for the coupling of organic materials.^[34] Noble metals (Au, Pt) were chemically^[35] or electrochemically^[36] pre-treated to generate such surface hydroxyl functions.^[37] Carbon electrodes, after appropriate chemical treatment, contain different surface-associated functional groups (carboxylic, carbonyl, lactone, hydroxyl, etc.) capable of attachment to proteins.^[38] To control the surface density of functional groups on a graphite surface and their chemical activity, O₂-plasma,^[39] strong oxidants,^[40] or electrochemical oxidation^[41] were applied. Amino functions were introduced onto graphite electrodes by their treatment with NH₃-plasma.^[42] Some other electrode materials, for example, p-InP, were functionalized by applying special chemical treatment.^[43] The following section will summarize different routes used for the activation of solid surfaces for the covalent attachment of proteins.

Cyanuril chloride (2,4,6-trichlorotriazine, **1**), is a versatile reagent for the activation of surfaces and subsequent immobilization of enzyme layers.^[44] Electrode surfaces functionalized by hydroxyl groups, such as glassy carbon, pyrographite, or metal oxides, such as SnO₂, In₂O₃, TiO₂, react with **1** to form oxy-substituted mono- and dichlorotriazine layers (Figure 2). These residues react with amino or hydroxyl groups on the lysine and tyrosine residues of the protein. The resulting protein monolayer is linked to the electrode by a single anchoring site or by multiple sites involving several amino acid residues and triazine units. Table 1 summarizes several enzymes and proteins that were anchored as monolayers to different electrode supports using the triazine as a linking unit.

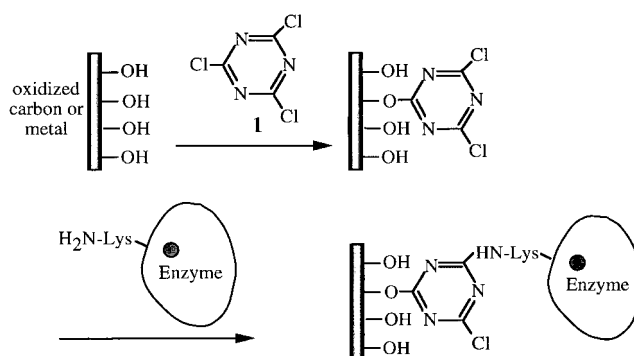


Figure 2. Assembly of enzyme-layered electrodes by the functionalization of the conductive support with cyanuril chloride (**1**).

Table 1. Enzymes linked to electrode surfaces through cyanuril chloride (**1**).

Enzyme	Electrode material	Enzyme loading [mol cm ⁻²]	Electrochemical response	Substrate	Analyzed concentration range [M]	Response time [s]	Optimal pH	Electrode stability	Ref.
glucose oxidase (EC 1.1.3.4) from <i>Aspergillus niger</i>	pyrographite	–	amperometric	glucose	$2 \times 10^{-5} - 5 \times 10^{-2}$	25	7.0	20 d	[45a]
	pyrographite	–	differential pulse voltammetry	glucose	–	–	–	–	[45b]
	pyrographite	–	amperometric	glucose	–	–	–	–	[45c]
L-amino acid oxidase (EC 1.4.3.2) from <i>Crotalus atrox</i> venom	pyrographite	–	amperometric	L-phenylalanine	$1 \times 10^{-4} - 5 \times 10^{-2}$	25	7.5	30 d	[45a]
	pyrographite	–	potentiometric	L-phenylalanine, L-methionine, L-leucine	$1 \times 10^{-5} - 1 \times 10^{-2}$	2–2.5	7.0–7.5	75 d	[46]
alkaline phosphatase (EC 3.1.3.1) from <i>E. Coli</i>	glassy carbon	$(1.4 - 9.7) \times 10^{-12}$	amperometric, RDE	catechol phosphate	$1 \times 10^{-3} - 1 \times 10^{-2}$	30	–	–	[47]
α -chymotrypsin (EC 3.4.21.1)	IrO ₂	–	potentiometric, flow-injection	N-benzoyl-L-tyrosine ethyl ester	–	12	7.8	–	[48]
ferritin (type 1) from horse spleen	pyrographite	$(7.7 - 20) \times 10^{-11}$	–	–	–	–	–	–	[49]
urease (EC 3.5.1.5)	IrO ₂	–	potentiometric	urea	$5 \times 10^{-5} - 1 \times 10^{-3}$	100	7.0	12 d	[50]

Carboxylic acid groups or amine functions, directly attached to the conducting support can be used for the covalent coupling of complementary amino groups on the lysine residues or carboxylic acid groups of aspartic/glutaric acid residues, respectively. Oxidation of carbon surfaces yields surface-associated carboxylic acid functions.^[38a] The carboxylic acid residues are functionalized to an active ester using carbodiimide reagents,^[51] to acyl halides using thionyl chloride,^[52] or to a mixed anhydride by the reaction with an anhydride^[53] prior to the coupling of the functionalized monolayer associated with the electrode to the protein (Figure 3A). The surface density of carboxylic acid residues on the electrode is an important parameter in controlling the effectiveness of covalent attachment of the protein. It was suggested that the electrode area equivalent to the footprint of the protein molecule should

include at least ten carboxylic acid residues to achieve an efficient coupling of the protein.^[24b] The average distance, about 5 Å, between surface carboxylic groups was determined^[54] by labeling experiments and X-ray analysis. The deposition of albumin on the electrode surface as a sub-monolayer resulted in an increase in the amount of the peroxidase linked to it as a secondary monolayer.^[55] This effect was attributed to the increase in the number of functional groups available for the peroxidase coupling. It was reported that enzymes also link to carbon surfaces functionalized with carboxylic acid groups in the absence of appropriate activation reagents.^[52, 53, 56] This was attributed to the possible availability of anhydride groups on the carbon surface, which were formed during the oxidation of the support.^[38a] Amino-functionalized graphite electrodes^[43] were used for covalent coupling with carboxylic groups of enzymes (Figure 3B).^[51] Table 2 summarizes some of the enzymes immobilized onto carbon electrodes through amide bonds.

The attachment of functionalized olefins or acetylenes to Pt surfaces^[61] or carbon electrodes^[62] allows the activation of the support for the secondary coupling of organic molecules, particularly enzymes.^[51] Pretreatment of the electrodes yields radical sites that react with π bonds and result in their attachment to the electrode surface. Different redox groups were immobilized at Pt and graphite electrode surfaces by this method, and the technique was also applied for the immobilization of enzymes (for example, glucose oxidase^[51]). Figure 4 shows such an immobilization by the primary activation of the surface with (ω - 1)-vinylcarboxylic acids or amines and the subsequent coupling of the enzyme to the base layer.^[51]

The strong π - π interactions between the hydrophobic basal surface of graphite electrodes (highly oriented pyrographite monocrystals) and polycyclic aromatic systems allow the stable immobilization of functionalized aromatic systems on the conductive support.^[63] The functionalized surfaces were used for the covalent immobilization of many organic and bioorganic materials (Figure 5).^[64]

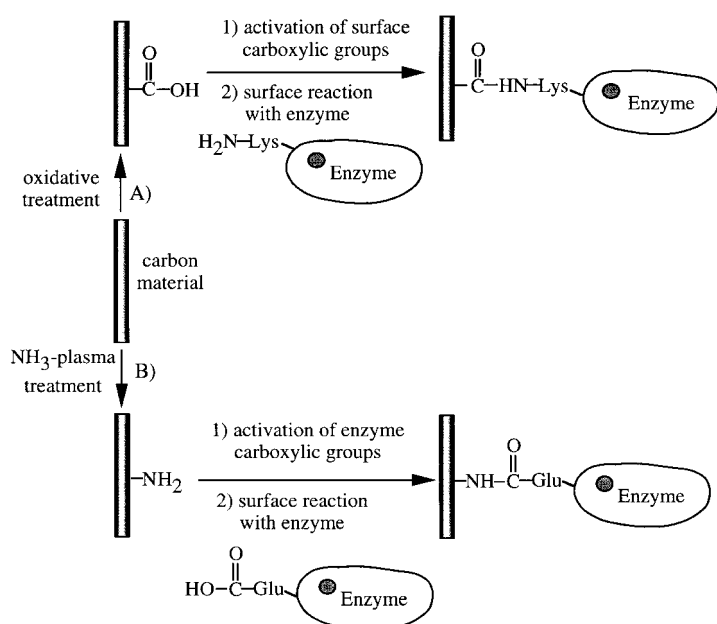
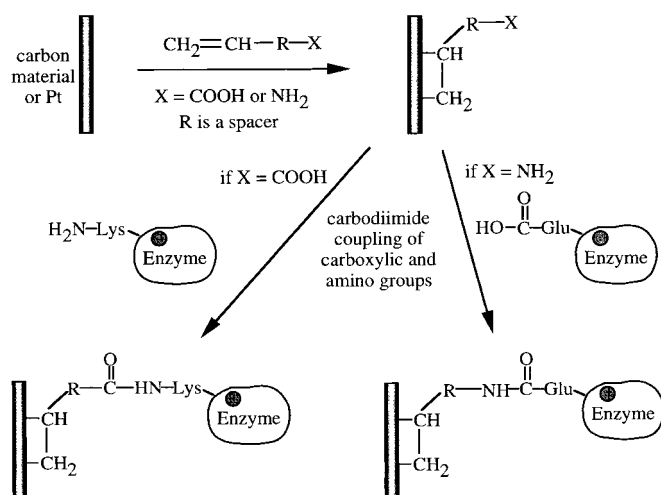
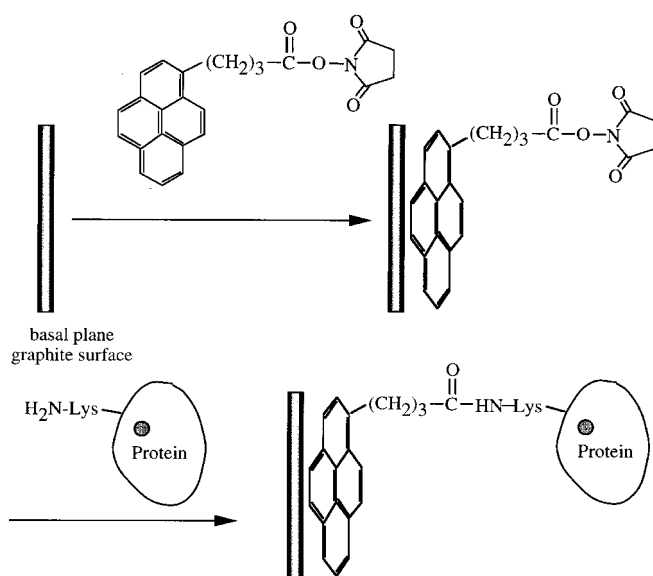


Figure 3. Covalent linkage of enzyme layers to carbon electrodes by coupling of amino and carboxylic functions.

Table 2. Enzymes linked to carbon electrodes through amide bonds.

Enzyme	Enzyme loading [mol cm ⁻²]	Electrochemical response	Substrate	Analyzed concentration range [M]	Optimal pH	Electrode stability	Ref.
glucose oxidase (EC 1.1.3.4) from <i>Aspergillus niger</i>	$(0.4-3.5) \times 10^{-12}$	amperometric	glucose	–	4.5–6.0	12–15 d	[24a–c, 41a, 51, 57–59]
xanthine oxidase (EC 1.2.3.2) from buttermilk	–	amperometric, potentiometric	xanthine	$7 \times 10^{-6} - 6 \times 10^{-6}$	–	7 d	[10, 38b]
horseradish peroxidase (EC 1.11.1.7)	–	amperometric	H ₂ O ₂	–	3.8	10 d	[38b]
lactoperoxidase (EC 1.11.1.7) from bovine milk	–	amperometric	lactate	–	4.5	10 d	[38b]
α -Chymotrypsin (EC 3.4.21.1) from bovine pancreas	–	–	acetyl-L-tyrosine ethyl ester	–	–	–	[41a]
lactate dehydrogenase (EC 1.1.1.27) from rabbit skeletal muscle	1.4×10^{-13}	amperometric	lactate	–	6.0–7.5	21 d	[60]

Figure 4. Modification of electrodes with functionalized π adsorbates for the covalent linkage of enzymes. $R = (CH_2)_n$, $n = 0-8$.Figure 5. Functionalization of graphite electrodes with polyaromatic π -electron modifiers for protein immobilization.

Alkoxy- or halosilanes are reactive substances for the derivatization of hydroxy-functionalized supports, and their hydrolysis by the hydroxyl groups yields siloxane monolayers

or multilayers on the conductive or semiconductive surfaces. Metallo-oxide electrodes, such as SnO₂,^[65] TiO₂,^[66] RuO₂,^[67] and In_xSn_yO_z,^[68] represent suitable hydroxylated supports. Silanization of metal electrodes, such as Pt, requires electrochemical oxidation of the surface to an oxide monolayer that provides hydroxyl functions.^[37] Non-metal oxidized electrode surfaces (for example, glassy carbon electrodes) were also successfully silanized.^[69] Different functional groups (usually amino, but also thiol, ester, etc.) can be introduced onto hydroxylated electrode surfaces by the application of functionalized silane reagents. These modified electrode surfaces were used for immobilization of numerous organic and bioorganic compounds with electrochemical, photochemical, catalytic, and biocatalytic properties.^[70] Several of the enzymes (proteins) assembled by this method (Figure 6) are summarized in Table 3.

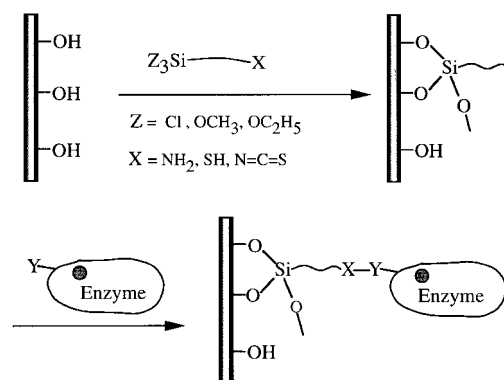


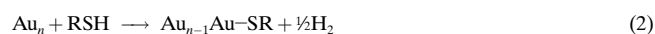
Figure 6. Assembly of functionalized, layered siloxane assemblies on electrodes for the immobilization of enzymes. Y is a complementary functional group for X.

The self-assembly of thiol^[73] or disulfide^[74] (and less commonly sulfide,^[75] thione,^[76] S-heterocycle,^[77] and isothiocyanate^[78]) monolayers on various conductive supports, mainly Au^[79, 80] but also Pt,^[81] Ag,^[82] Cu^[82c-g] (and less frequently Ir,^[83] Fe,^[84] Hg,^[85] amalgamated Pt,^[86] etc.) or semiconductive materials such as GaAs^[87] and InP^[88] have been the subject of extensive recent research efforts.^[2, 3, 79, 89] Thiolated monolayers on Au surfaces were extensively characterized in respect to their structural features^[79] and dynamics of formation^[90] by using various physical methods such as XPS (X-ray photoelectron spectroscopy),^[91] FTIR

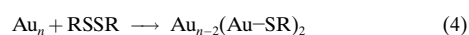
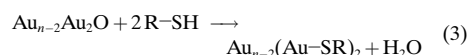
Table 3. Enzymes (proteins) covalently linked to electrode surfaces through functionalized silanes.

Enzyme/protein	Electrode material	Protein loading [mol cm ⁻²]	Electrochemical response	Substrate	Analyzed concentration range	Response time	Optimal pH	Electrode stability	Ref.
glucose oxidase (EC 1.1.3.4) from <i>Aspergillus niger</i>	Pt	–	amperometric	glucose	1–4 mM	40 s	–	9 months	[24d]
horseradish peroxidase (EC 1.1.1.7)	SnO ₂	–	amperometric	H ₂ O ₂	–	–	–	–	[71]
acetylcholinesterase (EC 3.1.1.7), electric eel, type VI-S	Pt	–	–	acetylcholine	–	–	7.2–7.8	–	[72]
Photosynthetic reaction centers from bacteria <i>Rhodospirillum rubrum</i> R-26	Pt	1.5 × 10 ⁻¹²	amperometric or potentiometric	light and reduced cytochrome c	–	3 min	8.0	7 d	[19a–e]

spectroscopy,^[92] contact-angle determination,^[93] ellipsometry,^[94] surface plasmon resonance,^[95] quartz-crystal microbalance,^[96] electrochemical methods,^[97] STM (scanning tunneling microscopy),^[98] AFM (atomic force microscopy),^[99] and others.^[100] Formation of Au-thiolate monolayers from thiols was attributed to oxidation of the Au surface by the thiol [Eq. (2)].^[73, 79a] The reduction of an oxide layer associ-



ated with the Au surface by the thiol was suggested as an alternative route [Eq. (3)].^[101] Formation of the thiolate monolayer on Au surfaces from the disulfide precursor was attributed to the reduction of the disulfide bond by the Au surface [Eq. (4)].^[74, 79a]



A variety of redox species, for example, ferrocenes,^[102] *N,N'*-dialkyl-4,4'-bipyridinium,^[75b, 103] quinones,^[81e, 86, 104] porphyrins and phthalocyanines,^[86, 105] heterocyclic dyes,^[106] metal complexes,^[107] molecular receptors such as cyclodextrins,^[108] calixarenes,^[75c, 109] supramolecular complexes,^[110] and bulky organic molecules,^[111] such as fullerene (C₆₀)^[111a–c] and dendrimers,^[111d] were anchored to Au supports by thiolate bridging groups. Thiolate monolayers associated with metal surfaces or semiconductor surfaces (GaAs, CdS) were used to generate nanostructures of colloids and clusters.^[112] The self-assembly of thiolate monolayers on Au supports was used to generate microscopic patterns^[113] and to tailor interfaces of controllable hydrophobic/hydrophilic domains.^[114] The assembly of photoisomerizable monolayers on Au surfaces through thiolate bonds was used to organize surfaces for the amperometric transduction of optical signals recorded by the monolayer interface.^[115] Different aspects of the assembly of thiolate monolayers have been reviewed.^[2, 3, 79, 89]

Amino- or carboxylic acid-functionalized thiolate monolayers associated with Au electrodes were covalently coupled to complementary carboxylic or amino groups of glutaric/aspartic or lysine residues of enzymes and redox proteins, respectively (Figure 7A).^[116] To prevent the enzyme deactivating upon linkage to short thiolate spacers, through interaction of the protein with bare Au domains, stepwise construction of thiolate layers with long spacers on electrode supports was performed.^[117] For example, coupling of glutaric dialdehyde to a cystamine monolayer associated with an Au electrode, followed by the coupling of lysine residues of the protein through formation of a Schiff base, yields a long-spaced protein monolayer.^[18c] Similarly, linkage of diisothiocyanatostilbene disulfonate to a cystamine monolayer, followed by

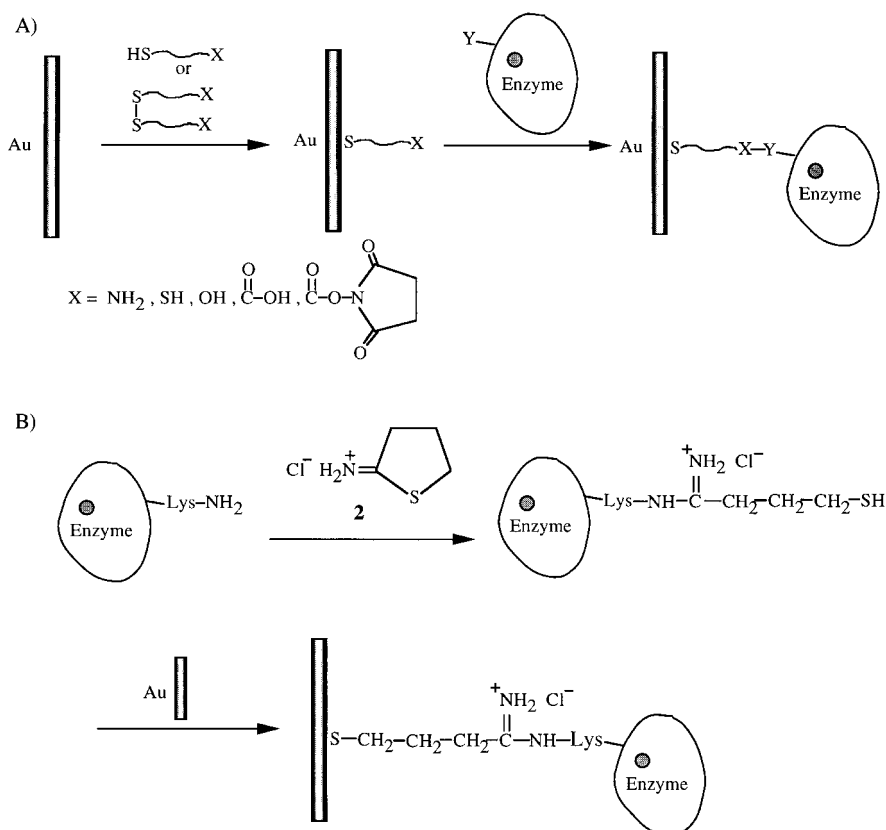


Figure 7. A) Self-assembly of functionalized, thiolated monolayers on Au electrodes for the covalent linkage of enzymes. X is a functional group for coupling with a protein. Y is a complementary functional group to X. B) Modification of proteins with thiol functionalities for self-assembly on Au supports.

the coupling of the protein glutathione reductase to the thiocyanate function by a thiourea bond, generates an enzyme monolayer separated by a stilbene unit.^[118] Table 4 summarizes different proteins that were assembled onto Au electrodes as monolayers through thiolate bridging spacers. The surface coverage of the protein on the electrode is controlled by the footprint of the protein, and in the case of the nondensely packed protein monolayers, by the density of the sublayer associated with the conductive solid support.

Direct modification of solid supports by proteins is often associated with the denaturation of the protein in the primary adsorbate layer associated with the surface. Chemical modification of the abundant lysine residues associated with proteins with thiol tethers allows the selective association of the thiol groups to gold surfaces without denaturation of the biomaterial. Reaction of the lysine residues with Traut's salt (**2**) yields the thiol-tethered protein that binds spontaneously to Au supports.^[126b] Catalase was functionalized and linked to a gold electrode by using this method (Figure 7B).

An enzyme base layer associated with a conductive support was used as an active interface for the stepwise construction of three-dimensional, multilayer protein arrays. Figure 8 shows a method to organize a multilayer network of glucose oxidase (GOx) on a gold electrode through a primary thiolate bridging unit.^[118] The primary enzyme layer is treated by a two-step synthesis with 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid (**3**) and the enzyme GOx. The number of repeated steps controls the number of layers associated with

the electrode. It was shown that the surface density of the enzyme in each layer is almost identical, approximately 5×10^{-11} mol cm⁻² per layer up to a network of 12 layers. A similar approach was used to assemble layered protein electrodes composed of two enzymes in an ordered manner.^[119b] Choline oxidase was assembled in the form of two consecutive protein layers and acetylcholine esterase was covalently linked to the base enzyme array in a further two-layered structure (Figure 9). Other multilayer enzyme networks on a base-thiolated bridging monolayer were also reported.^[119d, 120] A nonorganized enzyme multilayer assembly of glucose oxidase (GOx) was produced by cross-linking the enzyme in the presence of an amino-functionalized electron-transfer mediator on top of a primary thiolated monolayer associated with the electrode, using glutaric dialdehyde as the cross-linker.^[119d]

3. Chemical Modification of Surfaces and Proteins to Yield Layered Enzyme Electrodes

The previous section emphasized the nature of chemical bonds between the monolayer spacer units and the electrode that led to the linkage of proteins to the solid support. The surface functions associated with different supports, or with the monolayer(s) assembled on the electrodes, can be further modified by a variety of chemical functions that allow subsequent covalent coupling of proteins. Also, chemical

Table 4. Enzymes (proteins) covalently linked to Au electrodes by functionalized thiolated monolayers.

Enzyme/protein	Enzyme/protein loading [mol cm ⁻²]	Electrochemical response	Substrate	Analyzed concentration range	Response time	Optimal pH	Electrode stability	Ref.
glucose oxidase (EC 1.1.3.4) from <i>Aspergillus niger</i>	–	amperometric	glucose	–	–	7.0	–	[18c]
	7.5×10^{-12}	amperometric	glucose	1–20 mM	–	7.3	14 d	[118]
	$(1-4) \times 10^{-11}$	amperometric	glucose	1–25 mM	–	7.0	20 d	[119a,b]
	–	amperometric	glucose	$1 \times 10^{-5} - 6 \times 10^{-3}$ M	10 s	–	–	[119c]
	–	amperometric	glucose	–	–	–	–	[119e]
glucose dehydrogenase (EC 1.1.99.17) from <i>Acinetobacter calcoaceticus</i>	–	amperometric	glucose	–	10 s	6.0–9.5	60 d	[120]
bilirubin oxidase (EC 1.3.3.5) from <i>Myrothecium verrucaria</i>	6×10^{-12}	amperometric	bilirubin	10–120 μ M	20 s	8.0	75 d	[121]
malic enzyme (EC 1.1.1.40) from chicken liver	4×10^{-12}	amperometric	malate	$1 \times 10^{-7} - 1 \times 10^{-3}$ M	–	7.2	–	[122]
diaphorase (EC 1.6.99) from <i>Bacillus stearothermophilus</i>	6×10^{-12}	amperometric	NADH	$1 \times 10^{-5} - 5 \times 10^{-4}$ M	–	7.5	–	[123]
glutathione reductase (EC 1.6.4.2)	2×10^{-11}	–[a]	glutathione oxidized	–	30 min	7.2	–	[116]
microperoxidase 11	$(0.8-2.4) \times 10^{-10}$	amperometric	H ₂ O ₂	–	–	7.0	30 d	[125a]
			organic peroxides	$5 \times 10^{-5} - 3 \times 10^{-3}$ M	–	non-aqueous	–	[125b]
			hemoproteins	$5 \times 10^{-5} - 1 \times 10^{-3}$ M	–	7.0	–	[125c]
catalase (EC 1.11.1.6) from bovine liver	–	–[b]	–	–	–	–	–	[126]
acetylcholinesterase (EC 3.1.1.8)	–	amperometric	acetyl choline	8–80 mM	–	7.8	–	[119b]
choline oxidase (EC 1.1.3.17)	–	amperometric	choline	10–60 mM	–	7.8	–	[119b]

[a] Spectral detection of the product. [b] Scanning tunneling microscopy (STM) study.

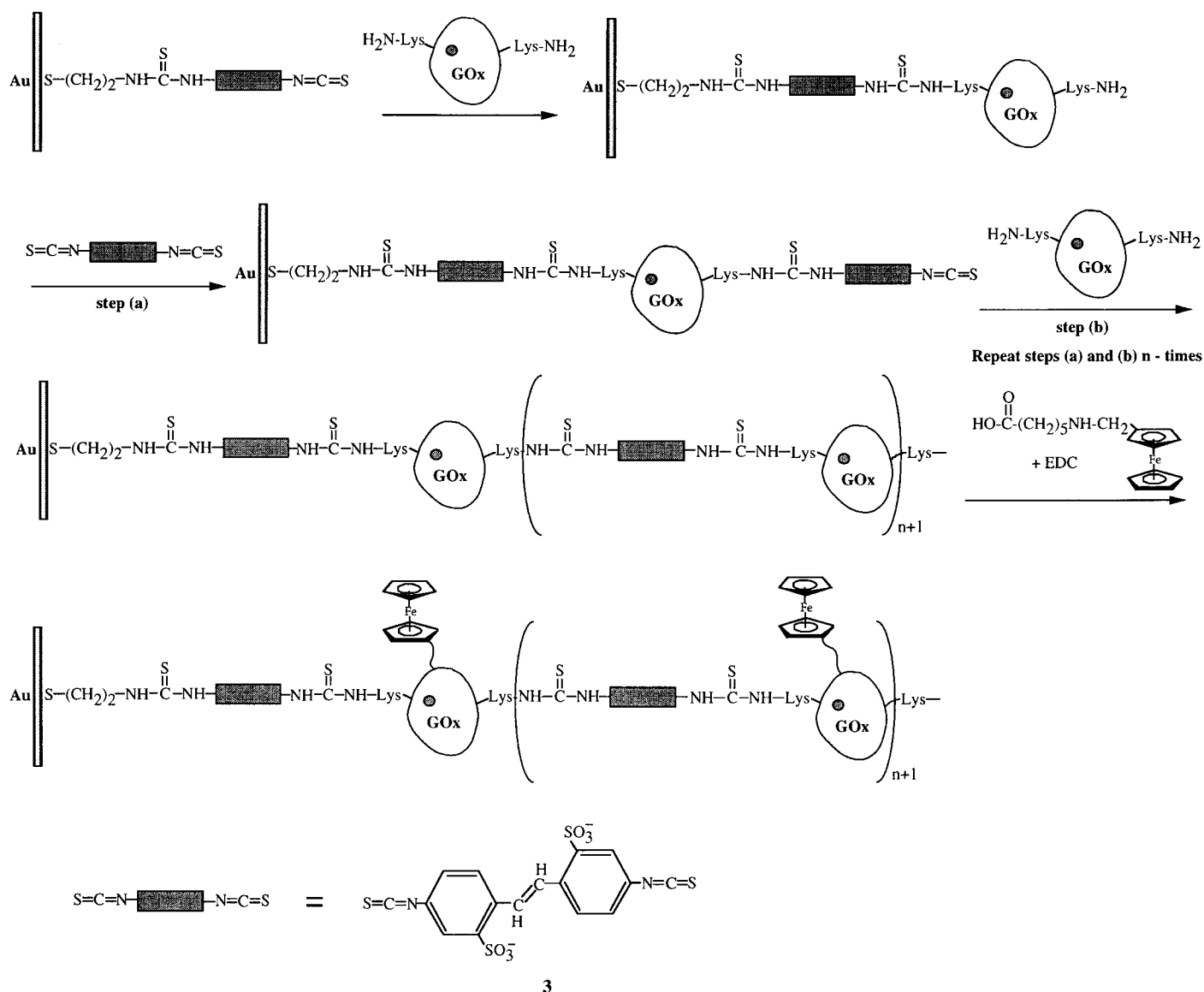


Figure 8. Stepwise assembly and electrical contacting of a cross-linked multilayer array of glucose oxidase (GOx) on a Au electrode.

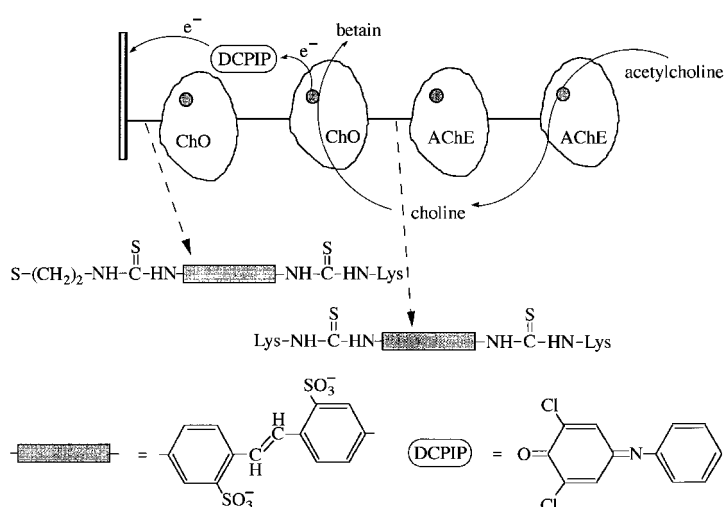


Figure 9. Assembly of a layered array of organized multienzymes for the amperometric sensing of acetylcholine: ChO = choline oxidase; AChE = acetylcholine esterase.

modification of the protein allows the generation of chemical functions that can be linked to the activated monolayer.^[126a] Figure 10 lists a series of functional units used for the modification of conductive supports and applied to the secondary coupling of proteins. The amino functions of lysine residues on the proteins can be linked to surface carboxylic groups generating amide bonds (Figure 10a) or to surface aldehyde functions to yield imine bonds^[24a,b, 124a] (Figure 10b).^[71, 127] Alternative means for attaching proteins to conductive surfaces include nucleophilic substitution of surfaces functionalized with cyanuric chloride (Figure 10c),^[45–50] incorporation of the isothiocyanate functionalities (Figure 10d),^[116c, 118] and Michael additions to quinone functions linked to electrodes (Figure 10e). The latter quinone–enzyme monolayer assembly represents an enzyme layer that is bridged to the electrode by a redox-active component.^[128] Aromatic amines linked to surfaces enable the generation of the surface-bound diazonium salt, which reacts with tyrosine or histidine residues to form proteins linked to

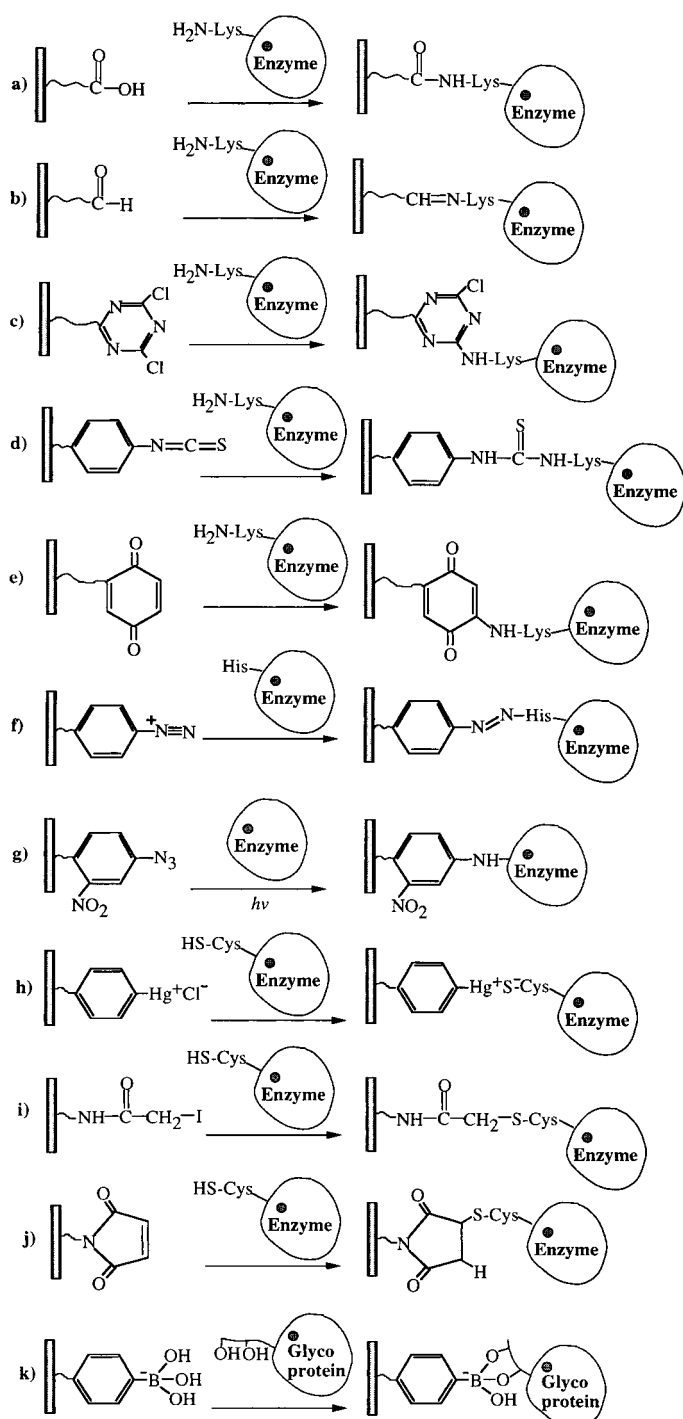


Figure 10. a)–k) Different monolayer-functionalized electrodes for the covalent linkage of enzymes.

the solid support through azo groups (Figure 10 f).^[127c] Arylazides are frequently used as photoactivated labels of proteins. Accordingly, the photochemical activation of a phenylazide monolayer yields the respective nitrene, which reacts with the amino group of lysine residues (Figure 10 g).^[129]

The linkage of proteins to solid supports through lysine (or glutamic/aspartic residues) is limited by the fact that proteins usually include many of these hydrophilic residues on the protein periphery. As a result, a heterogeneity in the modes of

protein linkage and orientation in respect to the surface is obtained. The structural alignment of the redox protein relative to the conductive support is essential for many bioelectronic applications, and hence the development of methods for specific binding and alignment of proteins on surfaces is important. Cysteine is usually an uncommon amino acid residue in proteins. A single cysteine residue on the protein periphery, or a genetically engineered cysteine component in the protein, allows the linkage of proteins to surfaces at a single point. Solid supports functionalized by *p*-mercurybenzoate,^[19c] iodoacetamide layers,^[64] or maleimide,^[130] were applied for the covalent linkage of cysteine residues as monolayers on surfaces (Figure 10 h–j). As examples, the cysteine site of the photosynthetic reaction center (from *Rhodospirillum rubrum* R-26) was covalently linked to an iodoacetamide monolayer immobilized onto a pyrolytic graphite electrode.^[19c] Genetically engineered cytochrome *b*₅ (in which threonine 8 or threonine 65 were replaced with cysteine units) was immobilized onto glass by a siloxane bridging layer.^[72, 130] The bifunctional reagent, *N*-succinimidyl-3-maleimidopropionate, was covalently linked to an aminosiloxane layer associated with a glass surface, and the cysteine-modified proteins were bound to the maleimide sites by a nucleophilic Michael addition. Similarly, genetically engineered myoglobin was bound to a haloalkylsilylated glass support.^[130c] A similar approach was used to immobilize a synthetic de novo protein consisting of 128 amino acids (14728 Da) in a four-helix-bundle configuration, in which their flexible Gly-Gly-Cys units were attached to the surface maleimido groups.^[131] An oriented genetically engineered cytochrome *b*₅ was generated on an electrode^[132] by treating the thiol groups of the cysteine residue with terminal thiol groups of the monolayer to produce disulfide bonds. Glycoproteins (for example, GOx^[133]) exhibiting protein-associated sugar sites allow the binding of *cis*-diol sugar sites to a surface functionalized with phenyl boronic acid groups (Figure 10 k).

Potential-induced covalent attachment of proteins was suggested as a means to align and orient redox proteins on conductive supports.^[124a] A glassy carbon electrode was activated with a water-soluble carbodiimide, and cytochrome *c* was coupled to the functionalized electrode with an applied potential. Cytochrome *c* includes positively charged sites at the position where the edge of the heme is associated with the protein and where electron tunneling proceeds at a maximum rate.^[124b] Coupling of cytochrome *c* to the electrode at potentials more negative in respect to the zero charge potential (0.31 V versus the standard hydrogen electrode) was found to yield a cytochrome *c*-modified electrode that exhibits an effective electrical contact. Covalent attachment of the hemoprotein at potentials more positive than the potential of zero charge, generates a hemoprotein electrode that lacks direct electrical communication with the conductive support. The enhanced electrical contact of cytochrome *c* with the electrodes, upon the application of a negative potential in respect to the zero-charge value, was attributed to the alignment of the monolayer and the orientation of the hemoprotein by facing the heme site relative to the electrode

4. Noncovalent Coupling of Proteins to Solid Supports by Electrostatic, Hydrophobic, and Hydrophilic Interactions

Hydrophobic and hydrophilic interactions of enzymes with membranelike layered assemblies, or electrostatic interactions between charged interfaces and proteins, can lead to organized, supramolecular layered protein interfaces. A mixed, self-assembled monolayer consisting of octadecylthiol and dodecyl thiol was assembled on Au electrodes. The short-chain, charged thiols provide defect sites (or “pockets”) for the association of the enzyme fumarate reductase.^[134] The resulting enzyme electrode exhibits direct electrical contact between the redox site and the electrode surface, and the bioelectrocatalyzed reduction of fumarate enables the application of the modified electrode as an amperometric fumaric acid sensor.

Hydrophobic membrane proteins incorporate into a lipid layer supported on surfaces only if an aqueous layer separates the lipid layer from the substrate. This separation was achieved by transferring lipids to hydrophilic surfaces either by the Langmuir–Blodgett technique^[135] or by the fusion of liposomes.^[136] Incorporation of the membrane protein ATPase into a lipid layer associated with an Au surface was accomplished by the fusion of ATPase-containing liposomes with a functionalized lipid layer (Figure 11).^[137] A thiol-functionalized, helix-forming polypeptide was assembled onto

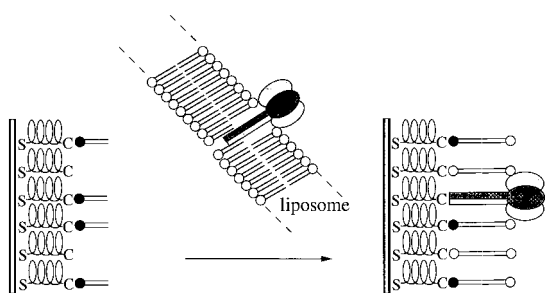


Figure 11. Hydrophobic association of liposome-bound ATPase onto thiolated, amphiphilic, helical oligopeptides.

an Au surface and the lipid DMPE (dimyristoylphosphatidyl ethanolamine) was covalently coupled to the carboxylic acid terminus of the peptide. The resulting lipid layer was mixed with liposomes that contain ATPase and spontaneous fusion of the liposomes with the lipid layer resulted in the incorporation of ATPase into the bilayer. The ATPase bilayer assembly was used as a semisynthetic proton-pump system.

Hydrophobic proteins such as fibrinogen, lysozyme, pyruvate kinase, or RNAase were adsorbed onto alkylthiolates associated with Au surfaces.^[138] Mixed monolayers consisting of the oligo(ethylene oxide) and alkane thiols were found to resist nonspecific hydrophobic adsorption of the proteins when a sufficiently high mole fraction of the ethylene oxide was included in the monolayer.

Electrostatic interactions combined with hydrophilic adhesion may lead to irreversible adsorption and alignment of proteins on monolayers terminated with carboxylic acids.^[139] Cytochrome c was adsorbed onto a 16-sulfanylhaxadecanoic

acid ($\text{HS}(\text{CH}_2)_{15}\text{CO}_2\text{H}$) monolayer associated with an Au surface. The resulting protein-functionalized electrode exhibits electrical contact with the electrode support, and from the rate constant for the electron transfer at the interface, $k_{\text{et}}^0 = 0.1 \text{ s}^{-1}$, a distance between the heme center of cytochrome c and the electrode of 31 Å was estimated.

5. Noncovalent Coupling of Proteins to Surfaces through Affinity Interactions

Affinity interactions between an enzyme and its substrate, a receptor protein and its recognition pair, or antigen–antibody pairs are often characterized by high association constants of the resulting complexes, which has enabled the use of specific recognition interactions to construct protein layers on solid supports. Furthermore, as the native receptor proteins often include more than one binding site for the substrates, and antibodies can be coupled to anti-antibodies, complex arrays of proteins can be tailored, and, specifically, multilayers of enzymes can be organized in a controllable order and structure.

Antigen–antibody interactions were used to organize layers and multilayers of glucose oxidase on glassy carbon electrodes (Figure 12).^[4] A glassy carbon electrode was coated with gelatin, and rabbit IgG antibodies were adsorbed onto the gelatin. A conjugate consisting of glucose oxidase linked to the anti-rabbit IgG antibody derived from goats was linked to the antibody associated with the gelatin to yield an enzyme-layered electrode (Figure 12A). This concept was further developed to construct multilayers of the enzyme on electrodes

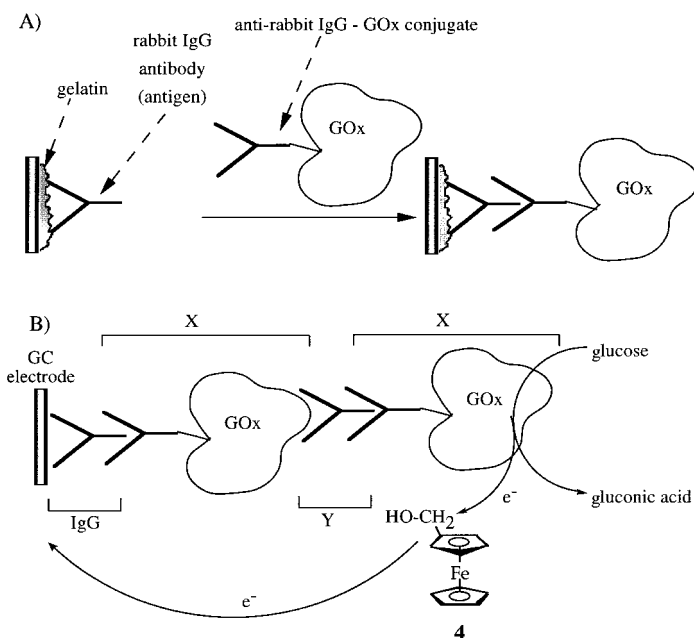
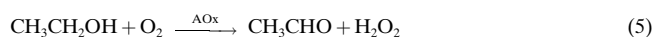


Figure 12. Assembly of enzyme layers on electrodes by noncovalent antigen–antibody interactions: A) Association of an antibody–enzyme conjugate to an antigen-monolayer electrode. B) Generation of an enzyme multilayer electrode (GOx multilayer glassy carbon electrode) by the application of an anti-IgG-GOx conjugate (X) and an IgG and anti-GOx antibody (Y) as linking components (>). The enzyme electrode is electrically contacted by the diffusional electron mediator ferrocenylmethanol (4).

(Figure 12B): Mouse IgG antibodies were adsorbed onto a gelatin layer associated with a glassy carbon electrode. The conjugate X consisting of glucose oxidase and an anti-mouse IgG antibody derived from goats was linked to the primary mouse antibody that acts as the antigen. A monoclonal mouse anti-GOx IgG antibody (Y), was then linked to the primary GOx layer. By the repeated interaction of the electrode with X and Y, a controllable number of layers could be deposited on the electrode. The resulting enzyme multilayer electrode was electrically contacted with the electrode, using ferrocenylmethanol (**4**) as a diffusional electron mediator. The effectiveness of the bioelectrocatalyzed oxidation of glucose is controlled by the number of layers deposited onto the electrode support. The transduced currents are enhanced as the number of enzyme layers associated with the electrode are increased, which implies that the sensitivity of the sensing electrode can be tuned by the number of enzyme layers assembled onto the electrode.

Biotin–avidin affinity interactions were used to assemble monolayer and multilayer enzyme electrodes (Figure 13).^[7] From the covalent immobilization of avidin on a glassy carbon electrode was studied and the importance of a long spacer to preserve the affinity properties was demonstrated.^[140] A monolayer of horseradish peroxidase (HRP) was deposited onto a carbon electrode using biotin-avidin affinity interactions^[7a] (Figure 13 A). Poly(oxyalkylene)diamine (Jeff-

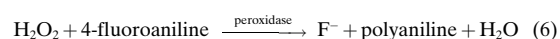
amine ED-600) was coupled to carboxylic acid residues associated with the carbon surface as a hydrophilic spacer, and the resulting surface amino functionalities were biotinylated. Biotinylated HRP was linked to the modified surface using avidin as a polydentate linker for the biotin units (Figure 13 B). The resulting HRP monolayer electrode stimulated the bioelectrocatalyzed reduction of H_2O_2 and the oxidation of *ortho*-hydrobenzoquinone. Biotin–avidin interactions were also used to assemble monolayer and multilayer enzyme arrays on other conductive supports.^[7b,c] Avidin was adsorbed onto a Pt electrode and biotinylated alcohol oxidase (AOx) linked to the avidin layer. By the sequential reaction of the enzyme layer with avidin and biotinylated AOx, a controllable number of enzyme layers was deposited onto the electrode. The enzyme electrode biocatalyzes the oxidation of ethanol to acetaldehyde [Eq. (5)]. The amperometric



response of the electrode as a result of the oxidation of H_2O_2 was used to quantitatively sense ethanol in blood and liquor samples in the concentration range 10^{-4} – 10^{-1} mg mL⁻¹. The sensitivity of the enzyme electrode was controlled by the number of enzyme layers associated with the electrode.

A thin layer of poly(L-lysine) (PL) assembled on gold surfaces was found to control the specific adsorption of proteins.^[141] PL functionalized with biotin units was electro-

statically associated with a base thiolate monolayer of 11-sulfanylundecanoic acid. Avidin was found to bind selectively to the biotin sites. By using surface plasmon resonance measurements and fluorescence-probe labeling the surface coverage of lysine residues was found to be 4×10^{14} lysine residues per cm², and that of avidin molecules 3×10^{12} molecules per cm². The thickness of an avidin monolayer was estimated to be 41 Å. Affinity interactions in biotin/avidin/enzyme systems were studied using nano-techniques (STM and AFM) and used to prepare nanostructures with maskless photolithography.^[142] Affinity interactions of glycoproteins and the respective lectins were similarly used to organize protein layers on solid supports.^[143] The glycoprotein glucose oxidase forms an affinity complex with concanavalin A. Accordingly, a cross-linked glucose oxidase/peroxidase monolayer was assembled on the lectin layer (concanavalin A) associated with a fluoride-sensitive field-effect-transistor (FET; Si/SiO₂/Si₃N₄/LaF₃ layers) to sense glucose.^[143a] The oxygen-mediated biocatalyzed oxidation of glucose generates H_2O_2 , which is transformed in the presence of peroxidase and *p*-fluoroaniline to fluoride ions [Eq. (6)] that are sensed by the FET device.



Upon the deactivation of the enzyme, the sensing interface associated with the FET device can be replaced and reloaded by interaction of the sensing matrix with α -D-mannopyranose. This sugar exhibits a high affinity for concanavalin A, and thus the

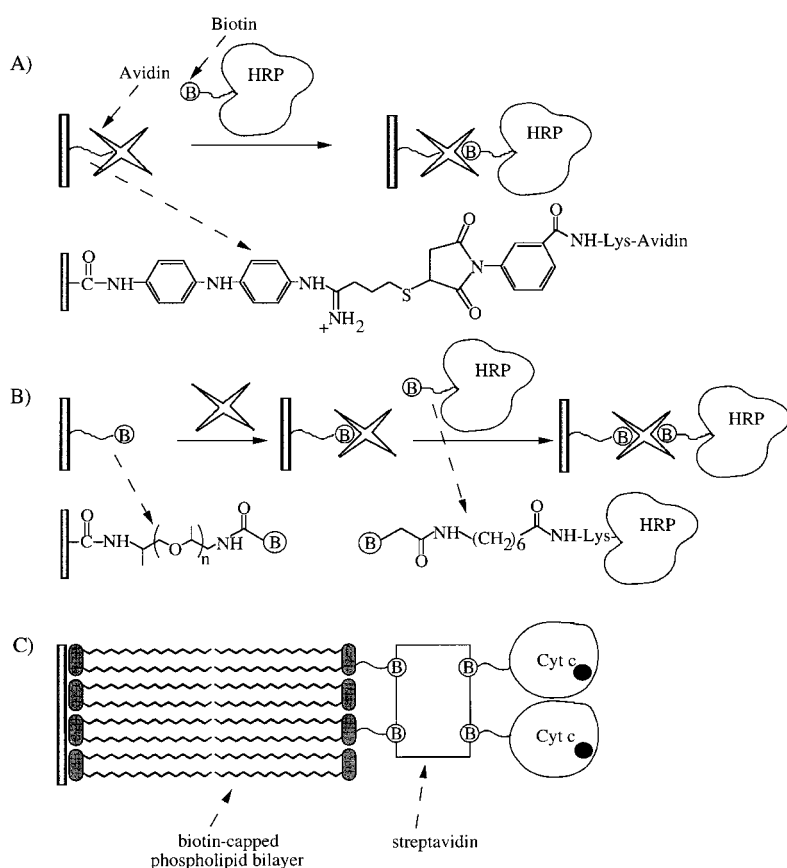


Figure 13. Organization of enzyme electrodes based on avidin–biotin interactions: A) Using a biotinylated enzyme and an avidin-monolayer electrode, B) using a biotinylated enzyme, a biotinylated monolayer electrode, and avidin as a cross-linker, C) aligned deposition of a biotin site-specific functionalized cytochrome c onto a biotin-capped phospholipid bilayer through a streptavidin linker.

original glycoprotein is removed from the sensing interface.

Biotin–avidin (or streptavidin) interactions were used to align and orient redox proteins (Figure 13C).^[143b] A bilayer consisting of 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[biotinyl] and 1,2-di[*cis*-9-octadecenoyl]-*sn*-glycero-3-phosphocholine was deposited onto a glass substrate. Avidin or streptavidin were used as cross-linkers for the alignment of the cytochrome *c* after the site-specific biotinylation at the cysteine residue 102 with *N*-[6-(biotinamido)hexyl]-3'-(2'-pyridyldithio)propionamide. Linear dichroism and fluorescence anisotropy measurements enabled one to conclude that the cytochrome *c* is oriented, and its tilt-angle is $(41 \pm 11)^\circ$ relative to the bilayer matrix.

Choline-functionalized monolayers assembled on a gold electrode demonstrated affinity for a chimera protein made by the fusion of the β -galactosidase and the choline-binding domain.^[144] The enzyme immobilized through affinity interactions was biocatalytically active for the hydrolysis of (*p*-aminophenyl)- β -D-galactopyranoside, a synthetic substrate of β -galactosidase, and the released *p*-aminophenol was detected electrochemically.

Cofactor–protein interactions can be used to assemble enzymes on solid supports. Redox cofactors such as flavin adenine dinucleotide phosphate (FAD) or pyrroloquinoline quinone (PQQ, **5**) are tightly associated with the protein by noncovalent interactions. Other redox cofactors, such as nicotinamide adenine dinucleotide (NAD^+ , **6**), and nicotinamide adenine dinucleotide phosphate (NADP^+ , **7**), operate by a diffusional route and form temporary affinity complexes with the respective NAD(P)^+ -dependent enzymes that enable cofactor-mediated electron transfer. The affinity interactions between cofactors and proteins enable the assembly of redox-enzyme electrodes (Figure 14A).

A monolayer of **5**, covalently linked to the amino-derivatized flavin adenine dinucleotide **8**, was assembled on an Au surface. Apo-glucose oxidase (apo-GOx), which lacks its native FAD cofactor, was reconstituted onto the semi-synthetic FAD cofactor associated with the electrode.^[145] The PQQ component was found to mediate the electron transfer from the FAD unit to the electrode surface, and the reconstituted enzyme revealed an unprecedentedly high bioelectrocatalytic activity for the oxidation of glucose (see Section 8). A PQQ monolayer assembled onto an Au electrode was similarly employed to reconstitute the PQQ-dependent apo-glucose dehydrogenase.^[2c, 146] The electrochemical oxidation of glucose was stimulated by the reconstituted biocatalyst in the presence of a diffusional electron-transfer mediator.

Redox proteins such as myoglobin were also reconstituted on conductive supports.^[147] For example, a Fe^{III} -protoporphyrin IX complex was assembled as a monolayer on an Au electrode and apo-myoglobin was reconstituted with this heme-cofactor monolayer. Although native myoglobin usu-

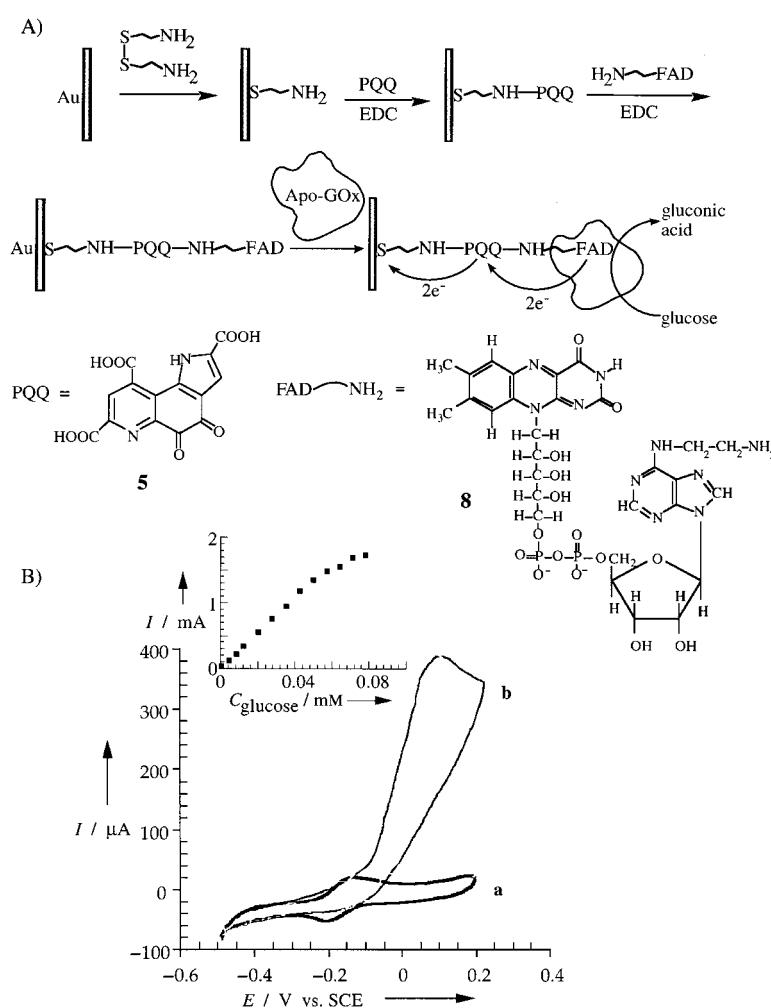


Figure 14. A) Reconstitution of apo-glucose oxidase on a PQQ-FAD monolayer assembled on a Au electrode. B) Cyclic voltammograms of the reconstituted glucose oxidase on a Au-electrode a) in the absence of glucose and b) with glucose (80 mM); potential scan rate: 5 mV s^{-1} . Inset: Calibration curve corresponding to the amperometric responses (measured by chronoamperometry) of the enzyme electrode at different concentrations of glucose.

ally lacks direct electrical communication with electrode supports because of insulation of the heme center, electrical contact between the surface-reconstituted myoglobin and the electrode was evident. This property was attributed to the alignment of the heme center on the electrode surface in a structural orientation that facilitates electron transfer to and from the electrode.

Artificial compounds capable of substituting for natural materials and exhibiting affinity interactions to proteins were immobilized as monolayers on electrodes and used as “instruction matrices” for assembling further protein layers. Artificial dyes exhibiting affinity interactions to NAD(P)^+ -dependent enzymes (for example, cibacron blue F3G-A) were assembled as monolayers on Au electrodes, and used for the anchoring of NAD^+ -dependent enzymes.^[148] The affinity complexes consisting of the layered dye–enzyme matrices exist in a bioactive configuration, but lack electrical contact with the electrode. Addition of the diffusional NAD^+ -cofactor was found to trigger the biocatalytic activities of the enzyme electrode.

6. Cross-Linking of Protein (Enzyme) Layers Stabilized by Affinity Interactions on Electrodes

Electrically contacted biocatalytic electrodes of NAD^+ -dependent enzymes were organized by generating affinity complexes between a catalyst/ NAD^+ monolayer and the respective enzymes.^[6] A PQQ monolayer covalently linked to an amino-functionalized nicotinamide adenine dinucleotide (9) was assembled onto an Au electrode. The resulting monolayer-functionalized electrode binds NAD^+ -dependent enzymes such as lactate dehydrogenase (LDH) or alcohol dehydrogenase (AlcDH) by affinity interactions between the cofactor and biocatalyst (Figure 15 A). These enzyme electrodes electrocatalyze the oxidation of the respective substrates,

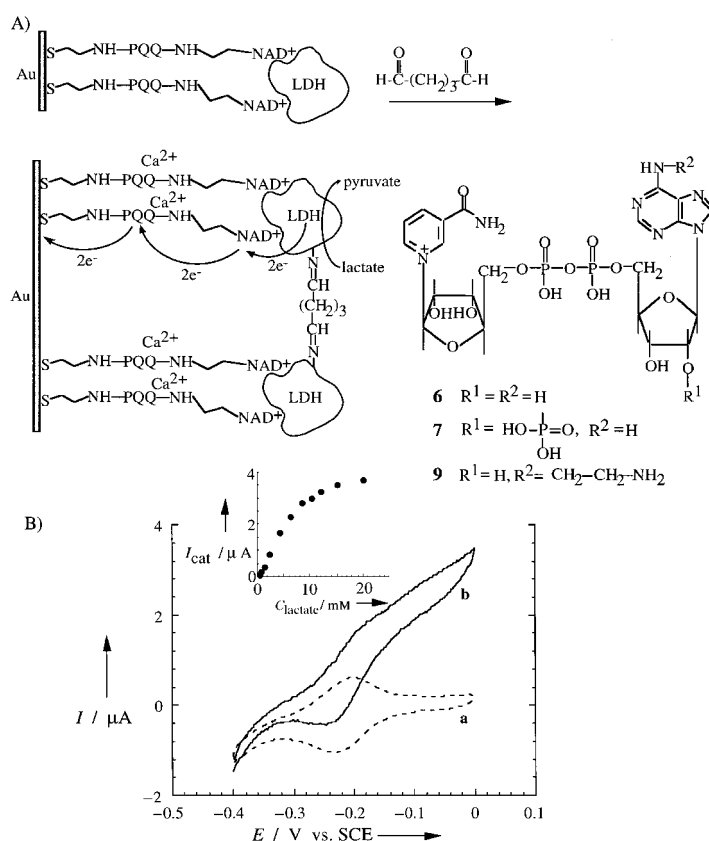


Figure 15. A) Assembly of an integrated LDH-monolayer electrode by cross-linking an affinity complex formed between the enzyme and a PQQ- NAD^+ monolayer Au electrode. B) Cyclic voltammograms of this electrode: a) in the absence of lactate and b) with lactate (20 mM); potential scan rate: 2 mV s^{-1} . Inset: amperometric responses of the integrated LDH layered electrode at different concentrations of lactate.

lactic acid or ethanol. The bioelectrocatalytic transformations proceed via the biocatalyzed substrate-induced formation of NADH and its oxidation by the PQQ catalytic site. The resulting enzyme electrode revealed only temporary stability and approximately 25% of the biocatalyst dissociated from the monolayer to the electrolyte solution within 30 min. Cross-linking the enzyme layer associated with the PQQ/ NAD^+ -cofactor monolayer with glutaric dialdehyde generated a stable, integrated, electrically contacted, cofactor-enzyme electrode (Figure 15 A).

Protein-protein affinity interactions play a major role in biological electron transfer. For example, cytochrome c mediates electron transfer to different redox enzymes, such as cytochrome oxidase, lactate dehydrogenase, or copper enzymes.^[149] These mediated electron transfer reactions proceed within the protein-protein affinity complexes.^[150] Microperoxidase-11 (MP-11, 10, see Figure 16) is a heme-containing oligopeptide consisting of 11 amino acid residues that compose the microenvironment of the active site of cytochrome c.^[151] It is obtained by digestion of the native cytochrome c with trypsin. Despite the structural similarities between MP-11 and cytochrome c, the heme sites of the oligopeptide and the native protein differ substantially in their redox potentials, $E^\circ = -0.40 \text{ V}$ for MP-11^[125a] and $E^\circ = +0.012 \text{ V}$ (versus SCE) for cytochrome c.^[149] Microperoxidase-11 was assembled as a monolayer on an Au electrode,^[152] and this functionalized electrode stimulated electron transfer to hemoproteins such as myoglobin, hemoglobin, and cytochrome c.^[125c] The mediated electron transfer was attributed to the formation of affinity complexes between the proteins and MP-11 at the electrode interface. The affinity interactions between MP-11 and hemoproteins or cytochrome-dependent enzymes were used to assemble a nitrate reductase enzyme electrode (Figure 16).^[152] The cytochrome-dependent nitrate reductase (NR, E.C. 1.9.6.1 from *Escherichia coli*) forms an affinity complex with the MP-11 monolayer associated with the electrode. Cross-linking of the enzyme-MP-11 affinity complex layer with glutaric dialdehyde generated a stable, enzyme-layered electrode that effected the bioelectrocatalyzed reduction of nitrate to nitrite. The bioelectrocatalyzed transformation proceeds with a current efficiency of approximately 85%, and the electrode was applied as an amperometric nitrate sensor.

Cobalt(II)-protoporphyrin IX reconstituted myoglobin was also found to form an affinity complex with the MP-11 monolayer electrode (association constant $K_a = 1.6 \times 10^5 \text{ M}^{-1}$, electron-transfer rate constant in the resulting supramolecular complex $k_{et} = 0.3 \text{ s}^{-1}$).^[153] The MP-11 mediates the electrocatalyzed reduction of Co^{II} -myoglobin and the resulting cobalt hydride hydrogenates alkynes, for example, acetylene dicarboxylic acid to maleic acid. The cross-linking of the Co^{II} -reconstituted myoglobin affinity complex at the MP-11 monolayer with glutaric dialdehyde generated an integrated, stable, layered electrode for the electrocatalytic hydrogenation of acetylene dicarboxylic acid with a current yield of approximately 80%.

Recently, de novo synthesized four-helix polypeptides were applied to mimic functions of cytochrome b and to tailor layered cross-linked electrocatalytic electrodes. One such protein (14728 Da) that includes four histidine units in the respective "A"-helices was assembled onto Au electrodes (Figure 17). Two units of Fe^{III} -protoporphyrin IX were reconstituted into the assembly to yield a vectorial electron-transfer cascade.^[131] The affinity complexes formed between the de novo synthesized protein and the cytochrome-dependent nitrate reductase (NR) or with Co^{II} -protoporphyrin IX-reconstituted myoglobin^[154] were cross-linked with glutaric dialdehyde to yield electrically contacted electrocatalytic electrodes. The Fe^{III} -de novo protein/NR-electrode assembly

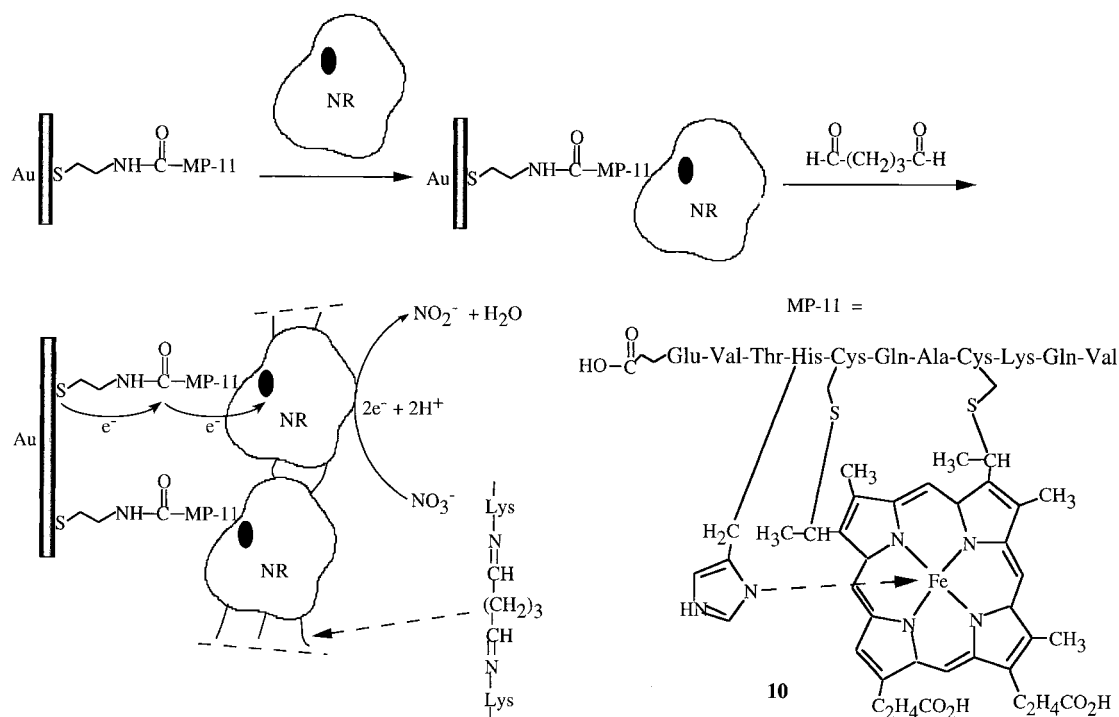


Figure 16. Assembly of an integrated nitrate sensor electrode by cross-linking of an affinity complex formed between MP-11 and nitrate reductase on a Au electrode.

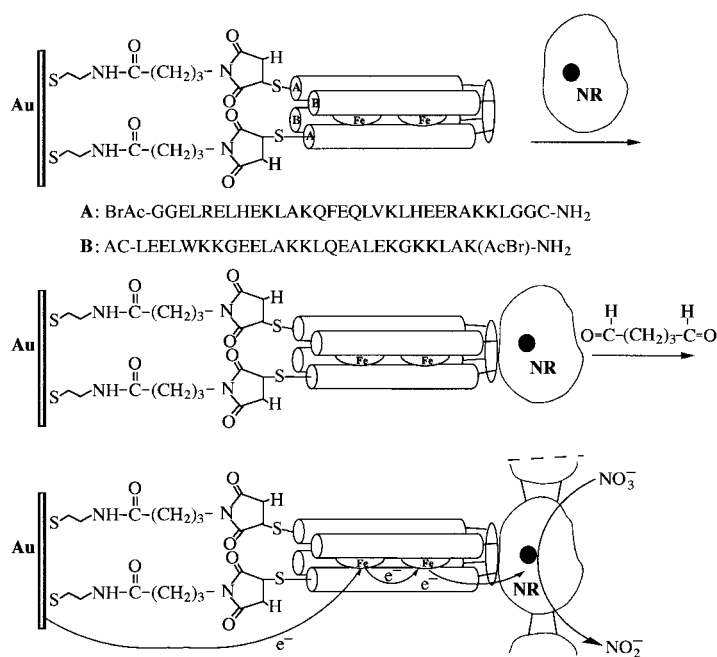


Figure 17. Assembly of a nitrate-sensing electrode by the cross-linking of an affinity complex formed between nitrate reductase and a de novo four helix-bundle protein reconstituted with Fe^{III}-protoporphyrin.

was applied to the electrocatalyzed reduction of NO_3^- to NO_2^- and acted as an amperometric NO_3^- sensor. The Fe^{III}-de novo protein/Co^{II} reconstituted myoglobin integrated electrode stimulated the electrocatalyzed hydrogenation of acetylene dicarboxylic acid to maleic acid.

7. Electron Transfer in Layered Enzyme Electrode Assemblies

The electrical contacting of redox proteins and the electrode supports is the essence of any biosensor or bioelectronic device. The direct electron transfer between redox-active sites of proteins and the electrode is usually prohibited since the redox center is sterically insulated by the protein matrices (see Introduction). Early studies have demonstrated that certain enzymes or redox proteins exhibit electrical communication with electrode supports, and biocatalyzed electrically stimulated transformations are driven by these enzymes.^[155] The direct electroreduction of H_2O_2 by horseradish peroxidase (HRP [Eq. (7)]) was demonstrated,^[156] and related heme-

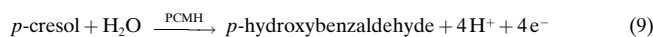


containing oxidases, for example, cytochrome c peroxidase,^[157] lactoperoxidase,^[158] chloroperoxidase,^[159] showed similar direct electron transfer with electrode surfaces. Laccase (a copper-containing polyphenol oxidase) was found to electrocatalyze the reduction of molecular oxygen [Eq. (8)].^[160] The direct electron transfer in these enzymes is



attributed to the location of the redox-active center at the protein periphery. For example, a detailed kinetic study^[161] of the peroxidase-catalyzed reduction of H_2O_2 revealed that 42% of the total enzyme molecules are aligned on the electrode surface in a configuration where the redox heme site is accessible for electron transfer. Some of the enzymes include two redox sites within the protein, and electron

transfer proceeds vectorially from a peripheral redox site to an inner redox-active component. For example, *p*-cresolmethyl hydroxylase (PCMH), an FAD- and heme-containing redox enzyme, effects the direct oxidation of *p*-cresol to *p*-hydroxybenzaldehyde [Eq. (9)].^[162] Similarly, flavocytochrome *c*₅₅₂

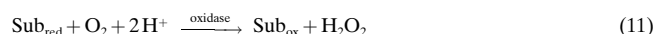


(sulfide cytochrome *c* oxidoreductase), which contains a FAD and two covalently linked heme groups, is bioelectrocatalytically active in the oxidation of sulfide to sulfur [Eq. (10)].^[163]



The direct electron transfer of this series of redox enzymes allows their application as bioactive sensing interfaces in amperometric biosensor devices. Detection of *p*-cresol,^[162] methylamine,^[164] and fructose^[165] was reported in the presence of *p*-cresolmethyl hydroxylase, methylamine dehydrogenase, and fructose dehydrogenase, respectively.

The direct electrical contact of certain enzymes with electrodes can be used to tailor bioelectrocatalytic assemblies for sensor applications. A variety of oxidases utilize molecular oxygen as the electron acceptor for the oxidation of their substrates (Sub). Enzymes such as catechol oxidase, amino acid oxidase, glucose oxidase, lactate oxidase, pyruvate oxidase, alcohol oxidase, xanthine oxidase, and cholesterol oxidase catalyze the O₂-oxidation of the respective substrates with the concomitant formation of H₂O₂ [Eq. (11)]. The



direct electron transfer between HRP and electrodes enables the electroreduction of H₂O₂ in the range −0.2 to 0 V (versus SCE) and allows for the coupling of HRP to these oxidases to yield amperometric biosensors. The amount of generated H₂O₂ is controlled by the substrate concentration and, hence the resulting current provides a quantitative measurement of the analyzed substrate. Accordingly, amperometric biosensors based on HRP coupled with glucose oxidase for glucose analysis,^[166] with alcohol oxidase for alcohol detection,^[167] with choline oxidase for choline analysis,^[166a] and with amino acid oxidase for amino acids determination^[168] were constructed. Various conducting materials such as carbon black,^[156] pyrolytic graphite,^[169] platinized carbon particles,^[170] and colloidal gold^[171] were used to support the enzymes, and carbon paste^[172] or polypyrrole^[166e, 172a] were used to entrap the biocatalysts.

Electrical contact of redox enzymes that lack direct electrical communication with electrodes can be established by mediated electron transfer using synthetic or biologically active charge carriers. Mediated electron transfer (MET) can be effected by a diffusional mechanism (Figure 18A). The electron relay is oxidized at the electrode surface (in an oxidative biotransformation) or reduced at the electrode (in a reductive biotransformation). Diffusional penetration of the reduced or oxidized relays into the protein yields sufficiently short electron-transfer distances in respect to the active redox center for MET and the electrical activation of the biocatalyst. Ferrocene derivatives, ferricyanide, quinones, *N,N'*-dialkyl-

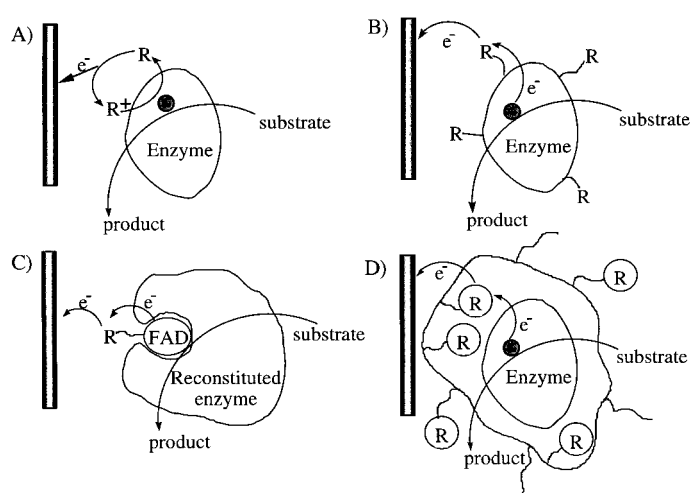


Figure 18. Electrical contacting of redox enzymes and electrode supports (R is an electron relay): A) Using a diffusional electron relay, B) by chemical modification of the protein with electron relay units, C) by reconstitution of an apo-flavoenzyme with a synthetic electron-relay-FAD dyad, D) by immobilization of the biocatalyst into a redox polymer.

4,4'-bipyridinium, and other electroactive molecular substrates were employed for MET and electrical activation of redox enzymes.^[9b] Table 5 gives a representative summary of bioelectrocatalytic transformations stimulated by diffusional MET.

Chiroselective mediated electron transfer has been addressed in a series of studies using diffusional chiral electron mediators.^[185] The chiral electron relays (*S*)- or (*R*)-*N,N*-dimethyl-1-ferrocenyl-ethylamine [(*S*)- or (*R*)-(Fc)] were reported to stimulate chiroselective bioelectrocatalyzed oxidation of glucose in the presence of glucose oxidase,^[185a] whereby the oxidation in the presence of (*S*)-(Fc) was double that in the presence of (*R*)-(Fc). Kinetic analysis of the bioelectrocatalyzed oxidation of glucose by the two enantiomeric electron relays suggests that the protein induces chiral discrimination through diastereoisomeric interaction with the penetration–dissociation routes of the electron mediator, to and from the biocatalyst. Chiral discrimination in the MET, and the subsequent bioelectrocatalyzed transformations, were observed using different diffusional electron relays and various enzymes.^[185c, 185d]

The concept of enantioselective electrical contacting of redox enzymes and electrode surfaces was further developed by the organization of a chiral electron mediator monolayer on an electrode.^[186] (*S*)- or (*R*)-2-Methylferrocene carboxylic acid was assembled as a monolayer on an Au electrode (Figure 19). The monolayer-mediated chiroselective oxidation of glucose in the presence of glucose oxidase and an approximate 1.9-fold enhanced biocatalytic oxidation of glucose was observed in the presence of the monolayer electrode functionalized with the (*S*)-relay enantiomer.

Chemical modification of redox enzymes with electron-relay groups enables the mediated electron transfer and the electrical wiring of the proteins (Figure 18B).^[187] Covalent attachment of electron-transfer units at the protein periphery, as well as inner sites, yields short inter-relay electron-transfer distances. Electron “hopping” or tunneling from the periph-

Table 5. Diffusional electron-transfer mediators applied to the immobilized enzymes.

Enzyme	Mediator	Mediator redox potential [mV versus SCE]	Ref.
glucose oxidase (EC 1.1.3.4) from <i>Aspergillus niger</i>	1,4-benzoquinone	39	[173]
	1,1-dimethylferrocene	100	[174]
	ferrocenecarboxylic acid	275	[175]
	phenazine methosulphate	–161	[176]
	tetrathiofulvalene	300	[177]
	tetracyanoquinodimethane	127	[178]
xanthine oxidase (EC 1.2.3.3) from buttermilk	[Fe(CN) ₆] ^{4–}	180	[10a]
cholesterol oxidase (EC 1.1.3.6) from <i>Pseudomonas sp.</i>	ferrocenecarboxylic acid	275	[179]
hydrogenase (Fe/S type)	dimethylviologen	–681	[180]
horseradish peroxidase (EC 1.11.1.7)	[Fe(CN) ₆] ^{4–}	180	[181]
lactate dehydrogenase (EC 1.1.2.3) from yeast	[Fe(CN) ₆] ^{4–}	180	[173a]
glucose dehydrogenase (EC 1.1.99.17) from <i>A. Calcoaceticus</i>	1,1'-dimethylferrocene	100	[182]
	phenazine ethosulfate	–172	[183]
	ferrocenylmethanol	185	[184]
NADH dehydrogenase (EC 1.6.99) from <i>Bacillus stearothermophilus</i>	ferrocenecarboxylic acid	275	[184]

ery to the active site, or vice versa, enables electron transfer between the redox enzyme and its environment. Glucose oxidase was covalently modified with ferrocene electron-relay groups by carbodiimide coupling of ferrocenecarboxylic acid to the amino groups of the lysine functions of the protein backbone.^[187a,b] Some other chemical procedures were also used to produce relay groups peripherally bound to proteins. For example, carbonyl groups, generated in glycoproteins (for example, glucose oxidase) by oxidative treatment with periodate were coupled to the amino-functionalized ferrocene through the formation of Schiff bases.^[187c] A ruthenium complex was assembled on the glucose oxidase backbone that was pre-modified with pyridine units.^[187b] The relay groups randomly distributed on the protein provided electrical contact between the diffusional enzyme and the unmodified electrode surface. It has been demonstrated that longer spacer groups bridging the electron-relay groups and the enzyme provide higher mobility, shorten the electron-transfer distance, and enhance the enzyme bioelectrocatalytic activity.^[187c] Partial and reversible unfolding of the enzyme by urea during the covalent

modification of the protein with the relay is also important since it allows the attachment of the electron mediator to inter-protein positions close to the enzyme active site.^[188] The electron-relay-tethered enzymes were also cross-linked on an electrode surface, producing a nonorganized multi-layer,^[119d] or incorporated into a conductive polymer on electrode supports.^[189] The immobilized enzymes were electrically contacted through the electron-relay groups to provide electron propagation through the layer.

Chemical modification of redox proteins with synthetic electron mediators is always accompanied by the partial degradation of the native biocatalyst. The effectiveness of electrical contacting is enhanced upon increasing the loading of the electron mediator on the protein, since electron-transfer distances are shortened. The increase of the loading, however, partially deactivates of the enzyme. With glucose oxidase, the optimal MET was found at a loading corresponding to 12–13 ferrocene units per molecule.^[188] The rate constant of the electron transfer between the enzyme FAD site and the nearest electron-relay group was found to be

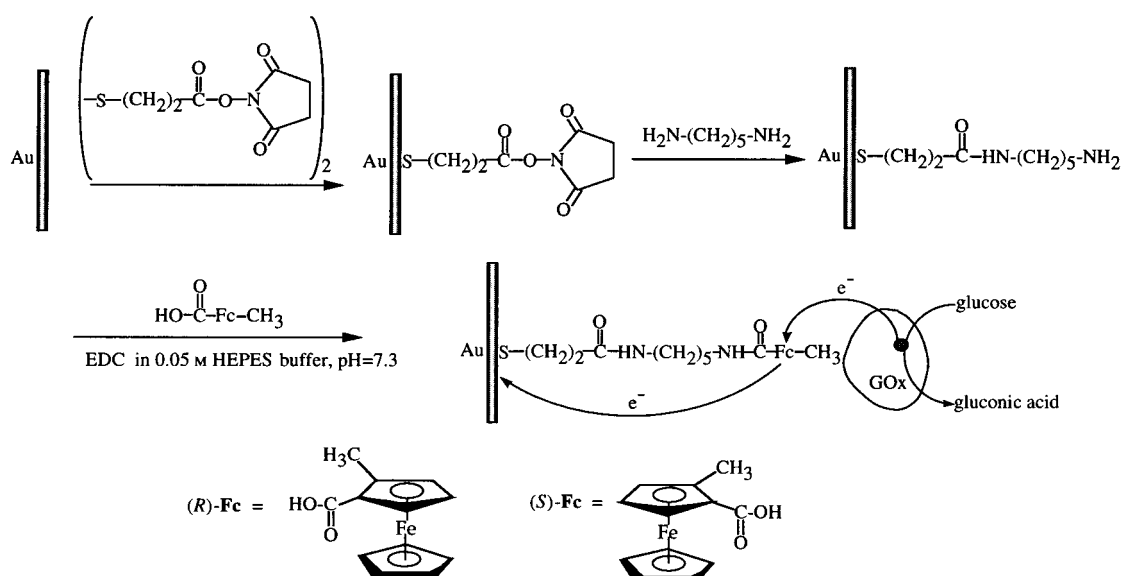


Figure 19. Organization of a chiral ferrocene monolayer on an electrode.

about 0.9 s^{-1} , that is, substantially lower than the electron transfer to the native dioxygen electron acceptor of the enzyme, which proceeds with a rate constant of about $5 \times 10^3 \text{ s}^{-1}$.^[188] Improvement of the electrical contact between the active center of the enzyme and the electrode can be envisaged by two complementary modes: 1) modification of the redox protein with relay units at optimal positions for mediated electron transfer, and 2) alignment of the relay-functionalized bioelectrocatalyst in respect to the electrode surface.

A novel means for the electrical wiring of redox enzymes and, specifically, flavo-redox-proteins was reported by the site-specific modification of the redox enzyme with the electron-relay group, and by using a reconstitution method (Figure 18C).^[190] The native cofactor, for example, flavin adenine dinucleotide phosphate (FAD) is substituted with a semisynthetic FAD cofactor tethered to an electron relay group to yield an electrically contacted biocatalyst. The semisynthetic cofactor composed of *N*-(ferrocenylmethyl)aminohexanoic acid (**11**) covalently linked to *N*⁶-(2-aminoethyl)-FAD (**8**; Figure 20) was used to reconstitute apo-glucose oxidase or apo-D-amino acid oxidase. The resulting reconstituted enzymes revealed direct electrical contact with electrode surfaces and acted as “electroenzymes” for the electroinduced biocatalyzed oxidation of glucose or D-alanine.^[190]

A further approach for bringing redox enzymes in contact with electrode supports is the entrapment of the protein in redox-tethered polymers or conductive polymers (Figure 18D).^[25, 31c, 191] The redox relay groups tethered to the polymer penetrate into the redox protein and reach appropriate distances to mediate electron transfer. It has been shown that the chain lengths tethering the redox mediator to the polymer control the efficiency of mediated electron transfer.^[192] Polylysine was functionalized with *N*-carboxyal-kyl-*N'*-methyl-4,4'-bipyridinium (**12**) redox-active groups. Mediated electron transfer to glutathione reductase and the bioelectrocatalyzed reduction of oxidized glutathione (GSSG) were examined with different chain lengths that tether the bipyridinium group to the polymer (Figure 21). Mediated electron transfer was found to be enhanced when the tethering chain is longer. The bioelectrocatalyzed reduction of GSSG in the presence of the enzyme and the functionalized polymer was attributed to the formation of a complex between the positively charged polylysine and the negatively charged glutathione reductase (GR), where long tethering bridges attain short distances of the redox relay in respect to the protein active center, thereby enhancing the MET.

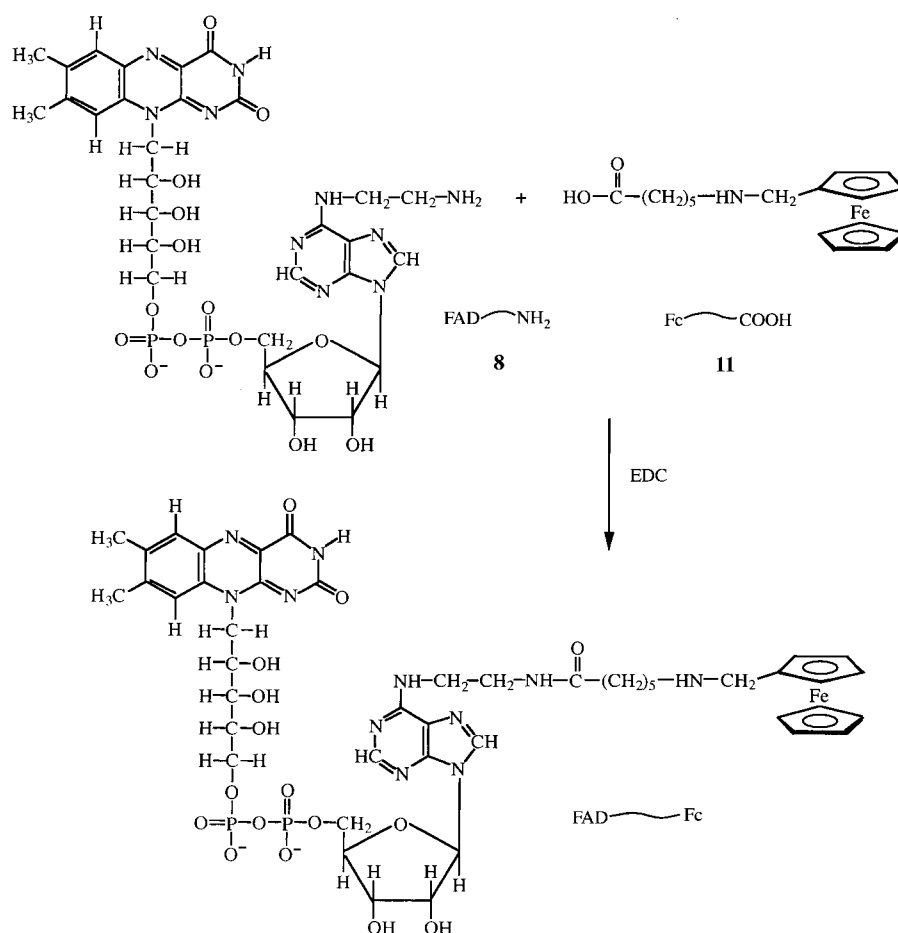


Figure 20. Synthesis of the FAD-ferrocene dyad.

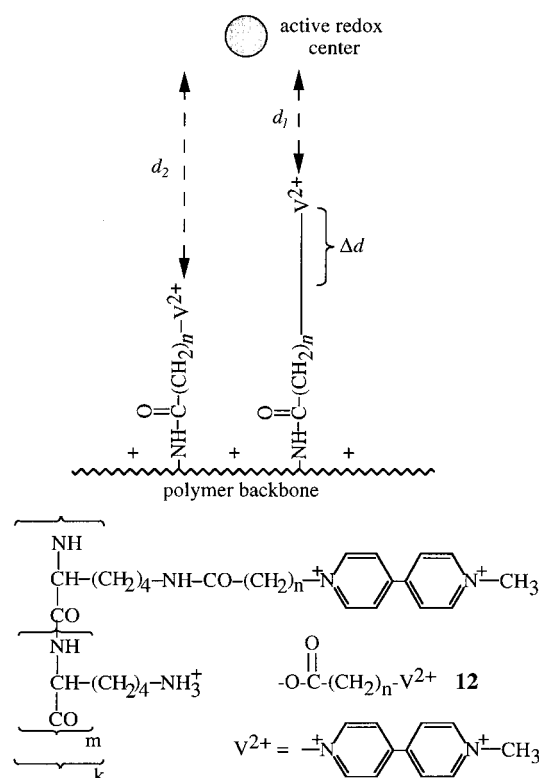


Figure 21. Schematic model for the spatial orientation of a redox center in a protein relative to a positively charged redox-tethered polymer.

Many examples of thin-film bioelectrocatalytic electrodes with the enzyme embedded in the polymer exist.^[31c] The amphiphilic polymers for the complementary immobilization and electrical wiring of enzymes are usually based on polypyrroles,^[193] polythiophenes,^[31d] siloxanes,^[29d, 31g] polyamines,^[31h] and copolymers of 4-vinylpyridine and 4-aminostyrene.^[25] The polymeric backbone was modified with ferrocene groups,^[31g, 193a, 194] Os(bpy)₂ complexes,^[25] or quinones^[195] to establish electrical contact with oxidative enzymes, for example, glucose oxidase, glutamate oxidase, or polyphenol oxidase. Viologens (*N,N'*-dialkyl-4,4'-bipyridinium salts) tethered to the polymer matrices were applied to electrically contact reductive enzymes, such as nitrate reductase^[31d, 193c] and pyridine nucleotide oxidoreductase.^[196]

8. Electrical Contact of Redox Proteins at Monolayer-Functionalized Electrodes

Functionalization of electrodes with low molecular weight, electrochemically inactive compounds was found to affect the electrical communication between redox proteins or redox enzymes and electrodes. Reversible electrochemistry of cytochrome *c*, which includes a partially exposed heme site,^[197] was observed at Au electrodes (in some investigations at Pt or Ag electrodes) modified with monolayers of different promoters.^[149c, 198] These promoters usually include a sulfur group as an anchor on the surface (thiol or disulfide) and an organic functional unit that interacts with the cytochrome *c* protein backbone. The promoter–monolayer prohibits the direct contact between the protein and the metal electrode surface, thus preventing irreversible unfolding and denaturation of the protein. The interactions between the promoter and the protein molecules are based on hydrogen bonds and/or attractive electrostatic association, which result in the specific alignment of the protein at the electrode surface. In the aligned configuration the proteins exhibit short electron-transfer distances that allow efficient electrical contact and electrochemical processes. The most common promoter for the activation of the interfacial electrochemistry of cytochrome *c* is bis(4-pyridyl)disulfide.^[199] Several other thiol- or disulfide-derivatized molecules also act as efficient promoters.^[200] Amino acid and oligopeptide monolayers were used as promoters for interfacial electrochemistry with cytochrome *c*^[201] as well as for reversible electrochemical activation of other cytochromes.^[202] Other promoters, such as imidazole,^[203] thiophene,^[204] and iodide^[205] deposited as monolayers onto Au or Ag electrodes were also applied to facilitate the electrochemistry of cytochrome *c*. A monolayer of colloidal Au particles with diameters of 12 nm on a SnO₂ electrode was demonstrated to be an efficient promoter for cytochrome *c* electrochemistry.^[206] The nanometer-scale morphology of the metal particles plays a key role in the electrical contacting of the protein. A similar methodology was applied to activate the interfacial electrochemistry of other redox proteins and enzymes such as ferritin, blue copper proteins, azurin, pseudoazurin, umecyanin, stellacyanin, plantacyanin, plastocyanin, and cucumber ascorbate oxidase^[207] on Au electrodes modified with 4-pyridinethiol (or some other thiol

and disulfide derivatives) monolayers. Protonated amino-siloxane-modified indium oxide electrodes were reported to be efficient interfaces for stimulating electron transfer to the negatively charged ferredoxin.^[208] These promoters apparently align the protein molecules on the electrode surface to an orientation that facilitates electron transfer.

Low molecular weight, redox-active oligopeptides containing redox groups derived from native biomaterials may establish direct electron-transfer communication with electrodes. Microperoxidase-11 (**10**; see Figure 16) is a heme-undecapeptide, which constitutes the active-site microenvironment of cytochrome *c*.^[151] Since the active site of MP-11 is not sufficiently isolated by the oligopeptide chain the direct electrochemistry of MP-11 was observed in aqueous^[209a] and nonaqueous^[209b] solutions at unmodified electrodes. Microperoxidase-11 was covalently linked to amino-^[125a] and carboxyl-functionalized^[125d] Au electrodes through carboxylic or amino groups of MP-11, respectively. The MP-11 monolayer revealed electrocatalytic activities for H₂O₂ reduction^[125a] and organic peroxide reduction in nonaqueous solutions.^[125b]

The MP-11 monolayer forms affinity complexes with hemoproteins such as cytochrome *c*, myoglobin, and hemoglobin.^[125c] Microgravimetric analysis enabled the association constant of myoglobin to the MP-11 monolayer to be determined as $K_a = 3.9 \times 10^2 \text{ M}^{-1}$. The MP-11 and hemoprotein affinity complexes enable the mediated reduction of the heme sites in the different proteins (Figure 22 A). The MP-11 monolayer was found to yield an affinity complex with the native cytochrome *b*₅-dependent nitrate reductase (NR, E.C. 1.9.6.1 from *Escherichia coli*).^[152] The association constant of the MP-11/NR complex was determined by quartz-crystal-microbalance measurements to be $K_a = 3.7 \times 10^3 \text{ M}^{-1}$, and the surface coverage of the enzyme on the surface was estimated to be $3.8 \times 10^{-12} \text{ mol cm}^{-2}$. The layered affinity complex was cross-linked to yield an integrated, stable, electrically contacted layered electrode (see Figure 16). Figure 22 B shows the electrocatalytic currents transduced by the MP-11/NR layered-electrode in the presence of nitrate. The transduced currents are controlled by the nitrate concentration in the electrolyte sample, (Figure 22 B, inset), and thus the functionalized electrode acts as an amperometric biosensor for nitrate.

Low molecular weight native cofactors such as PQQ (**5**) were reported to form an electrical contact between NAD(P)⁺-dependent enzymes and electrode supports. The PQQ cofactor was linked to a cystamine monolayer^[104b, 122] and was found to act as an electrocatalyst for the electro-oxidation of NAD(P)H, especially in the presence of Ca²⁺ ions.^[210a] Accordingly, a PQQ monolayer covalently linked to malate dehydrogenase (MalDH; Figure 23) was used to electrically activate the enzyme.^[122] The biocatalyzed oxidation of malic acid by MalDH generates diffusional NADPH that is oxidized by the PQQ electrocatalyst. The transduced current relates to the concentration of NADPH (or malic acid) and thus the layered enzyme electrode exhibits elements of an amperometric biosensor. The use of NAD(P)⁺-dependent enzymes as bioactive materials for amperometric biosensor devices requires, however, the integration of the cofactor and

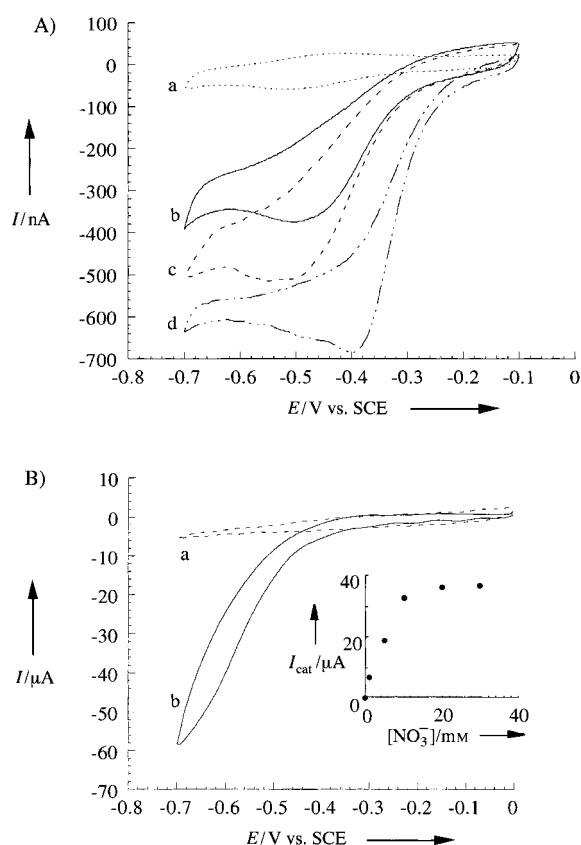


Figure 22. A) Cyclic voltammograms of a MP-11-monolayer electrode: a) in the absence and b) with hemoglobin (6×10^{-5} M); c) with myoglobin (2×10^{-4} M); d) with cytochrome c (2×10^{-4} M); scan-rate: 5 mV s^{-1} . B) Cyclic voltammograms of the electrode with a cross-linked MP-11/nitrate reductase monolayer: a) in the absence of nitrate, b) with nitrate (20 mM); potential scan rate: 5 mV s^{-1} . Inset: amperometric responses of the integrated electrode at different concentrations of nitrate.

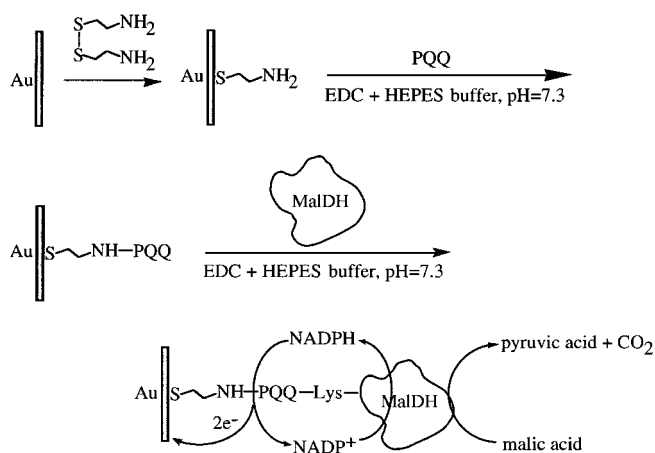


Figure 23. Assembly of a PQQ-MalDH monolayer electrode, and the amperometric sensing of malic acid using NADP^+ as a diffusional cofactor.

the enzyme in a rigid configuration, as a result of the high cost of the NAD(P)^+ -cofactors, which prevents their use as diffusional components. The NAD(P)^+ -dependent enzymes operate in nature by a diffusional route in which the oxidized cofactor penetrates into the protein, accepts the electrons (as a hydride equivalent), and diffuses from the protein matrices. Further oxidation of the NAD(P)H by the electrode requires

a catalyst.^[210] The affinity interactions between the NAD^+ -cofactor and the respective cofactor-dependent enzymes were used to assemble integrated electrodes with layers of cofactors and enzymes exhibiting electrical communication.^[6] The semisynthetic NAD^+ -cofactor **9** was covalently linked to a PQQ monolayer (see Figure 15 A). The NAD^+ -dependent enzymes lactate dehydrogenase (LDH) or alcohol dehydrogenase (AlcDH) bind to the PQQ- NAD^+ monolayer by affinity interactions. Microgravimetric, quartz-crystal-microbalance studies revealed the coverage of LDH to be $3.5 \times 10^{-12} \text{ mol cm}^{-2}$. The cross-linking of the enzyme layer with glutaric dialdehyde yields a stable, layered cofactor–enzyme electrode that stimulates the electrooxidation of lactic acid (see Figure 15 B). The biocatalyzed oxidation of lactate proceeds by the integrated cofactor–enzyme assembly where the enzyme-generated NADH is oxidized by PQQ in the presence of Ca^{2+} ions. The amount of reduced NADH cofactor is controlled by the concentration of lactate, and thus the transduced currents correlate with the concentration of lactate. The electrode thus provides a general configuration for biosensor electrodes employing NAD^+ -dependent enzymes.^[6]

The covalent attachment of electron relays to layered enzyme electrodes provides a means to facilitate electrical communication between the enzyme layer(s) and the electrode, and to electrically activate the biocatalyst.^[116] A glutathione reductase monolayer was assembled onto Au electrodes through a thiolate bridging unit (Figure 24 A).^[116a,b] The enzyme layer was functionalized with **12-H**, where the chain length tethering the electron relay was systematically lengthened. Electroreduction of the bipyridinium unit was found to activate the enzyme for the reduction of oxidized glutathione (GSSG). The effectiveness of GSSG reduction was controlled by the length of the chain tethering the electron relay to the protein, with longer bridging chains enhancing the bioelectrocatalyzed reduction of glutathione (Figure 24 B). This result was rationalized in terms of shorter electron-transfer distances between the electron-relay sites and the enzyme redox center for the systems with bipyridinium units tethered by long chains. It was found that it is important to modify the protein with the bipyridinium components in the presence of urea to attain electron transfer between the enzyme redox center and the electrode. Added urea partially unfolds the protein and enables the substitution of inner-protein lysine residues with the bipyridinium electroactive sites (see Section 7).^[116a,b]

A multilayer of glucose oxidase (GOx, see Figure 8) was similarly modified with a carboxyferrocene derivative (**11**).^[118] The electroactive ferrocene relay units are oxidized by the electrode, and these then oxidize the redox sites of the enzyme. The amperometric response of the layered electrodes was found to be controlled by the number of protein layers,^[119b] implying that all of the enzyme layers are electrically contacted with the electrode by the ferrocene units. The rate-limiting process in the oxidation of glucose is the electron transfer between the substrate and the active center. This results in different amperometric responses of the electrode at variable glucose concentrations, and allows the application of the layered enzyme electrode as an amperometric glucose

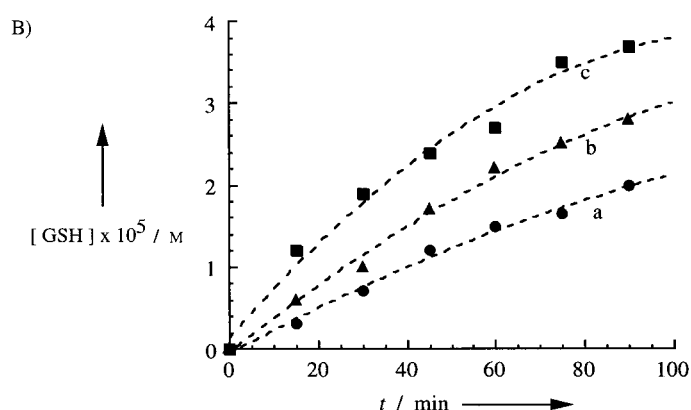
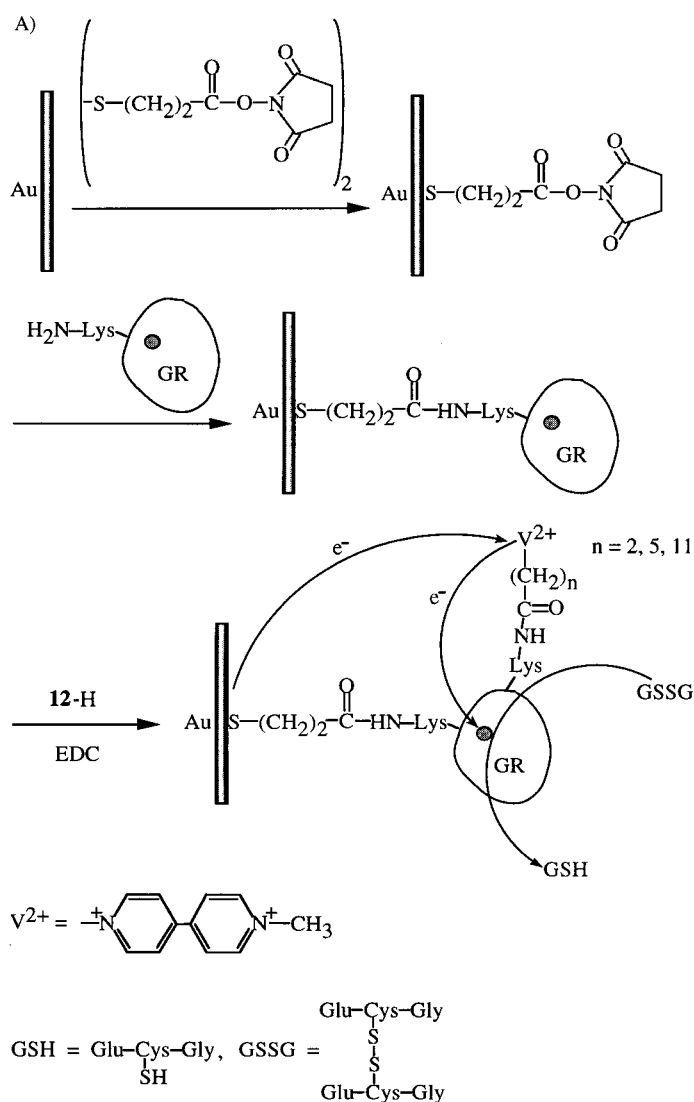


Figure 24. A) Assembly of an electrically contacted glutathione reductase electrode. B) Rate of bioelectrocatalyzed reduction of oxidized glutathione (GSSG) by this electrode using different tethering chain lengths of the contacting relay units: a) $n = 2$, b) $n = 5$, c) $n = 11$.

biosensor. A related thin layer of glucose oxidase, electrically contacted by ferrocene units, was assembled on an Au electrode by the cross-linking of GOx, 2-aminofluorene, and a monolayer of *p*-mercaptoaniline with glutaric dialdehyde.^[17b]

The reconstitution of apo-GOx on the PQQ-FAD monolayer (see Figure 14A) yields a stable, electrically contacted, bioelectrocatalytically active layer.^[145] The current densities transduced by the electrode appear to be unprecedentedly high in the area of bioelectronic devices: A current density of $300 \mu\text{A cm}^{-2}$ at a glucose concentration corresponding to 80 mM and at 35°C was found. The theoretical turnover rate of GOx at 35°C in the presence of molecular oxygen as an electron acceptor is approximately 900 s^{-1} ,^[145] while the calculated value of the current to be transduced by a densely packed GOx monolayer ($2.9 \times 10^{-10} \text{ mol cm}^{-2}$) operating at this maximal electron transfer turnover rate is approximately $300 \mu\text{A cm}^{-2}$, which is in excellent agreement with the experimental value. It was concluded that the reconstituted biocatalyst reveals the theoretical value for MET as a result of the alignment of the enzyme onto the electrode surface. The aligned enzyme allows the effective oxidation of the reduced FAD cofactor by the PQQ electron-relay unit and the oxidation of glucose by MET. The high current densities transduced by the GOx reconstituted onto the PQQ-FAD monolayer, and the insensitivity of the enzyme electrode to oxygen and other biological interferences, led to the suggestion that these functionalized enzyme electrodes could be miniaturized into implanted invasive microelectrodes for in vivo continuous monitoring of glucose levels in blood.

9. Biomaterial-Based Electrodes for Biofuel Cells

One of the attractive applications of bioelectrocatalytic electrodes is the development of biofuel cell elements. The biofuel cell utilizes biocatalysts for the conversion of chemical energy into electrical energy.^[211] Since many organic substrates undergo combustion in oxygen or are oxidized with the release of energy, the biocatalyzed oxidation of the organic material at two compartmentalized electrode interfaces could lead to the conversion of chemical energy into electrical energy. Abundant raw materials, such as methanol or glucose, can be used as fuel substrates for the oxidation, and molecular oxygen or H_2O_2 can act as the oxidizer. The extractable power (P) of a fuel cell is the product of the cell voltage (V_{cell}) and the cell current (I_{cell}). Although the ideal cell voltage is affected by the difference in the formal potential of the fuel and oxidizer substrates, irreversible losses in the cell voltage originate from kinetic limitations associated with the electron transfer, ohmic resistances, and concentration gradients. Similarly, the cell current is controlled by the size of the electrodes, the ion permeability, and transport across the membrane separating the cathodic and anodic compartments, and specifically, the rates of electron transfer at the anode and cathode interfaces. All of these parameters collectively influence the resulting cell power, and the V_{cell} and I_{cell} values should be optimized to obtain improved efficiencies.

The fact that layered biomaterial-functionalized electrodes catalyze the oxidation of substrates such as glucose, methanol, and lactic acid, or catalyze the reduction of substrates such as H_2O_2 , enables these electrodes to be used as key elements of biofuel cells. Accordingly, a biofuel cell element based on the bioelectrocatalytic oxidation of glucose by H_2O_2 was con-

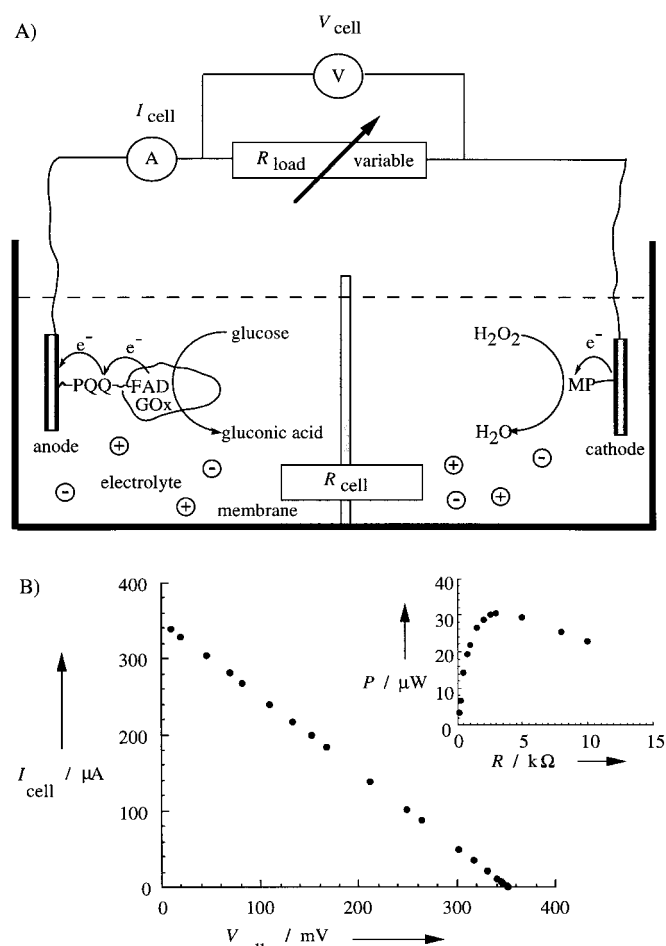


Figure 25. A) Schematic configuration of a biofuel cell employing glucose and H_2O_2 as a fuel and an oxidizer, respectively, and PQQ-FAD/reconstituted GOx MP-11-functionalized electrodes as biocatalytic anode and cathode, respectively. B) Current–voltage behavior of the biofuel cell at different external loads. Inset: electrical power P extracted from the biofuel cell at different external loads.

structured (Figure 25 A).^[212a] An electrically contacted glucose oxidase monolayer assembled on an electrode by the reconstitution of apo-glucose oxidase on a PQQ-FAD layer (see Figure 14 A) was used as the anode, whereas a MP-11-functionalized electrode acted as the cathode in the system. The bioelectrocatalyzed oxidation of glucose proceeds at the anode, while the MP-11-catalyzed reduction of H_2O_2 occurs in the cathodic compartment. The current–voltage behavior of the biofuel cell and the power extracted from the cell at different external loads and at optimized concentrations of the oxidizer and fuel substrates are shown in Figure 25 B. The maximum extracted power corresponds to $32\text{ }\mu\text{W}$ at an external load of $3\text{ k}\Omega$ (inset in Figure 25 B). The configuration of this biofuel cell represents a very general method for developing biofuel cell elements, and it can be extended to other oxidative enzymes and fuel substrates such as methanol oxidase or lactate oxidase and the respective alcohol or lactic acid fuel substances.

A different general approach to tailor biofuel cells is based on the bioelectrocatalyzed oxidation of 1,4-dihydronicotinamide cofactors. Various substrates, for example, alcohols,

hydroxy acids, or sugars, undergo biocatalyzed oxidation by enzymes dependent on the NAD(P)^+ cofactor. The bioelectrocatalytic oxidation of the resulting dihydronicotinamide cofactors (NAD(P)H) at the anode, with the concomitant reduction of the oxidizer (H_2O_2) at the cathode, could provide a general configuration for a biofuel cell (Figure 26 A).^[212b] The bioelectrocatalyzed oxidation of NADH by the PQQ-functionalized electrode represents the electrochemical transformation in the anodic compartment, while the MP-11-catalyzed reduction of H_2O_2 is the complementary process at the cathode interface. Figure 26 B shows the current–voltage behavior and the electrical power extracted from the cell at different external loads. The maximum extractable power from the cell was estimated to be $8\text{ }\mu\text{W}$ at an external load of $3\text{ k}\Omega$ (inset of Figure 26 B). Although the system represents a general methodology that utilizes NAD(P)^+ cofactors as the fuel of a biofuel cell, it is essential to further develop this system for future practical use. The cost of NAD(P)^+ cofactors prohibits their use as the primary fuels of the biofuel cell. It is essential to immobilize the cofactor on the anode interface and to couple it to a primary abundant fuel, for example, an alcohol, and the respective enzyme, namely

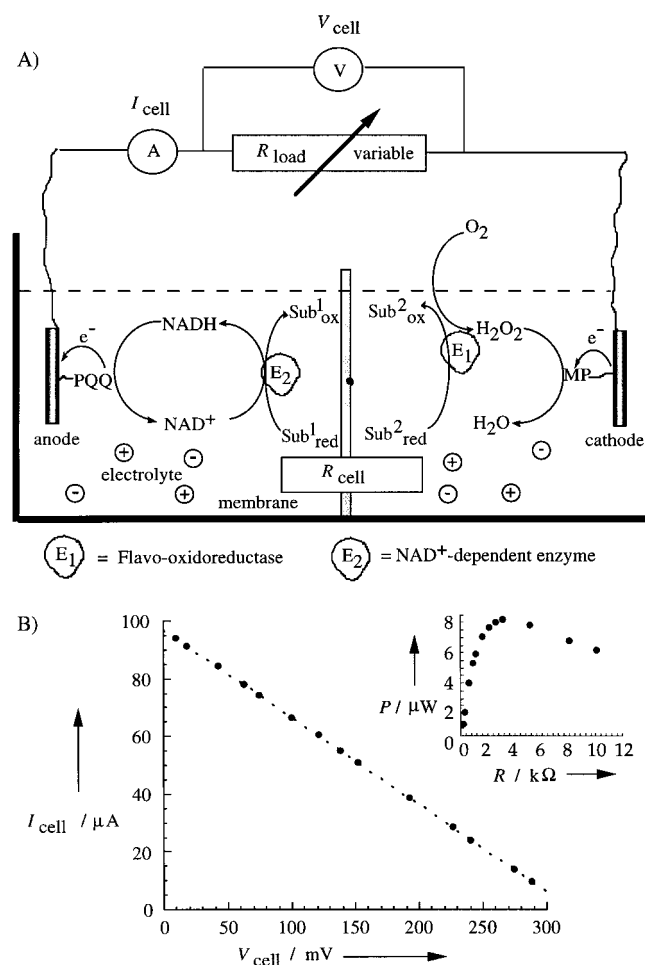


Figure 26. A) Schematic configuration of a biofuel cell employing NADH and H_2O_2 as a fuel and an oxidizer, respectively, and a PQQ-functionalized anode and a MP-11-functionalized cathode. B) Current–voltage behavior and electrical power P (inset) of the biofuel cell at different external loads.

alcohol dehydrogenase, for the in situ generation of the NAD(P)H cofactor. The progress in the organization of integrated, electrically contacted, bioelectrocatalytic NAD(P)⁺ electrodes (see Figure 15) paves the way toward engineering new layered enzyme electrodes for biofuel cells.

10. Microscale Patterning and Structuring of Biomaterials on Surfaces

The potential applications of biosensors and bioelectronic devices could be expanded to novel horizons if biomolecules, and specifically, enzymes, antigens, antibodies, and receptors, could be organized in ordered microstructured arrays on surfaces.^[213] The tailoring of multisensing surfaces (sensor batteries) for the simultaneous addressable detection of several analytes or the analysis of spatial distributions and gradients of analytes in samples could be envisaged by microstructured arrays of bioactive sensing materials. Also, patterned sensor arrays of spatially resolved biomaterials could act as self-calibrated sensor arrays, where one sensor domain is used to calibrate a secondary sensing interface. A further application of structurally ordered domains of biomaterials could include the organization of interacting arrays that respond to external physical or chemical stimuli. A series of enzymes in the appropriate ordering could lead to the transformation of the analyte substrate to a redox-active species that is electronically transduced by the conductive support. Similarly, a chemical reaction of two species generated by spatially separated biocatalysts could generate a product that activates a third spatially organized electroactive enzyme (gated bioelectronics).

The generation of microstructures consisting of conductive materials is a mature research field that has led to tremendous developments in microelectronics and information storage. Microscale lithography using UV irradiation, electron beams, and X-rays are common technologies for surface patterning.^[214] The addressing of biomaterials to target surface domains and their specific chemical or physical deposition in biologically active forms on these defined areas on the support represent scientific challenges of interdisciplinary interests. Substantial research efforts have recently been directed to the microscale-patterning of monolayers^[215a,b] and functionalized thin films on solid supports.^[215c,d]

Photolithography^[214] and micromachining of monolayers,^[216] microstamping of solid supports,^[215a,b, 217] and micro-writing on surfaces^[218] were often applied to generate patterned monolayers of controlled wettability,^[216b–d, 219] or chemical and electrical properties.^[220] The controlled etching of metals^[218] or the selective deposition of metals^[221] enabled the microscopic structuring of surfaces by a variety of polymeric, organic, conductive, and inorganic materials.

Several of the concepts of patterning surfaces with microscale chemical functions were used to generate arrays of biomaterials. Some of these methods were used to pattern oligonucleotide arrays^[213c, 222] or antigen–antibody structures.^[223] Other studies have used redox-inactive or model proteins to demonstrate the strategies of assembling protein structures on solid supports.^[224] Although the present review

emphasizes the use of redox proteins for bioelectronic applications, we take the liberty of surveying recent advances in the patterning of proteins on surfaces. We believe that these approaches may find central roles in tailoring future bioelectronic systems of different functions.

10.1. Patterning of Surfaces with Biomaterials by Covalent Bonding

Modification of the surface of solid supports with photoactivable groups allows the light-induced generation of reactive intermediates, for example, radicals, carbenes, nitrenes, that react with proteins to yield covalent bonds.^[129] Photoirradiation of the photosensitive monolayer on the solid support through a mask yields patterned domains of the reactive intermediates, which allow the covalent attachment of biomaterials to the activated surfaces. Figure 27 summarizes several photochemical routes to generate reactive

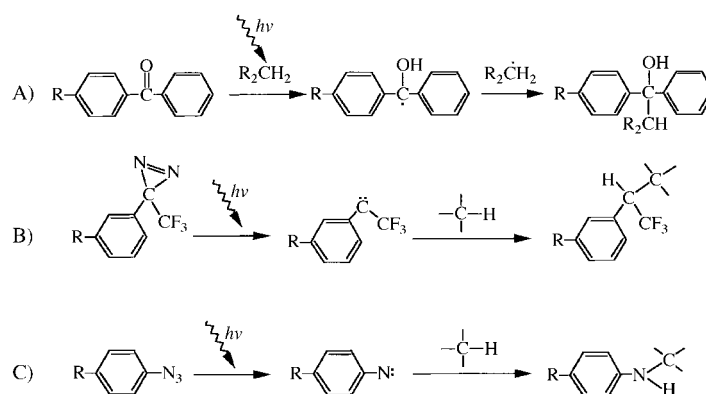


Figure 27. Photochemical generation of: A) benzhydrol radicals. B) carbenes, C) nitrenes, for covalent linkage to proteins.

intermediates. Benzophenone undergoes photochemical activation in the presence of a proton source to form the ketyl radical, and the recombination of the two radicals permits the formation of a new bond. Photolysis of aryldiazine generates the carbene and its insertion into a C–H bond allows proteins to be linked to the reactive intermediate. Irradiation of azides produces the aryl nitrene that reacts with C–H bonds to form the stable amine. Accordingly, Si chips were silylated by aminopropyltriethoxysilane to yield the amino-functionalized Si surface, which was then treated with benzophenone-4-isothiocyanate (**13**) or with 3-(*m*-isothiocyanatophenyl)-3-trifluoromethyldiazirine (**14**) to yield the thiourea-linked, photosensitive benzophenone or diazirine layers, respectively (Figure 28).^[225] Photolysis of the respective monolayers through masks produces the ketyl or carbene species that link biomaterials (proteins) to the Si surface. Aryl azides were used for the photochemical patterning of polymer-functionalized surfaces with proteins.^[226] By one approach, an aryl azide functionalized bovine serum albumin (BSA) was prepared by the reaction of BSA with *N*-(4-azidobenzoyloxy)-succinimide (**15**; Figure 29 A) and deposited onto a polyvinyl alcohol film. Irradiation of the resulting assembly

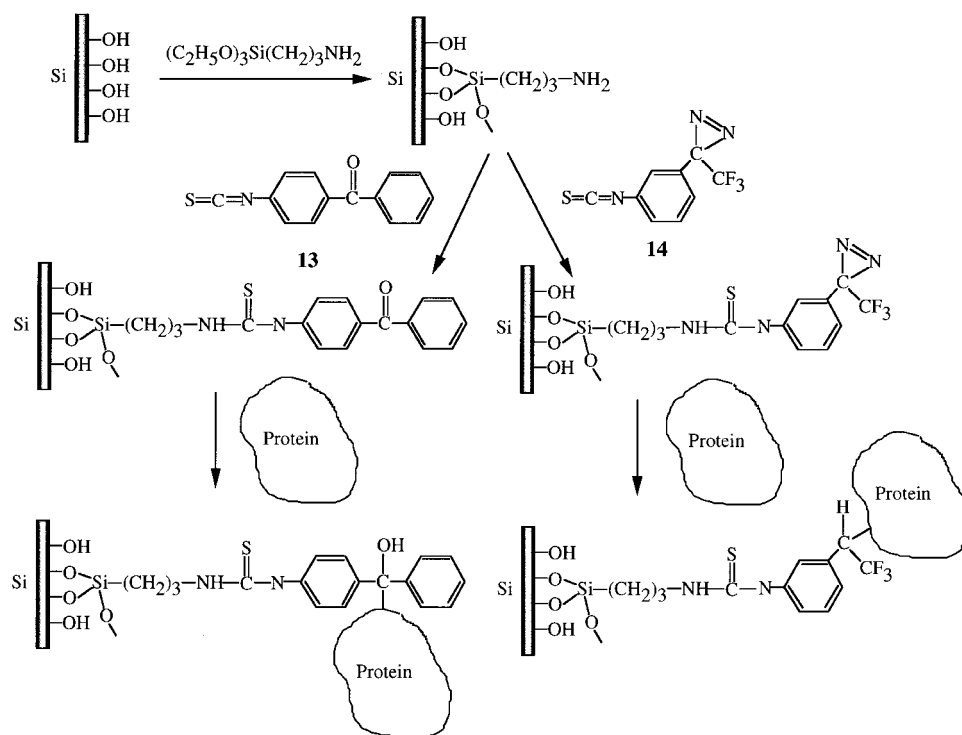


Figure 28. Photostimulated covalent attachment of proteins to a benzophenone- or a diazidine-functionalized layered support.

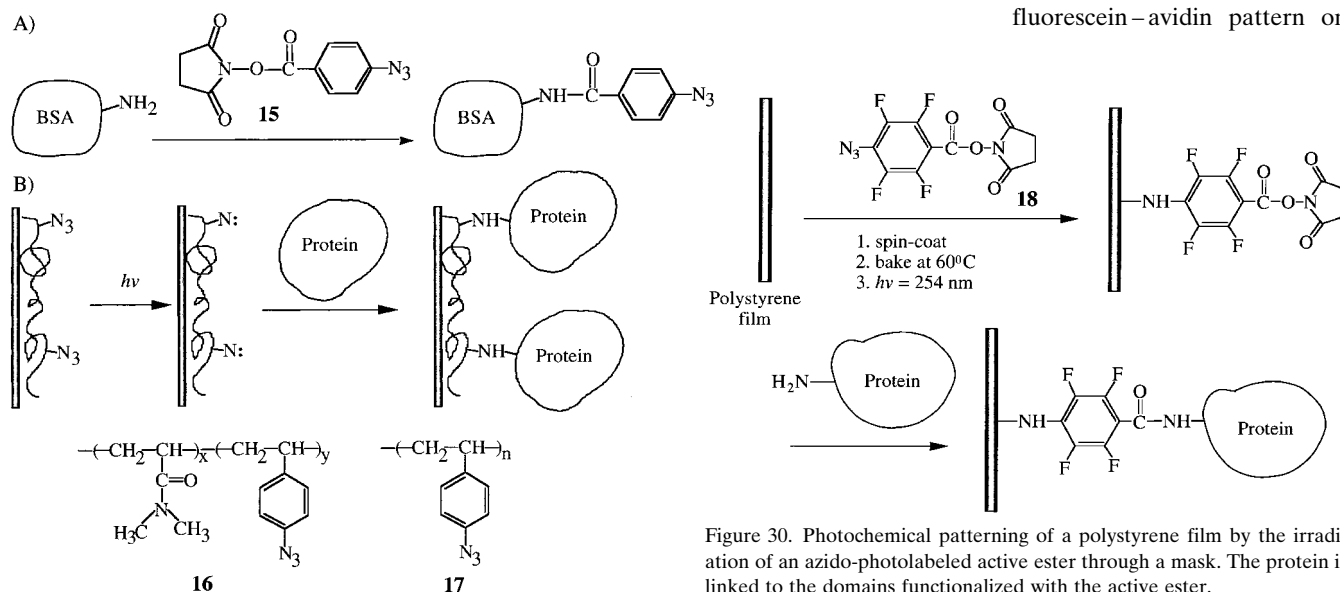


Figure 29. A) Preparation of a photolabile azido-functionalized protein. B) Photoinduced covalent linkage of a protein to an azido-functionalized polymer film.

through a mask results in the covalent attachment of the protein to the base polymer layer, and the BSA from the areas that were not exposed to light was washed off. A related approach used aryl azide functionalized polymers as photoactive matrices for the covalent attachment of the protein at irradiated surface domains (Figure 29B). Two polymers, for example, the copolymer poly(*N,N*-dimethylacrylamide-*co*-4-azidostyrene) (**16**) and poly(3-azidostyrene) (**17**) were deposited as thin films on solid supports, and the protein was spread on the respective polymer films. Irradiation of the assemblies

through a mask results in the covalent linkage of the protein to the polymer via the intermediate generation of phenylnitrene species. Using a similar approach, an aryl azide functionalized layer that includes an active ester moiety was photolithographically deposited onto a polystyrene (PS) film (Figure 30). *N*-(4-azido-2,3,5,6-tetrafluorobenzoyloxy)succinimide (**18**) was deposited on the polymer. The film irradiated through a mask yielded a pattern of the reactive *N*-hydroxy-succinimide groups that was subsequently linked to horse radish peroxidase (HRP) or avidin.^[227] Alternatively, *N*-(5-aminopentyl) biotinamide was treated with the patterned active ester and fluorescein-labeled avidin was associated to the biotin domains. Figure 31 A shows the micrograph of the fluorescein-avidin pattern on

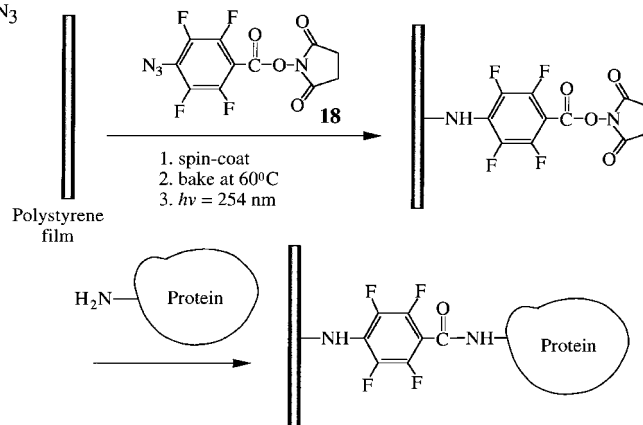


Figure 30. Photochemical patterning of a polystyrene film by the irradiation of an azido-photolabeled active ester through a mask. The protein is linked to the domains functionalized with the active ester.

a glass support. Note that the avidin pattern enables the secondary attachment of any enzyme by using biotinylated proteins (see Section 10.2). Photochemical deprotection of functional groups that can be linked to proteins allows the micropatterning of surfaces with enzymes or proteins. The *ortho*-nitrobenzyl ester unit is one of the most studied photosensitive protective groups for functional groups, particularly carboxylic acids.^[228] A copolymer consisting of protected acrylic acid, *co*-poly-*ortho*-nitrobenzyl acrylate poly(*N,N*-dimethylacrylamide (**19**) was used as an active matrix for microdeposition of protein structures.^[226] Irradiation of the polymer layer through a mask results in the

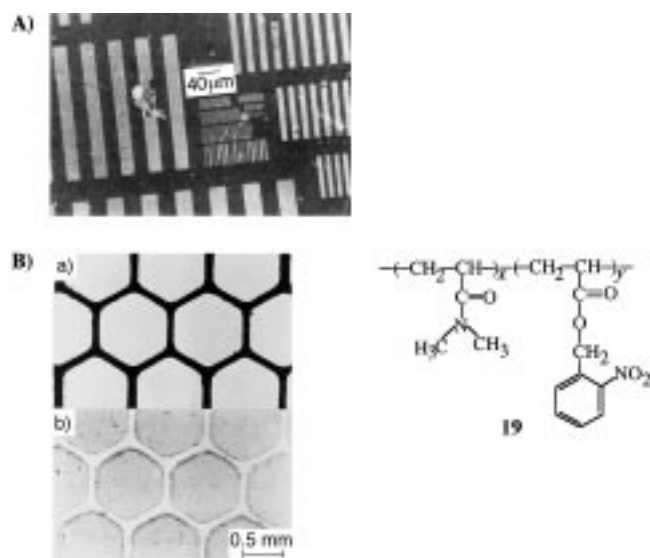


Figure 31. A) Micrograph of a fluorescein-labeled avidin attached to a patterned active ester monolayer generated by the irradiation of polystyrene through a mask in the presence of an azido-labeled active ester (see Figure 30, from ref. [227]). B) Photolithographic activation of a polymer film and site-specific covalent attachment of BSA to the patterned polymer (**19**). a) The structure of the mask, b) Patterned BSA/polymer surface obtained upon irradiation of a thin film of **19** on glass in the presence of BSA. The image (from ref. [226]) was recorded by the staining of the resulting pattern with the respective enzyme-labeled antibody using Vectastain ABC-AP (Vector Laboratories, Burlingame).

photodeprotection of acrylic acid residues. Covalent attachment of bovine serum albumin to the carboxylic acid residues using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide as the coupling reagent yields the protein pattern shown in Figure 31B. This method can be extended to immobilize any redox protein in a patterned, well-defined, configuration.

A different approach involves “negative photolithography”, namely, the photochemical deactivation of functional groups associated with a monolayer for the secondary covalent immobilization of proteins.^[223b] A silylated, sulfuranlypropyl-functionalized surface was irradiated under oxygen through a mask, and the areas exposed to light were oxidized to the sulfonated functionalized monolayer. The resulting patterned monolayer was then treated with the bifunctional reagent *N*-4-maleimidobutyryloxysuccinimide ester (GMBS, **20**), which allows the covalent linkage of proteins to the patterned interface (Figure 32). Different antibodies, for example, anti-goat IgG from rabbits or phycoerythrin, were linked to the patterned interfaces, and protein microstructures exhibiting a resolution of approximately 25 μm were tailored. Note that the patterning of antibodies on surfaces enables the organization of any protein (enzyme) pattern by the secondary noncovalent association of antigen-labeled proteins to the base antibody pattern.

10.2. Patterning of Surfaces by Layered Biomaterials through Noncovalent Interactions

The patterning of surfaces with molecular components that allow the formation of host–guest complexes with biomate-

rial receptors provides a general means of generating bioactive microstructures. Of specific interest is the patterning of addressable multidentate bio-receptors such as avidin, concanavalin A, and antibodies, that allows the secondary association of any appropriately labeled biomaterial to the patterned layered assembly. Biotin/avidin affinity interactions were used to generate micropatterns of proteins and, specifically, enzyme patterns.^[229]

A layer of deglycosylated avidin (avidin D) was covalently linked^[229a] to Au or SiO₂ surfaces, and the photoactive azide-functionalized biotin (photobiotin, **21**) was bound to the avidin layer by noncovalent interactions (Figure 33). Irradiation of the monolayer through a mask in the presence of a protein yields the nitrene biotin that reacts with the protein through nitrene insertion. By the two-step irradiation of two addressable domains in the presence of two different proteins, for example, rabbit IgG and rat IgG, the antibodies were assembled on the respective spatially addressed surfaces. By the further irradiation of the resulting protein-functionalized layer, the nonmodified photobiotin sites were activated towards the reaction with casein, which resulted in the

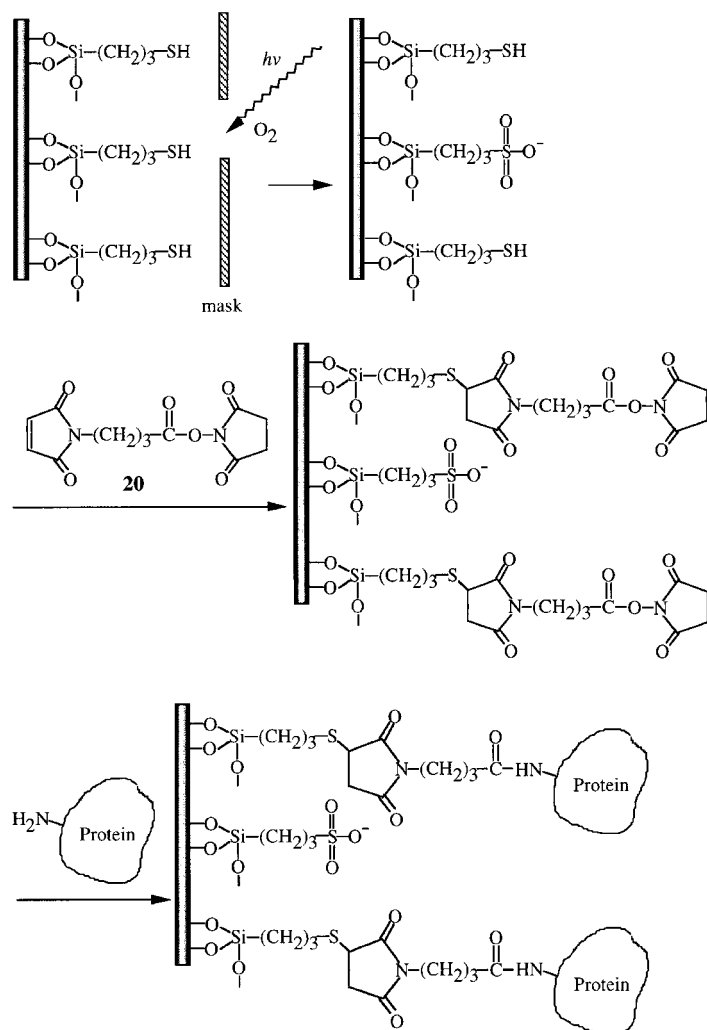


Figure 32. Photolithographic patterning of a thiol-functionalized surface with a protein by the light-stimulated deactivation of surface functionalities by irradiation through a mask.

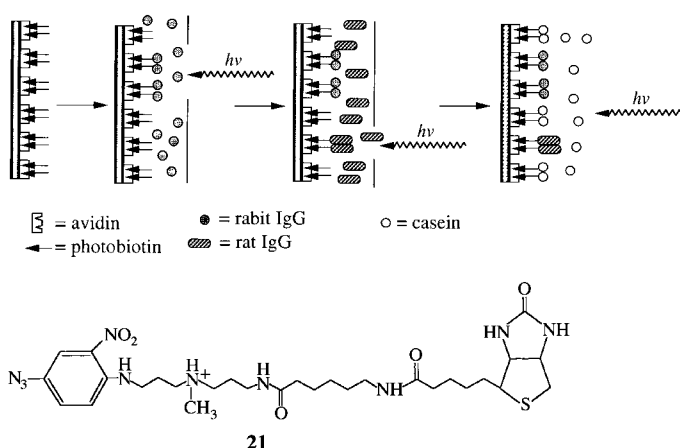


Figure 33. Sequential photochemical patterning of a surface with different proteins by site-specific irradiation of surface domains functionalized with an avidin/photolabeled biotin layer.

assembly of an ordered three-protein composite. The resulting antibody-patterned surface was imaged by the reaction with rhodamine-labeled anti-rabbit IgG derived from goats and fluorescein-labeled anti-rat IgG derived from rabbits, respectively. By using this method lines of biomaterials with a resolution corresponding to $1.5\ \mu\text{m}$ could be written. A related method of patterning polymers with biomaterials using photobiotin (as the acetate salt) as the active component was reported.^[229b] Photobiotin was physically adsorbed onto a nitrocellulose membrane or a polystyrene film. The polymer was irradiated through a mask, and the photoactivation of biotin generated a polymer-linked biotin pattern. The binding of the multidentate avidin to the biotin binding sites linked to the polymer matrices enabled the secondary association of biotinylated alkaline phosphatase or biotinylated HRP.

A similar approach was used to generate patterns of enzymes on glassy carbon surfaces (Figure 34).^[142b] Photo-sensitive biotin (**21**) was cast onto the glassy carbon surface. The pattern of biotin on the surface was generated by an interference pattern on the substrate rather than the irradiation through the mask. Subsequent interaction of the biotin-

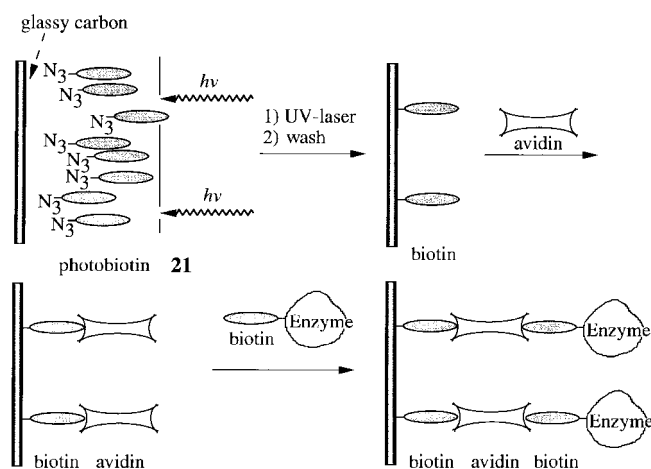


Figure 34. Photochemical patterning of a glassy carbon electrode with biotin and a secondary avidin/biotinylated enzyme layer by the irradiation of the surface through a mask in the presence of photolabeled biotin.

layer pattern with avidin yields the protein pattern. The microstructured avidin layer was imaged by fluorescence microscopy by the application of fluorescein-labeled avidin or avidin labeled with Texas Red. The tetramer ligation ability of avidin allows the secondary binding of biotinylated enzymes (for example, alkaline phosphatase) to the base avidin pattern.

Photoisomerizable antigens were used to tailor reversible immunosensors by controlling the antigen–antibody interactions with light.^[230] In one photoisomer state the molecular substrate exhibits antigen features for the antibody, while in the secondary photoisomer configuration a molecular species lacking antigen properties is generated (Figure 35 A). A cyclic, light-induced association and dissociation of the

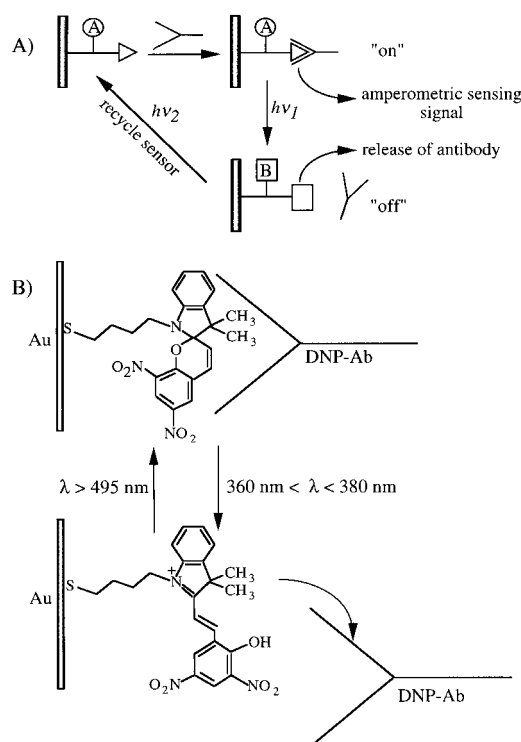


Figure 35. A) Photocontrolled association and dissociation of an antibody to and from an electrode with a photoisomerizable antigen monolayer. This is a model for a reversible immunosensor electrode, and the light-induced regeneration of an immunosensor. B) Photoinduced binding and dissociation of DNP-Ab to and from an electrode with a photoisomerizable dinitrospiropyran/protonated dinitromerocyanine monolayer.

antigen–antibody complex was stimulated by the reversible photoisomerization of the photoactive molecular substrate between the two states. It was shown that a dinitrospiropyran monolayer associated with an Au electrode or a conductive ITO electrode reveals photochemically controlled binding and dissociation of the dinitrophenyl antibody (DNP-Ab, Figure 35 B).^[230] The dinitrospiropyran monolayer acts as an antigen for the DNP-Ab, whereas the protonated dinitromerocyanine lacks antigen features. This difference enabled the photolithographic patterning of surfaces with DNP-Ab.^[230b,c, 231] A glass surface was silylated with aminopropyltriethoxysilane, and dinitrospiropyran (SP) **22a** was covalently coupled to the surface (Figure 36 A). The resulting antigen

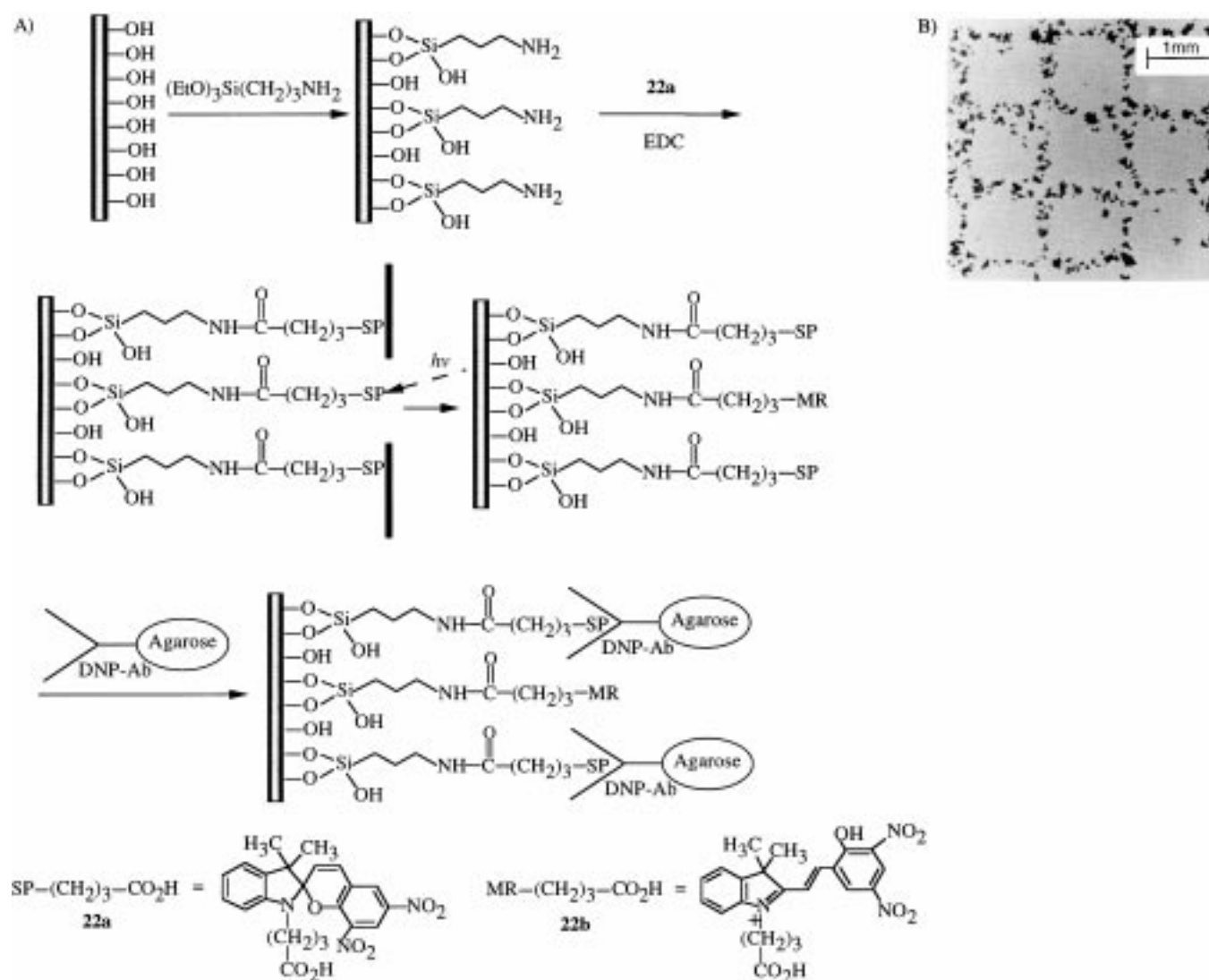


Figure 36. A) Assembly of a photoisomerizable dinitrospiropyran (SP) antigen monolayer on a glass support, the photolithographic patterning of the monolayer by irradiation through a mask, and the selective binding of DNP-Ab-functionalized agarose beads to the patterned surface. B) The pattern of DNP-Ab covalently linked to agarose beads formed upon the selective deposition of the particles to a photolithographic patterned dinitrospiropyran monolayer. Particles are deposited onto the dinitrospiropyran sites, whereas the vacant domains are in the dinitromerocyanine (MR) state (from ref. [231]).

monolayer was irradiated through a mask and all of the illuminated domains were transformed to protonated dinitromerocyanine (**22b**) areas lacking antigen features. The resulting patterned antigen layer was then interacted with DNP-Ab-functionalized agarose particles. The domains that include the dinitrospiropyran antigen units associate with the antibody–agarose particles. Figure 36B shows the pattern of the antibody–agarose particles formed upon irradiation of the base dinitrospiropyran layer through a grid. This system enables, in principle, the secondary microstructuring of surfaces with any enzyme, and the organization of a three-dimensional array of different biomaterials. For example, any dinitrophenyl-functionalized enzyme will link by noncovalent interactions to the base DNP-Ab-patterned microstructure since the agarose beads include vacant DNP-Ab sites.

Proteins may be spatially patterned by the organization of patterned monolayers on solid supports that have the appropriate hydrophilic/hydrophobic balance for the specific adsorption of the biomaterial. Monolayers consisting of oligo(ethylene glycol) terminated thiols (HS(CH₂)₁₁(OCH₂CH₂)₆OH) resist the adsorption of proteins, whereas hydrophobic monolayers (for example, HS(CH₂)₁₅CH₃) adsorb proteins such as avidin, hexokinase, pyruvate kinase, ribonuclease A, lysozyme, and fibrinogen effectively.^[232] Several techniques, including microwriting,^[232c, 233] micromachining,^[216d] stamping,^[215b] and UV photolithography^[100d] were used to generate the respective patterns of oligo(ethylene glycol) and hexadecylthiol.^[224] Adsorption of the proteins to the patterned hydrophobic domains was imaged by scanning electron microscopy (SEM). The relative brightness of a micrograph area relates to the secondary electron emission

from that domain. The association of the protein to the hydrophobic monolayer is reflected by a decrease in the brightness of the domain in the micrograph.^[215b] A pattern of lines was written on an Au film using $\text{HS}(\text{CH}_2)_{15}\text{CH}_3$ as the ink solution, and the background surface was treated with the oligo(ethylene glycol).^[232c]

Irradiation of the hexadecylthiol monolayer through a mask (UV light, under oxygen) results in the oxidation of the thiolate to the sulfonate. Desorption of the latter product and specific association of $\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_6\text{OH}$ with the bare Au domains (Figure 37) enabled the specific adsorption of pyruvate kinase to the patterned hydrophobic domains.^[224] The stamping of an Au surface with a stamp molded from

A micromachining approach^[215a, 216, 218] was similarly applied to generate patterns of pyruvate kinase. An Au surface was functionalized with the hydrophilic sulfanyl oligo(ethylene glycol). The resulting monolayer was scratched with a scalpel blade and the scratched domain was then treated with the hydrophobic thiol to which pyruvate kinase was specifically associated. Different proteins such as fibronectin, streptavidin, and antibodies were selectively associated on the patterned hydrophobic layer. It was possible to distinguish between proteins associated with stamped hydrophobic domains by the relative intensities of the SEM images. The larger the protein, the darker is the SEM image.

11. Photoactivated Layered Enzyme Electrodes for Optobioelectronics: Amperometric Transduction of Recorded Optical Signals

Photoactivated layered redox enzymes on conductive supports enable the amperometric transduction of optical signals recorded by the bioactive interfaces.^[20, 234] Figure 38 A shows the application of a layered, photoswitchable redox enzyme on an electrode as an optobioelectronic assembly for the amplified amperometric transduction of recorded optical signals. The enzyme is functionalized by a photoisomerizable unit (**A**) that distorts the protein structure and prohibits the bioelectrocatalyzed oxidation (or reduction) of the respective substrate. Photoisomerization of the light-active groups to state **B** restores the bioactive tertiary structure of the enzyme. This process activates the bioelectrocatalytic transformation and the photonic information recorded is transduced as an amperometric output. As the optical signal activates an electrocatalytic process the resulting current represents an amplified response to the recorded photonic signal. Such systems can be used as optical memories (write-read-erase), where the optical signal represents the writing process, the electrocatalytic reaction the reading mechanism, and the reversible photoisomerization the erasure step. Similarly, the use of photoactivated redox enzymes on electrodes as actinometric devices, biomolecular amplifiers of weak light signals, and logic gates,^[115] were recently addressed.

The enzyme glucose oxidase (GOx) was modified chemically with nitrospiropyran photoisomerizable units (**23a**) and assembled as a monolayer onto an Au electrode (Figure 38 B).^[18a] In the presence of the diffusional electron mediator, ferrocenecarboxylic acid (**24**) the nitrospiropyran-functionalized GOx is activated for the oxidation of glucose, as evidenced by the resulting high electrocatalytic current (Figure 39). Photoisomerization of the monolayer to the protonated merocyanine (**23b**) results in the distortion of the protein that perturbs the electrical contact by the electron mediator. This process results in a substantially lower amperometric response. Reversible “high” and “low” amperometric responses of the functionalized electrode are transduced upon cyclic photoisomerization of the enzyme monolayer between the two states. The photoisomerizable enzyme electrode revealed photoswitchable transduction of recorded optical signals (Figure 39). However, the “switched-off” state does not reveal complete blocking of the

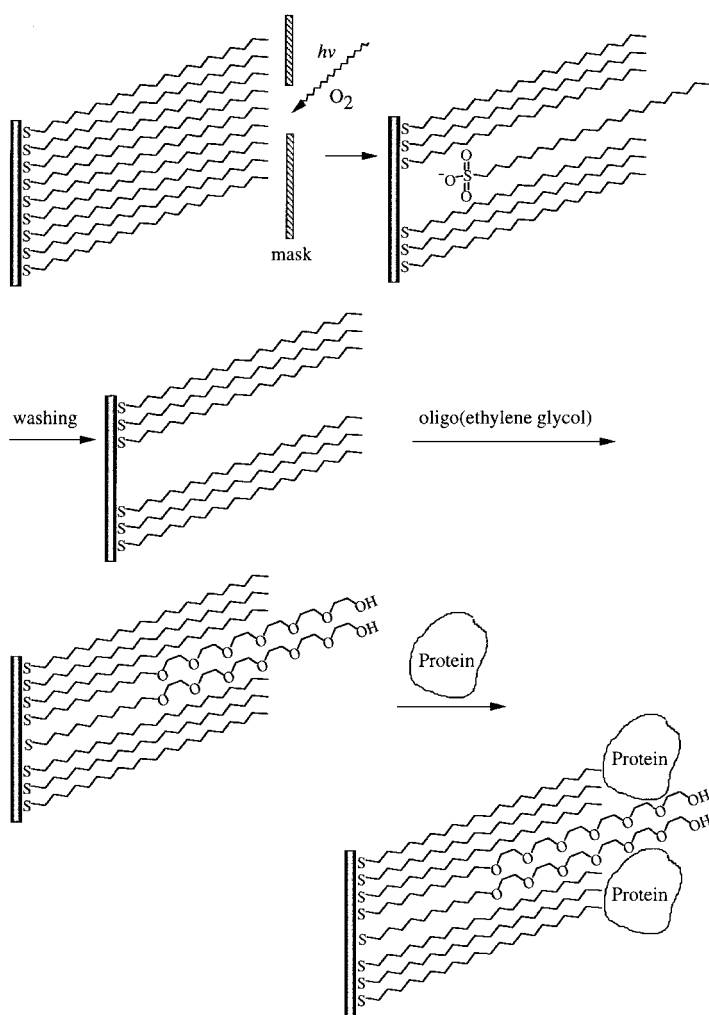


Figure 37. Photolithographic oxidative desorption of a thiol monolayer followed by the filling of empty domains with a hydrophilic oligo(ethylene glycol) terminated thiol for the noncovalent patterning of proteins on the surface. The alkyl chains are only representative.

poly(dimethylsiloxane) and functionalized with the hydrophobic thiol was used to generate a pattern of hexadecylthiol, and the remainder of the base surface was derivatized with the sulfanyl oligo(ethylene glycol). Selective association of pyruvate kinase to the hydrophobic domains resulted in the protein pattern.^[224]

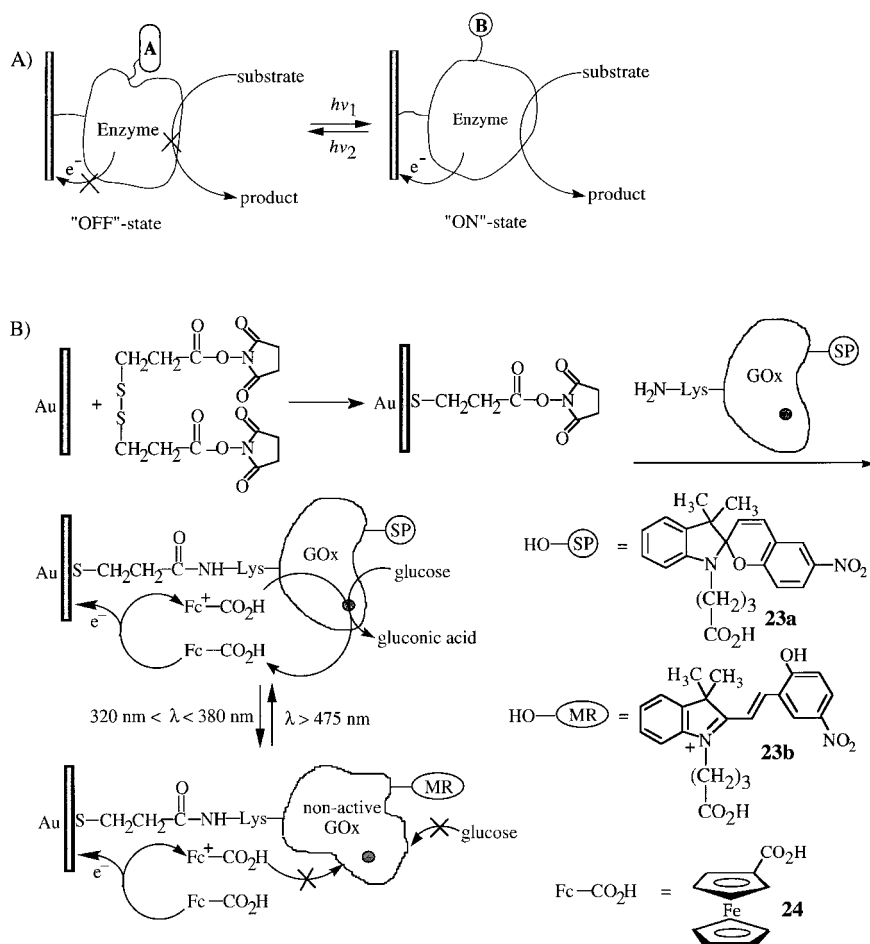


Figure 38. A) Assembly of an optobioelectronic system by the organization of a layer of photoisomerizable redox enzyme on an electrode support. B) Assembly of a nitrospiropyran-tethered glucose oxidase layer on a Au electrode for the photoswitchable, bioelectrocatalyzed oxidation of glucose. Ferrocenecarboxylic acid is used as a diffusional electron mediator to provide an electrical contact between the redox enzyme and the electrode support.

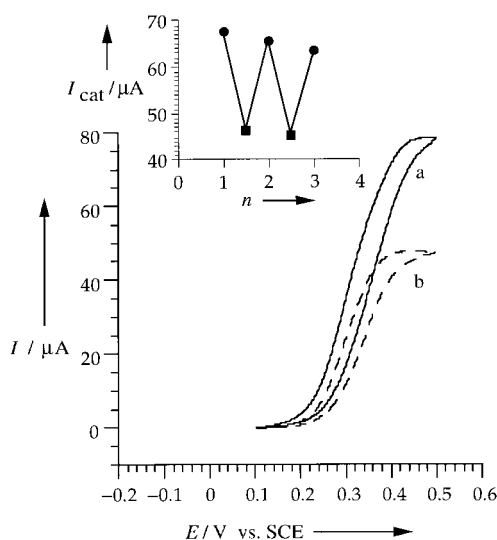


Figure 39. Cyclic voltammograms of the photoswitchable bioelectrocatalyzed oxidation of glucose (2.5 × 10⁻² M) as described in Figure 38B using a photoisomerizable GOx monolayer electrode (in the presence of **24**, 5 × 10⁻³ M): a) in the SP form, b) in the MR form; potential scan rate: 5 mV s⁻¹. Inset: Cyclic amperometric responses of the electrode with a photoisomerizable enzyme monolayer upon reversible light-induced isomerization of the protein layer between the SP (●) and MR form (■).

bioelectrocatalytic functions of the enzyme. This was attributed to the insufficient structural distortion of the protein by the covalent attachment of the photoisomerizable units. That is, attachment of photoisomerizable components to amino acid residues far from the enzyme redox center, or the channel pathway of the electron mediator, is not sufficient to effectively perturb the electrical contact between the enzyme and the electrode.

One approach of improving the photo-switchable functions of a redox enzyme to complete "ON" and "OFF" states involved the introduction of the photoisomerizable unit close to the biocatalytic redox active site by a reconstitution process (Figure 40). The native FAD-cofactor associated with GOx was excluded from the enzyme and substituted with the semisynthetic nitrospiropyran-FAD cofactor (25a).^[18d, 235] The reconstituted photoisomerizable enzyme was then assembled as a monolayer on an Au electrode. In the presence of the electron mediator **24** the bioelectrocatalyzed oxidation of glucose was fully switched to "ON" or "OFF" positions (Figure 41). In the nitrospiropyran state of the enzyme (25a-GOx) the mediated electron transfer by **24** is blocked. Upon photoisomerization of the enzyme monolayer, 25b-GOx state, the diffusion path of the electron mediator is opened, and the bioelectrocatalytic oxidation of glucose is activated (Figure 42).

The partially photostimulated properties of glucose oxidase that had been substituted randomly by photoisomerizable groups were used to design a three-state switch by the coupling of the photoisomerizable enzyme with an antibody (Figure 43).^[18c] Glucose oxidase was modified with dinitrospiropyran units, and the resulting photoisomerizable enzyme was assembled as a monolayer on an Au electrode. The resulting monolayer enzyme electrode was activated for the bioelectrocatalyzed oxidation of glucose in the dinitrospiropyran photoisomer state (SP-GOx) and using ferrocenecarboxylic acid (**24**) as an electron transfer mediator (switch "ON"). Photoisomerization of the monolayer to the protonated dinitromerocyanine state (MR-GOx) results in the partial deactivation of the bioelectrocatalytic features of the enzyme electrode (partial switch "OFF"). The photoisomerizable units of dinitrospiropyran and protonated dinitromerocyanine, however, exhibit light-stimulated binding affinities to the dinitrophenyl-antibody (DNP-Ab, see Section 10.2). The SP state acts as an antigen for DNP-Ab, while the MR state lacks antigen features for DNP-Ab. The binding of the DNP-Ab to the SP-GOx insulates the diffusion path of the electron-transfer mediator, and the electrical contact of the enzyme and the electrode is blocked. This process yields the

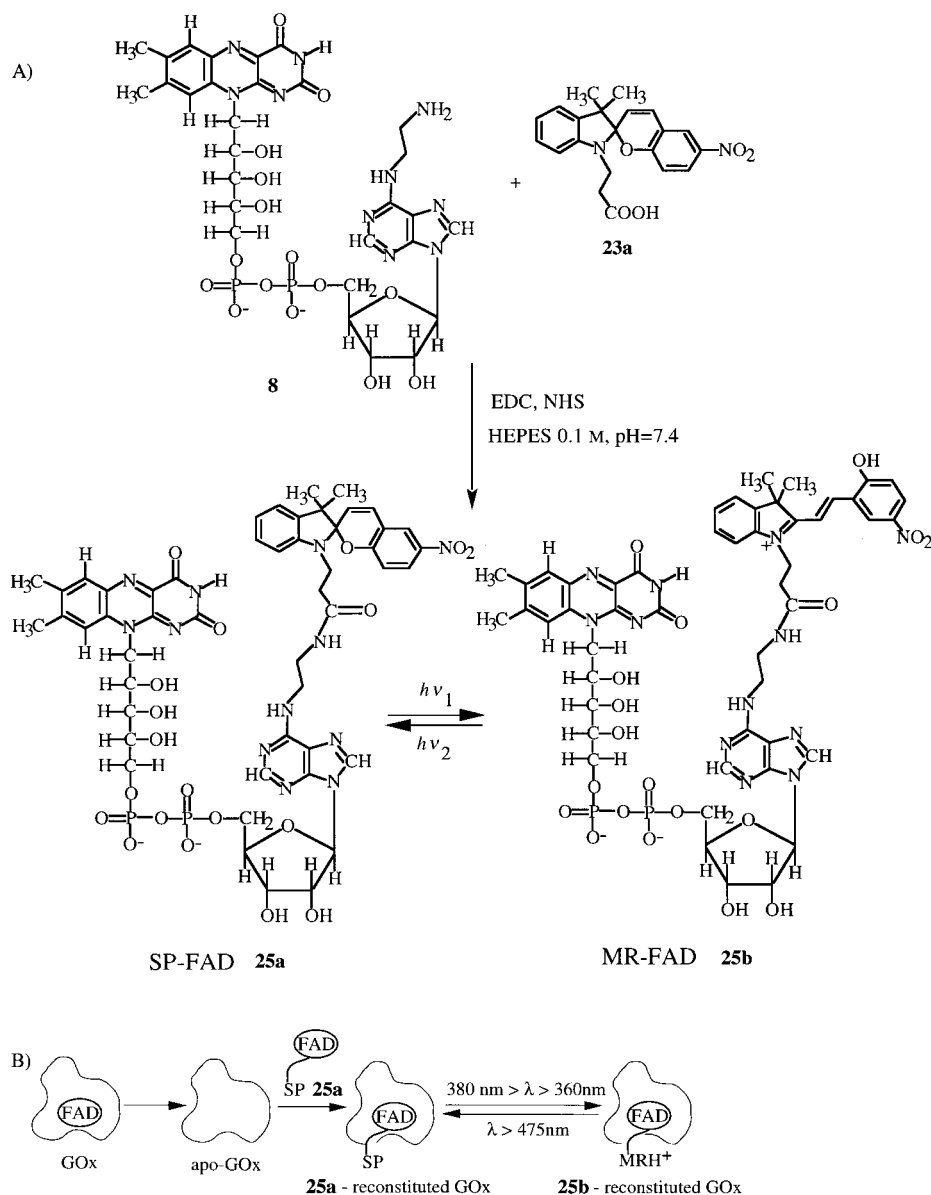


Figure 40. A) Synthesis of a semisynthetic nitrospiropyran-FAD cofactor. B) Reconstitution of apo-GOx with the photoisomerizable cofactor.

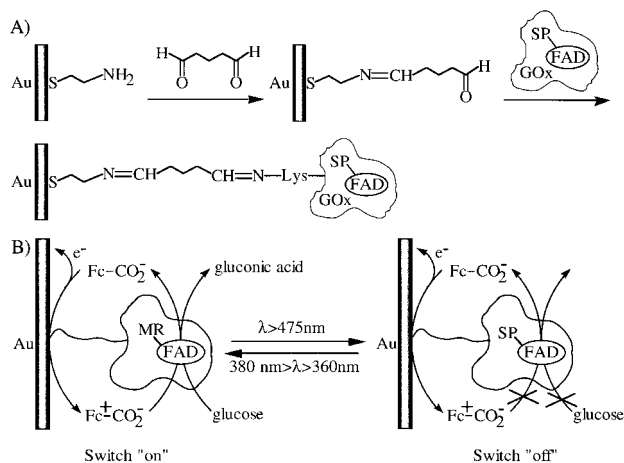


Figure 41. A) Assembly of the photoisomerizable enzyme layer in accordance with Figure 40B on an Au electrode. B) Photoswitchable bioelectrocatalyzed oxidation of glucose by this electrode in the presence of ferrocenecarboxylic acid as a diffusional electron mediator.

complete switching-off of the electrobiocatalytic properties of the enzyme electrode. The MR-GOx photoisomer state of the monolayer is not affected by DNP-Ab, since the photoisomer sites lack antigen features for the antibody. By reversible photoisomerization of the enzyme monolayer between the SP-GOx and MR-GOx states in the presence or absence of DNP-Ab, the system is cycled through the switch-ON, switch-OFF, and switch partial-ON states (Figure 44). The layered enzyme-antibody and electrode assembly mimics functions of an electronic logic gate of “AND” characteristics. The amperometric response of the photoisomerizable monolayer-electrode is turned to the switched-off position when two conditions are met: The monolayer is photochemically transformed to the SP-GOx state *and* the monolayer interacts with the DNP-Ab to yield the complex layer on the electrode.

The electrical contact of the layered enzyme assembly and the conductive support is driven by a diffusional electron mediator, which enables the photostimulation of the bioelectrocatalytic functions of the enzyme layer by the application of a photoisomerizable electron mediator (Figure 45; p. 1211).^[127b] In one photoisomer state (SP) of the electron mediator the relay establishes the electrical contact between the enzyme layer and the electrode support and acti-

vates the bioelectrocatalyzed transformation. In the complementary photoisomerizable state (MR) the electron transfer between the biocatalyst layer and the conductive support is blocked, as a result of steric or electrostatic barriers for diffusion of the relay into the protein. Two photoisomerizable relays, the covalently linked SP-ferrocene derivative **26** and the SP-bipyridinium salt **27**, were reported to photostimulate the activities of glucose oxidase (GOx) and glutathione reductase (GR), respectively.^[127b] The enzyme GOx was assembled as a five-layer array on an Au electrode. The SP-ferrocene **26a** forms an electrical contact to the enzyme multilayer and the electrode surface, and results in the bioelectrocatalyzed oxidation of glucose. The protonated MR-ferrocene **26b** does not mediate the electron transfer, and its diffusion to the protein is sterically (or electrostatically) hindered. By the reversible photoisomerization of the electron relay between **26a** and **26b**, the cyclic activation and deactivation of the enzyme was induced by light. Similarly, the

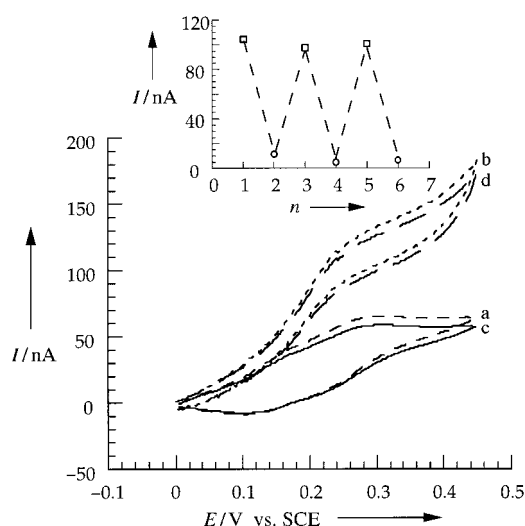


Figure 42. Cyclic voltammograms corresponding to the bioelectrocatalyzed oxidation of glucose described in Figure 41 B by the photoisomerizable GOx-monolayer electrode a) and c) in the SP state, b) and d) in the MR state. Inset: Cyclic amperometric responses of the electrode upon reversible photoisomerization of the monolayer between the protonated MR (□) and SP state (○).

photoisomerizable SP-bipyridinium relay **27** allows the photochemical activation and deactivation of glutathione reductase assembled in a layer on an Au electrode.

12. Conclusion and Perspectives

This review has addressed recent advances in the organization of redox proteins as monolayer or multilayer assemblies on solid conductive supports for bioelectronic applications. Specifically, the electrical contacting of the protein layers with the electrode supports and the spatially controlled deposition of proteins as integrated micropatterned arrays were discussed. The potential use of electrically contacted redox proteins as future biosensor devices was addressed. In

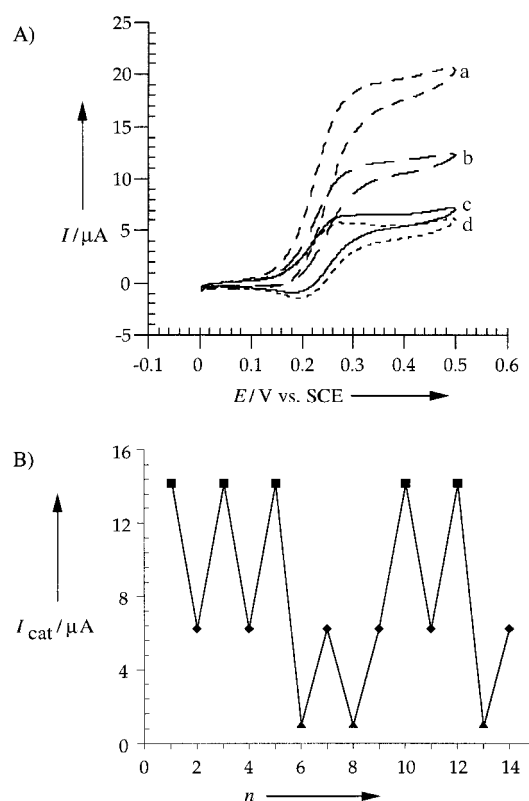


Figure 44. A) Cyclic voltammograms of the two-phase switch described in Figure 43 in the presence of ferrocenecarboxylic acid (4×10^{-4} M) a) in the SP state and in the presence of glucose (5×10^{-2} M), b) in the MR state, c) in the presence of the SP state and DNP-Ab (20 mg mL^{-1}), d) in the SP or MR state and in the absence of glucose. B) Cyclic amperometric transduction of the biphasic switch composed as a result of the reversible light-induced isomerization of the protein layer between the SP and MR states in the absence and presence of DNP-Ab: (■) SP-GOx monolayer without DNP-Ab, (♦) MR-GOx monolayer with or without DNP-Ab, (▲) SP-GOx monolayer in the presence of DNP-Ab.

contrast to the previous methods that used random, non-organized, deposition of proteins onto surfaces, for example, encapsulation or immobilization in polymer matrices, we have emphasized the basic scientific interests and the practical implications of tailoring organized protein architectures in ordered and defined nanostructures. The key elements in the integration of redox proteins with electronic transducers include the physical or chemical deposition of the proteins on the solid supports, the electrical communication between the biomaterials and the transducers, and the electronic transduction of the biocatalyzed transformation that occurs at the biomaterial/transducer interfaces. Monolayer and multilayer arrays of proteins can be organized on transducers using covalent bonds, affinity interactions, or hydrophobic/hydrophilic interactions. Theoretical understanding of electron-transfer processes in proteins and the availability of chemical and biological means to modify biomaterials have enabled us to improve the electronic coupling between the redox proteins and the transducer

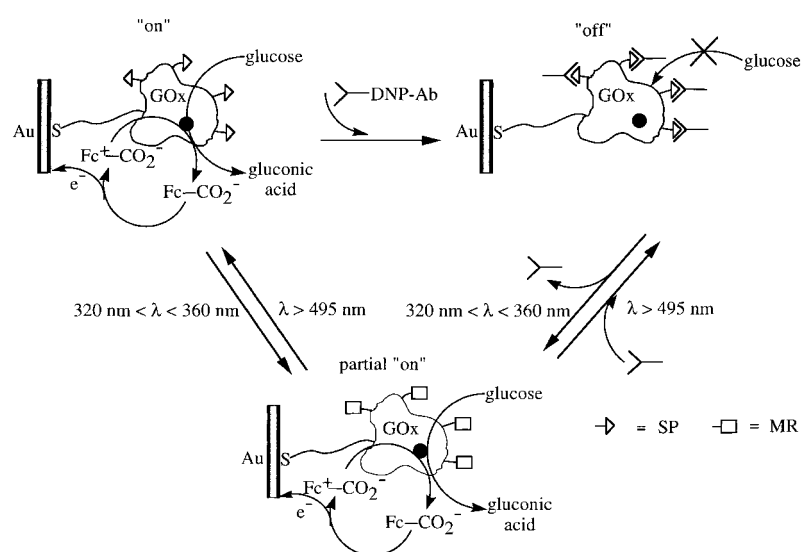


Figure 43. Schematic operation of a biphasic photobiological switch based on a SP-GOx-monolayer electrode and DNP-Ab.

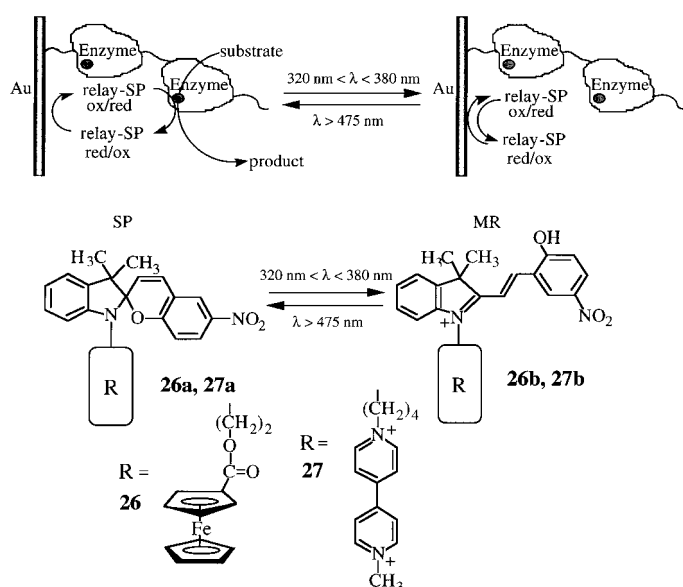


Figure 45. Photostimulation of redox-enzyme electrodes by photoisomerizable electron relays.

element. Site-specific modification of redox proteins, genetic engineering of protein structures, and surface-reconstitution of proteins, represent novel and attractive means to align and orient redox proteins on surfaces. The effective electrical contact of aligned proteins with electrodes suggests that future efforts should be directed at engineering further structural mutations in proteins in order to further develop ordered nanostructures of proteins on surfaces. Although our report has emphasized the electronic coupling of redox proteins and transducer elements, the concept can be further adopted to organize monolayer and multilayer systems using other biomaterials, such as antigens, antibodies,^[236] oligonucleotides (or DNA),^[5, 237] or bioreceptors.^[8, 238] Indeed, recent reports have demonstrated the electronic coupling of antibody–antigen complexes with electrode supports^[21, 239] or with piezoelectric quartz crystals.^[13b, 240] Also, the electronic transduction of photoswitchable formation and dissociation of antigen–antibody complexes using photoisomerizable antigen monolayers was reported.^[230] The formation of oligonucleotide–DNA double-stranded assemblies in monolayer assemblies was electronically^[21c, 241] and microgravimetrically^[242] transduced. These systems were suggested as future bioelectronic devices for the detection of genetic disorders (for example, Tay–Sachs).^[243] The continuous interest in the development of antigen/antibody-based sensors (immunosensors) and the growing demand for sensitive electronic DNA sensors suggest that integration of these biomaterials as monolayer/multilayer assemblies on transducer elements will expand and will be utilized as a general immobilization strategy.

Another aspect that will require future development involves the integration of the biomaterial–monolayer assemblies with other transducers capable of signaling the biological events at the biointerface by other electronic, photoelectric, or optical means. In this context the organization of the bioactive materials on field-effect-transistor

devices (FET),^[14] the use of impedance spectroscopy,^[12, 244] or surface plasmon resonance,^[245] to probe biointeractions at the monolayer interface seems to be attractive.

The electrical contacting of protein layers associated with electrodes for sensing applications and for the tailoring of optoelectronic assemblies are already mature research areas of solid scientific frames. The concept of integrating biomaterial monolayers with solid supports leads, however, to new bioelectronic applications. The effective electrical contact of surface-reconstituted flavoenzyme monolayers on electrodes, and the ability to assemble electrocatalytic monolayer electrodes, led to the use of the functionalized electrodes as active components in biofuel cells.^[212]

The concepts of monolayer assembly on solid supports were extended to the functionalization of surfaces with metal and semiconductor nanoparticles.^[112a,f, 246] By the appropriate design of complementary affinity interactions between biomaterial-capped metal particles (for example, Au particles) three-dimensional superlattices were assembled.^[246k] The organization of similar superlattices on transducer elements is anticipated to yield novel sensing matrices.^[247] The unique photonic and electronic features of nanoparticles^[248] suggest that the organization of biomaterial/nanoparticle composites would yield novel optobioelectronic systems, such as new photo-cells for the effective light-to-electrical energy conversion or optoelectronic sensors. Double-stranded oligonucleotide assemblies with sub-monolayer coverage were used as a mold for the deposition of metal nanowires.^[249] This opens up novel routes for the generation of nanoscale metal networks with nanometric spatial resolution.

Finally, the spatial patterning of surfaces with chemical functionalities, and the ability to modify surfaces with biomaterials with micro- or nanoscale structures, has made tremendous progress in recent years. This opens the way to construct parallel multisensor systems, biosensing libraries, and bioelectronic arrays for parallel or consecutive operation. It is, however, mandatory to develop further chemical methods to specifically address the target domains on the patterned transducer element. The photochemical activation of nano-domains,^[213b] or electrochemically driven synthesis at microelectrodes,^[92d, 97g, 144a,c, 250] could provide future challenging goals. The development of the various scanning microscopy techniques, such as atomic force microscopy (AFM) or scanning tunneling microscopy (STM) has enabled the microscopic imaging of biomaterial patterns.^[251] The ability to follow complementary affinity force interactions of biomaterials by AFM permits not only the basic understanding of the molecular forces characterizing the macroscopic bioelectronic systems,^[252] but also allows the patterning of microstructures using these forces.^[98g, 113a,b, 253] The possibility of illuminating nano-domains using a near-field-scanning optical microscope (NSOM) opens the way to activate layered photoswitchable biomaterials associated with electrodes for dense optical recording and electronic transduction.^[254] Clearly, the architecture of biomaterial layers on transducer elements is envisaged to offer exciting perspectives at the frontiers of chemistry, biology, physics, medicine, and material science.

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Recent Trends in the Application of Evanescent Wave Biosensors

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Evanescent Waves and Biosensors

During the last few years biosensors have become important for the investigation of biomolecular interactions. In particular surface plasmon resonance (SPR) and resonant mirror (RM) techniques^[1] are frequently used in biosensors. More than one thousand publications concerning the use of SPR or RM biosensors underline the importance of these techniques in the analysis of interactions between biomolecules.

SPR and RM techniques are optical methods which use evanescent waves^[1] to primarily determine the refractive index of an (aqueous) solution. As a consequence, these methods are unspecific, however they have the advantage of being very sensitive. Specificity can be introduced by modification of the surface facing the solution, for example, by immobilization of a receptor protein. Extremely thin layers of gold, other precious metals or glasslike materials may be used as supporting surfaces. Due to the interaction with the immobilized protein a bioactive molecule, present in solution above the sensor, will be attracted to the surface. The obtained change of the refractive index of the solution close to the sensor surface is directly proportional to the increase or decrease in mass of the sensor during the ligand–receptor binding process (Figure 1).

The experiments can be performed within minutes and need only very small amounts of sample, making them interesting as pharmaceutical screening processes. However, for biological aspects the signal progress over time is much more interesting, since one can determine the equilibrium and time constants (the association rate constant or “on-rate”, and the dissociation rate constant or “off-rate”) of the ligand–receptor binding process from the curves. Due to the optical detection mode, one obtains insights into the time scale of the processes being monitored without labeling the molecules. The collected kinetic and thermodynamic information complement structural data of the systems under investigation, thus being of great importance for structure activity relationship (SAR) studies of biomolecular complexes.

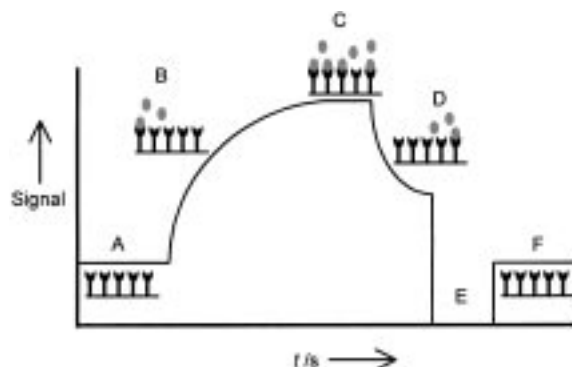


Figure 1. Schematic representation of the dependence of signal intensity on the surface properties during a resonant mirror or surface plasmon resonance experiment. A) Baseline after preparation of the sensor surface, for example, by immobilization of a protein. B) Addition of a binding partner to the solution results in complex formation. This process changes the refractive index at the sensor surface and the experimental signal increases. C) If the experiment is continued until equilibrium, a plateau is reached. D) Removal of the binding partner from solution results in complex dissociation. The experimental signal decreases. E), F) Termination of the experiment and regeneration of the surface without deactivation of the protein leads back to the baseline level. The association and dissociation rate constants of the ligand receptor binding process can be mathematically determined from the slopes of the curve.

Membrane Systems on Sensor Surfaces

Immobilization of a molecule onto the sensor surface results in reduced translational and rotational degrees of freedom. This fact distinguishes SPR and RM techniques from other biophysical methods where all interacting partners are dissolved. However, many important biomolecular recognition processes take place on surfaces, such as cell membranes. The logical consequence is, therefore, to build artificial membranes on sensor surfaces to study receptor–ligand interactions in an environment most closely resembling the natural one. To achieve this goal, different concepts have been developed to immobilize membranes and embedded proteins on sensor surfaces. The most apparent and simple one is to couple alkanes through a thiol group directly to the gold surface. These functionalized alkanes create a hydrophobic, self-assembling monolayer on the sensor surface, on which a lipid bilayer can be formed (Figure 2a). The use of these membrane systems allowed the study of interactions such as the binding of factor VIII^[2] and antibacterial peptides^[3] to membranes, the interaction of a protein kinase with phospholipids,^[4] and the binding of lectins^[5] and cholera-

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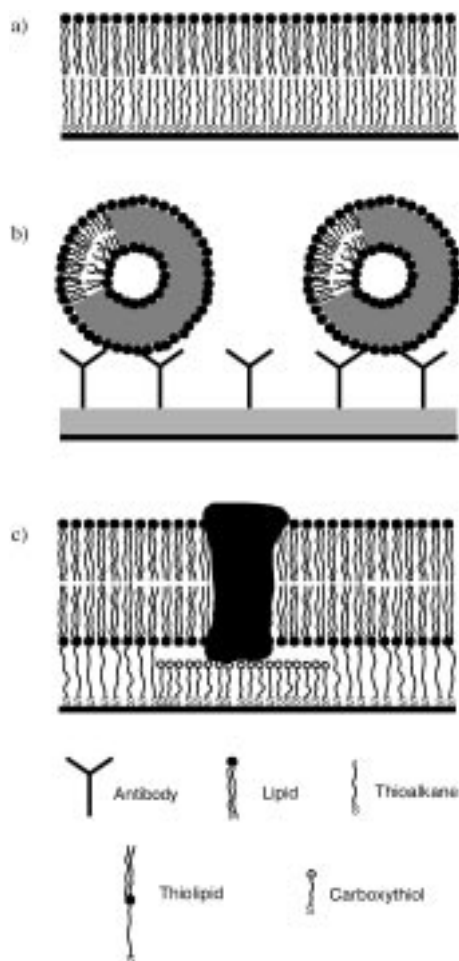


Figure 2. Different strategies for creation of artificial membrane systems on sensor surfaces. a) Thioalkanes directly immobilized on the sensor provide a hydrophobic surface, on which a lipid bilayer can be formed. Transmembrane proteins can not be introduced into this artificial membrane. b) Anti-lipopolysaccharide antibodies are immobilized on a modified dextrane matrix, to which liposomes containing lipopolysaccharides can bind.^[10] This allows the study of molecules binding to the liposomes or membrane associated proteins. c) Special thiolipids and carboxythiols are used to build bilayers with fixed distances to the surface of the biosensor.^[14] This is also a method to introduce transmembrane proteins into an artificial membrane and study it as a receptor.

toxin^[6] to glycolipid systems. Furthermore, it was possible to place a functionally intact nicotinic acetylcholine receptor^[7] as well as cytochrome C oxidase^[8] in such artificial membranes. Recently, the formation of a multicatalytic protease complex (20-S-proteasom), which consists of 28 subunits, was achieved on such a lipid bilayer.^[9]

A lipid bilayer which is attached directly to the sensor surface has the drawback that membrane-spanning proteins may not be introduced. If such proteins are to be studied in a bilayer system, one must fix the membrane at a certain distance above the sensor surface by special spacer molecules. One such spacer is the monoclonal *anti*-lipopolysaccharide antibody SE155-4, since its ligand, the lipopolysaccharide, possesses optimal properties to anchor micelles or lipid bilayers onto the biosensor (Figure 2b).^[10] Alternatively, it is also possible to attach biotinylated lipids to the surface by immobilized avidin or streptavidin. Vesicles immobilized in

this manner were used for binding mitochondrial creatin kinase^[11] and recoverin.^[12]

A new development is the direct modification of a gold-attached dextrane matrix with hydrophobic anchors through which liposomes may be immobilized.^[13] Furthermore, special thiolipids were employed to fix the lipid bilayer to the sensor surface at a certain distance (Figure 2c). This way it was possible to position rhodopsin in predefined regions of a membrane and investigate the light-induced transformation of transducin by rhodopsin.^[14]

Sample Volume and Sensitivity

In the meantime, recent developments in SPR technology by Biacore AB have lead to decisive improvements concerning sample consumption and sensitivity of the instruments. With current instruments the detection of mass changes of the sensor surface in the picogram range is possible. The surface of such a sensor equals approximately 1 mm². In addition, the volume within the flow cell could be decreased to approximately 21 nL, greatly reducing the consumption of the solubilized binding partner. Working with these SPR instruments, one can now study the binding of compounds with molecular weights considerably below 1000 Da and dissociation constants in the millimolar range to immobilized proteins. This was demonstrated with a monoclonal antibody raised against oligoglucose and small (di- to tetrasaccharide) ligands.^[15] From these improvements new applications for the use of SPR instruments in screening processes or in binding studies of small, low-affinity ligands to receptor proteins will emerge.

Coupling of SPR Techniques and Mass Spectrometry

The use of SPR technology in the quest for bioactive compounds from libraries allows the determination of binding activity of one or more substances from such a mixture. However, it is not possible to unambiguously identify the bioactive compound directly from the complex mixture. Since mass spectrometry is one of the most sensitive analytical methods for providing information on structure and composition of a molecule, the coupling of SPR and MALDI-TOF (Matrix-assisted laser desorption/ionization time-of-flight) techniques enables the characterization of bioactive substances immediately following an SPR experiment. For this purpose, the sensor surface is treated with the matrix needed for the MALDI-TOF experiment and subsequently analyzed. This way, bioactive compounds may be characterized directly from the surface of the biosensor even in the subfemtomolar range.^[16] However, the biosensor must be removed from the instrument after each positive SPR result and prepared for the MALDI-TOF experiment. This is time consuming and can become quite expensive, since the biosensor can not be used repeatedly after it has been modified for the MALDI-TOF experiment. Therefore, a new development concerning the SPR–MALDI-TOF coupling allows the recovery of the bioactive compound in a small volume directly from the biosensor.^[17] The recovered substances can subsequently be analyzed by MALDI-TOF spectrometry, also in concentra-

tions reaching the femtomolar range. This way, the biosensor is not destroyed and can be used for further experiments.

Mobile SPR Sensors

A wide-spread distribution of SPR and RM instruments to determine refractive indexes and applications derived thereof is often opposed by the size and, in particular, the price of the instruments. Here, an alternative are the SPREETA sensors developed by Texas Instruments.^[18] These devices combine the sensor surface with all the optic and electronic components required for SPR experiments in a compact (approx. $3 \times 4.2 \times 1.5$ cm) and lightweight (approx. 7 g) assembly which can be produced cost efficiently (Figure 3). A likewise

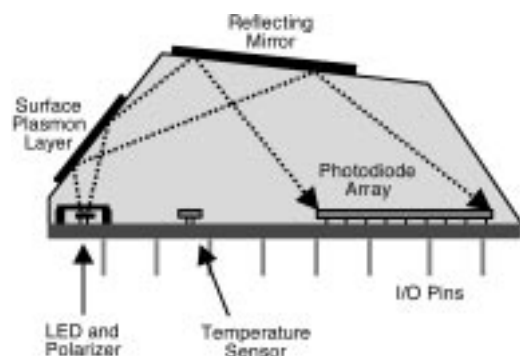


Figure 3. Structure and path of rays of a SPREETA sensor (kindly provided by Texas Instruments, Dallas, TX).

transportable interface handles data acquisition and data transfer to a personal computer, where the evaluation is achieved by use of an MS Windows program. The SPREETA sensors also allow the determination of the refractive index of a solution, and are hence useful for different purposes, such as monitoring the saccharide content of soft drinks. Analogous to the much larger stationary SPR instruments, these sensors may also be used to study biomolecular interactions. This was demonstrated for the binding of creatine kinase to an immobilized *anti*-creatine kinase antibody on the sensor surface.^[19] Although, the sensitivity of state of the art SPR instruments may not be reached by the SPREETA sensors, these cost-effective and small SPR sensors will provide the basis for the development of a wide range of applications with SPR biosensor technology.

Conclusions

Since their presentation, SPR and RM biosensors have been continuously improved, and can thus be employed in different analytical areas. In many of these areas, such as environmental monitoring or product control in the food or

beverage industry, custom-designed biosensor solutions already exist. For biologically oriented chemists or biochemists, the described advances in biosensor technology open new perspectives for the investigation of protein–ligand or other biomolecular interactions. Therefore, these techniques will become part of the standard equipment of biologically oriented laboratories in the near future.

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Polysaccharide Sequencing

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Chemical compounds whose names begin with the prefix “oligo” or “poly” broaden questions of structure to include aspects of sequencing. At the constitutional level, natural products that serve as skeletal compounds or energy depots usually demand little more than orderly building plans with which, for example, the requirements for mechanical rigidity or osmotic inactivity can be fulfilled. Instances of this are the polysaccharides cellulose and starch, which are composed solely of glucose. A different situation appears if phenomena such as molecular recognition or information storage come into play. Here the different monomers serve as an alphabet with which exact instructions can be written by means of an inexhaustible combination of letters, or as modular systems for distinctive macromolecular structures that recognize receptors or substrates with high selectivity. Prime examples of this are nucleic acids and proteins whose sequencing has long been established. On the other hand, work published recently in *Science* by Sasisekharan and co-workers under the title “Sequencing Complex Polysaccharides” has attracted attention.^[1] There are several reasons for this: The polyfunctionality of carbohydrates allows more diverse coupling possibilities than is the case with nucleotides and amino acids, and includes branching such as additional substitutions. Furthermore, the biological significance of carbohydrates for, for example, cell recognition and adhesion, inflammatory processes, or the regulation of enzymatic reactions, and hence also the analytical challenge, has been recognized only relatively recently.

What makes sequence analysis of oligo- and polysaccharides so difficult? To start with, one is almost always confronted with structural diversity. N- and O-glycans of glycoproteins differ from each other according to species, tissue, cell type, and protein. In the biosynthesis of the glycosaminoglycans heparin and heparan sulfate the situation is further complicated by polymer-like, enzymatic modification of (D-GlcA β 1,4-D-GlcNAc α 1,4)_n, which leads to the partial isomerization of the repeating units to (L-IdoA α 1,4-D-GlcNAc α 1,4)_n, to N-deacetylation/N-sulfation, and to different O-sulfation patterns (Figure 1).^[2] Likewise, the polyfunctionality of carbohydrates also hampers stepwise chemical degradation from one chain terminus, as is the case for the Edman degradation of peptides. Moreover, amplification of certain structures, as with the polymerase chain reaction (PCR) in the case of nucleic acids, cannot be carried out with polysaccharides.

Initial advances were made with the development of “soft” ionization methods in mass spectrometry, first with FAB, and

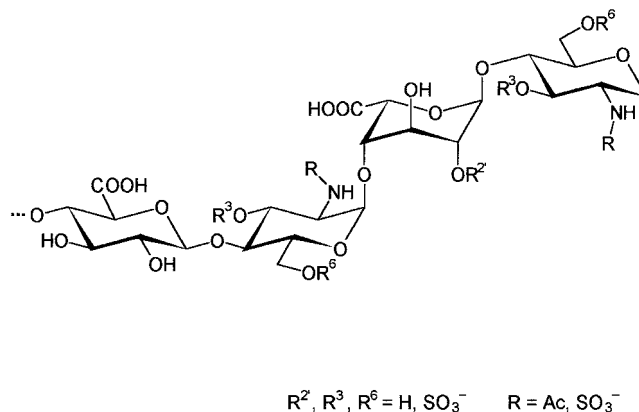


Figure 1. Possible section of a heparin or a heparan sulfate molecule (D-GlcA β 1,4-D-GlcNAc α 1,4-L-IdoA α 1,4-D-GlcNAc α 1,4-). GlcA = glucuronic acid, GlcNH₂ = 2-amino-2-deoxyglucose, IdoA = iduronic acid.

then later with MALDI-MS and ESI-MS (FAB = fast atom bombardment, MALDI = matrix assisted laser desorption/ionization, ESI = electrospray ionization). In principle, these methods make it possible to determine the molecular mass as well as the order of the sugar building blocks, which may be identified from the sequential cleavage of glycoside bonds.^[3] However, because of the large number of possible stereoisomers, it is not possible to decide which hexose is involved, or which deoxy or amino sugar, as long as the building block composition does not impose any restrictions. Furthermore, branching-specific fragment ions, which provide further structural information, are formed by high-energy collision activation.^[4] With all these ionization methods carbohydrates bring up the rear since they are ionized in much lower yield than peptides or oligonucleotides. Fundamental to the successful sequencing strategy of Sasisekharan et al.^[1] was therefore the procedure of Juhasz and Biemann^[5] in which an increase in the sensitivity of MALDI-TOF-MS into the 100-fmol range was achieved by complexation of the sulfated heparin-like oligosaccharides with basic proteins of defined molecular mass, and sulfate loss could be avoided.

Because of their manifold biological functions and high structural diversification, O- and N-glycans and heparin/heparan sulfate are very frequently both topic and stimulus for powerful, sensitive, and practical carbohydrate analysis. Glycans from glycoproteins have been sequenced by their fragmentation behavior under CID conditions (CID = collision-induced fragmentation) by means of MALDI-MS^[6] as well as through the use of metastable ions (post source decay, PSD-MALDI-MS),^[7] or after stepwise enzymatic degradation with exoglycosidases.^[9–11] It has also been possible to obtain new information on the complexity of saccharides from human milk by this strategy.^[12]

Which are now the key steps in the new sequence strategy described above? The authors investigated hexa- to deca-saccharides with heparin-like structures. The starting point for

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Table 1. Sequencing example from ref. [1]

Example 1		$n^{[a]}$
a)	MALDI-MS: $M = 2230 \rightarrow$ octasaccharide- $S_{11}Ac_0$	
b)	exhaustive enzymatic degradation to disaccharides with heparinases: $CE \rightarrow \Delta U_{2S}H_{NS,6S}, \Delta UH_{NS,6S} (3:1)^{[b]}$	32
c ₁)	heparinase I: MALDI-MS $\rightarrow$ tetrasaccharide- S_5 , disaccharide- S_3	4
c ₂)	heparinase II: MALDI-MS $\rightarrow$ hexasaccharide- $S_9 \rightarrow \Delta U_{2S}H_{NS,6S}I_{2S}H_{NS,6S}I_{2S}H_{NS,6S}GH_{NS,6S}^{[b]}$	1
Example 2		
a)	MALDI-MS: $\rightarrow$ decasaccharide- $S_{13}Ac_1$	
b)	exhaustive enzymatic degradation to disaccharides with heparinases: $CE \rightarrow \Delta U_{2S}H_{NS,6S}, \Delta UH_{NAc,6S}, \Delta UH_{NS,3S,6S} (3:1:1)$	320
c ₁)	heparinase I ("mild"): $\rightarrow$ MALDI-MS	52
	heparinase I ("exhaustive"): $\rightarrow$ MALDI-MS	28
d)	labeling of the decasaccharide at the reducing terminus	
e ₁)	heparinase II: $\rightarrow$ MALDI-MS	6
e ₂)	exhaustive degradation by deamination: $\rightarrow$ MALDI-MS $\rightarrow$ localization of H_{NAc}	6
f)	successive treatment with exoenzymes $\rightarrow \Delta U_{2S}H_{NS,6S}I_{2S}H_{NS,6S}I_{2S}H_{NS,6S}IH_{NAc,6S}GH_{NS,3S,6S}$	1

[a] n = calculated number of sequences which are in agreement with the experimental data. [b] U = uronic acid (I or G), $\Delta U = 4,5$ -unsaturated uronic acid from enzymatic cleavage, I = iduronic acid, G = glucuronic, H = hexosamine, index: 2S sulfated at O2, NS: sulfated at N, etc.

their deliberations are the possible sequences that can be constructed from the disaccharide building blocks (Figure 1), which consist of an uronic acid and a hexosamine. When the possible sulfation and N-acetylation patterns are taken into consideration, there are 32 building blocks which are coded for the computer-aided calculations. This is absolutely necessary since even for one octasaccharide constructed from these units there are theoretically more than a million possible structures (32^4). Exhaustive degradation with heparinases gives the building blocks, the composition of which may be analyzed by capillary electrophoresis (CE) and comparison with standard substances. Determination of the molecular mass by MALDI-MS supplies information on the possible combinations of the coded disaccharide units. A clear limitation is now possible on the basis of the variation in masses in relation to the degree of sulfation and acetylation together with knowledge gained from the building block analysis. By selective chemical or enzymatic partial degradation new fragments are obtained in each case, whose molecular masses are also determined by MALDI-MS. In this way the possibilities of suitable precursors are restricted stepwise. Commercially available exoenzymes have been used for identifying the configuration of the uronic acid at the nonreducing terminus. The authors' procedure is illustrated in Table 1 with the example of an octasaccharide. After nitrous acid deamination and ring contraction to 2,5-anhydromannose, chain-cleaving deamination, commonly used for 2-amino-2-desoxy sugars, allows localization of the N-sulfate and N-acetyl groups in the hexosamine. Labeling of the reducing terminus permits its differentiation from the internal building blocks. Successful elucidation of the whole sequence is made possible by selection of suitable degradation methods and mass spectrometric analysis with verification through calculations which of the coded disaccharide structures are in agreement with the experimental results.

That the detailed structural elucidation of heparin and heparan sulfate is highly topical and is being intensively investigated is demonstrated by two further papers which were published in 1999 and which herald "Sequence analysis..."^[13] or "A strategy for rapid sequencing..."^[14] in their titles. The chemical (deaminative cleavage) and enzymatic

methods are the same as in the *Science* work cited above,^[11] but in the first case^[13] the analysis of the degradation products is carried out by anion-exchange chromatography of the tritium-labeled oligosaccharides, and in the second example^[14] by gel electrophoresis after reductive amination with a fluorophore. Neither study involves mass spectrometry.

All the applications described involve isolated, chemically uniform hexa- and deca-saccharides. Isolates of natural oligosaccharides are frequently microheterogeneous and must normally be carefully purified first. Even for Sasisekharan and co-workers, building block analysis by capillary electrophoresis is essential for the restriction of possible sequences. Wherein lies the progress of this strategy? According to the statements of the authors, MALDI-MS does not require renewed isolation and purification of the cleavage products after the different manipulations. Moreover, they see in their approach potential for a fully automated sequencing method, when with better investigated and more specific enzymes the tools for a defined partial degradation of complex polysaccharides are available and thus a more refined and more efficient algorithm can be developed. This is all the more important if the future goal is to analyze larger sequences and mixtures of oligosaccharides in a similar manner and thus reduce the effort of fractionation of biological material, a challenge whose accomplishment is awaited with anticipation.

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Direct Detection of Hydrogen Bonds in Biopolymers by NMR Spectroscopy

Gerd Gemmecker*

Dedicated to Professor Horst Kessler on the occasion of his 60th birthday

Today every chemist knows about the existence and importance of hydrogen bonds. The concept of hydrogen bonding plays a major role in the understanding of the physicochemical properties of water, inorganic and organic acids, as well as acid–base catalysis. Hydrogen bonds influence the conformational preferences and reactivity of many classes of organic molecules.

In the field of biochemistry, hydrogen bonds are responsible for the selectivity of base pairing in nucleic acids—the basis for the preservation and propagation of genetic information. Furthermore, hydrogen bonds play a crucial role in the three-dimensional folding of proteins: the most prominent structural features of proteins—helical and β -sheet regions—are defined and stabilized by their unique pattern of hydrogen bonds.

Finally, intermolecular hydrogen bonds contribute to the affinity and selectivity of molecular recognition, from simple host–guest systems all the way up to the multi-component complexes of proteins, nucleic acids, etc., which are at the heart of so many biological functions.

However, in the course of structure determinations by X-ray diffraction or NMR spectroscopy, the existence of hydrogen bonds is usually only inferred in a rather indirect way from an appropriate spatial arrangement of possible hydrogen donors and acceptors that is already known to exist in high-resolution molecular structures. Particularly in the field of NMR spectroscopy, several approaches have been proposed to deduce the existence and localization of hydrogen bonds indirectly from parameters such as hydrogen-exchange rates, isotropic and anisotropic chemical shifts, ^2H quadrupolar splittings, and $^1\text{H}/^2\text{H}$ isotope shifts.

At the XVIIIth International Conference on Magnetic Resonance in Biological Systems (ICMRBS) in Tokyo in August 1998 Andrew Dingley and Stephan Grzesiek reported the observation of scalar couplings across the hydrogen bonds

in the Watson–Crick base pairs of a ^{15}N -labeled 69 nucleotide RNA (their paper appeared in print the same month).^[1] In an experiment set up for the detection of scalar couplings between two ^{15}N spins (a type of ^{15}N -COSY spectrum), several fairly intense cross-peaks had been observed (Figure 1) that could only be assigned to correlations between N3 of a uridine and N1 of an adenosine group, and N1 of a guanosine and N3 of a cytosine group, each across the hydrogen bonds within a U–A or G–C Watson–Crick base pair, respectively (Figure 2).

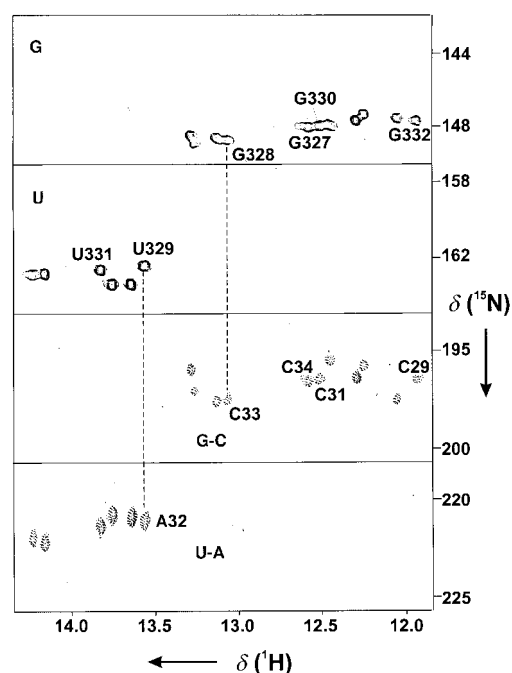


Figure 1. Strips from an HNN-COSY spectrum of a $^{13}\text{C},^{15}\text{N}$ -labeled 69-nucleotide RNA domain.^[1] The upper two panels show the COSY “diagonal peaks”, that is, the ^{15}N spins (in F1) correlated with their directly bound proton (F2). The cross-peaks in the lower two panels are caused by ^{15}N - ^{15}N correlations through a $^2J_{^{15}\text{N},^{15}\text{N}}$ coupling across the hydrogen bonds within Watson–Crick base pairs; the correlations G328-N1/C33-N3 and U329-N3/A32-N1 are indicated by dashed lines. (Reproduced with permission from the American Chemical Society 1998.)

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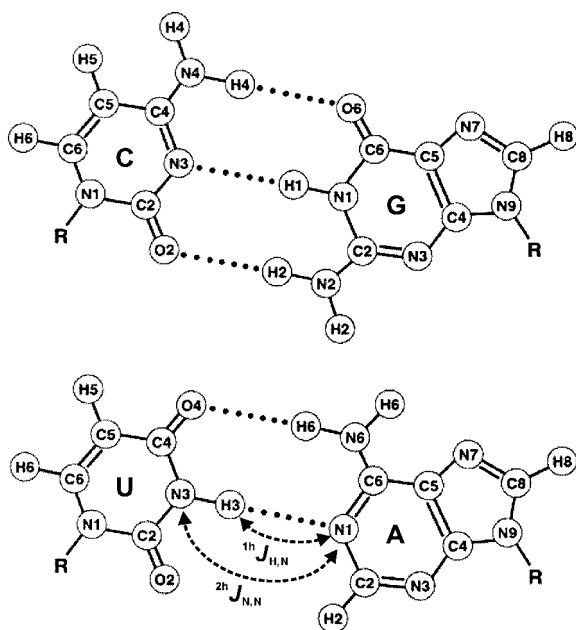


Figure 2. Hydrogen-bonding pattern in the Watson-Crick base pairs uridine-adenosine (U-A) and cytidine-guanosine (C-G).

Grzesiek's revelations caused quite a lively discussion and, of course, several critical questions as to whether the observed correlations could be explained by some other mechanism, for example, dipolar cross-correlation. However, Grzesiek's experimental data were quite thorough and proved that the mysterious correlation across the hydrogen bond behaves exactly like a scalar coupling of 6.5–7.0 Hz.

It is well known that hydrogen bonds are not just purely ionic bonds based only on electrostatic attraction, but can exhibit a considerable covalent character. Hence, the existence of a scalar coupling across the hydrogen bond could, in principle, be expected. What came as a big surprise in Grzesiek's work was the size of the observed coupling: the measured values are comparable to the average vicinal coupling between protons in a H-C-C-H fragment—couplings involving ^{15}N are usually much smaller. The observed coupling could be called a $^2J_{^{15}\text{N},^{15}\text{N}}$, that is, a two-bond coupling; however, to emphasize the fact that these are not two ordinary bonds, but hydrogen bonds, it was suggested by Kurt Wüthrich (who confirmed the original findings) to use the symbol $^2J_{^{15}\text{N},^{15}\text{N}}$.^[2]

Considering the size of the $^2J_{\text{N,N}}$ coupling, the idea to look for $^1J_{\text{H,N}}$ couplings across the hydrogen bonds arose; these should be even easier to detect. However, the Wüthrich group found these values to be in the order of only 2–4 Hz.^[2]

Scalar couplings between two spatially close spins that are not transmitted through ordinary covalent bonds have been reported before in the literature (for example, between ^{15}N and ^{19}F atoms)^[3, 4] and dubbed with the rather misleading term “through-space J couplings”, although they are real scalar couplings transmitted by the valence electrons. A few years ago such a scalar coupling had even been detected and measured between the amide proton and ^{113}Cd in an N-H...S-Cd hydrogen bond in a Cd-substituted iron-sulfur protein.^[5] Recently, the groups of Limbach and Denisov investigated

the $^{19}\text{F}\cdots\text{H}\cdots^{15}\text{N}$ hydrogen bond in the complex between hydrogen fluoride and trimethylpyridine at low temperature. They found a similar pattern of (temperature dependent) scalar couplings: $^1J_{\text{H,N}} = 39\text{--}54\text{ Hz}$, $^1J_{\text{F,H}} = 15\text{--}105\text{ Hz}$, and $^2J_{\text{F,N}} = 96\text{ Hz}$.^[6] Again, the two-bond coupling was clearly larger than each of the one-bond couplings (on average), which suggested that the molecular orbitals with large s character at ^{19}F and ^{15}N exhibit only a weak s character at the bridging hydrogen atom itself.

Recently, the phenomenon of scalar couplings across N-H...N hydrogen bonds in nucleic acids and its dependence on bond geometry has been analyzed in detail, and the experimental values could be reproduced and “explained” by density functional calculations.^[7] These calculations agreed with the experimental findings that the $^2J_{\text{N,N}}$ coupling is much larger, and also much less dependent, on the N-N distance than the $^1J_{\text{H,N}}$ coupling (Figure 3).

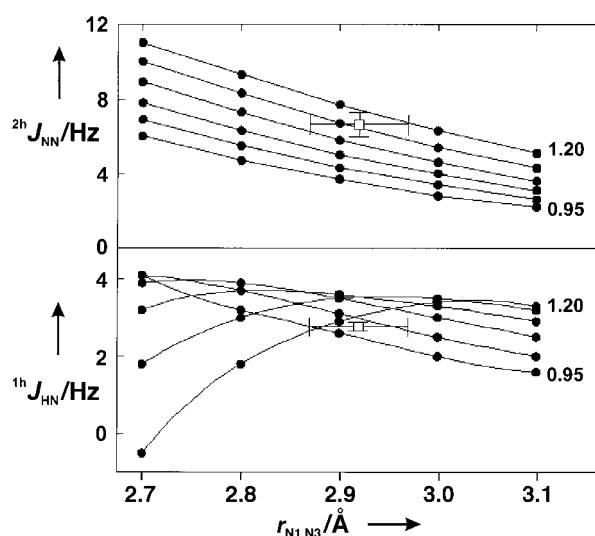


Figure 3. Dependence of $^2J_{^{15}\text{N}_1,^{15}\text{N}_3}$ (top) and $^1J_{^1\text{H}_1,^{15}\text{N}_3}$ (bottom) on the length of the hydrogen bond $r_{\text{N}_1, \text{N}_3}$, calculated by density functional theory for a G-C fragment, and $r_{\text{N}_1, \text{H}_1}$ distances from 0.95 to 1.20 Å (indicated on the right).^[7] The open boxes and error bars represent mean values and deviations for $r_{\text{N}_1, \text{N}_3}$ distances as deduced from DNA crystal structures. (Reproduced with permission from the American Chemical Society 1999.)

With the existence and accessibility of the scalar couplings in hydrogen bonds confirmed, several groups immediately went to work to look for similar couplings in proteins. Here, the hydrogen acceptor atom is usually the oxygen atom of a carbonyl group in the peptide backbone, instead of a nitrogen atom in nucleic acids (however, a $^2J_{\text{N,N}}$ coupling has recently been detected between two histidine side chains in apomyoglobin^[8]). Unfortunately, there is no oxygen isotope that is suitable for NMR measurements as ^{15}N : the main isotope ^{16}O is magnetically inactive, and the other stable isotopes ^{17}O and ^{18}O are quadrupolar nuclei. The closest suitable spin on the acceptor side of a hydrogen bond in isotopically $^{15}\text{N},^{13}\text{C}$ -enriched proteins (as generally used for NMR studies) is the carbonyl carbon atom $^{13}\text{C}'$. The hydrogen bond scalar couplings to be expected in an N-H...O=C arrangement are thus the two-bond coupling $^2J_{\text{H,C}}$ and the three-bond coupling $^3J_{\text{N,C}}$ (Figure 4).

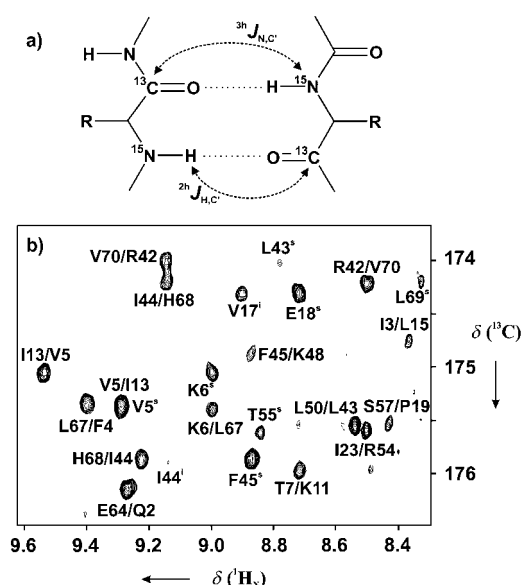


Figure 4. a) Nomenclature for hydrogen-bond couplings in proteins. b) Region from an HNCO spectrum of human ubiquitin tuned for the detection of small $^{15}\text{N},^{13}\text{C}$ couplings.^[9] Some cross-peaks arise from incomplete suppression of either $^1J_{\text{NC}}$ (superscript s) or $^2J_{\text{NC}}$ couplings (superscript i). However, the majority of peaks correlate two hydrogen-bonded residues through a $^3J_{\text{NC}}$ scalar coupling ranging from 0.3 to 0.9 Hz. (Reproduced with permission from the American Chemical Society 1999.)

Again, the bond over the longer distance, $^3J_{\text{NC}}$, was the first to be reported by Cordier and Grzesiek,^[9] followed shortly afterwards by similar results from the group of Ad Bax.^[10] The detection did not even require a completely new pulse scheme, but relied on the HNCO experiment, well known and widely used in protein NMR for correlating the amide proton to the amide nitrogen atom and on to the carbonyl carbon atom of the adjacent $i-1$ amino acid through the one-bond couplings $^1J_{\text{NH},^{15}\text{N}}$ (ca. 92 Hz) and $^1J_{^{15}\text{N},^{13}\text{C}}$ (ca. 15 Hz; Figure 4). The transfer efficiency in these experiments is at a maximum with a delay of $1/2J$ and zero for an integer multiple of $1/J$. Therefore, for the detection of the much smaller coupling $^3J_{^{15}\text{N},^{13}\text{C}}$, only the delay for the transfer from ^{15}N to ^{13}C had to be adjusted from about 33 ms (optimum for $^1J_{^{15}\text{N},^{13}\text{C}}$) to the rather lengthy 133 ms (optimum for a 3–4 Hz coupling and zero for $^1J_{^{15}\text{N},^{13}\text{C}}$). As a result, the direct ^1J correlation between $^{15}\text{N}_i$ and $^{13}\text{C}_{i-1}$ was suppressed and another weaker correlation could indeed be seen: from the amide nitrogen atom to the ^{13}C spin of the acceptor carbonyl group of a hydrogen bond!

These first experiments were performed on the small protein ubiquitin, which has a well-known assignment of all ^{15}N and ^{13}C spins and 3D structure. The correlations found in the HNCO spectrum tuned for small $^3J_{^{15}\text{N},^{13}\text{C}}$ couplings proved to agree perfectly with the known pattern of hydrogen bonds. The size of the coupling constant, however, was rather small, only 0.3–0.5 Hz for α -helical regions and 0.5–0.9 Hz for β -sheets—an extremely small coupling for proteins with line widths usually exceeding 10 Hz, and it is not surprising that they had not been discovered by chance before.

Again from extensive experimental data, a quantitative relationship could be established between the length of the

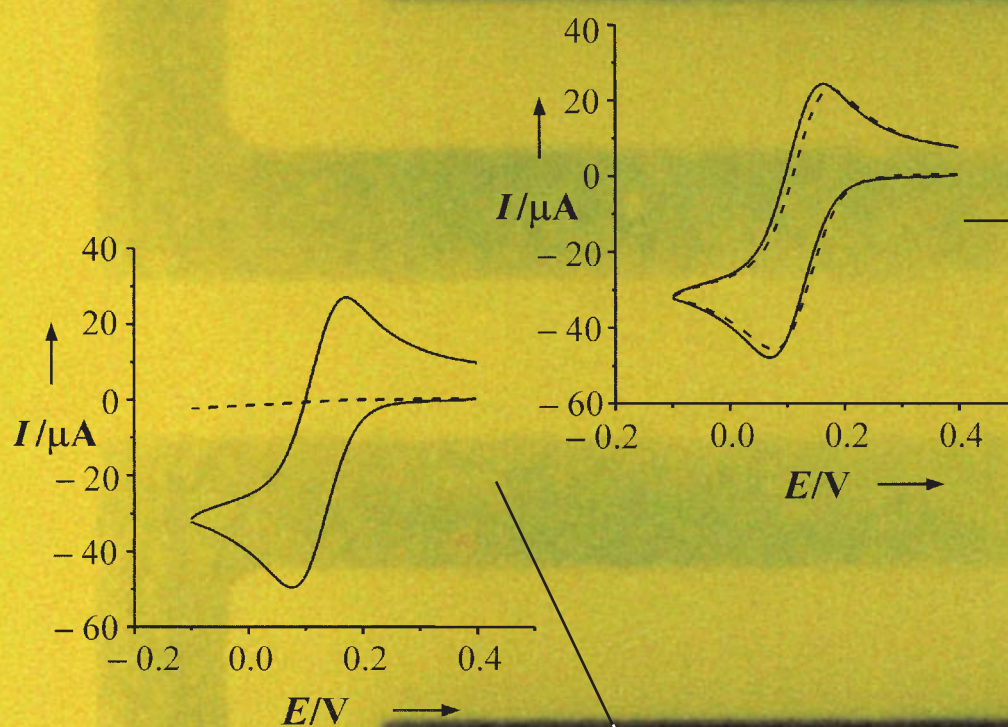
hydrogen bond (namely, the $^{15}\text{N}-^{13}\text{C}$ distance) and the size of the $^3J_{^{15}\text{N},^{13}\text{C}}$ value, with the coupling constant dropping below 0.2 Hz for $^{15}\text{N}-^{13}\text{C}$ distances larger than about 3.2 Å.^[11]

In the meantime the two-bond coupling $^2J_{\text{NH},^{13}\text{C}}$ had also been observed, with coupling constants slightly smaller than the 0.4–0.6 Hz of the three-bond coupling.^[12] However, the $^2J_{\text{NH},^{13}\text{C}}$ coupling is technically much more difficult to detect than $^3J_{^{15}\text{N},^{13}\text{C}}$, as a result of the presence of the larger “ordinary” ^2J and ^3J couplings between the amide protons and ^{13}C in the protein backbone. Recently, also the $^3J_{\text{NH},^{13}\text{C}}$ coupling has been detected and quantified by Meissner and Sørensen.^[13]

It is clear that the direct detection of hydrogen bond donors and acceptors will greatly facilitate the NMR investigation of nucleic acid structures by revealing the presence, localization, and even the length of hydrogen bonds involved in base pairing.^[14] The applications to proteins are more problematic because of the small size of the accessible hydrogen-bond couplings. However, it is reasonable to expect that these couplings will also prove useful with much larger proteins by using the TROSY approach. The TROSY (Transverse Relaxation Optimized Spectroscopy) concept was introduced by the Wüthrich group about two years ago and allows for a significant reduction in the line width and relaxation rates, which usually increase with molecule size.^[15] For the very long delays required for the detection of small hydrogen-bond couplings, the reduction in relaxation losses is essential, and TROSY versions have been applied almost from the beginning.^[1, 2] In combination with protein samples which are perdeuterated (except for the exchangeable protons), it can be expected that the measurement of hydrogen-bond couplings will soon also play an important role in structural studies for medium-sized proteins.

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A fluorescence-microscopy photograph of a triple-track tester overlaid with a thin film of a fluorescent dye. Electrode B, modified by an electrochemically adsorbed sodium *n*-dodecylsulfate layer, is hydrophobic and repels the dye solution. In contrast, the unmodified electrodes, A, are wetted with the dye.



The cyclic voltammogram shows the behavior of both types of electrodes before and after modification as the solid and broken lines, respectively. More details are given in the following pages.

Electrochemically Directed Self-Assembly on Gold**

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One of the most attractive characteristics of self-assembled monolayers (SAMs) is the simplicity of their preparation: simply expose a substrate surface to an appropriate adsorbate.^[1–3] This facility unfortunately prevents selective monolayer formation on particular substrates in the presence of others of the same composition. While contact printing of SAMs has proven useful in preparing mesoscale patterns on various substrates,^[4] the formation of monolayers on particular features of a preexisting pattern—such as an electrode array, an integrated circuit, or a microelectronic systems (MEMS) device—remains challenging. Advances have been made using the oxidation of alkyl thiolates on gold electrodes to control the formation of SAMs,^[5] and reductive desorption^[6, 7] of monolayers from modified electrodes.^[8] In this paper, we report a new method for forming SAMs by the electrochemical oxidation of alkyl thiosulfates on gold electrodes and demonstrate their selective formation in specific locations on a set of closely spaced microelectrodes.^[9]

The chemical^[10–13] or electrochemical^[14, 15] oxidations of alkyl thiosulfates (Bunte salts) are known to produce disulfides. We hypothesized that the proposed intermediate of the electrochemical reaction, an alkylsulfide radical,^[14] or the disulfide produced at a gold electrode could be trapped and form stable gold–thiolate bonds.^[16] In preliminary experiments,^[17] this synthetic strategy resulted in the successful formation of a SAM on a gold electrode in a Galvanic cell, in which iodine was used as a remote oxidant in an aqueous solution. A monolayer did not form under analogous open-circuit conditions. Using a Galvanic cell or potentiometric conditions to drive the oxidation of alkyl thiosulfates in an

aqueous solution did not provide adequate reproducibility or control over the electrochemisorption process. These results prompted us to explore the use of nonaqueous systems to characterize the redox chemistry involved.

Figure 1a shows a cyclic voltammogram of sodium *n*-hexadecylthiosulfate in THF at a gold electrode. The inset magnifies the range from –0.80 to +0.50 V (versus Ag/AgNO₃) of the anodic scan. Clearly, the onset of current flow

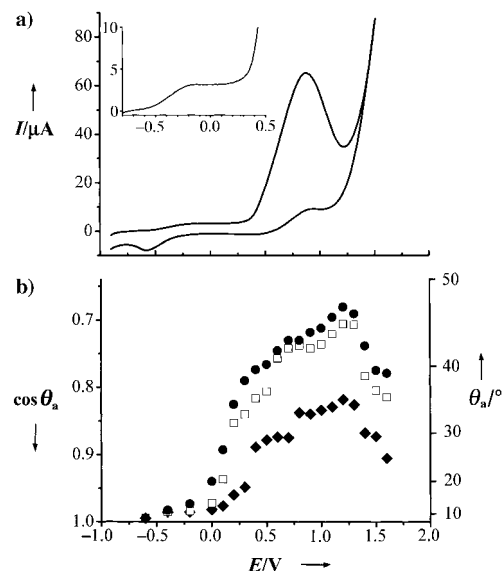


Figure 1. a) Cyclic voltammogram for a 10 mM solution of sodium hexadecylthiosulfate in THF (0.1 M Bu₄NBF₄, 100 mV s^{–1}) using a gold working electrode and a Ag/AgNO₃ reference electrode (3 mm in CH₃CN). Inset: the onset of current flow in the anodic scan. b) Advancing contact angles of hexadecane on SAMs formed by electrochemical oxidation of hexadecylthiosulfate using one (◆), three (□), and five (●) voltametric pulses to different potentials.

begins at about –0.50 V. For the results shown in Figure 1b, a gold electrode was immersed into the sodium *n*-hexadecylthiosulfate solution and its potential stepped from –0.90 V to a particular value in the range producing an anodic current. After 5 s at this potential, it was stepped back to the –0.90 V resting potential. This process was repeated using a separate sample for each potential. The advancing contact angle of hexadecane provided a convenient measure of the degree of completeness of the resulting monolayer films as a function of the applied potential and number of pulses used in their formation. In all cases, the onset of anodic current at about –0.50 V corresponded closely with the appearance of a finite contact angle of hexadecane on the film produced. The peak contact angles (45–47°) compared favorably with those reported for complete, well-ordered SAMs prepared by the self-assembly of hexadecanethiol.^[2] The loss of lipophobicity at higher potentials corresponded to a strong anodic current (Figure 1a), probably reflecting oxidation of the thiolate groups, the gold electrode, or THF, and concomitant disordering of the films.

We followed the growth of monolayers formed at 1.20 V as a function of the number of potentiometric pulses by monitoring monolayer thickness and wettability. As the number of pulses was increased on a single electrode, the contact angles of both water and hexadecane rose (Figure 2b)

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

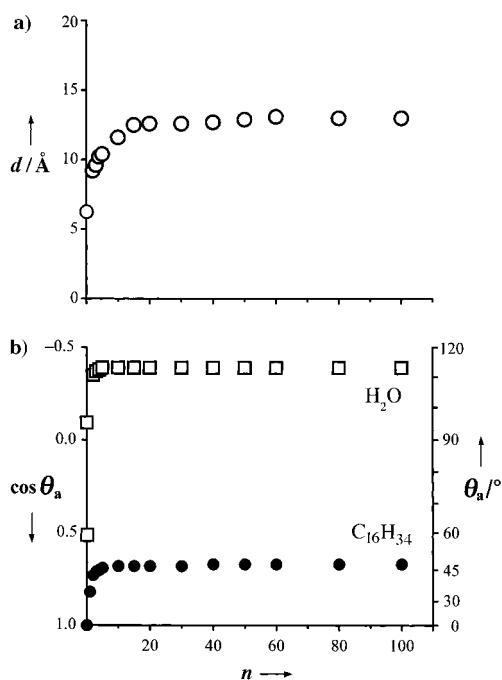


Figure 2. a) Ellipsometric thickness d and b) advancing contact angles θ_a of water and of hexadecane on a gold electrode as a function of the number n of potential pulses (1.20 V versus Ag/AgNO₃) in a 10 mM solution of sodium *n*-hexadecylthiosulfate in THF (0.1 M Bu₄NBF₄).

and reached limiting values consistent with a well-ordered monolayer (water 112–114°; hexadecane 45–47°).^[2] The ellipsometric thickness of the monolayer also increased as a function of the number of pulses to approximately 13 Å (Figure 2a). A monolayer formed at the same time by self-assembly of hexadecanethiol had the same thickness. X-ray photoelectron spectra of a monolayer formed by the electrolysis of hexadecylthiosulfate at 1.20 V (five pulses) and of one formed by adsorption of hexadecanethiol from ethanol were nearly indistinguishable.^[18] High-resolution spectra (sulfur 2p region) showed that both samples contained only thiolate sulfur; no evidence indicated higher oxidation states arising from either incomplete reduction of the thiosulfate or oxidation of the thiolate by air.^[18, 19]

The key advantage of this electrochemical synthesis over the conventional chemisorption of alkanethiols and -disulfides is that it provides *selectivity* in the placement of a SAM only on electrodes with potentials high enough to oxidize the thiosulfate precursor. We demonstrated this feature by selectively modifying one electrode in the close proximity of another: The samples used in these studies were triple-track testers,^[20] comprising a serpentine pattern of three 70–80-μm wide gold lines spaced 70–80 μm apart on an alumina substrate. The two outer lines (electrode A) were connected at one end; the central line (electrode B) was electronically isolated. The device was immersed into a 10-mM sodium *n*-dodecylthiosulfate solution (THF, 0.1 M Bu₄NBF₄) and the potential of electrode B was stepped from –0.90 V (versus Ag/AgNO₃) to +0.90 V. After 200 ms at this potential, it was stepped back to the –0.90 V resting potential. This process was repeated through 150 pulses, with a interval of 6 s between pulses; electrode A was electronically isolated

throughout this process. The differences between this protocol and that used to form the SAMs of hexadecylthiosulfate (Figures 1 and 2) reflect optimization to minimize cross-contamination of the nearby electrode in this experiment, as well as the difference in the chain lengths (C₁₂ versus C₁₆) of the precursors.

This process left the two electrodes on the device strongly differentiated, both in surface energy and electrochemical activity. Figure 3 shows a fluorescence micrograph (×100 magnification) of the device coated with a thin layer of a

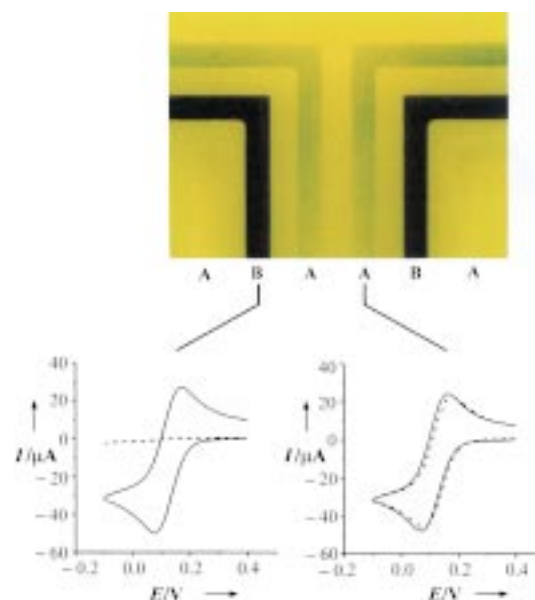


Figure 3. Top: A fluorescence micrograph (×100 magnification; Nikon Microflex UFX-II microscope; Nikon FX35a camera) of a triple-track tester covered with a thin layer of a 1.06 mM aqueous solution of the fluorescent dye rhodamine-6G. The central electrode (B) is hydrophobic resulting from electrochemisorption of sodium *n*-dodecylthiosulfate and repels the dye solution. The outer electrode (A; two outer lines) is unmodified and covered by the dye solution. Both the widths of the gold lines and the spacings between them were in the range of 70–80 μm. Under: cyclic voltammograms (1.0 mM K₃Fe(CN)₆, 0.1 M KCl, scan rate 100 mV s^{–1}; silver quasi-reference electrode, AgQRE) beneath the micrograph show the responses of both electrodes before (—) and after (---) modification of the electrode B.

1.06 mM aqueous solution of the fluorescent dye rhodamine-6G. The modified electrode B repels the solution and thus appears black due to the absence of the dye. The unmodified electrode A is coated with the dye solution and thus appears greenish-yellow. Below the micrograph in Figure 3 are cyclic voltammograms for a second triple-track tester immersed in aqueous solutions of ferricyanide, before and after electrode modification. The modified electrode B showed a normal response prior to modification but was electrochemically inactive after coating with a dodecanethiolate monolayer. In contrast, the response of the unmodified electrode A at this scan rate did not change significantly before and after treatment of electrode B.

In contrast to these electrochemically directed adsorption processes, treatment of a gold electrode by solutions of hexadecylthiosulfate in THF with (90 h) or without (5 min) Bu₄NBF₄ led to the spontaneous, nonselective adsorption of a

SAM.^[9] This kinetic inhibition towards spontaneous adsorption was not observed when Bu₄NPF₆ was used instead of Bu₄NBF₄. The rate of spontaneous adsorption in the presence of tetrafluoroborate is sufficiently slow to allow the selective electrochemisorption described herein.

We have developed an electrochemical method for the selective formation of self-assembled monolayers on a particular gold electrode in the presence of another nearby electrode. The monolayers produced are very similar in thickness, wettability, blocking of heterogeneous electron transfer, and elemental composition to analogous SAMs formed by the chemisorption of alkanethiols. The selectivity of this synthetic method should allow the preparation of microelectrode arrays with differentiated surface chemistry, a goal of great importance in the fabrication of sophisticated sensor arrays.^[5–7, 21, 22] Other attractive features of this electro-synthesis of SAMs are: a) the control it provides over the degree of coverage; b) the short time (less than a minute) needed to form a SAM; c) the ability to form SAMs easily on gold that is not freshly evaporated; and d) the use of precursors without an unpleasant odor (for precursor alkyl groups containing more than about ten carbon atoms). The formation of SAMs by the electrochemical oxidation of alkyl thiosulfates may be extendable to other metals, as long as anodic dissolution of the metal does not interfere at the potential necessary to oxidize the Bunte salts. In preliminary experiments, we found that SAMs can also be formed from aqueous solutions by the reduction of an alkyl thiosulfate, a process known to produce thiols.^[10]

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Building Supramolecular Nanostructures at Surfaces by Hydrogen Bonding**

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Supramolecular structures formed by the self-assembly of functional molecular building blocks are a promising class of materials for future technologies.^[1–3] Particularly useful for their fabrication is hydrogen bonding,^[4] which provides both high selectivity and directionality.^[5] Hydrogen-bonded archi-

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structures are abundant in biological systems, which has motivated their exploitation in supramolecular chemistry.^[6] This has been demonstrated particularly for systems in solution, molecular crystals, and for two-dimensional layers.^[1, 3, 4, 7–10] Herein we demonstrate that novel supramolecular nanostructures can be generated at surfaces on the basis of this concept. Scanning tunneling microscopy experiments were performed on 4-[*trans*-2-(pyrid-4-yl-vinyl)]benzoic acid adsorbed onto a metal surface.^[11, 12] A one-dimensional supramolecular nanograting was fabricated at a Ag(111) surface by cooperative self-assembly.

Molecular self-assembly at surfaces is governed by the subtle balance between intermolecular and molecule–surface interactions, which can be tuned by the appropriate choice of substrate material and symmetry. Promising achievements have been reported in this field.^[13–16] For the present study we employed 4-[*trans*-2-(pyrid-4-yl-vinyl)]benzoic acid (PVBA, Figure 1a), which has been specifically designed to form

onto different well-defined single-crystal metal surfaces by organic molecular beam epitaxy.^[17, 18] The resulting molecular arrangements were subsequently characterized in situ by temperature-controlled scanning tunneling microscopy (STM).

The molecules experience the potential energy surface of the metal substrate upon adsorption, which makes specific geometries energetically favorable. The ease with which these sites can be changed by either translational or rotational processes, that is, the surface mobility, is a key parameter for the arrangement of molecules at surfaces. Similarly important is the strength and nature of the intermolecular interactions that compete with the molecule–substrate interactions. As a third parameter, the magnitude of the thermal energy governs the level of ordering that can be achieved. The balance of these factors controls molecular self-assembly at surfaces. The STM data reproduced in Figure 1b–d demonstrate how self-assembly can be tuned for a given molecule by the choice of substrate material and symmetry. The interaction of PVBA with the transition metal surface Pd(110) is visualized in Figure 1b. The two-lobe shape of the individual molecules resolved in the image is associated with the pyridyl and phenylene rings. Strong π bonding to Pd surface atoms enforces a flat adsorption geometry. Two distinct molecular orientations exist exclusively which allow for the accommodation of the molecular units at sites on the anisotropic substrate with high symmetry.^[19, 20] At small coverages a random distribution of isolated molecules is found even well above room temperature where thermal mobility becomes appreciable, which demonstrates the dominance of the adsorbate–substrate interactions with this system.^[19, 20] Low-temperature aggregation and growth of dendritic molecular islands is observed on switching to the more inert Cu(111) surface (Figure 1c), which is indicative of a higher surface mobility and greater lateral interactions. However, the PVBA adsorption geometry is not unique as is deduced from the irregularities in the dendritic arms and the coexistence of the flat adsorbed molecules with single ones in upright orientations,^[21] which are imaged as spherically symmetrical protrusions. Annealing the sample results in only flat lying species, however, a regular molecular ordering is obstructed by strong lateral interactions with Cu adatoms evaporated from the substrate steps. These complications are absent at the Ag(111) surface. The STM topograph in Figure 1d reveals that flat adsorption of PVBA prevails on Ag(111). Again, island formation is already found at low temperatures, and inspection of the island shapes reveals that their formation must be a result of attractive interactions between the molecular endgroups. This observation is in line with the directional interactions expected from the formation of hydrogen bonds. Molecular strings thus evolve at the surface, and their curved shape signals that the substrate corrugation experienced by the molecules must be rather weak. This effect is attributed to the smoothness of the close-packed geometry of the substrate and the weak bonding between the adsorbate and the noble metal surface. The observed growth scenario can be considered as a diffusion-limited aggregation of rodlike particles, which is subject to anisotropic interactions. Accordingly, the irregularity of the formed agglomerates suggests that their

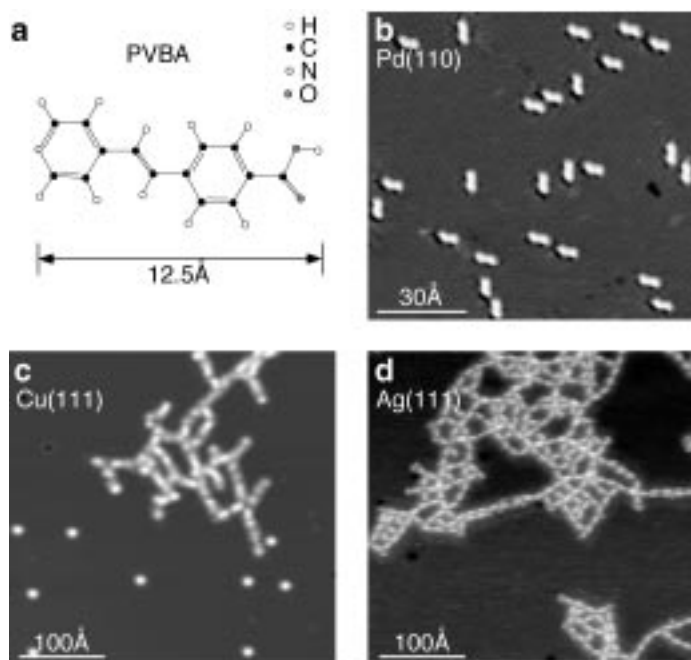


Figure 1. a) Molecular structure of 4-[*trans*-2-(pyrid-4-yl-vinyl)]benzoic acid (PVBA) with a pyridyl group at the head and a benzoic acid moiety at the tail. Pictures b–d show STM topographs of PVBA on different single-crystal metal substrates: b) Strong adsorbate–substrate interaction on a Pd(110) surface: isolated, immobile PVBA molecules lie flat in two distinct orientations (measured at 325 K) and remain randomly distributed upon annealing at 450 K. c) On a Cu(111) surface flat molecules in dendritic islands coexist with isolated molecules in an upright bonding configuration (single protrusions) after adsorption at 160 K. d) The complex aggregation of PVBA lying flat on Ag(111) reflects the surface mobility and attractive interactions between molecular endgroups at 125 K.

strong hydrogen bonds and has been used to form thin films for application in nonlinear optics.^[11, 12] This planar and rigid molecule comprises a pyridyl group as the head and a carboxylic acid group as the tail and is ideal for self-assembly by head-to-tail hydrogen bonding.^[11, 12] Small amounts of PVBA were evaporated under ultra-high vacuum conditions

shape results from kinetic limitations, whereby thermal equilibrium is not attained.

The data reproduced in Figure 2 show that well-ordered supramolecular structures evolve on Ag(111) when the thermal energy is augmented by adsorption or annealing at

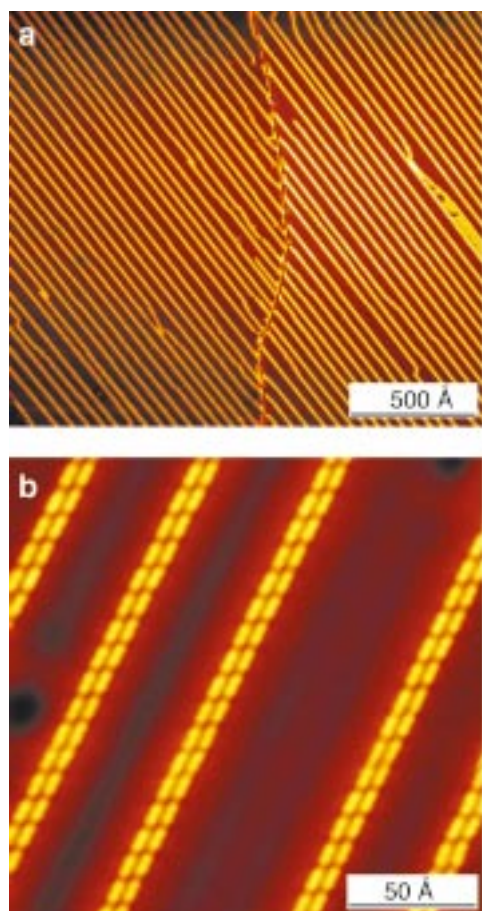


Figure 2. Formation of a one-dimensional supramolecular PVBA superstructure by self-assembly mediated by H-bond formation on an Ag(111) surface at 300 K (measured at 77 K). a) An STM topograph of a single domain extending over two terraces demonstrates ordering at the μm scale. b) A close-up image of the self-assembled twin chains reveals that they consist of coupled rows of PVBA molecules.

300 K. The overview picture (Figure 2a) reveals the formation of highly regular, one-dimensional supramolecular arrangements in a domain that extends over two neighboring terraces that are separated by an atomic step. The molecular stripes run straight along a $\langle 11\bar{2} \rangle$ direction of the Ag lattice. In agreement with the threefold symmetry of Ag(111) three rotational domains of this structure exist, which usually extend in the μm -range on the surface. A close-up view of some molecular stripes (Figure 2b) reveals that the one-dimensional superstructure actually consists of two chains of PVBA.^[22] The molecular axis is oriented along the chain direction, in agreement with the expected formation of hydrogen bonds between the PVBA end groups. The chain periodicity amounts to $15.0 \text{ \AA}$, that is $p = 3\sqrt{3}a$, where a is the Ag(111) surface lattice constant ($2.89 \text{ \AA}$). The rows of PVBA within the twin chains are shifted by $\Delta p \approx 3.7 \text{ \AA}$ with respect

to each other. This observation suggests an intricate coupling mechanism between adjacent rows separated by $d \approx 2.4a$. The extreme stability of the low-temperature scanning tunneling micrograph^[23, 24] employed for this study allows for the elucidation of fine chain details, as demonstrated by the high-resolution data shown in Figure 3. Firstly, a slight

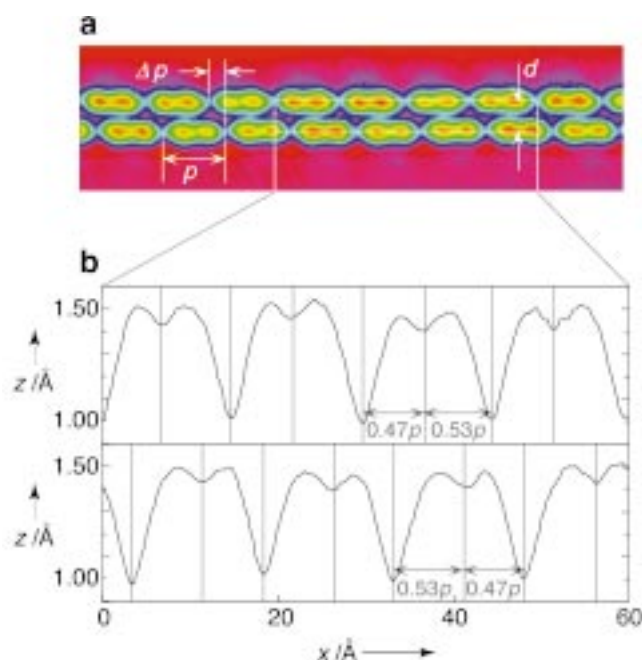


Figure 3. High-resolution STM data of a PVBA twin chain. a) The chain periodicity p in the $[11\bar{2}]$ direction is $3a\sqrt{3} = 15 \text{ \AA}$, the PVBA inter-row distance d is $\approx 2.4a$. b) The STM contours along the lines indicated in (a) demonstrate the head-to-tail coupling of the PVBA molecules along the rows and the antiparallel molecular alignment in adjacent rows.

asymmetry of the molecules becomes apparent in the topograph (Figure 3a), namely, in the upper row the right lobes of all the molecules appear oval, while the left lobes have a round shape. This inequality is elucidated by the STM contour lines shown in Figure 3b. The longer, oval lobe is associated with the benzoic acid moiety of PVBA. Hence, there is indeed a head-to-tail coupling of PVBA in the chains. Secondly, the data reveal that in the lower row the left lobe of all the PVBA molecules is more extended, opposite to the configuration in the upper row. Hence, the molecules in adjacent rows exhibit antiparallel alignment.

The observed features of the supramolecular structure are rationalized by the model proposed in Figure 4a, where a montage of an Ag(111) atomic resolution image with a self-assembled twin chain drawn to scale is shown. The orientation of the molecular chains reflects a good match between the PVBA subunits and the high-symmetry lattice positions. This result also accounts for the chain periodicity being a multiple of Ag lattice units. When an unrelaxed molecular configuration is assumed,^[25] the length of the $\text{OH} \cdots \text{N}$ hydrogen bond is $2.5 \text{ \AA}$. This distance is larger than those of similar types of H-bonds in crystals of nucleic acid components and isonicotinic acid (a lower analogue of PVBA), where values in the range of $1.5\text{--}2.1 \text{ \AA}$ exist.^[26, 27] Nevertheless, the proximity of the coupled groups can be associated with the formation of

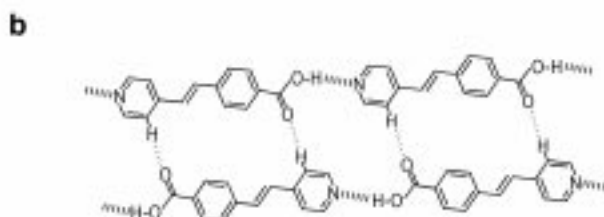
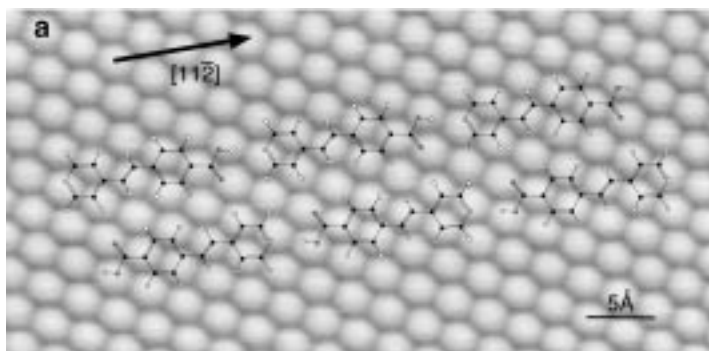


Figure 4. a) Montage of an atomic-resolution image of Ag(111) with a proposed model of the self-assembled twin chain of PVBA drawn to scale illustrating the match of the molecular geometry and substrate lattice. b) Repeat motif of the PVBA supramolecular twin chains with weak OH...N and possible weak CH...OC hydrogen bonds indicated.

weak H-bonds (Figure 4b).^[5] It is possible that the presence of the metal surface electrons might influence the hydrogen bonding. Solid-state ^{15}N NMR spectroscopy has demonstrated that proton transfer does not occur with PVBA in crystallites.^[11] The coupling of the PVBA in adjacent rows is associated with weak intermolecular attractions. The antiparallel alignment and the relative displacement allow for a complementary assembly of two equivalent PVBA molecules, which are accommodated in similar adsorption geometries. In addition to the expected electrostatic interactions between the polar molecules, a weak CH...OC hydrogen bonding is feasible. The corresponding CH...OC distance is approximately 2.9 Å, close enough for a weak interaction.^[28] The geometrical arrangement is a compromise between the lateral intermolecular interaction and the bonding to the substrate.^[29] There is a slight outward relaxation of the rows away from the centers of the hollow-site positions as a result of the inter-row distance of $2.4a$. This relaxation and the suggested inward orientation of the C=O group prevent two-dimensional growth and thus account for the directional self-assembly of the twin chain. The rather regular mesoscopic ordering of the supramolecular chains into a grating, reminiscent of mesoscopic superstructures induced by relaxation of surface strain,^[30, 31] can be rationalized by the operation of weak, long-range repulsive dipole–dipole interactions between the twin chains.^[32]

It is interesting to note that chiral species of PVBA exist at the surface which undergo spontaneous enantioresolution in the self-assembly process. Only one enantiomer is present in the model shown in Figure 4 (while arrangements are feasible with a combination of different enantiomers, they lead to energetically less-favorable structures^[33]). This observation is related to the distinct directional shift in the twin chains: it is

always the right PVBA row that appears to be displaced by the distance Δp in the chain direction. Accordingly the opposite shift is encountered, and was indeed observed, with the other enantiomer.

Our findings suggest that the self-assembly of properly designed molecules by noncovalent bonding opens up novel avenues for the positioning of functional units in supramolecular architectures at surfaces by organic molecular beam epitaxy. It is believed that this approach will be valuable for the future fabrication of nanoscale devices and supramolecular engineering.

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Ring-Closing Alkyne Metathesis: Application to the Stereoselective Total Synthesis of Prostaglandin E₂-1,15-Lactone**

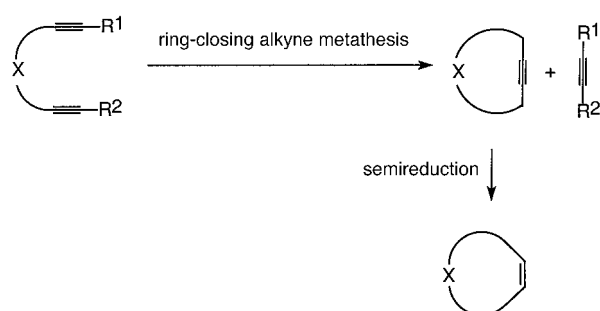
Alois Fürstner* and Karol Grela

Dedicated to Professor Günther Wilke on the occasion of his 75th birthday

Among the few limitations that infringe upon the superb overall application profile of ring-closing olefin metathesis (RCM), the lack of control over the configuration of the newly formed double bond constitutes a significant handicap when applied to the macrocyclic series.^[1] The cycloalkenes formed are usually obtained as mixtures of the *E* and *Z* isomers, with the *E* isomers dominating in most of the recorded examples.^[1, 2] This constitutes a significant drawback in many natural product syntheses as can be clearly seen, for example, from the epothilone case.^[3]

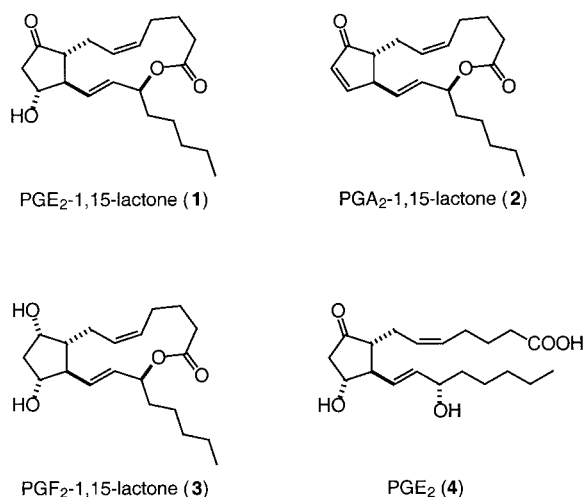
To circumvent this inherent problem, we have recently proposed an indirect but stereoselective approach to macrocyclic *Z* alkenes which comprises a ring-closing metathesis reaction of diyne substrates followed by semireduction of the resulting cycloalkyne products (Scheme 1).^[4] Schrock-type tungsten alkylidyne complexes such as [W(=CCMe₃)(*Or*Bu)₃]^[5] as well as a newly discovered molybdenum chloride species formed in situ from [Mo{N(*t*Bu)(Ar)}₃] and CH₂Cl₂^[6, 7] were found to be efficient precatalysts for this unprecedented type of ring-forming reaction.^[8] In terms of functional group compatibility, these initiator systems exhibit complementary behavior.

To gain a better understanding of the relevance and scope of this conceptually new approach, we were prompted to



Scheme 1. Stereoselective synthesis of macrocyclic *Z* alkenes by ring-closing alkyne metathesis and subsequent semireduction.

extend our studies beyond model compounds and to venture into the total synthesis of biologically significant and structurally more demanding targets. We felt that prostaglandin lactones such as **1–3**, a rather unique class of natural products isolated from the nudibranch *Tethys fimbria*,^[9, 10] would provide an ideal testing ground in this respect.

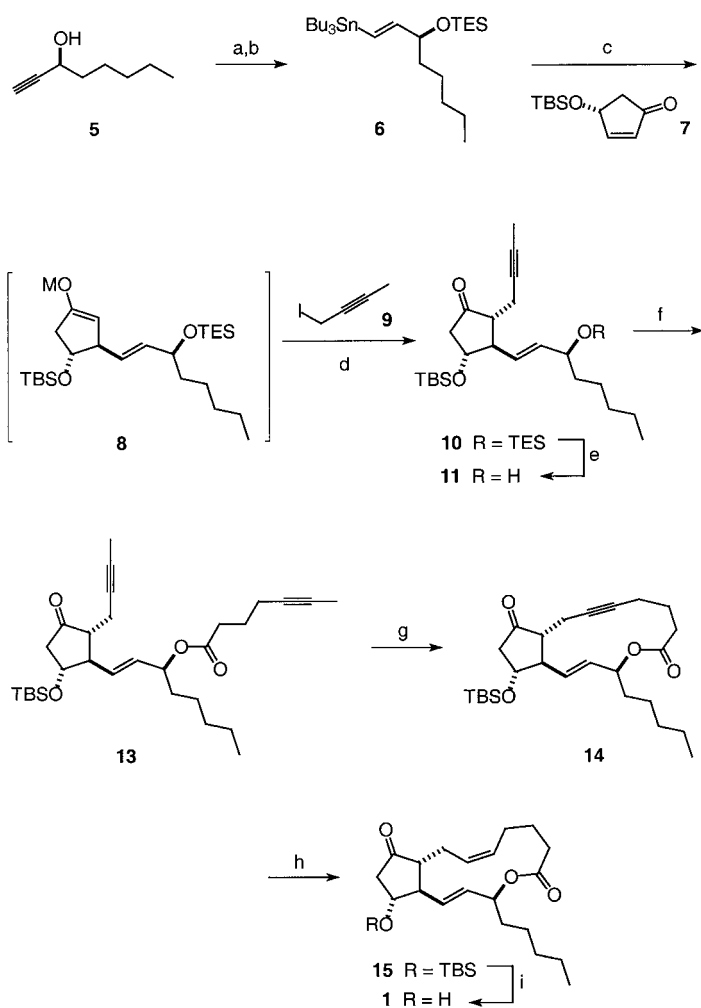


PGE₂-1,15-lactone **1** as a prototype member of this family exerts strong biological effects in vitro and in vivo, including a significant decrease of gastric secretion when administered intravenously in dogs (90 % at a dose of 100 $\mu\text{g kg}^{-1}$)^[10c] as well as ichthyotoxic properties at 1–10 $\mu\text{g mL}^{-1}$ concentrations.^[9] Furthermore, **1** is readily hydrolyzed into parent prostaglandin E₂ **4** by various esterases and therefore constitutes an attractive prodrug for this physiologically highly active metabolite.^[10c, 11] In view of differing enzyme activity distribution in tissue, one may even envisage its sustained and localized release. From the chemical point of view, the intrinsically labile β -hydroxy ketone substructure of all members of the PGE series towards acid as well as base renders lactone **1** a formidable probe for the applicability of the alkyne metathesis/Lindlar reduction strategy to sensitive compounds in general.

The results of our investigations are summarized in Scheme 2. Three-component coupling^[12] as the most elegant method for the construction of prostaglandin skeletons accounts for a straightforward formation of the required cyclization precursor **13**. Thus, commercially available prop-

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Scheme 2. a) Et₃SiCl, imidazole, DMF, room temperature, 24 h; b) *n*Bu₃SnH, azoisobutyronitrile (AIBN; cat.), 130 °C, 2 h, 73% (over both steps); c) 1.) *n*BuLi, THF, −78 °C, 1 h; 2.) Me₂Zn, −78 °C → 0 °C, 15 min; 3.) compound **7**, −78 °C, 1 h; d) THF/HMPA, then compound **9**, −78 °C → −40 °C, 19 h; e) HOAc, THF/H₂O, room temperature, 3 h, 74% (over steps c–e); f) 5-heptynoic acid (**12**), diisopropyl carbodiimide, DMAP cat., CH₂Cl₂, room temperature, 3 h, 94%; g) [Mo{N(*t*Bu)(Ar)}₃] (Ar = 3,5-dimethylphenyl) (7.5 mol %), CH₂Cl₂/toluene, 80 °C, 16 h, 68–73%; h) H₂ (1 atm), Lindlar catalyst, quinoline cat., hexane, room temperature, 2 h, 86%; i) aq. HF, MeCN, room temperature, 1 h, 88%.

argyl alcohol **5** (ee = 98%) is protected as a triethylsilyl (TES) ether prior to conversion into vinylstannane **6** under free-radical conditions.^[13] Tin for lithium exchange on exposure of substrate **6** to *n*BuLi at low temperature followed by addition of Me₂Zn affords a zincate intermediate which undergoes smooth conjugate addition to the known Michael acceptor **7** (ee = 94%).^[14] Enolate **8** thus formed is quenched with propargyl iodide **9**^[15] to afford adduct **10**.^[16] Selective deprotection of the TES group of the crude material with dilute HOAc in aqueous THF delivers compound **11** in diastereomerically and enantiomerically pure form in 74% yield over both steps (ee ≥ 99%).^[17a] This excellent result reflects the high reactivity of **9** as the electrophile in this three-component assembly. Subsequent esterification of the free OH group of **11** with 5-heptynoic acid (**12**)^[15b] in the presence of diisopropyl carbodiimide and catalytic amounts of 4-dimethylaminopyridine (DMAP) readily provides diyne **13** and sets the stage for

the crucial macrocyclization by ring-closing alkyne metathesis.

Gratifyingly, this key transformation proceeds very well using the catalyst formed in situ from [Mo{N(*t*Bu)(Ar)}₃] (Ar = 3,5-dimethylphenyl) and CH₂Cl₂ in toluene at 80 °C,^[6] affording the desired cycloalkyne **14** in 68–73% yield (four runs).^[18] Several aspects are noteworthy: The [Mo{N(*t*Bu)(Ar)}₃]-derived catalyst was previously shown to tolerate esters, ethers, silyl ethers, *tert*-amides, thioethers, and pyridine groups,^[6] but its reactivity towards ketones was unknown. Since the rather labile aldol substructure of substrate **13** is fully preserved in the product, this example not only extends this list by an additional electrophilic group, but clearly attests to the mildness of the method in general terms. Careful chromatographic inspection of the reaction mixture reveals that no racemization takes place before or after ring closure and the ee of the substrate (ee = 99%)^[17a] and of the product (ee = 98%)^[17b] are also virtually identical. Finally, this example nicely demonstrates that the catalyst rigorously distinguishes between the triple bonds (reactive) and a preexisting double bond (inert) of the substrate.

Standard Lindlar hydrogenation of cycloalkyne **14** followed by deprotection of the residual TBS ether with aqueous HF in acetonitrile^[19] completes this total synthesis of the marine natural product prostaglandin E₂-1,15-lactone **1** which is obtained in 28% yield over the entire eight-step sequence.^[20] Its 600 MHz NMR spectra are in full agreement with the data reported in the literature.^[9, 21] By virtue of the known enzymatic hydrolysis of this compound into prostaglandin E₂ **4** as well as by the known transformation of **1** into PGA₂-1,15-lactone **2**,^[10c] formal total syntheses of these interesting natural products have also been accomplished.

From the conceptual point of view it should be emphasized that this novel entry into the prostaglandin series is inherently flexible and has therefore *strategic* advantages over more conventional approaches: esterification of compound **13** with alkyne acids other than **12** followed by ring closure of the resulting diynes by alkyne metathesis opens a rather general way for the assembly of prostaglandin libraries differing in the α-chain which are difficult to prepare otherwise.^[22]

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- [17] a) Determined by HPLC on a Chiralcel OD-H column with *n*-heptane/2-propanol as mobile phase. b) Determined by HPLC on a Chiralpak AD column with *n*-heptane/2-propanol (95:5) as mobile phase.
- [18] Compound **14**: colorless syrup; [α]_D²⁰ = –189.7 (*c* = 0.23, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ = 0.03 (3 H, s), 0.04 (3 H, s), 0.87 (9 H, s), 1.20–2.50 (21 H, m), 2.69 (1 H, dd, *J* = 18.4, 7.8 Hz), 2.98 (1 H, d, *J* = 15.4 Hz), 4.0 (1 H, m), 5.10 (1 H, dt, *J* = 8.0, 5.2 Hz), 5.88 (2 H, m); ¹³C NMR (75 MHz, CDCl₃): δ = –4.8, –4.6, 14.0, 17.5, 18.0, 19.0, 22.5, 22.6, 25.5, 25.7, 31.6, 34.1, 34.9, 46.6, 54.8, 56.1, 72.2, 73.0, 79.3, 79.6, 130.4, 132.3, 172.4, 211.8; IR (neat): $\tilde{\nu}$ = 2955, 2930, 2857, 1746, 1252, 1154, 1115, 964, 839, 778 cm^{–1}; MS (EI): *m/z*: 446 ([*M*⁺], 1), 431 (1), 389 (33), 317 (18), 297 (8), 225 (5), 155 (5), 129 (10), 91(12), 75 (100), 55 (21); HRMS (C₂₆H₄₂O₄Si): *m/z*: 446.2850 (calcd: 446.2852); elemental analysis (%) calcd for C₂₆H₄₂O₄Si (446.71): C 69.91, H 9.48; found: C 70.08, H 9.42.
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- [21] Compound **1**: colorless needles; mp 76.5–77.5 °C (Et₂O/pentane) [ref [10c] 73–76 °C (Et₂O/hexane)]; [α]_D²⁰ = –185.0 (0.15, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ = 0.89 (3 H, t, *J* = 6.8 Hz), 1.20–2.18 (16 H, m), 2.20 (1 H, ddd, *J* = 13.2, 9.4, 3.3 Hz), 2.21 (1 H, dd, *J* = 18.9, 9.3 Hz), 2.29 (1 H, dt, *J* = 13.2, 8.8 Hz), 2.40 (1 H, ddd, *J* = 13.3, 8.7, 3.2 Hz), 2.80 (1 H, ddd, *J* = 18.8, 7.8, 1.2 Hz), 4.14 (1 H, dt, *J* = 7.9, 9.2 Hz), 5.20 (1 H, dt, *J* = 8.5, 6.0 Hz), 5.35 (1 H, ddd, *J* = 10.4, 9.6, 5.5 Hz), 5.60 (1 H, dt, *J* = 10.5, 5.9 Hz), 5.81 (1 H, dd, *J* = 15.9, 8.7 Hz), 6.11 (1 H, dd, *J* = 15.8, 6.6 Hz); ¹³C NMR (150 MHz, CDCl₃): δ = 14.0, 22.5, 23.9, 25.3, 25.5, 25.6, 31.5, 34.0, 34.2, 45.5, 55.0, 57.9, 71.7, 71.8, 128.9, 129.3, 131.9, 134.7, 173.2, 213.1. IR (KBr): $\tilde{\nu}$ = 3431, 3002, 2938, 2857, 1726, 1377, 1243, 1160, 1041, 728 cm^{–1}. MS (EI): *m/z*: 334 ([*M*⁺], 24), 316 (38), 298 (13), 262 (39), 208 (63), 163 (64), 151 (22), 145 (15), 133 (25), 121 (28), 107 (42), 91 (78), 79 (100), 67 (83), 55 (93).
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IR-Thermographic Screening of Thermoneutral or Endothermic Transformations: The Ring-Closing Olefin Metathesis Reaction

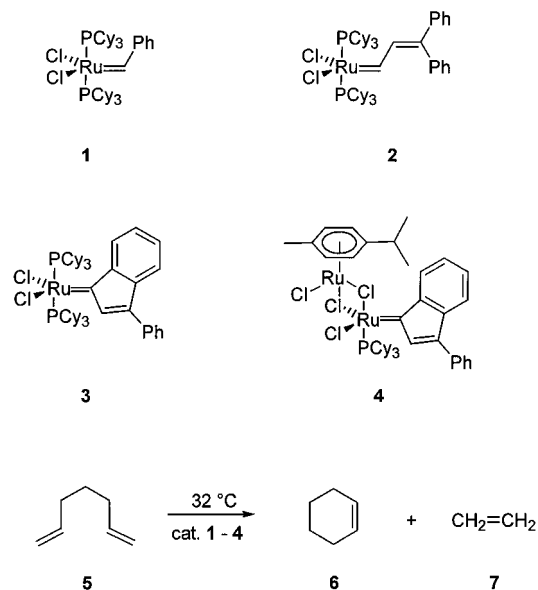
Manfred T. Reetz,* Michael H. Becker, Monika Liebl, and Alois Fürstner

Whereas combinatorial chemistry in the area of pharmaceutical research has reached maturity,^[1] the use of appropriate systems in catalysis still poses challenges.^[2] Recently we reported the first cases of IR-thermographic detection and parallel screening of enantioselectivity in transition metal catalyzed and biocatalyzed organic transformations.^[3] The test reactions chosen were all exothermic processes, enantioselectivity showing up as “hot spots” in the respective IR-thermographic images. IR-thermography had previously been used as a detection and/or screening system in achiral exothermic reactions mediated by heterogeneous catalysts.^[4] Indeed, it was quietly assumed that only exothermic processes can be assayed by this method.^[2, 4, 5] We now report that exothermicity is not a requirement in IR-thermographic screening of catalysts. Specifically, we demonstrate for the first time that in appropriate systems endothermic or even thermoneutral reactions can be successfully screened by time-

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resolved detection of “cold spots” in IR-thermographic images.

We chose the well-known Ru-catalyzed ring-closing olefin metathesis (RCM)^[6] as the reaction to be scrutinized IR-thermographically, not knowing at the outset whether this is actually an exo- or endothermic process. In an exploratory study using the same instrument and method as previously described,^[3, 4a] the known reaction^[6] of 1,7-octadiene (**5**) with formation of cyclohexene (**6**) and ethylene (**7**) was carried out at 32 °C on a 24-well microtiter plate employing the conventional Grubbs precatalysts **1** and **2** and the more recently developed complexes **3** and **4**.^[7]



Four wells of the microtiter plate were charged with a solution of **5** in toluene (wells 1–4), the fifth one (well C) containing octane in place of **5** as a control. Once the temperature was thermostatically set at 32 °C, 250 IR-thermographic pictures were taken within 5 s, the average of which is shown in Figure 1a.^[8] The solutions in wells 1–4 were then treated with precatalysts **1**–**4**, respectively. Precatalyst **1** was also added to the control well C. After one minute, shaking was interrupted and the IR-thermographic pictures were taken (average of 250 recordings), resulting in the image shown in Figure 1b. Shaking was then resumed and the process repeated after one more minute (Figure 1c). Using the temperature/color key of the temperature window (bar on far right), several remarkable features immediately become apparent. Whereas the emissivities of wells C and 4 remain approximately constant, those of wells 1–3 clearly reveal “cold spots”, implying heat uptake. This shows that the RCM of **5** leads to an endothermic effect on the microtiter plate, suggesting that the Grubbs precatalyst **1** as well as complexes **2** and **3** are considerably more active than precatalyst **4**. Close inspection of the emissivities of wells 1–3 in Figure 1c leads to the qualitative conclusion that precatalyst **2** is somewhat less active than **1** or **3**. These conjectures were tested by

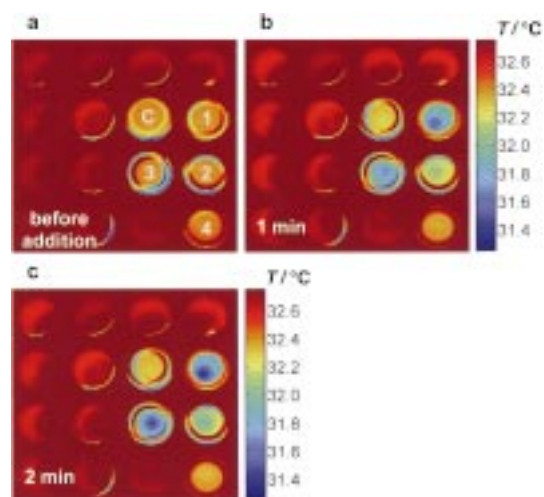


Figure 1. Time-resolved IR-thermographic imaging of the Ru-catalyzed RCM reaction of diene **5**.

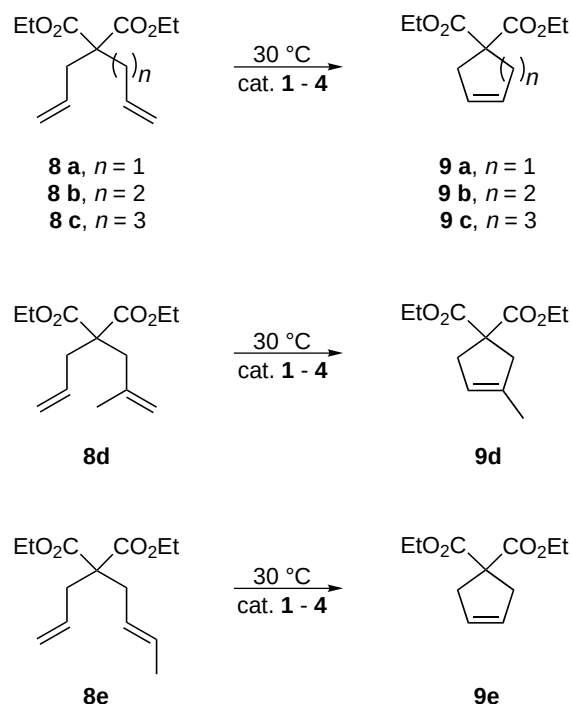
studying lab-scale reactions of diene **5** with precatalysts **1**–**4**. Indeed, complete correspondence was observed. Thus, it was found that under standard conditions the reactions catalyzed by **1**–**3** are essentially over within 1 min at 25 °C, whereas the reaction catalyzed by **4** requires 10 min for complete conversion under otherwise identical conditions.

Unfortunately, thermodynamic data for the reaction **5**→**6**+**7** are not available. However, application of the ASPIN program for calculating thermodynamic data predicts a heat of reaction (reaction enthalpy) of 4.8 kJ mol^{−1}, indicating that the reaction of interest should be slightly endothermic or nearly thermoneutral.^[9] Thus the present data can be interpreted on the basis of slight endothermicity, differences in the IR-thermographic images being due to differences in catalyst activity. However, it is not clear how much of the liberated ethylene (**6**) actually evaporates from the solutions, a process that would also lead to “cold spots”. It is likely that at least some of the effects seen in the IR-thermographic images are in fact due to the heat of vaporization of ethylene from the reaction mixture.^[10] Indeed, upon gently blowing ethylene through a toluene-containing well on the microtiter plate comparable to the bubbling observed during an actual reaction, a “cold spot” immediately became visible. For the purpose of screening, the relative importance of the origins of the “cold spots” is not decisive. It is the sum of the two effects in the overall process which comprises the detection system.

According to the mechanistic work of Grubbs et al. concerning RCM,^[11] compounds **1** and **2** are precatalysts. Following initial [2+2] cycloaddition of the ruthenium–carbene complex with an olefinic function, the primary metal–cyclobutane undergoes cycloreversion with formation of a new carbene complex which then adds intramolecularly to the second olefin function. The final step is cycloreversion with formation of the cyclic olefin (e.g., **6**), ethylene (**7**), and yet another carbene complex [L_nRu=CH₂], which then mediates more than 95 % of the reaction.^[11] It is therefore clear that “catalyst activity” as observed in the present IR-thermographic study or in conventional detection of lab-scale reactions reflects the ease of initiation of RCM by the

carbene complexes **1–4**. Stated in different terms, it simply means that in the present study most or all of the precatalyst **1** or **3** has been consumed within the first two minutes, allowing the reaction of $[L_nRu=CH_2]$ to proceed. In contrast, a considerable (or major) portion of the less reactive complexes **2** or **4** did not react at all under the same conditions.

We then proceeded to screen the reaction of other substrates **8a–8e** by employing the same set of precatalysts **1–4**. By using a modified setup,^[12] the wells of a polypropylene microtiter plate were filled row by row with substrates **8a–8e**



according to the arrangement shown in Figure 2a. After calibration the precatalysts were added simultaneously with an Eppendorf multipipette to the wells of one specific diene, starting with the least reactive substrate **8e** and ending with the most reactive substrate **8a**. All additions were completed within 90 s. Figure 2 summarizes the time-resolved IR-thermographic screening of these reactions.

Again, several noteworthy features become visible. The substrates **8a** and **8b** are by far the most active ones yielding the five- and six-membered cyclic olefins **9a** and **9b**, respectively. As before, precatalysts **1–3** are considerably more active than **4**. Especially the reaction of precatalyst **1** with **8a** and **8b** is essentially complete within 2 min, which was also demonstrated in additional experiments of **1** and **3** with these substrates on a shorter time scale. Figure 2 also shows that the reaction of **8c** with precatalysts **1–4**, leading to the seven-membered product **9c** is considerably slower. The rate of RCM as indicated by heat uptake is lowest in the case of diene **8e** having an internal olefinic double bond. This corresponds to the results of lab-scale reactions. This also appears to be the case in the reaction of substrate **8d** which likewise contains a disubstituted olefinic function. However, since propylene rather than ethylene is liberated, direct

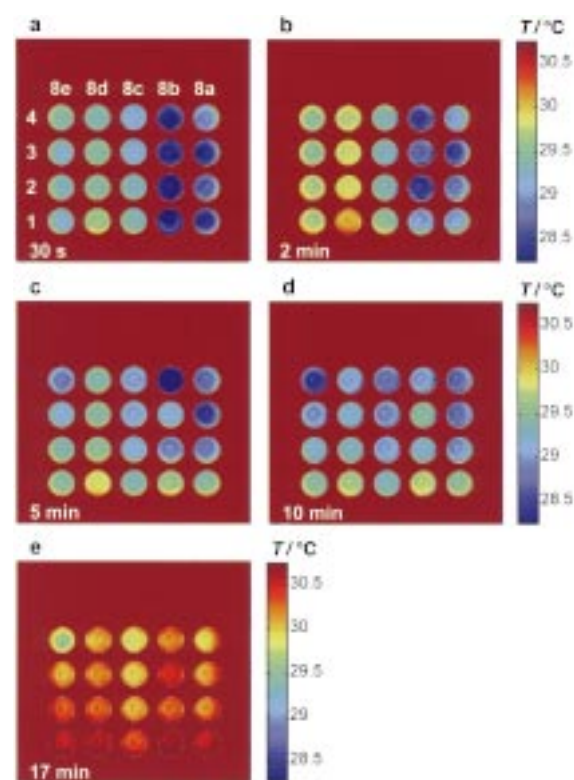


Figure 2. Time-resolved IR-thermographic imaging of the Ru-catalyzed RCM reaction of dienes **8a–8e** with precatalysts **1–4**.

comparison should not be made. In these experiments complex **4** seems to be the most active catalyst. However, caution must be exercised because the results suggested by the IR-thermographic images are in fact due to the delay associated with the row-wise addition of catalysts. In reality the major part of dienes **8d** and **8e** has been converted to the cyclic products **9d** and **9e** by the time the first thermographic image is taken, conversion then being in the phase of leveling off. Precatalyst **4** is actually considerably less active than complexes **1–3**, the system reaching maximum activity only after about 10 min (Figure 2d). At this time the reactions of substrates **8d** and **8e** catalyzed by **1–3** are almost over. When the order of catalyst addition to the wells on the microtiter plate was reversed starting with **8a** and ending with **8e**, heat uptake turned out to be more pronounced in reactions of substrates **8d** and **8e** catalyzed by complexes **1–3** (images not shown). The reactions of the more reactive substrates had proceeded to such an extent that no significant heat uptake was actually detectable at the time of recording. These observations show that two sets of experiments are necessary for correct conclusions (unless of course the precatalysts were to be added simultaneously to all wells with an appropriate multichannel pipette robot). Our conclusions concerning “catalyst activity” were fully corroborated by lab-scale kinetic studies of the reaction of diene **8e** catalyzed by complexes **1–4** (Figure 3). It is clear that precatalyst **4** is least active.

We have devised an efficient screening system for catalytic reactions based on IR-thermography in which high catalyst activity is identified by heat uptake from the surroundings as monitored by the appearance of “cold spots”. The heat of vaporization of one of the (gaseous) reaction products

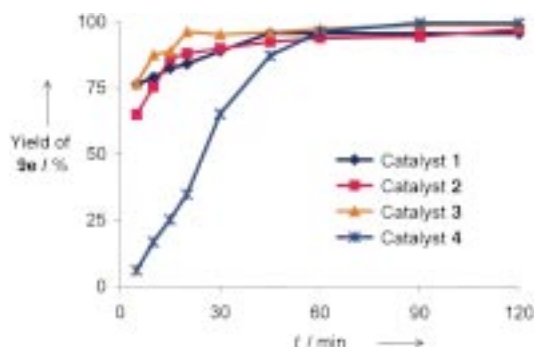
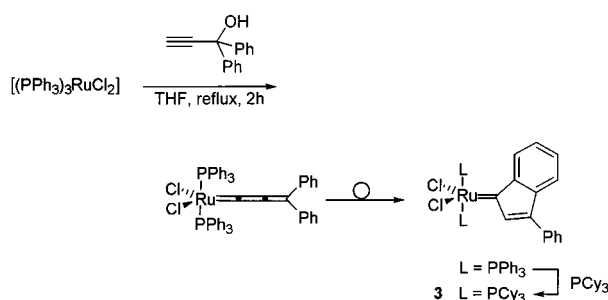


Figure 3. Kinetics of the RCM reaction of **8e** catalyzed by the Ru complexes **1–4**.

(ethylene or propylene) plays a pivotal role.^[10] These findings add a new dimension to the evolving area of high-throughput catalyst or reagent screening based on IR-thermography.^[2–4] Moreover, this study shows that IR-thermography constitutes a simple way to assess the relative rate of initiation of RCM events by different precatalysts as well as the inherent reactivity of variously substituted diene substrates towards the reaction. Therefore the method will greatly facilitate further investigations in this timely field of research.^[6]

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thus formed was a ruthenium allenylidene species, cf. K. J. Harlow, A. F. Hill, J. D. E. T. Wilton-Ely, *J. Chem. Soc. Dalton Trans.* **1999**, 285–292. More detailed studies, however, have shown that the stable product formed in this reaction is the rearranged compound, that is the indenylidene ruthenium complex **3**; the same applies to the synthesis of **4**. Cf. A. F. Hill, A. Fürstner, M. Liebl, R. Mynott, B. Gabor, L. Jafarpour, S. P. Nolan, unpublished results.

- [8] To prevent uncontrolled evaporation of solvent, screening was performed in a closed fume hood without ventilation.
- [9] We thank Dr. P. Schwab and Dr. G. Kautz (BASF AG, Ludwigshafen) for this calculation.
- [10] Strictly speaking one also has to consider various other enthalpies (i.e. enthalpy of mixing, enthalpy of solvation) which contribute to the effects seen in the thermographic images.
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- [12] For the substrate/catalyst screening the substrates were placed in the wells of a 96-well polypropylene microtiter plate (100 μ L substrate per well). The temperature was calibrated in the range of 25–35 °C. The reaction was initiated by the simultaneous addition of 100 μ L of the four different precatalyst solutions (**1–4**) in toluene (0.01 M corresponding to 0.26 mol% precatalyst) at 30 °C to each substrate using a multiple pipette (the addition of the precatalyst solutions was completed within 90 s). As before, the temperature changes were detected periodically, shaking being interrupted. The detection time was 5 s, resulting in 250 recordings which were averaged.

Host within a Host: Encapsulation of Alkali Ion – Crown Ether Complexes into a $[Ga_4L_6]^{12-}$ Supramolecular Cluster**

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We have constructed structures based on supramolecular clusters found in nature and shown that they encapsulate molecular cations.^[1] The origins of supramolecular chemistry

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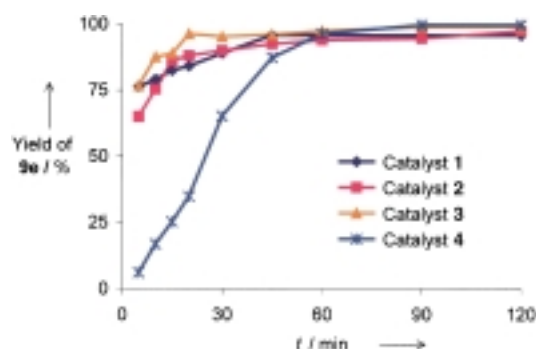
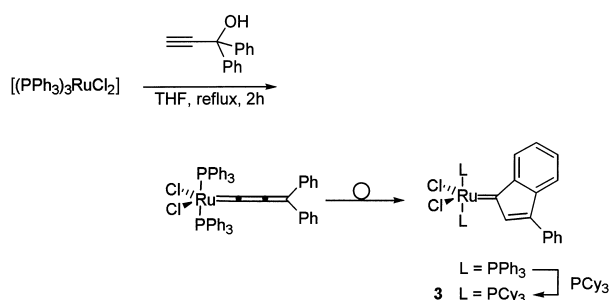


Figure 3. Kinetics of the RCM reaction of **8e** catalyzed by the Ru complexes **1–4**.

(ethylene or propylene) plays a pivotal role.^[10] These findings add a new dimension to the evolving area of high-throughput catalyst or reagent screening based on IR-thermography.^[2–4] Moreover, this study shows that IR-thermography constitutes a simple way to assess the relative rate of initiation of RCM events by different precatalysts as well as the inherent reactivity of variously substituted diene substrates towards the reaction. Therefore the method will greatly facilitate further investigations in this timely field of research.^[6]

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thus formed was a ruthenium allenylidene species, cf. K. J. Harlow, A. F. Hill, J. D. E. T. Wilton-Ely, *J. Chem. Soc. Dalton Trans.* **1999**, 285–292. More detailed studies, however, have shown that the stable product formed in this reaction is the rearranged compound, that is the indenylidene ruthenium complex **3**; the same applies to the synthesis of **4**. Cf. A. F. Hill, A. Fürstner, M. Liebl, R. Mynott, B. Gabor, L. Jafarpour, S. P. Nolan, unpublished results.

- [8] To prevent uncontrolled evaporation of solvent, screening was performed in a closed fume hood without ventilation.
- [9] We thank Dr. P. Schwab and Dr. G. Kautz (BASF AG, Ludwigshafen) for this calculation.
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Host within a Host: Encapsulation of Alkali Ion – Crown Ether Complexes into a $[Ga_4L_6]^{12-}$ Supramolecular Cluster**

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We have constructed structures based on supramolecular clusters found in nature and shown that they encapsulate molecular cations.^[1] The origins of supramolecular chemistry

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can be traced to the synthesis of hosts for simple ionic species. Examples include amongst others crown ethers, acyclic podands, calixarenes, macropolycyclic cryptands, and spherands.^[2] Here we report the combination of these two types of host–guest interactions: alkali cations are incorporated into the large anionic host as a crown ether complex.

Examples in which supramolecular metal clusters act as host molecules include being hosts for small inorganic ions such as Li^+ , Na^+ , Cl^- , NH_4^+ , or BF_4^- ,^[3] while Fujita et al. have shown that larger guests can induce organization of three-dimensional cage-like complexes.^[4] An example of designed self-assembled metal clusters^[4] is $\text{K}_5(\text{Et}_4\text{N})_7[\text{M}_4\text{L}_6]$ ($\text{M} = \text{Ga}^{\text{III}}$, Fe^{III} , $\text{L} = 1,5\text{-bis}(2,3\text{-dihydroxybenzamido})\text{naphthalene}$; Figure 1). Both solution and solid-state studies reveal that one of the Et_4N^+ counterions is located inside the tetrahedral cluster

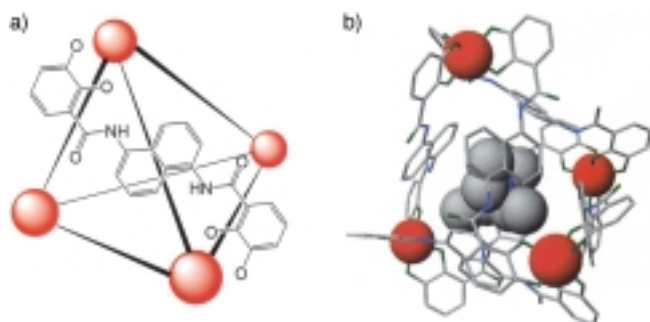


Figure 1. a) A schematic drawing of the tetrahedral $[\text{Ga}_4\text{L}_6]^{12-}$ host as determined from the crystal structure of the $\text{K}_5(\text{Et}_4\text{N})_7[\text{FeL}_6]$ salt (the rods represent the ligands and the spheres represent the metal ions). b) A view of the crystal structure of $[\text{Ga}_4\text{L}_6]^{12-}$ showing the encapsulated Et_4N^+ ion (the other counterions are omitted for clarity).

cavity.^[5] The driving force for the reaction is the gain in entropy associated with solvent release.^[6] The positive enthalpy of this host–guest complexation results from desolvation of the guest and the cluster interior, hence cations with small solvation enthalpies are preferentially encapsulated by the $[\text{Ga}_4\text{L}_6]^{12-}$ host. Increasing the charge of a cation of constant size from +1 to +2 increases the solvation enthalpy approximately fourfold. Hence, singly charged guests are encapsulated into $[\text{Ga}_4\text{L}_6]^{12-}$ while more highly charged guests are not,^[6] and highly solvated, singly charged cations (namely, K^+ , Na^+ , or Li^+), are very poor guests. This has been confirmed by studies involving ^{39}K NMR spectroscopy, which indicate that the cavity of $[\text{Ga}_4\text{L}_6]^{12-}$ does not incorporate K^+ ions; the solvated K^+ ions remain exclusively outside the cavity.^[6]

Crown ethers are well known as effective hosts for small supramolecular cationic guests.^[7] The high enthalpies of cation desolvation are compensated by strong intermolecular interactions between the cation and the crown ether such that the overall enthalpies are negative.^[8] Therefore small cations complexed by crown ethers should be suitable guests for encapsulation into the cavity of $\text{M}_{12}[\text{Ga}_4\text{L}_6]$, since the desolvation enthalpy cost has been paid. Herein we, indeed, demonstrate the inclusion of cation complexes of [12]crown-4, [15]crown-5, and [18]crown-6 ethers into $[\text{Ga}_4\text{L}_6]^{12-}$.

The three salts of $\text{M}_{12}[\text{Ga}_4\text{L}_6]$ ($\text{M} = \text{Li}^+$, Na^+ , or K^+) were synthesized by the procedure reported earlier;^[6] their ^1H NMR spectra in D_2O and D_3COD are identical. The fact that the spectra show no dependence on the cation is consistent with our previous finding that the cations are located outside the cavity.^[6] Electrospray ionization (ESI) mass spectra studies on a similar cluster reveal that the metal cations are located outside the cluster and interact with the oxygen atoms at the corners of the tetrahedral cluster.^[9]

The addition of $\text{M}_{12}[\text{Ga}_4\text{L}_6]$ ($\text{M} = \text{Li}^+$, Na^+ , or K^+) to [12]crown-4, [15]crown-5, or [18]crown-6 results in a decrease in the intensities of the ^1H NMR signals of the crown ethers and the appearance of new peaks at higher fields.^[10] The new, high-field ^1H NMR resonances are a clear indication of encapsulation: the magnetically shielded cluster cavity, surrounded by naphthalene and phenyl groups of the ligand, shifts the proton resonances of the encapsulated guest to much higher field.^[11] Additional evidence for the formation of the host–guest complex is provided by the 2D NOESY NMR spectra, which show cross-peaks between the naphthalene resonances of the cluster and the new, high-field peaks, which implies close proximity of these protons (Figure 2).

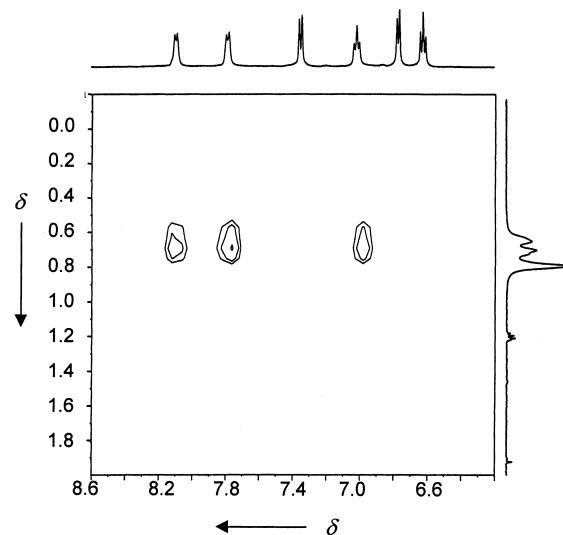


Figure 2. A 2D NOESY spectrum of a mixture containing $\text{K}_{12}[\text{Ga}_4\text{L}_6]$ and [12]crown-4 in D_3COD . The horizontal scale represents proton resonances of the naphthalene ligand in the metal cluster, and the vertical scale represents proton resonances of the encapsulated crown ether.

Significantly, the crown ethers are incorporated into the cavity in each of the $\text{M}_{12}[\text{Ga}_4\text{L}_6]$ salts even though no extra M^+ is added to the solution. Since only positively charged molecules are incorporated into the cluster,^[5,6] the crown ether must have complexed one of the twelve cations from $\text{M}_{12}[\text{Ga}_4\text{L}_6]$, to form a positively charged guest which enters the cluster. Specific evidence for the formation of the cation–crown ether complex is provided by the ^7Li NMR spectrum of the Li^+ –crown ether complex: in the absence of the cluster only one peak is seen for the solvated Li^+ ion, since the exchange between the complexed and solvated Li^+ ions in D_2O and D_3COD is fast on the NMR scale. In contrast, the ^7Li NMR spectra of [12]crown-4 and [15]crown-5 solutions upon

addition of $\text{Li}_{12}[\text{Ga}_4\text{L}_6]$ (Figure 3) show a strong peak for the solvated Li^+ ions (referenced at 0.0 ppm) and one new peak at $\delta = -3.20$ or -4.05 . The appearance of new ^7Li resonances at higher field is consistent with complexation of the Li^+ ion by the crown ether.^[12] Incorporation of the Li^+ –crown ether complex into the cluster cavity slows exchange between the crown-complexed Li^+ ion and aqueous Li^+ ions in solution, so that both species are seen in the ^7Li NMR spectrum.

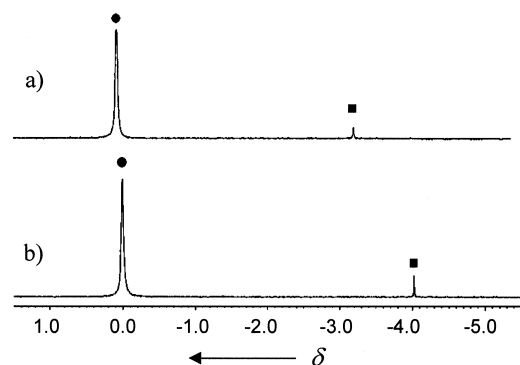
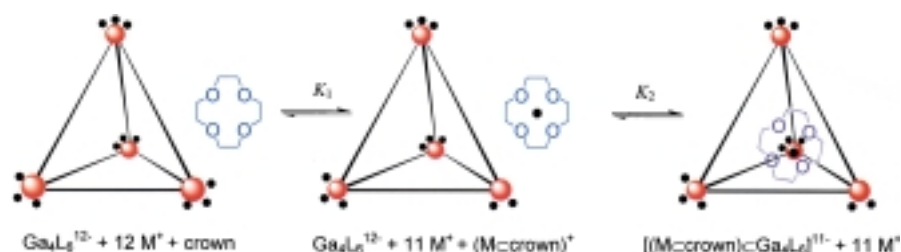


Figure 3. ^7Li NMR spectra of a) $\text{Li}_{11}[(\text{Li}^+ \subset [12]\text{crown-4}) \subset \text{Ga}_4\text{L}_6]$ and b) $\text{Li}_{11}[(\text{Li}^+ \subset [15]\text{crown-5}) \subset \text{Ga}_4\text{L}_6]$. The filled circle represents fully solvated Li^+ ions located outside the cluster, and the filled squares represent Li^+ ions complexed to the crown ether and encapsulated inside the cluster cavity.

Equilibrium constants for the encapsulation of crown ethers into the host were determined on the basis of the reaction sequence shown in Scheme 1. The first step is



Scheme 1. The encapsulation of an alkali metal cation from $\text{M}_{12}[\text{Ga}_4\text{L}_6]$, ($\text{M} = \text{Li}^+, \text{Na}^+, \text{or } \text{K}^+$) by a crown ether (equilibrium constant K_1) is followed by encapsulation of the crown ether complex into the cluster cavity (K_2).

coordination of the aqueous cation by the crown ether to form the metal–crown ether complex $\text{M}^+ \subset \text{crown}$ ($\text{M}^+ = \text{K}^+, \text{Na}^+, \text{Li}^+$), for which the equilibrium constant is designated K_1 [Eq. (1)]. (We have used the literature values for K_1 .^[13] Although interaction between M^+ and the catecholate oxygen

$$K_1 = \frac{[\text{M}^+ \subset \text{crown}]}{[\text{crown}][\text{M}^+]} \quad (1)$$

atoms has been observed in the ESI-mass spectra, this binding does not affect all 12 of the counterions and in any case is much smaller than the formation constants of the macrocyclic ether. We have therefore assumed no significant reduction in the concentration of M^+ by ion-pair formation in these calculations.) The next step is the inclusion of $\text{M}^+ \subset \text{crown}$ into the tetrahedral host cluster (Ga_4L_6) to form

$[(\text{M}^+ \subset \text{crown}) \subset \text{Ga}_4\text{L}_6]^{11-}$ for which the equilibrium constant is K_2 [Eq. (2)].

$$K_2 = \frac{[(\text{M}^+ \subset \text{crown}) \subset \text{Ga}_4\text{L}_6]}{[\text{Ga}_4\text{L}_6][\text{M}^+ \subset \text{crown}]} \quad (2)$$

The concentration of all the species included in the equation are determined from the ^1H NMR spectra and the values of K_2 are calculated.^[14] The results in Table 1 show that

Table 1. The equilibrium constants [$\text{mol}^{-1} \text{dm}^3$] for the inclusion of various M^+ –crown ether complexes ($\text{M} = \text{Na}^+$ or K^+) into $[\text{Ga}_4\text{L}_6]^{12-}$ in D_3COD at 298 K. For the definition of K_1 and K_2 see Scheme 1.

Guest	K_1 ^[a]		K_2	
	Na^+	K^+	Na^+	K^+
[12]crown-4	29	38	3400	2700
[15]crown-5	1400	3900	21	18
[18]crown-6	2300	1.4×10^6	< 0.1	< 0.1

[a] The K_1 values are taken from ref. [13]. Values for Li^+ are not included because the differences in literature values are too large to consider these values reliable.

K_2 decreases as the size of the crown ether increases. This trend is similar to that previously observed in the encapsulation of amines, in which equilibrium constants decrease in the order $\text{Et}_4\text{N}^+ > \text{Pr}_4\text{N}^+$ (while Bu_4N^+ was not encapsulated at all). The weaker binding of the larger crown complex guests is attributed to their inability to fit into the host cavity.^[5]

The conformational freedom of crown ethers in solution results in a single, dynamically averaged proton resonance in the NMR spectra of both the free ligands and cation complexes of [12]crown-4, [15]crown-5, and [18]crown-6. However, inclusion of the cation–crown ether complex into the $[\text{Ga}_4\text{L}_6]^{12-}$ cavity results in a splitting of this single resonance into multiple peaks, which implies that there is a conformational constraint of the encapsulated cation–crown ether complex. This splitting of the NMR resonances occurs regardless of the particular cation ($\text{M}^+ = \text{Li}^+, \text{Na}^+, \text{or } \text{K}^+$). The

limited volume of the cluster interior evidently locks the M^+ –crown ether complex in a fixed conformation. The variable temperature studies shown in Figure 4 show a general trend: the constrained conformation of encapsulated [12]crown-4 completely relaxes at 353 K (as indicated by the coalescence of multiple resonances into a singlet), while the encapsulated [15]crown-5 remains in a constrained conformation even at 363 K. The larger volume of [15]crown-5 apparently makes it more constrained inside the host cavity.

The coordination of solvated cations by crown ethers requires complete or partial desolvation of the cation. It has been found that cation complexation by small crown ethers such as [12]crown-4 and [15]crown-5 does not completely remove the solvation shell of the cation.^[15] Thus, the inclusion reactions were performed in different solvents to test whether solvent molecules are part of the encapsulated cation–crown

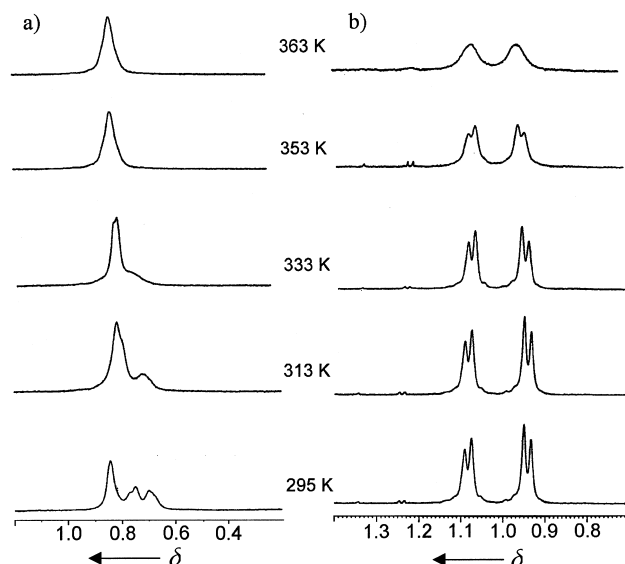


Figure 4. Variable-temperature ^1H NMR spectra of a) $\text{Li}_{11}[(\text{Li}^+ \subset [12]\text{crown-4}) \subset \text{Ga}_4\text{L}_6]$ and b) $\text{Li}_{11}[(\text{Li}^+ \subset [15]\text{crown-5}) \subset \text{Ga}_4\text{L}_6]$ in D_2O . Only the NMR resonances of the encapsulated crown ether are shown.

ether complex. Figure 5 shows that the ^1H NMR resonances of the encapsulated crown ethers differ significantly depending on the solvent. While a set of sharp doublets and doublets of doublets is seen for the encapsulated crown ether of

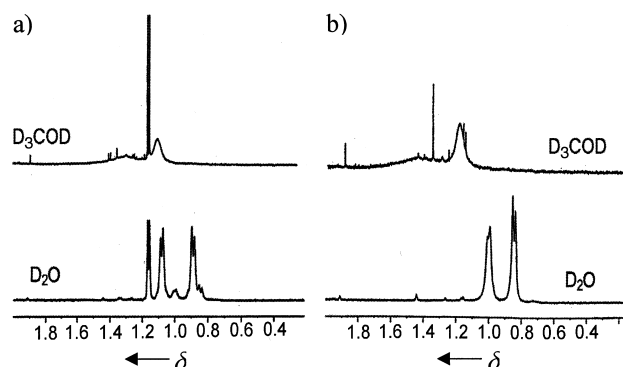


Figure 5. ^1H NMR spectra of a) $\text{Li}_{11}[(\text{Li}^+ \subset [12]\text{crown-4}) \subset \text{Ga}_4\text{L}_6]$ and b) $\text{Na}_{11}[(\text{Na}^+ \subset [15]\text{crown-5}) \subset \text{Ga}_4\text{L}_6]$ in D_2O and D_3COD . Only the NMR resonances of the encapsulated crown ether are shown.

$\text{M}_{11}[(\text{M}^+ \subset [15]\text{crown-5}) \subset \text{Ga}_4\text{L}_6]$ in D_2O , only one sharp doublet and a broad peak for the encapsulated ether are observed in D_3COD . The proton NMR spectrum of $\text{M}_{11}[(\text{M}^+ \subset [12]\text{crown-4}) \subset \text{Ga}_4\text{L}_6]$ shows a similar trend. In each case examined the solvent affects both the chemical shift and the conformation of the included crown ethers, which implies that the encapsulated metal–crown ether complex is interacting with the solvent. We interpret this as showing that the solvent molecule is incorporated in the inner coordination sphere of the alkali ion–crown complex. The volume of the cluster cavity, estimated as $350 \text{ \AA}^3$,^[6] should be able to accommodate one [12]crown-4 or [15]crown-5 moiety along with one or two solvent molecules. The ability of the naphthalene bridging groups of the host to bend outward apparently

allows accommodation of guests even as large as $[\text{C}_5(\text{CH}_3)_5\text{Co}]^+$.^[16]

The host–guest chemistry presented in this study involves multiple recognition events: the cations from the metal cluster complex are first encapsulated by the crown ether host, and subsequently the cation–crown ether host–guest complex is encapsulated into the metal cluster. While the first type of recognition has been well known and thoroughly studied, this is the first example of selective cation incorporation into a metal cluster host by a cation–crown ether: a host within a host.

Experimental Section

The ligand L and the supramolecular cluster $\text{M}_{12}[\text{Ga}_4\text{L}_6]$ ($\text{M} = \text{Li}^+$, Na^+ , or K^+) were synthesized according to previously reported procedures.^[5, 6] The crown ethers were purchased and used as such. All NMR measurements were done on a Bruker DRX 500 MHz instrument. For the determination of the equilibrium rate constants, 1×10^{-6} mol of $\text{M}_{12}[\text{Ga}_4\text{L}_6]$ was dissolved in 200 μL of D_3COD , and an equimolar amount of crown ether (10 μL of 100 mM solution in D_3COD) was added to this solution. The total volume was adjusted to 600 μL by addition of D_3COD . For 2D NOESY measurements the sample was prepared in a similar way, except that the crown ether was present in twofold excess with respect to the cluster. 2D NOESY spectra were obtained at 300 K using standard NOESY sequences, with $d_1 = 2$ sec and $d_8 = 100$ msec.

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Substituted Diazadibenzoperylenes: New Functional Building Blocks for Supramolecular Chemistry**

Frank Würthner,* Armin Sautter, and Christoph Thalacker

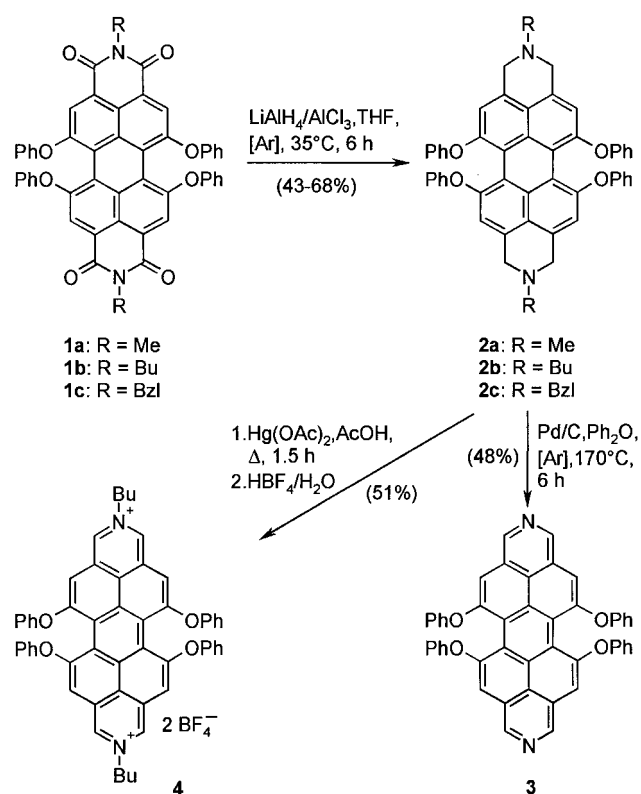
Dedicated to Professor Franz Effenberger on the occasion of his 70th birthday

Supramolecular structures are often compared to non-covalently assembled functional units in nature. To introduce functionality in artificial superstructures, building blocks are required that exhibit suitably positioned receptor groups, good solubility, as well as optical or electrical properties. Among the most widely used receptor groups in supramolecular chemistry are azaaromatic Lewis bases that can form strong intermolecular interactions with carboxylic acids, Lewis acidic boron compounds, and metal centers.^[1] In particular ditopic building blocks such as pyrazine, 4,4'-bipyridine, and diazapyrene have been used to construct sandwich complexes with coordinated metalloporphyrins, molecular squares with ligand-bridged Pd and Pt corners, cage compounds, polymeric aggregates, and solid-state networks.^[2] Herein we describe the synthesis of a new "expanded" building block, 5,6,12,13-tetraphenoxy-2,9-diazadibenzo[*cd,l*m]perylene (**3**), and its functional and coordinative properties.

Our synthesis starts with phenoxy-substituted perylene bisimides **1a–c**,^[3, 4] which could be reduced to the amines **2a–c** with lithium aluminum hydride/ AlCl_3 .^[5a] The subsequent aromatization reaction turned out to be critical, because amines **2a–c** decompose under the drastic reaction conditions which are typically used to accomplish dehydrogenation and dealkylation.^[5a–c] Finally **3** could be obtained under comparably mild reaction conditions from **2c** because the benzyl (Bzl) groups were readily removed in the presence of Pd/C (Scheme 1).

Diazadibenzoperylene **3** is isolated as a bright red, poorly crystallizing solid and shows an intense yellow-green fluorescence in solution and a red solid-state fluorescence. The compound exhibits excellent solubility in halogenated hydrocarbons and is even soluble in aliphatic solvents ($> 300 \text{ g L}^{-1}$ in CH_2Cl_2 ; 0.6 g L^{-1} in cyclohexane).

Oxidation of dibutyl-substituted perylene **2b** with mercury(II) acetate^[5a] affords the dibutyldiazadibenzoperylenium dication which crystallizes readily as tetrafluoroborate salt **4**



Scheme 1. Synthesis of substituted diazadibenzoperylenes **3** and **4**.

(Scheme 1). Single crystals suitable for X-ray crystal structure analysis were obtained by layering a solution of **4** in dichloromethane/methanol with diethyl ether (Figure 1). As expected all C–C bond lengths of the diazadibenzoperylene backbone

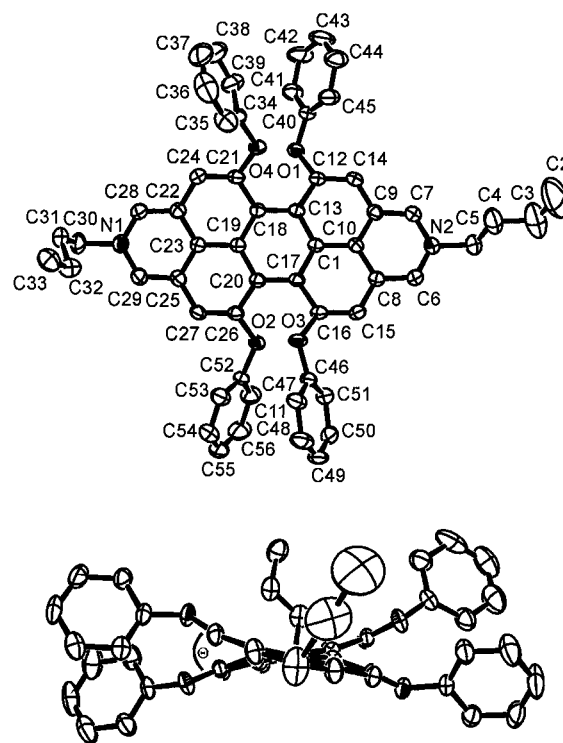


Figure 1. Structure of **4** in the crystal (ORTEP plot). The hydrogen atoms and BF_4^- counterions were omitted for clarity (top). View along the N–N axis showing the twisted perylene backbone ($\theta = 25^\circ$) (bottom).

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are between 1.35 and 1.45 Å, which confirms a high degree of conjugation. Owing to the electrostatic repulsion between the oxygen atoms of the phenoxy substituents, the central six-membered ring is twisted by 25° (Figure 1). This twisting, which interferes with π - π stacking of the extended aromatic surfaces, is considered to be important for the excellent solubility properties of **3** and **4**.

The absorption spectra are characterized by intense absorption bands with maxima at 496 nm (**3**) and 501 nm (**4**). The emission spectra show Stokes shifts of 26 nm (**3**) and 30 nm (**4**) (Figure 2), and the fluorescence quantum yields are

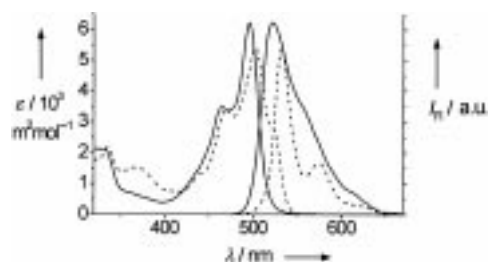


Figure 2. UV/Vis absorption and fluorescence spectra of **3** (—) and **4** (---) in dichloromethane.

0.75 for **3** and 0.50 for **4** in chloroform.^[6, 7] The cyclic voltammogram^[8] of diaza ligand **3** (Figure 3) shows one reversible wave in the reductive cycle where reduction to the

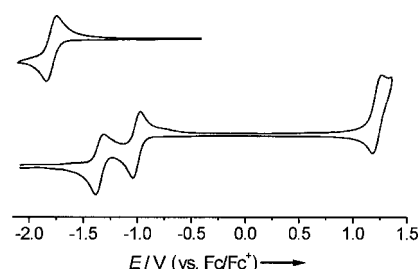
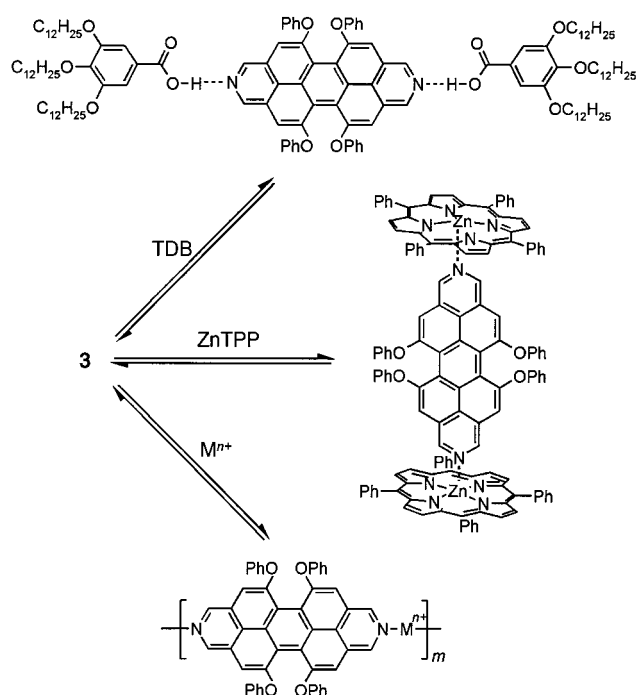


Figure 3. Cyclic voltammogram of **3** (top) and **4** (bottom) in dichloromethane (sweep rate 100 mV s⁻¹).

radical anions **3**^{•-} takes place (−1.79 V versus ferrocene/ferrocenium (Fc/Fc⁺)). Oxidation is irreversible and accompanied by adsorption of **3** on the electrode surface. After several oxidation cycles a stable film is deposited on the platinum electrode which itself exhibits electrochemical activity. For the alkylated ligand **4** which bears two positive charges, two reversible waves are observed in the reductive cycle, reducing **4** via the radical cation to the neutral compound (−1.01 V, −1.35 V versus Fc/Fc⁺). In the oxidative cycle, a reversible oxidation to the radical trication becomes possible (+1.23 V versus Fc/Fc⁺), because **4**, in contrast to **3**, does not contain lone pairs of electrons at the nitrogen atom.

The suitability of the new diaza ligand **3** as a photo- and redox-active supramolecular building block was investigated by complexation experiments with carboxylic acids (3,4,5-trisdodecyloxy benzoic acid, TDB), zinc tetraphenylporphyrin (ZnTPP), Pd²⁺ metal ions (*trans*-[Pd(PPh₃)₂(OTf)₂])(Tf = F₃CSO₂) and Ag⁺ ions (AgOTf) (Scheme 2). When available,



Scheme 2. Assembly of supramolecular structures by different intermolecular interactions.

highly soluble monotopic binding partners were used and the binding constants were determined by means of titration experiments monitored by NMR and UV/Vis spectroscopy.

For the hydrogen-bonding interaction of **3** with the carboxylic acid TDB we determined a binding constant of 140 M⁻¹ in deuterated chloroform. The interaction between **3** and ZnTPP is considerably stronger revealing binding constants of 1500 M⁻¹ in chloroform and 3900 M⁻¹ in the less polar solvent CCl₄ according to UV/Vis and NMR titrations (Figure 4).^[9] The binding constants for the interaction be-

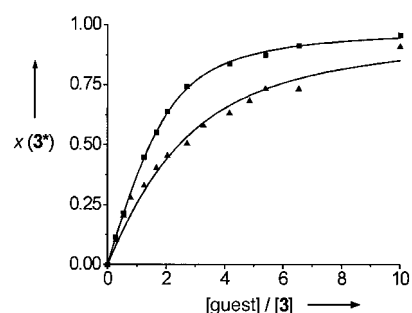


Figure 4. Amount (%) of complexed aza receptors (**3**^{*}) during titration experiments with ZnTPP (■) and TDB (▲) in CDCl₃. The chemical shifts of the CH protons in α -position to the nitrogen atom were monitored; they changed from δ = 9.22 to 9.28 (TDB) and 3.53 (ZnTPP), respectively.

tween **3** and *trans*-[Pd(PPh₃)₂(OTf)₂] as well as AgOTf (CDCl₃/CD₃NO₂) are too high to be determined by NMR titration experiments. During the NMR titration of **3** with Ag⁺ ions a distinct signal broadening and an increase of the solvent viscosity in the NMR tube is noted when a 1:1 stoichiometry is approached. Both observations indicate the formation of a coordination polymer.

Experimental Section

2c: AlCl₃ (7.48 g, 56 mmol) and LiAlH₄ (2.13 g, 56 mmol) were added to cooled (ice bath) dry THF (300 mL) under argon. After removal of the cooling bath, perylene bisimide **1c** (6.56 g, 7 mmol) was added in small portions. The mixture was stirred at 35 °C for 6 h and then poured into 1.4 L of cold 0.3 N hydrochloric acid and stirred for 1 h. The precipitate was suction filtered, washed with H₂O and dried. It was suspended in methanol (200 mL) and 1 N NaOH (50 mL) was added to precipitate the yellow amine **2c** which was collected, washed neutral, dried, and purified by chromatography on a Merck Lobar C column (4.20 g, 68 %): m. p. 252 °C (decomp); ¹H NMR (500 MHz, CDCl₃, 20 °C, TMS): δ = 7.34–7.21 (m, 10H), 7.16 (t, *J* = 8.0 Hz, 8H), 6.97 (tt, *J* = 7.4, 1.1 Hz, 4H), 6.82 (md, *J* = 8.6 Hz, 8H), 6.80 (s, 4H), 3.82 (s, 8H), 3.71 (s, 4H); ¹³C NMR (50 MHz, CDCl₃, 20 °C): δ = 157.0, 152.9, 137.7, 135.0, 133.1, 129.24, 129.19, 128.4, 127.3, 122.6, 120.5, 119.4, 115.7, 114.5, 61.9, 56.0; UV/Vis (CH₂Cl₂): λ_{max}(ε) = 453 (26200), 429 (22100), 381 (5200), 360 (3700), 298 (57000), 259 (31000) nm; field desorption (FD) MS (8 kV): *m/z* (%): 882 ([*M*]⁺, 100); elemental analysis (%): calcd for C₆₂H₄₆N₂O₄ (883.06): C 84.33, H 5.25, N 3.17; found: C 84.33, H 5.26, N 3.07.

2b: As described for **2c** but the reaction was carried out under reflux for 3 h. 50 %: m. p. 208–210 °C (decomp); ¹H NMR (200 MHz, CDCl₃, 20 °C, TMS): δ = 7.16 (m, 8H), 6.96 (m, 4H), 6.84–6.82 (m, 12H), 3.79 (s, 8H), 2.52 (t, *J* = 7.4 Hz, 4H), 1.55 (m, 4H), 1.32 (m, 4H), 0.89 (t, *J* = 7.3 Hz); UV/Vis (CH₂Cl₂): λ_{max}(ε) = 454 (24800), 430 (20600), 362 (3700), 300 (55500), 258 (30600) nm; elemental analysis (%): calcd for C₅₆H₅₀N₂O₄ (815.03): C 82.53, H 6.18, N 3.44; found: C 82.40, H 6.30, N 3.40.

3: A mixture of **2c** (2.65 g, 3 mmol) and 0.32 g Pd/C (10 % Pd) was stirred under argon in diphenyl ether (150 mL) for 6 h at 170 °C. After cooling, the mixture was filtered over celite/silica gel (each ca. 5 cm), and diphenyl ether was eluted with CH₂Cl₂. The product was eluted with an increasing amount of methanol, and the solvent was evaporated. After chromatography on a Merck Lobar C column (CH₂Cl₂/MeOH 97:3) **3** was isolated as a bright red solid (1.00 g, 48 %): m. p. 273 °C; ¹H NMR (500 MHz, CDCl₃, 20 °C, TMS): δ = 9.21 (s, 4H), 7.52 (s, 4H), 7.34 (t, *J* = 7.6 Hz, 8H), 7.18 (tt, *J* = 7.5, 1.1 Hz, 4H), 7.13 (md, *J* = 7.6 Hz, 8H); ¹³C NMR (126 MHz, CDCl₃, 20 °C): δ = 156.6, 155.8, 143.3, 129.9, 126.8, 125.8, 124.4, 120.8, 120.2, 108.14, 108.13; UV/Vis (CH₂Cl₂): λ_{max}(ε) = 496 (62300), 465 (34900), 307 (22500), 294 (21800), 270 (47000) nm; EI-MS: *m/z* (%): 696 ([*M*]⁺, 100); elemental analysis (%): calcd for C₄₈H₂₈N₂O₄ (696.76): C 82.74, H 4.05, N 4.02; found: C 82.41, H 3.95, N 4.09.

4: A mixture of **2b** (0.41 g, 0.5 mmol) and Hg(OAc)₂ (0.64 g, 2.0 mmol) in acetic acid (20 mL) was stirred under reflux for 1.5 h. The mixture was cooled to room temperature, filtered, and H₂O (15 mL) and HBF₄ (1 mL; 50 % aqueous solution) were added to yield a brown precipitate which was separated and washed with a small amount of H₂O/MeOH (1:1). After drying, the crude product was purified by column chromatography on silica gel (CH₂Cl₂/MeOH 9:1) and recrystallized from methanol/diethyl ether. Compound **4** was isolated as an orange crystalline solid (0.25 g, 51 %): m. p. 272–275 °C (decomp); ¹H NMR (500 MHz, [D₆]acetone, 20 °C, δ = 2.04): δ = 9.92 (s, 4H), 8.03 (s, 4H), 7.50 (t, *J* = 7.9 Hz, 8H), 7.35 (t, *J* = 7.5 Hz, 4H), 7.30 (d, *J* = 7.8 Hz, 8H), 5.18 (t, *J* = 7.2 Hz, 4H), 2.29 (m, 4H), 1.50 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 6H); ¹³C NMR (126 MHz, [D₆]acetone, 20 °C): δ = 160.0, 155.5, 137.5, 131.3, 130.0, 127.1, 126.7, 123.1, 121.87, 121.83, 108.7, 63.7, 34.4, 20.0, 13.7; UV/Vis (CH₂Cl₂): λ_{max}(ε) = 502 (55000), 469 (35200), 367 (15500), 335 (22300), 301 (64700), 260 (51800) nm; elemental analysis (%): calcd for C₅₆H₄₆N₂O₃B₂F₈ (984.60): C 68.31, H 4.71, N 2.85; found: C 68.23, H 4.71, N 2.81.

Crystal structure analysis of **4**: C₅₆H₄₆N₂O₃B₂F₈, *M*_r = 984.60, monoclinic, space group *P*2₁/*n* (no. 14), *a* = 12.8868(16), *b* = 21.825(5), *c* = 17.688(2) Å, β = 99.743(14)°, *V* = 4903.2(14) Å³, *Z* = 4, ρ_{calcd} = 1.334 Mg m^{−3}, μ(MoKα) = 0.103 mm^{−1}, crystal size 0.19 × 0.31 × 0.62 mm, *T* = 220 K, 9285 independent reflections collected, 682 parameters, *R*1 = 0.0565 and *wR*2 = 0.1366 for reflections with *I* > 2σ(*I*), max./min. residual electron density 0.419/−0.306 e Å^{−3}. Data were collected using a STOE-IPDS-diffractometer with monochromatic (graphite monochromator) MoKα radiation (λ = 0.71073 Å, 2θ_{max} = 51.94°, 2θ_{min} = 4.08°); scan modulus rotation. The structure was solved by direct methods (SHELXS 97),^[10a] (refinement on *F*² using the full-matrix least-squares method (SHELXL 97).^[10b] Hydrogen atoms were set geometrically as idealized CH₂, CH₃, and aromatic CH

groups and treated using a riding model. The tetrafluoroborate anions showed a strong orientation disorder and were described and refined by using 10 and 12 fluorine split sets, respectively, but the exact positions of the fluorine atoms could not be determined.^[11] 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-133189. 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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A Unified Bonding Picture for the Metallic Triel Elements**

Ulrich Häussermann,* Sergei I. Simak, Rajeev Ahuja, and Börje Johansson

The elements of the boron group (the triel elements) have a unique position in the periodic table, being situated at the borderline between metallic bonded elements with either a close-packed or the body-centered cubic structure and the covalently bonded tetrel elements crystallizing in the diamond structure. As a peculiar consequence all the triels display different ground-state structures at ambient conditions^[1] (of which some are displayed in Figure 1): in α -rhombohedral

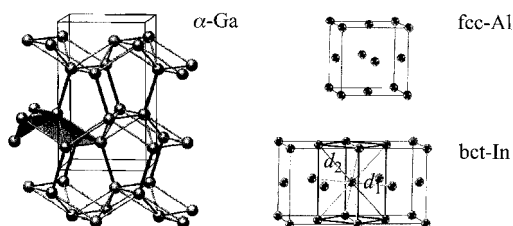


Figure 1. The structures of orthorhombic α -Ga (left), and fcc-Al and tetragonal In (right). In the α -Ga structure the local (1+6) coordination of the atoms is emphasized.

boron B_{12} icosahedra are arranged as in a cubic close-packing of spheres, whereas aluminum crystallizes in the simple face-centered cubic (fcc) structure type. α -Gallium again has a rather complicated, orthorhombic structure, consisting of corrugated 3^6 nets that are stacked and connected by short distances along the stacking direction yielding a local (1+6) coordination for each Ga atom. Indium adopts a tetragonal body-centered (bct) structure which corresponds to a distorted fcc arrangement in which the environment of 12 nearest neighbors is split into two sets. The c/a ratio is 1.521 and is thus larger than that for the ideal case of the fcc structure ($\sqrt{2}$). Finally, thallium attains an almost ideal hexagonal close-packed (hcp) structure with a c/a ratio of 1.598 (the ideal value is $\sqrt{8/3}$). The contrast to the simple structure – bonding situation of the neighboring tetrel group is striking and has fascinated chemists for a long time. There, the tetrahedral coordination of atoms is easily linked to the electron count of four which leads to the simplified picture of

covalent two-electron two-center bonds in solids formed by atomic sp^3 -hybrid orbitals. Prerequisite to this bonding picture is the strong interaction between the atomic valence states giving rise to an opening of a s – p hybridization gap in the band structure.^[2] The decrease of the number of valence electrons to three in the triels seems to terminate the clear link between electron count and geometrical structure in elemental solids and the obscure region of metallic bonding is entered. However, importantly the transition from covalent (saturated) bonding to metallic (unsaturated) bonding does not occur abruptly. For the two most electronegative triel elements, boron and gallium, a distinct relation between electron count and ground-state structure can still be established on the basis of (localized) multicenter bonding, which results in two structural solutions for an electron count of three, optimal structures are α -rhombohedral B (semiconducting) and α -Ga (metallic).^[3]

Herein we present an intriguing, general bonding picture for the metallic triels, which we have extracted from high-accuracy full-potential calculations of these elements in different structural variations (see Computational Methods). We will see that this bonding picture is astonishingly closely connected to the simple one of the tetrels. To make progress towards a unified bonding picture we state that from a chemical point of view the problem of structural stability of solids is preferably tackled by dividing the total energy into the band energy E^{band} , which represents the sum over the occupied one-electron states, and a part containing the remaining contributions, of which the electrostatic (Madelung) energy is the most significant. E^{band} favors the formation of open packed structures in which the atoms are closer to each other and thus covalent bonding can be realized. The electrostatic contributions display an antagonistic behavior with the tendency to stabilize high-symmetry close-packed structures. Therefore, we expect for the metallic triels with their distinguished location in the periodic table a delicate balance of these contributions to the total energy.

We computed the total energies and E^{band} of different structures for Al, Ga, In, and Tl at their experimental ground-state volumes. In the case of Tl a second set of calculations was performed with nonrelativistic radial functions within the muffin-tin spheres (NR-TI) in order to examine the influence of (scalar) relativistic effects on structural stability of this element. As competing structures we considered the fcc structure and its bct distorted variants with different c/a ratios around the ideal fcc value of $\sqrt{2}$, the hcp structure at different c/a ratios around the ideal value of $\sqrt{8/3}$, and finally the α -Ga structure. Figure 2 summarizes the total energy differences of the α -Ga structure and the two ideal close-packings. As expected, the energy differences between the close-packed structures are very small (≈ 25 meV per atom at the most (Al)), whereas the low-symmetry α -Ga structure is energetically clearly separated from the close-packings and is obtained correctly as the ground-state structure for gallium. In the left-hand panel of Figure 3 we focus on the structural competition between the fcc- and hcp-based structural variation for the metallic triels. We note that, with the exception of Tl, the fcc-related structures are always lower in energy than the hcp ones. For Al the tetragonal variations lead

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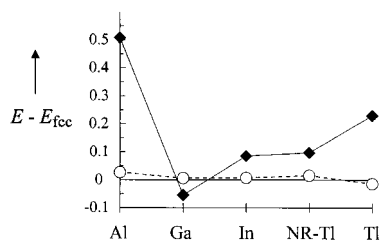


Figure 2. Total energy differences (in eV per atom) for the metallic triels in the α -Ga (solid diamonds), hcp (open circles), and fcc structure. The energy differences are referenced to the fcc structure.

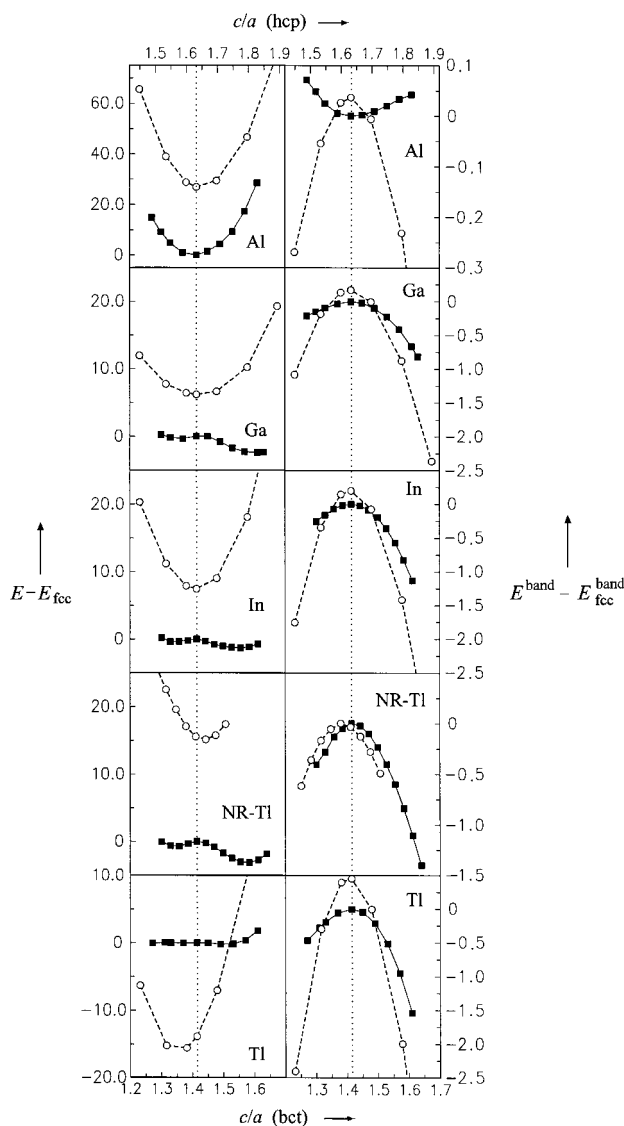


Figure 3. Left: Total energy changes (in meV per atom) as a function of c/a for the metallic triels in fcc- (solid squares) and hcp-based (open circles) structural variations; right: The corresponding changes in the band energies (in eV per atom!). The dotted lines mark the c/a ratios for ideal close-packings.

to a parabolic total energy versus c/a curve, where the minimum corresponds to the c/a ratio of the fcc structure, which is also the ground-state structure. For Ga and In, however, the bct energy curve exhibits double-well behavior with two minima and a local maximum exactly at a c/a ratio corresponding to the ideal fcc structure. In the case of In the

deeper minimum at a c/a ratio of 1.55 (at 0 K) is in agreement with the observed In ground-state structure and compares very well with the experimental value of 1.521 (at 298 K). The stabilizing energy of the ground-state structure with respect to the fcc structure is extremely small (below 2 meV per atom).^[4] For Ga the bct structure is a high-pressure modification (Ga-III) that appears at pressures around 15 GPa.^[5] The deeper minimum of the bct energy curve at $c/a \approx 1.61$ for the ground-state volume V_0 compares also well with that of the experimental Ga-III structure (1.58 at $V/V_0 = 0.9$). The stabilization energy with respect to the fcc structure is about 4 meV per atom.^[6,7] Finally, for Tl a remarkable result is obtained: the hcp ground-state structure appears as a consequence of scalar relativistic effects. Without considering these effects (NR-Tl), the bct-In structure with a c/a ratio of about 1.58 is almost 20 meV per atom more stable than the hcp structure. Interestingly, this stabilization of a close-packing by relativistic effects was also found for the neighboring element Pb.^[8] There the omission of relativistic effects reveals the diamond structure is more stable than the ground-state fcc packing. The trends in the band energies along the distortion paths of the close-packings are displayed in the right-hand panel of Figure 3. The E^{band} curves have—with the exception of bct-Al—a maximum at the c/a ratios corresponding to ideal close-packings thus favoring the formation of distorted structures. Therefore, we may identify E^{band} as the leading contribution to the stability of the ground-state structures of Al, Ga, In, and NR-Tl. E^{band} is optimized with respect to the counteracting (weaker) Madelung contribution to the total energy. Remarkably, for Al E^{band} attains a minimum for the ideal fcc structure with respect to the tetragonal distortion, that is for this element E^{band} supports a close-packed arrangement. For Tl however the electrostatic part overcompensates E^{band} : the (almost) ideal hcp structure is obtained as the ground-state structure despite a maximal value of E^{band} at the corresponding c/a ratio.

To proceed further to a unified bonding principle for the metallic triels we need to analyze E^{band} in more detail. An important feature influencing E^{band} in elemental main group solids is the interaction between the valence s and p bands. Generally, this interaction (s–p mixing or hybridization) can take place in the band structure of any structure, provided that the corresponding Bloch functions belong to the same irreducible representation of the space group. Figure 4 sketches roughly the consequences of s–p mixing. The pure s and p energy bands are bonding at their bottom and antibonding at their top (left part of Figure 4) and when the dispersion of the bands is large enough, their interaction leads to an opening of a hybridization gap (right part of Figure 4). Accompanied with the gap formation is a change in the bonding characteristics of the bands: the lower band becomes completely bonding, whereas the upper one turns into a completely antibonding one.^[9] Such hybridization gaps often correspond to only local band gaps at highly symmetrical k points and do not have to coincide with the Fermi level. While the occurrence of s–p mixing is determined by symmetry, the strength of s–p band interaction is dependent on the size of the energy separation between the atomic s and p levels, the kind of structure (in open packed structures interactions

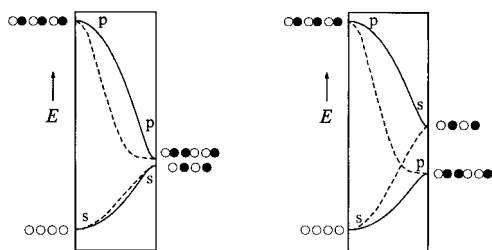


Figure 4. Schematic representation of the interaction between s and p valence bands in the band structures of main group elemental solids (based on ref.[9]). Weak interaction is shown in the left-hand part, strong interaction in the right-hand part. The dashed lines approximate the dispersion of the unhybridized (noninteracting) bands. The orbital combinations indicate the bonding character of the bands.

between atoms are stronger) and the volume (external pressure increases the band widths). The degree of stabilization by strong s–p mixing is crucially dependent on the electron count of the elements. Maximum stabilization is obtained for a band filling, which corresponds to a completely filled lower band in Figure 4. This is exactly the situation for the tetrrels in the diamond structure where the s–p hybridization gap corresponds to a real band gap at the Fermi level. The electron count of the triels, however, is not sufficient to produce a fully occupied completely bonding s–p hybridized band throughout the Brillouin zone. Nevertheless one might expect that s–p mixing is still a decisive ingredient to the bonding in the metallic triels. To corroborate this idea we calculated the ratio between the total number of p and s states (N_p/N_s) inside the muffin-tin spheres as a measure of the degree of s–p mixing in the structures under consideration.

In Figure 5 the N_p/N_s ratios for the metallic triels in the α -Ga structure and the two different close-packings are shown.^[10] Two important results can be extracted from

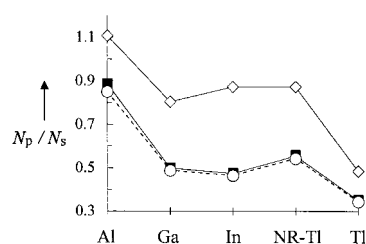


Figure 5. The ratio of the number of p states and s states in the muffin-tin spheres (N_p/N_s) for the metallic triels in the α -Ga (open diamonds), and the ideal fcc (solid squares) and hcp structures (open circles, broken line for clarity).

Figure 5. First, in the low-symmetry α -Ga structure the highest degree of s–p mixing (highest values of N_p/N_s) can be expressed and second the “inherent hybridization capacity” of the different atoms is revealed. Al shows the highest N_p/N_s values in the considered structures, whereas those for Ga, In, and NR-Tl are lower but in a quite narrow range. Clearly distinct from the other triels is Tl which attains very low N_p/N_s values. The trend in the “inherent hybridization capacity” of the triel elements, $\text{Al} > \text{Ga} \approx \text{In} \approx \text{NR-Tl} > \text{Tl}$, reflects exactly that of the separation of the atomic s and p valence states of

these elements: $\Delta\epsilon_{sp}(\text{Al}) = 3.60 \text{ eV} < \Delta\epsilon_{sp}(\text{Ga}) = 4.71 \text{ eV} \approx \Delta\epsilon_{sp}(\text{In}) = 4.34 \text{ eV} < \Delta\epsilon_{sp}(\text{Tl}) = 5.61 \text{ eV}$.^[11] Figure 6 displays the N_p/N_s ratios for the fcc and hcp structural variations. Again, two results are important. First the metallic triels in the fcc-related structures can express a slightly higher degree of s–p mixing than in the hcp-related ones and second the obtained N_p/N_s values as a function of c/a exhibit a trend that is reverse that for the corresponding band energies. For the favored tetragonal structural variations, the N_p/N_s ratio gains a maximum value for Al and a minimum value for Ga, In, and NR-Tl at $c/a = \sqrt{2}$. Consequently, taking the fcc structure as a reference, the apparent tendency for the metallic triel elements is to adopt a ground-state structure in which the N_p/N_s ratio is either maximal (Al) or increased by distortion (Ga, In, NR-Tl). The degree of distortion (bct or α -Ga structure), however, is governed by the counteracting electrostatic contributions. Only for the most electronegative metallic triel (Ga), where E^{band} is dominating most and the ability to form strong homonuclear bonds is highest, the α -Ga structure can be adopted.

With these results we may now formulate the bonding principle for the metallic triels Al, Ga, In, and NR-Tl:

Metallic triels adopt a ground-state structure in which s–p mixing of the valence bands (and thus E^{band}) is optimized with respect to the electrostatic contributions of the total energy. As shown in Figure 4, this optimization of s–p mixing raises s–s antibonding states above the Fermi level for the *largest* possible part of the Brillouin zone. It should be remembered that for the tetrrels in the diamond structure s–s antibonding states are situated above the Fermi level for *all* parts of the Brillouin zone. For a final elucidation of this bonding principle we compare a particular section (the direction L–W) of the fcc band structure of the considered elements (Figure 7). The direction L–W in these band structures mirrors perfectly the s–p band interaction as sketched in the simple Figure 4. For Al the relatively small s–p separation of the atomic levels

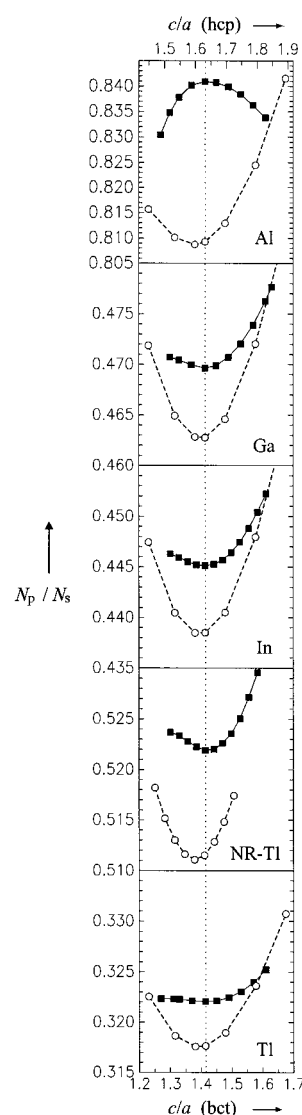


Figure 6. Ratio of the number of p states and s states in the muffin-tin spheres (N_p/N_s) as a function of c/a ratio for the metallic triels in fcc- (solid squares) and hcp-based (open circles) structural variations. The dotted line marks the c/a ratios for ideal close-packings.

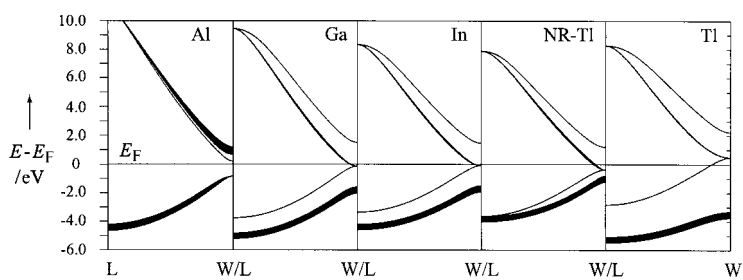


Figure 7. Band structure along the direction $L-W$ for the metallic triels in the fcc structure. The s orbital character of a band is proportional to the “fatness” of the lines used in the plots. Note that just one of the three p bands can interact with the s band. While for Al $s-p$ mixing is most effective, in Tl relativistic effects suppress completely this interaction.

ensures large $s-p$ mixing, which results in a $s-p$ hybridization gap (a local band gap) at the Fermi level at W . A distortion of the fcc structure decreases the amount of $s-p$ mixing for Al (see Figure 6). Thus, the fcc ground-state structure appears as most stable for *electronic* reasons.^[4] In Ga, In, and NR-Tl with a larger atomic $s-p$ separation, however, substantial $s-p$ mixing in the fcc structure is prohibited. As a consequence a distortion to a low-symmetry structure takes place where a higher degree of $s-p$ mixing can be achieved. Interestingly, with pressure the dispersion of s and p valence bands is increased and bct-Ga (Ga-III) and bct-In transform to the fcc structure at such a compressed volume that the amount of hybridization between the s and p valence bands becomes comparable to that for fcc-Al at ambient pressure.^[6] Thus, the structural phase transition bct $\rightarrow$ fcc for these elements is *electronically* driven. Finally, Tl does not follow the bonding principle of optimum hybridization. Relativistic effects increase the separation of the atomic $6s$ and $6p$ states to such a degree that effective $s-p$ mixing is virtually suppressed in all considered structural alternatives. Owing to this relativistic $s-p$ dehybridization^[12] E^{band} is overcompensated by the Madelung part of the total energy and the hcp ground state structure appears as most stable for *electrostatic* reasons.

Computational Methods

Total energy calculations for Al, Ga, In, NR-Tl, and Tl in the considered structural alternatives were performed at constant volumes which corresponded to the respective experimental ground-state volumes (V_0 (Al) = 16.617, V_0 (Ga) = 19.588, V_0 (In) = 26.164, V_0 (Tl) = 28.584 Å³ per atom). We applied the full-potential linearized augmented plane wave (FLAPW) method^[13] and the full-potential linear muffin-tin orbital (FP-LMTO) method.^[14] The size of the atomic muffin-tin sphere for a particular element was the same in all structures; between the sphere sizes of the different elements a certain relation was introduced.^[10] In full-potential techniques within the local-density approximation basis functions, electron densities, and potentials are calculated without any shape approximation. These methods belong to the most accurate ones to date concerning studies of structural stability.^[15] The calculated energy differences and band structures were found to be virtually identical for the two full-potential techniques. The presented energy differences for Al, Ga, In, and Tl were obtained from FP-LMTO calculations, the presented band structures and the energy differences for NR-Tl are results from FLAPW calculations.

Concerning the FLAPW calculations, well-converged plane wave sets with a cut-off parameter $R_{\text{mt}}K_{\text{max}} = 9.0$ were used for all elements. The Ga 3d, In 4d, and Tl 5d states were treated as local orbitals. The exchange–correlation potential was parametrized according to Perdew et al.^[16a] The

reciprocal space integrations in the irreducible tetragonal Brillouin zone were performed with the tetrahedron method. Concerning the FP-LMTO calculations, we made use of valence band s , p , and d basis functions for all elements. For Ga, In, and Tl pseudocore d states were included in the basis as well, that is the resulting basis always formed a single, fully hybridizing basis set. The exchange–correlation potential was parametrized according to Hedin and Lundqvist.^[16b] For sampling the irreducible wedge of the Brillouin zone we used the special k points with a Gaussian smearing of width 20 mRy. To ensure convergency several standard tests were performed for both methods, such as the effect of increasing the number of k points used in the summation over the Brillouin zone.

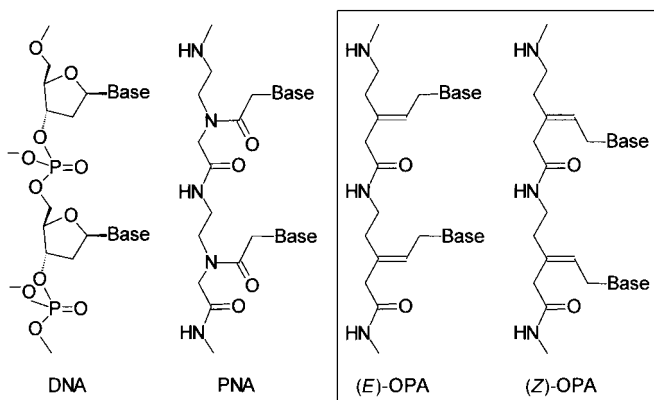
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Olefinic Peptide Nucleic Acids (OPAs): New Aspects of the Molecular Recognition of DNA by PNA**

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Christian Leumann*

Polyamide or peptide nucleic acids (PNAs), first described in 1991,^[1] are DNA analogues based entirely on an achiral polyamide backbone (Scheme 1). The PNAs undergo sequence-specific and efficient Watson–Crick base pairing with



Scheme 1. Sections of the chemical structures of deoxyribonucleic acids (DNAs), polyamide or peptide nucleic acids (PNAs), and (E)- and (Z)-olefinic polyamide nucleic acids ((E)- and (Z)-OPAs).

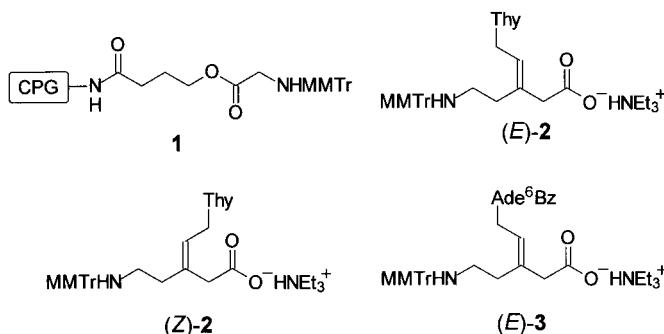
complementary DNA and RNA.^[2] Owing to their structural simplicity and their remarkable functional properties they have not only found application as tools in molecular biology,^[3] but also have a large impact on antisense research^[4] and prebiotic chemistry.^[5] The ample literature describing the chemical and biological properties of PNAs has recently been reviewed.^[6]

A key structural feature of PNAs is the central amide linker between the base and the backbone. This tertiary amide functionality is conformationally labile and occurs in both the *E*- and *Z*-rotameric forms in uncomplexed PNA.^[7] However, it is uniformly oriented in the *Z*-rotameric form in PNA/DNA,^[8, 9] PNA/RNA,^[7] and PNA/PNA complexes,^[10] as revealed by NMR and X-ray analysis. Early work on molecular modeling^[11, 12] suggested that intra- or interresidue

hydrogen bonds between the backbone and this tertiary amide group in the PNA strand might be important secondary structure-stabilizing elements—a statement that was not supported by the structural analyses.

To eliminate ambiguity regarding the conformation and to elucidate the structural and electrostatic role of this amide group on DNA and RNA binding, we designed olefinic polyamide nucleic acids (OPAs), in which this central amide functionality is replaced by an isostructural, configurationally stable C–C double bond in either the *Z* or *E* configuration (see Scheme 1). While we have already reported on the synthesis of the monomeric (*E*)- and (*Z*)-OPA building blocks containing the base thymine,^[13, 14] we describe here the synthesis of (*E*)- and (*Z*)-OPA oligomers as well as preliminary studies on pairing with complementary DNA.

The synthesis of chimaeric PNA–oligomers containing OPA units was performed using the building blocks (*E*)/(*Z*)-**2** and (*E*)-**3** and followed the MMTTr/acyl (MMTTr = monomethoxytrityl) protecting group strategy developed earlier for the synthesis of PNAs.^[15] This methodology was chosen because of its mild deprotection chemistry and its compatibility with DNA synthesis.



In a first set of experiments the PNA oligomers **5–9** (Table 1)—which contained single *t^E* ((*E*)-**2**) or *t^Z* mutations ((*Z*)-**2**) at various positions in the sequence, a hydroxyhexylamide C terminus, and a natural thymidine unit at the N terminus—were prepared according to published procedures,^[16] and their structural integrity was verified by electrospray (ESI) mass spectrometry. The N-terminal thymidine

Table 1. Mass spectrometry data and *T_m* values [°C] (UV-melting curves, 260 nm) of DNAs, PNAs, and PNA sequences containing (*E*)-**2** or (*Z*)-**2** units with antiparallel complementary DNA (*c* = 4 μM in 100 mM NaCl, 10 mM Na₂HPO₄, 0.1 mM EDTA, pH 7.0). Capital letters: deoxynucleotides; lowercase letters: PNA units; *t^Z* = (*Z*)-**2** unit, *t^E* = (*E*)-**2** unit, hex = *n*-hydroxyhexylamide; g = hydroxyethylglycyl variant of the PNA-guanine monomer ((guanin-9-yl)acetyl-*N*-2-hydroxyethylglycine).

		<i>m/z</i> calcd	<i>m/z</i> found (ESI ⁺ -MS)	<i>T_m</i> (antiparallel DNA) ^[a]
4	Tgtagatcact-hex	3132.0	3132.7	46.4
5	Tgt ^{t^Z} agatcact-hex	3115.0	3115.0	43.4
6	Tgtagat ^{t^Z} cact-hex	3115.0	3114.6	32.2
7	Tgtagat ^{t^E} cact-hex	3115.0	3115.1	39.9
8	Tgt ^{t^E} agatcact-hex	3115.0	3115.2	43.3
9	Tgtagatcact ^{t^E} -hex	3115.0	3115.0	47.7
10	d(GTAGATCACT)	–	–	33.5

[a] d(AGTGATCTAC).

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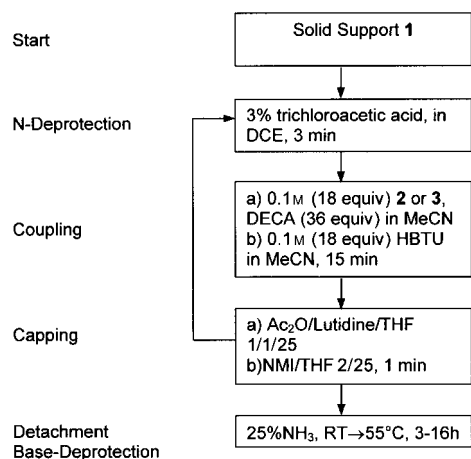
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unit was introduced in order to facilitate purification of the oligomers (gel electrophoresis) and to increase their solubility in water.

The syntheses of the fully modified (*E*)- and (*Z*)-OPA decapeptides **13–15**, **17**, and **18** (Table 2) started with the glycine-containing solid support **1** and were performed on a 1-μmol scale using a Pharmacia Gene Assembler DNA synthesizer that was reprogrammed accordingly (Scheme 2).



Scheme 2. Cycle and conditions for the solid-phase synthesis of OPA oligomers. DCE = dichloroethane, DECA = diethylcyclohexylamine, HBTU = *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, NMI = *N*-methylimidazole.

The coupling yields per step, as measured by MMTr assay, were in the range of 88–95% for **2** and **3**, and thus slightly lower than for the synthesis of the PNA control sequence **12** (>98% per step). Whereas oligomers **12–14** were prepared with free N termini, sequences **15–18** were treated in the last cycle with a thymidine or deoxycytidine phosphoramidite DNA building block under typical DNA synthesis conditions^[17] to produce a phosphonamidate cap. This step was again included in order to introduce a negative charge, which facilitates purification and enhances the solubility of the oligomer in water. Deprotection and detachment from the solid support was effected by treatment with concentrated NH₃, (room temperature (RT) or 55°C, 3 or 16 h) and produced oligomers with C-terminal glycine amide residues. The oligomers **12–14** were purified by HPLC, and **15–18** by polyacrylamide gel electrophoresis. Again, ESI or matrix-

assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry confirmed the structural integrity of the oligomers (Table 2).

Initially there was concern that migration of the C–C double bond (β,γ -unsaturated amide) could occur under the conditions of the synthesis and deprotection. The ¹H NMR spectrum of the crude trimer t^Zt^Zt^Z-Gly-NH₂, which was prepared manually on a 10-μmol scale to test this possibility, showed no signals for products arising from double-bond tautomerism (<1%).

The *T_m* analysis (UV-melting curves) of the chimaeric PNA/OPA oligomers **5–9** paired to their antiparallel DNA complements indicated a general decrease in affinity, relative to the unmodified PNA oligomer **4**, for those cases (**5–8**) where the modifications are not at the end of the sequence (Table 1). A dramatic decrease was observed for **6** and **7**, which display modification in the middle of the sequence. Oligomer **7**, which contains t^E-OPA and represents the geometry of the base-linker unit observed for PNA in complexed form, is less destabilized ($\Delta T_m = 6.5$ K) than **6**, which contains the geometrically mismatched monomeric unit t^Z ($\Delta T_m = 14.2$ K).

From these experiments, two conclusions can be drawn: 1) A geometric mismatch of the base-linker unit is associated with an energetic penalty on duplex formation; 2) stereochemical constriction of the base-linker unit into the pairing-competent geometry of PNA does not increase but rather decreases affinity. Assuming that replacement of the amide functionality by the double bond has a minor influence on the conformational preferences of the rest of the PNA unit, there exists a considerable electrostatic contribution of the amide functionality to pairing.

The pure (*Z*)-OPA and (*E*)-OPA decamers **13** and **14** also form complexes of comparable stability with the DNA complement d(A)₁₀, as inferred from UV-melting curves (Figure 1a). The *T_m* values are on the order of that of the DNA control duplex, but distinctly lower than that of the corresponding PNA₂/DNA triplex (Table 2).

Interestingly, neither the (*Z*)-OPA nor the (*E*)-OPA homodecamers **13–15** seem to form triplexes with d(A)₁₀. This was demonstrated in the case of **15** by a gel shift experiment (Figure 2). For a stoichiometric ratio of 2:1 for **15**:d(A)₁₀, a new band attributable to a complex arises on the gel together with a band for uncomplexed **15** (lane 3). At the same time, all the d(A)₁₀ was consumed. From this distribution of products we conclude that only a duplex had formed

Table 2. Mass spectrometry data and *T_m* values [°C] of DNAs, PNAs, and fully modified (*E*)- and (*Z*)-OPA sequences with antiparallel and parallel complementary DNA (*c* = 4 μM in 100 mM NaCl, 10 mM Na₂HPO₄, 0.1 mM EDTA, pH 7.0). a^E = (*E*)-**3** unit; see Table 1 for further abbreviations.

		<i>m/z</i> calcd	<i>m/z</i> found	antiparallel DNA	<i>T_m</i>	parallel DNA
11	d(T) ₁₀	2980.0	2977.2 ^[a]		20.7	
12	(t) ₁₀ -Gly-NH ₂	2736.7	2736.6 ^[a]		66.9	
13	(t ^Z) ₁₀ -Gly-NH ₂	2566.8	2568.5 ^[a]		23.0	
14	(t ^E) ₁₀ -Gly-NH ₂	2566.8	2566.6 ^[a]		23.5	
15	dT(t ^E) ₁₀ -Gly-NH ₂	2869.9	2890.3 ^[b]	n.d. ^[c]		n.d. ^[c]
16	dC(ttttaataa)-Gly-NH ₂	3060.9	3060.9 ^[b]	29.4		13.1
17	dC(t ^E t ^E t ^E t ^E a ^E a ^E t ^E a ^E t ^E a ^E)-Gly-NH ₂	2891.0	2891.3 ^[b]	< 0		16.0
18	dC(t ^E t ^E t ^E t ^E a ^E a ^E t ^E a ^E t ^E a ^E)-Gly-NH ₂	2891.0	2891.0 ^[b]	< 0		13.5

[a] MALDI-TOF-MS (positive-ion mode). [b] ESI⁺-MS. [c] n.d. = not determined.

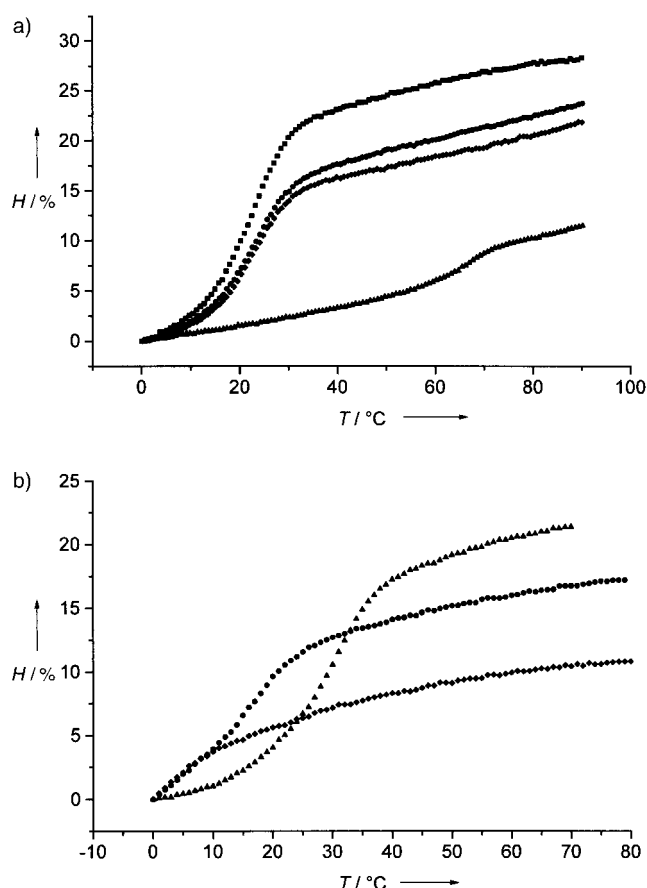


Figure 1. a) The UV-melting curves (H = relative hyperchromicity, $\lambda = 260$ nm) of a) $\bullet$ **11**/dA₁₀, $\blacktriangle$ **12**/dA₁₀, $\blacksquare$ (**13**)/dA₁₀, and $\blacklozenge$ **14**/dA₁₀ as well as b) $\blacktriangle$ **16**/antiparallel DNA, $\bullet$ **17**/parallel DNA, and $\blacklozenge$ **17**/antiparallel DNA. Oligonucleotide concentrations and buffer conditions as in Table 2.

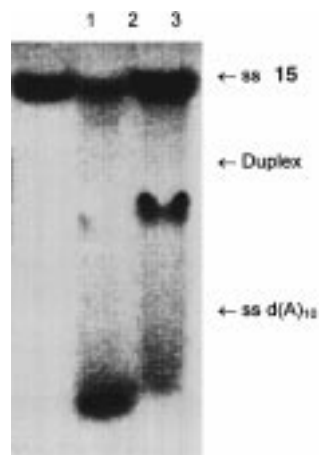


Figure 2. Binding of **15** to d(A)₁₀. UV shadowing of a 20% nondenaturing polyacrylamide gel. Buffer: 90 mM Tris · borate, pH 8.1, 10 mM MgCl₂. The samples were dissolved in 20 μ L of loading buffer (8% sucrose, 10 mM MgCl₂, 90 mM Tris · borate) and incubated at 0 °C for 20 min. The gel was run at 120 V for 1 h, then at 90 V for 12 h ($T = 5$ °C). Lane 1: **15**; lane 2: **15**:d(A)₁₀ 1:1; lane 3: **15**:d(A)₁₀ 2:1.

under these conditions. The fact that no triplex had formed is also supported by the very different shapes of the melting curves of OPA/DNA and PNA/DNA hybrids (Figure 1 a) as well as by the large differences in T_m between the PNA₂/DNA triplex (**12**)₂:d(A)₁₀ and PNA/DNA duplex **16**:d(TATAT-

TAAAA) compared to the relatively similar T_m values of the OPA/DNA duplexes of **13**, **14**, and **17** with the corresponding DNA complements (see Figure 1 and Table 2). Furthermore, in contrast to PNA, no hysteresis was observed in melting/renaturation cycles (rate = 0.5 K min⁻¹), which is again in accord with the fact that no triplex was formed. Thus the behavior of OPA seems to be distinctly different from that of PNA, in that it has lost its ability to form triplex structures with complementary homo-purine DNA sequences.

With oligomer **17**, having an asymmetric sequence distribution of thymine and adenine bases, we investigated the preferred strand orientation in OPA/DNA duplexes (Table 2). Surprisingly it was determined that **17**, in which the bases are preorganized in the same orientation as in PNA/nucleic acid complexes, only forms duplexes with the parallel DNA complement and thus deviates completely from the preferred pairing orientations in PNA/nucleic acid complexes.

Oligomer **18**, in which one t^E unit is replaced by a t^Z unit, was prepared in order to investigate the effect of one stereochemical mismatch in an OPA sequence. When paired to its parallel DNA complement, this structural mismatch results in a penalty of 2.5 K in T_m relative to **17** and highlights a nonnegligible preference for the stereochemically uniform arrangement of the base-linker units in OPA.

The key results obtained are: 1) Both (*E*)- and (*Z*)-OPA sequences bind to complementary DNA with similar affinities as DNA itself; 2) in contrast to PNA, there are no indications of OPA₂/DNA triplex formation with homobasic thymine-containing OPA sequences; 3) in contrast to PNA, OPA binds preferentially in the parallel mode to DNA; 4) sequences containing both (*E*)- and (*Z*)-OPA units in the same strand bind less efficiently than homoconfigured sequences.

The following conclusions can be drawn with respect to molecular recognition of DNA by PNA: The amide functionality in the base-linker unit in PNAs determines significantly the affinity and preferred strand orientation in PNA/DNA duplexes. Furthermore, it seems to be responsible for the propensity to form PNA₂/DNA triplexes. These properties do not depend on the conformational constraints that the amide functionality exerts on the base-linker unit,^[18] but rather on its electrostatic properties. Whether solvation, solvent-mediated intrastrand hydrogen bonding, or dipole effects in the OPA strands are responsible for the observed behavior remains open at this point and has to be clarified by further experiments.

With OPA, new and rather unexpected structure–activity relationships in PNA/DNA recognition could be obtained. The results are of importance for the further modification of the PNA skeleton in order to enhance its chemical and biological properties. Furthermore, OPA offers the unique possibility, with respect to PNA, to introduce a fourth substituent on the double bond. This could be of interest, for example, for improving binding or solubility properties, or for the attachment of functional units that may act on bound complementary RNA or DNA.

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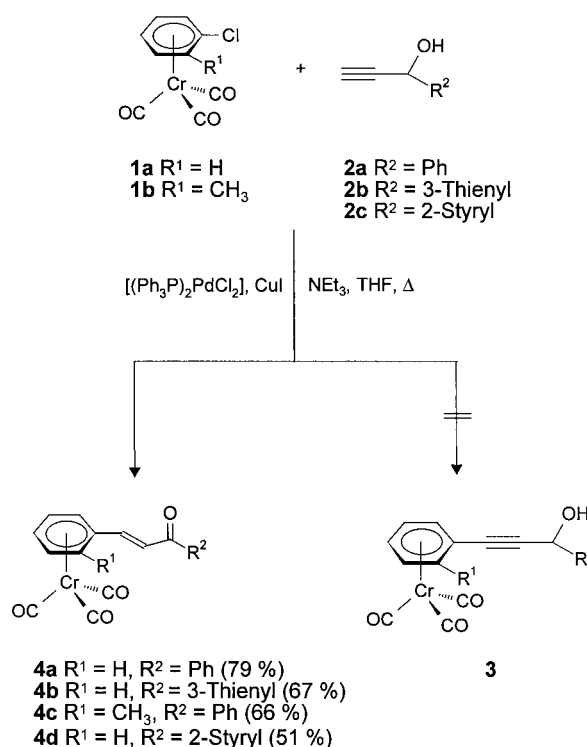
An Unexpected Coupling–Isomerization Sequence as an Entry to Novel Three-Component-Pyrazoline Syntheses**

Thomas J. J. Müller,* Markus Ansorge, and Daniel Aktah

Consecutive reactions^[1] have gained increasing importance and interest since efficient syntheses inherently claim to generate a maximum of structural complexity in few steps and in good yields from simple starting materials and with high chemo-, regio-, and stereoselectivity. In such reactions, the directly preceding step forms the functionality necessary for the following transformation. Particularly with regard to multicomponent reactions, the development of novel cascade

reactions for the in-situ-generation of reactive functional groups is an intensively pursued goal. Ideally, all these processes occur in a consecutive fashion, occasionally by successive addition of reagents, without the isolation of intermediates and in the sense of a “one-pot synthesis”. A model for these consecutive processes are multicomponent condensations^[2] as well as palladium-catalyzed cascade reactions,^[3] which have proved particularly useful in many cases owing to the mild reaction conditions and the pronounced tolerance for functional groups.

In the course of our work on the chemistry of (arene)Cr(CO)₃ complexes with conjugated side chains,^[4] we now have found that the usually reliable Sonogashira coupling^[5] of chloroarene complexes **1** with 1-aryl prop-2-ynols **2** does not furnish the expected alkyne coupling products, the propargyl alcohols **3**, but that the isomeric aryl complexed chalcones **4**^[6] are formed in good yields (Scheme 1).



Scheme 1. Synthesis of chromium carbonyl complexed chalcones by means of a coupling–isomerization sequence.

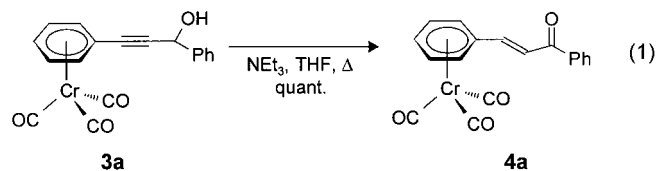
The constitution of the complexed chalcone **4a** was elucidated unambiguously by a selectively ¹H-decoupled ¹³C NMR experiment, and thus, a Meyer–Schuster rearrangement could be ruled out.^[7] Remarkably, the chalcones are formed with excellent *trans* selectivity (³J = 16 Hz), indicating a thermodynamically controlled double bond formation.

To the best of our knowledge this unusual reaction has so far only been observed for the coupling of 2-halogen-substituted pyrimidines.^[8] In this case the authors explained the mechanism by a coordination of an intermediate during a hydropalladation–dehydropalladation catalytic cycle to the heterocyclic nitrogen atom.^[8c] Additionally, some transition metal catalyzed redox isomerizations of propargyl alcohols to

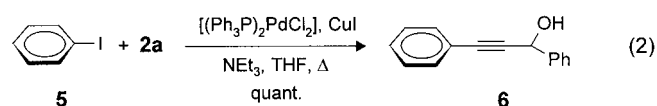
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α,β -unsaturated carbonyl compounds have been described.^[9] However, due to a lack of heteroatom coordination this explanation fails for the formation of the complexes **4**. Furthermore, we now could show that this isomerization exclusively occurs in a base-catalyzed manner. Thus, heating of the complexed diphenylpropargyl alcohol **3a** ($R^1 = H$, $R^2 = Ph$), the presumed primary product of the Sonogashira coupling of **1a** with **2a**, in THF in the presence of triethylamine gives rise to a rapid formation of the complexed chalcone **4a** [Eq. (1)]. On the other hand the coupling of



propargyl alcohol **2a** with iodobenzene (**5**) instead of a chlorobenzene complex, which undergoes the oxidative addition at the palladium complex at a comparable rate, exclusively gives rise to the formation of the diphenylpropargyl alcohol (**6**) [Eq. (2)]. Evidently, the electronic nature



of the halogen arene component plays a key role for the following isomerization. Therefore, we assume that this coupling–isomerization sequence is far more generally applicable than only for aromatic heterocycles and chromium carbonyl complexed arenes.

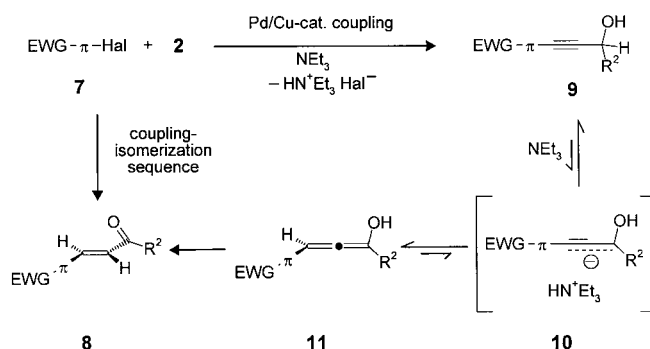
For halogen components **7** (π denotes a structural unit with a π -electron system) with electron-withdrawing groups in conjugation to the halogen carbon atom as, for example, in acceptor-substituted halogen (hetero)arenes, (*Z*)-3-bromomethyl acrylate, or 3-bromocyclohex-2-enone, and for extended π -substituents at the propargylic center of **2**, the enones **8** are formed in good to excellent yields [Eq. (3); Table 1].

According to the product analysis and the control experiment addressing the base-catalyzed isomerization of **3a** to **4a**, the mechanistic course of this coupling–isomerization sequence can be outlined as follows (Scheme 2). The Sonogashira coupling of the terminal arylpropargyl alcohol **2** with a sufficiently electron-poor sp^2 -hybridized halogen compound **7** results in the formation of an acceptor-substituted propargyl alcohol **9**. Upon deprotonation at the propargyl center with triethylamine under equilibrium conditions, a resonance-stabilized propargyl–allenyl anion **10** is formed that is protonated to give the thermodynamically more favored allene **11**. Finally, the sequence concludes with an allenol–enone tautomerism to furnish the *trans*-configured enone **8** selectively.

Under the mild reaction conditions the coupling–isomerization sequence turns out to be a competitive strategy for the

Table 1. Coupling–isomerization reaction.

$\text{EWG}-\pi-\text{Hal } \mathbf{7} + \mathbf{2a} / \mathbf{2b} \xrightarrow[\text{NEt}_3, \text{THF}, \Delta]{[(\text{Ph}_3\text{P})_2\text{PdCl}_2], \text{CuI}} \text{EWG}-\pi-\text{CH=CH-C(=O)R}^2 \quad (3)$			
No.	EWG- π -Hal 7	Propargyl alcohol 2	Enone 8 ^[10] Yield [%] ^[11]
1		2a $R^2 = Ph$	 8a 80
2		2a $R^2 = Ph$	 8b 57
3		2b $R^2 = 3\text{-Thienyl}$	 8c 100
4		2a $R^2 = Ph$	 8d 85
5		2b $R^2 = 3\text{-Thienyl}$	 8e 90
6		2b $R^2 = 3\text{-Thienyl}$	 8f 97



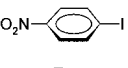
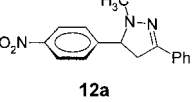
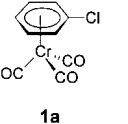
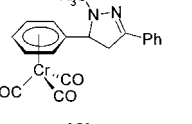
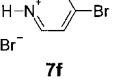
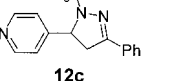
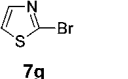
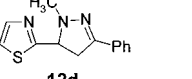
Scheme 2. Mechanistic rationale for the course of the coupling–isomerization sequence.

synthesis of enones in comparison to aldol condensations, especially, if the required aldehyde is difficult to prepare (e.g. the corresponding 3-formylcyclohex-2-enone^[12]) or if an alkaline-sensitive functionality (**7b**, **7c**, **7d**) needs to be carried through a reaction sequence without tedious protecting group manipulations. Additionally, propargyl alcohols are significantly easier to handle than vinyl ketones that can be coupled by Heck reactions to give enones but display a distinct propensity to polymerize. Interestingly, the coupling–isomerization reaction leads to a complete *Z*–*E* isomerization of the acrylate double bond (**8e**^[13]), which supports a thermodynamically controlled formation of the enone functionality (via delocalization of the propargyl anion intermediate). In contrast, Sonogashira couplings proceed stereospecifically with retention of alkene configuration.^[5] Accordingly,

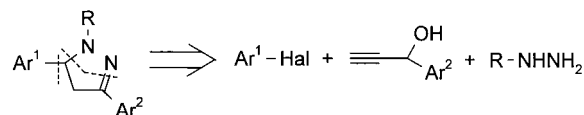
this is a facile and stereoselective access to electron-deficient dienes^[14] (**8e**, **8f**), a class of interesting substrates in Diels–Alder reactions with inverse-electron demand.^[15]

Furthermore, this mild enone synthesis enables the development of novel one-pot reactions taking advantage of the newly generated enone functionality. Thus, the addition of *N*-methylhydrazine is compatible with the reaction conditions after the coupling. Only after the base-catalyzed propargyl alcohol–enone isomerization the hydrazine enters the Michael-addition–cyclocondensation sequence with the α,β -unsaturated carbonyl compounds giving rise to the formation of 2-pyrazolines **12**^[16] [Eq. (4); Table 2].

Table 2. Three-component one-pot pyrazoline synthesis.

$\text{EWG}-\pi\text{-Hal} + \text{2a} \xrightarrow[\text{2) CH}_3\text{NHNH}_2]{\text{1) }[(\text{Ph}_3\text{P})_2\text{PdCl}_2], \text{CuI}, \text{NEt}_3, \text{THF}, \Delta} \text{EWG}-\pi\text{-} \begin{array}{c} \text{H}_3\text{C} \\ \diagup \quad \diagdown \\ \text{N} \quad \text{N} \\ \diagdown \quad \diagup \\ \text{CH} \quad \text{CH} \end{array} \text{Ph} \quad (4)$			
No.	EWG- π -Hal 7	Pyrazoline 12 ^[10]	Yield [%] ^[11]
1			90
2			63
3			77
4			69

Upon applying the coupling–isomerization sequence of a haloarene, a propargyl alcohol, and a hydrazine, we have developed a novel one-pot synthesis of 3,5-disubstituted 2-pyrazolines, an important class of pharmacophores,^[17] which allows unusual retrosynthetic cuts for the construction of heterocyclic systems (Scheme 3). Further heterocycle syntheses, even in a combinatorial sense, are now readily conceivable on the basis of this coupling–isomerization sequence.



Scheme 3. Retrosynthetic analysis of 3,5-diaryl-2-pyrazolines.

Experimental Section

Enone synthesis (8a): To a solution of **7a** (0.25 g, 1.00 mmol), [Pd(PPh₃)₂Cl₂] (22 mg, 0.02 mmol), and CuI (2 mg, 0.01 mmol) in anhydrous THF (10 mL) and triethylamine (5 mL) under nitrogen, a solution of **2a** (0.14 g, 1.05 mmol) in THF (10 mL) was added dropwise over a period

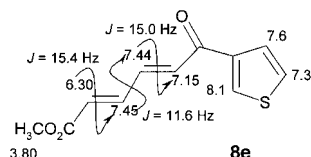
of 30 min. Then the reaction mixture was heated to reflux for 10 h. After the mixture had cooled to room temperature, diethyl ether (30 mL) was added and the suspension was filtered. The solvents were removed in vacuo and the crude product was flash chromatographed on silica gel (length: 10 cm, diameter: 1 cm) with diethyl ether/pentane to give **8a** (0.40 g; 80%), m.p. 161–162°C (ref. [18] 160–161°C). ¹H NMR (300 MHz, CDCl₃, 25°C): δ = 7.76 (dd, ³J(H,H) = 7.7 Hz, 2H; CH), 7.85 (m, 1H), 7.88 (d, ³J(H,H) = 15.8 Hz, 1H; CH), 8.01 (d, ³J(H,H) = 8.7 Hz, 2H; CH), 8.05 (d, ³J(H,H) = 15.4 Hz, 1H; CH), 8.27 (d, ³J(H,H) = 8.6 Hz, 2H; CH), 8.50 (d, ³J(H,H) = 8.8 Hz, 2H; CH); ¹³C NMR (75 MHz, CDCl₃, 25°C): δ = 124.14 (CH), 125.66 (CH), 128.52 (CH), 128.76 (CH), 128.88 (CH), 133.30 (CH), 137.47 (C_{quat}), 140.98 (C_{quat}), 141.41 (CH), 148.49 (C_{quat}), 189.55 (C_{quat}).

One-pot pyrazoline synthesis (12a): To a solution of **7a** (0.25 g, 1.00 mmol), [Pd(PPh₃)₂Cl₂] (22 mg, 0.02 mmol), and CuI (2 mg, 0.01 mmol) in anhydrous THF (10 mL) and triethylamine (5 mL) under nitrogen, a solution of **2a** (0.14 g, 1.05 mmol) in THF (10 mL) was added dropwise over a period of 30 min. Then the reaction mixture was heated to reflux for 10 h. After the mixture had been cooled, *N*-methylhydrazine (0.15 mL, 3.76 mmol) was added and heating was continued for 5 h. After removal of the solvents in vacuo the crude product was flash chromatographed on silica gel (length: 10 cm, diameter: 1 cm) with diethyl ether/pentane to furnish **12a** (0.26 g; 92%), m.p. 118–119°C. ¹H NMR (300 MHz, CDCl₃, 25°C): δ = 2.84 (s, 3H, CH₃), 2.96 (dd, ³J(H,H) = 14.0, 16.1 Hz, 1H; CH), 3.56 (dd, ³J(H,H) = 10.1, 16.1 Hz, 1H; CH), 4.25 (dd, ³J(H,H) = 10.1, 14.0 Hz, 1H; CH), 7.33–7.40 (m, 3H; CH), 7.61–7.68 (m, 4H; CH), 8.23 (d, ³J(H,H) = 6.8 Hz, 2H; CH); ¹³C NMR (75 MHz, CDCl₃, 25°C): δ = 41.78 (CH₃), 43.54 (CH₂), 72.63 (CH), 124.02 (CH), 125.88 (CH), 128.31 (CH), 128.61 (CH), 129.05 (CH), 132.27 (C_{quat}), 147.68 (C_{quat}), 148.16 (C_{quat}), 149.81 (C_{quat}); MS (70 eV, EI), *m/z* (%): 281 (100) [*M*⁺]; IR (KBr): $\tilde{\nu}$ = 1607 cm^{−1} (C=N); elemental analysis (%) calcd for C₁₆H₁₅N₃O₂: C 68.31, H 5.37, N 14.93; found: C 68.21, H 5.47, N 14.62.

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- Selected physical data of **4**. **4a**: ¹H NMR (300 MHz, [D₆]DMSO, 25°C): δ = 5.80 (dd, ³J(H,H) = 6.0, 6.1 Hz, 2H; CH), 5.87 (t, ³J(H,H) = 6.1 Hz, 1H; CH), 6.40 (d, ³J(H,H) = 6.3 Hz, 2H; CH), 7.36 (d, ³J(H,H) = 15.6 Hz, 1H; CH), 7.56 (dd, ³J(H,H) = 7.3, 7.4 Hz, 2H; CH), 7.67 (t, ³J(H,H) = 7.3 Hz, 1H; CH), 7.86 (d, ³J(H,H) = 15.6 Hz, 1H; CH), 8.12 (d, ³J(H,H) = 7.3 Hz, 2H; CH); ¹³C NMR (75 MHz, [D₆]DMSO, 25°C): δ = 94.02 (CH), 95.87 (CH), 95.91 (CH), 101.43 (C_{quat}), 123.24 (CH), 128.74 (CH), 129.00 (CH), 133.60 (CH), 137.32 (C_{quat}), 141.53 (CH), 188.66 (C_{quat}), 233.45 (C_{quat}); MS (70 eV, EI): *m/z* (%): 344 (13) [*M*⁺], 288 (6) [*M*⁺ − 2CO], 260 (100) [*M*⁺ − 3CO]; IR (KBr): $\tilde{\nu}$ = 1966 cm^{−1} (CO), 1891 (CO), 1667 (C=O), 1609 (C=C). **4b**: M.p. 141–143°C; ¹H NMR (300 MHz, [D₆]DMSO, 25°C): δ = 5.79–5.86 (m, ³J(H,H) = 6.2 Hz, 3H; CH), 6.36 (d, ³J(H,H) = 6.1 Hz, 2H; CH), 7.32 (d, ³J(H,H) = 15.4 Hz, 1H; CH), 7.64–7.68 (m, 2H; CH), 7.76 (d, ³J(H,H) = 15.5 Hz, 1H; CH), 8.78 (s, 1H; CH); ¹³C NMR (75 MHz, [D₆]DMSO, 25°C): δ = 94.10 (CH), 95.73 (CH), 95.77 (CH), 101.58 (C_{quat}), 124.32 (CH), 127.16 (CH), 128.09 (CH), 134.88 (CH), 140.52 (CH), 142.71 (C_{quat}), 182.35 (C_{quat}), 233.45 (C_{quat}); MS (70 eV, EI): *m/z* (%): 350 (17) [*M*⁺], 294 (11) [*M*⁺ − 2CO], 266 (100) [*M*⁺ − 3CO]; IR (KBr): $\tilde{\nu}$ = 1969 cm^{−1} (CO), 1883 (CO), 1656 (C=O), 1598 (C=C). **4c**: M.p. 92–93°C; ¹H NMR (300 MHz,

- [D₆]DMSO, 25 °C): δ = 2.34 (s, 3H; CH₃), 5.67–5.69 (m, 2H; CH), 5.96 (t, $^3J(\text{H,H})$ = 6.3 Hz, 1H; CH), 6.67 (d, $^3J(\text{H,H})$ = 6.8 Hz, 1H; CH), 7.55 (d, $^3J(\text{H,H})$ = 15.0 Hz, 1H; CH), 7.57 (dd, $^3J(\text{H,H})$ = 7.3, 7.4 Hz, 2H; CH), 7.67 (t, $^3J(\text{H,H})$ = 7.3 Hz, 1H; CH), 7.87 (d, $^3J(\text{H,H})$ = 15.3 Hz, 1H; CH), 8.13 (d, $^3J(\text{H,H})$ = 7.5 Hz, 2H; CH); ¹³C NMR (75 MHz, [D₆]DMSO, 25 °C): δ = 18.76 (CH₃), 91.77 (CH), 94.53 (CH), 95.39 (CH), 96.86 (CH), 100.11 (C_{quat}), 124.05 (CH), 128.75 (CH), 129.02 (CH), 133.64 (CH), 137.31 (C_{quat}), 138.32 (CH), 188.59 (C_{quat}), 233.65 (C_{quat}); MS (70 eV, EI): m/z (%): 358 (14) [M^+], 302 (5) [$M^+ - 2\text{CO}$], 274 (100) [$M^+ - 3\text{CO}$]; IR (KBr): $\tilde{\nu}$ = 1959 cm⁻¹ (CO), 1876 (CO), 1661 (C=O), 1588 (C=C). **4d**: M.p. 68 °C; ¹H NMR (300 MHz, [D₆]DMSO, 25 °C): δ = 5.64–5.84 (m, 5H, CH), 6.21 (d, $^3J(\text{H,H})$ = 16.0 Hz, 1H; CH), 6.30 (d, $^3J(\text{H,H})$ = 16.0 Hz, 1H; CH), 7.21 (d, $^3J(\text{H,H})$ = 16.1 Hz, 1H; CH), 7.31 (d, $^3J(\text{H,H})$ = 15.9 Hz, 1H; CH), 7.33–7.83 (m, 5H; CH); ¹³C NMR (75 MHz, [D₆]DMSO, 25 °C): δ = 94.19 (CH), 95.46 (CH), 95.75 (CH), 101.76 (C_{quat}), 125.70 (CH), 126.49 (CH), 128.74 (CH), 129.18 (CH), 130.86 (CH), 134.72 (C_{quat}), 140.30 (CH), 143.65 (CH), 188.06 (C_{quat}), 233.45 (C_{quat}); MS (70 eV, EI): m/z (%): 370 (19) [M^+], 314 (15) [$M^+ - 2\text{CO}$], 286 (100) [$M^+ - 3\text{CO}$]; IR (KBr): $\tilde{\nu}$ = 1965 cm⁻¹ (CO), 1886 (CO), 1651 (C=O), 1618 (C=C).
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- $^4J(\text{H,H})$ = 0.7 Hz, 1H; CH), 7.37 (dd, $^3J(\text{H,H})$ = 5.1, $^4J(\text{H,H})$ = 2.8 Hz, 1H; CH), 7.44 (m, $^3J(\text{H,H})$ = 11.6, 15.0, $^4J(\text{H,H})$ = 0.8 Hz, 1H; CH), 7.45 (m, $^3J(\text{H,H})$ = 11.6, 15.4, $^4J(\text{H,H})$ = 0.7 Hz, 1H; CH), 7.61 (dd, $^3J(\text{H,H})$ = 5.1, $^4J(\text{H,H})$ = 1.3 Hz, 1H; CH), 8.11 (dd, $^4J(\text{H,H})$ = 1.2, 2.8 Hz, 1H; CH); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 51.9 (CH₃), 126.8 (CH), 127.3 (CH), 128.6 (CH), 132.4 (CH), 132.7 (CH), 139.7 (CH), 141.5 (CH), 142.5 (C_{quat}), 166.4 (C_{quat}), 183.1 (C_{quat}); MS (70 eV, EI): m/z (%): 222 (83) [M^+], 163 (100) [$M^+ - \text{CH}_3\text{CO}_2$], 111 (88) [$\text{C}_5\text{H}_3\text{OS}^+$]; IR (KBr): $\tilde{\nu}$ = 1709 cm⁻¹ (C=O), 1653 (C=O), 1624 (C=C).
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Novel Water-Soluble Calix[4]arene Ligands with Phosphane-Containing Groups for Dual Functional Metal-Complex Catalysts: The Biphase Hydroformylation of Water-Insoluble Olefins**

Shoichi Shimizu,* Seiji Shirakawa, Yasuyuki Sasaki, and Choichiro Hirai

The design and development of environmentally benign chemical processes has been the subject of growing attention, given the growing international consensus on green chemistry.^[1] The Ruhrchemie–Rhône-Poulenc process^[2] for the hydroformylation of propene, catalyzed by a water-soluble rhodium complex with triphenylphosphane trisulfonate (TPPTS, see Scheme 1) as a ligand, has been repeatedly discussed in the literature^[3] because it allows the catalyst in the aqueous phase to be recycled by simple decantation, and the exclusive use of water as the reaction medium. However, its application is limited to olefins which have appreciable water solubility. To circumvent this problem, a variety of alternate strategies have been reported primarily for the hydroformylation of oct-1-ene. These include the addition of co-solvents,^[4] promoter ligands,^[5] or partially methylated β -cyclodextrins (β -CDs),^[6] and the use of surface-active phosphanes,^[7] thermoregulated phase-transfer catalysts,^[8] or β -CD-modified diphosphanes^[9] in place of TPPTS. None of these approaches have proved ideal, since all inevitably increase the difficulty of product separation^[10] and, in addition for certain cases, a substantial decrease in activity takes place over consecutive catalytic cycles.

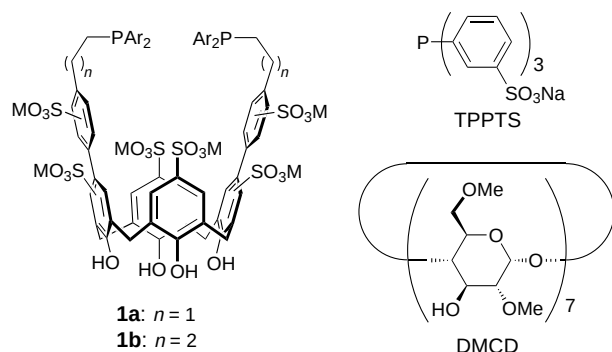
The approach described herein involves the use of novel water-soluble calix[4]arenes with phosphane-containing groups, named phosphacalix[4]arenes,^[11] as ligands for dual functional metal-complex catalysts. Our hypothesis was that water-soluble phosphacalix[*n*]arene–metal complexes would function not only as homogeneous metal catalysts but also as inverse phase-transfer catalysts,^[12, 13] which facilitate reactions

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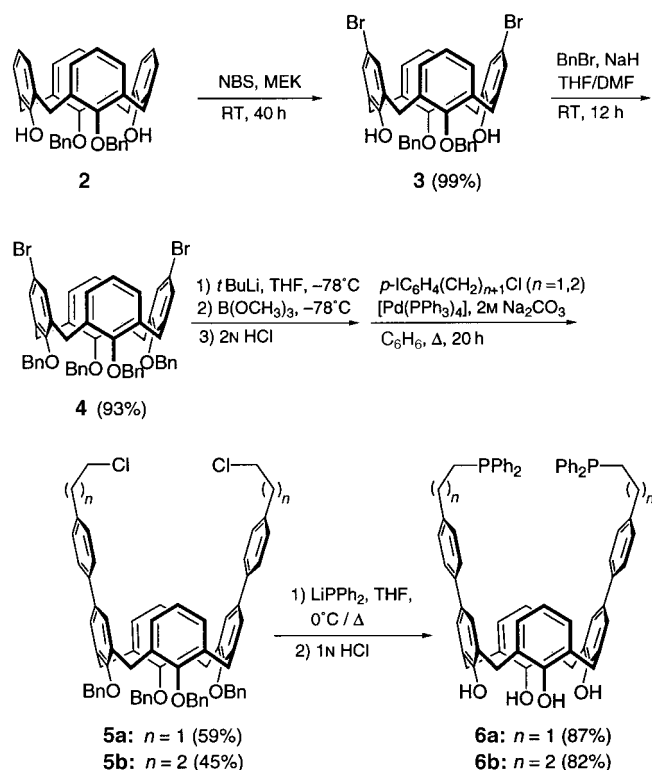
Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

through transporting an organic substrate into an aqueous phase. We report here on the catalytic behavior of complexes with ligands **1a** and **1b** (Scheme 1) in the aqueous biphasic hydroformylation of oct-1-ene and dec-1-ene. These phosphacalix[4]arene–rhodium complexes perform dual functional catalysis without the need for additives, thereby leading to enhanced catalytic activity.



Scheme 1. The structures of TPPTS and DMCD, and of the water-soluble phosphacalix[4]arenes **1a** and **1b** (Ar = *m*-MOSO₂C₆H₄). For **1a** and **1b**, the ten M are nine Na⁺ and one H⁺, or ten Na⁺, respectively.

A number of phosphacalix[*n*]arenes have already been prepared,^[14–16] but relatively few are known which contain phosphane moieties on the upper rim.^[16] We were interested in using the water-soluble phosphacalix[4]arenes **1a** and **1b**, which were synthesized starting from the known dibenzylphosphacalix[4]arene **2**^[17] (Scheme 2). We believed that the structure



Scheme 2. Synthesis of the upper-rim functionalized phosphacalix[4]arenes **6a** and **6b**, precursors to **1a** and **1b**. Bn = CH₂Ph; NBS = *N*-Bromosuccinimide; MEK = methyl ethyl ketone; RT = room temperature.

of **1a** and **1b** would enable an olefin to be included in the hydrophobic cavity and to simultaneously interact with a catalytic transition-metal center coordinated to the phosphane moieties.

Controlled sulfonations of the precursors **6a** and **6b** were conducted according to literature methods,^[18] that avoid phosphane oxidation and complex product mixtures. As a result, both **1a** and **1b** were obtained as precisely decasulfonated derivatives. Furthermore, the ³¹P NMR spectra of both products showed only two peaks. The most plausible structures are shown in Scheme 1, as deduced from the structures of analogous products obtained by sulfonations of triphenylphosphane^[18] and calix[4]arene.^[19]

The activity and selectivity of complexes with ligands **1a** and **1b**^[20] were tested using [Rh(acac)(CO)₂] (acac = acetylacetonate) as the metal complex for the biphasic hydroformylation of oct-1-ene and dec-1-ene. That, in all cases, high catalytic activities were observed was gratifying. For comparison purposes, a TPPTS ligand and the combination of TPPTS and 2,6-di-O-methyl-β-cyclodextrin (DMCD) as inverse phase-transfer catalysts were also examined under the same reaction conditions. These results are summarized in Table 1.

Table 1. The rhodium-catalyzed biphasic hydroformylation of water-insoluble olefins.^[a]

Entry	Ligand/Additive	Olefin	Conversion [%] ^[b]	Yield [%] ^[b,c]	l:b ^[d]
1	TPPTS ^[e]	oct-1-ene	trace	trace	–
2	TPPTS ^[e] /DMCD ^[f]	oct-1-ene	26	21	2.4
3	1a	oct-1-ene	55	40	3.0
4	1a	oct-1-ene	96	75	2.6
5	1b (1st use)	oct-1-ene	95	73	1.7
6	1b (2nd use) ^[h]	oct-1-ene	97	84	1.7
7	1b (3rd use) ^[i]	oct-1-ene	98	86	1.9
8	1b ^[j]	oct-1-ene	96	76	2.0
9	1b + TPPTS ^[k]	oct-1-ene	66	51	3.5
10	1b	dec-1-ene	94	52	2.3

[a] Reaction conditions: olefin (4.0 mmol), ligand (0.032 mmol), [Rh(acac)(CO)₂] (0.016 mmol), mole ratio olefin:P:Rh = 250:4:1, H₂O (3 mL), undecane (GC internal standard; 0.40 mmol), CO:H₂ = 1:1, *p* = 4.0 MPa, *T* = 100 °C, *t* = 12 h. [b] Determined by GC. [c] Yield of aldehydes. [d] Linear:branched ratio includes all branched aldehydes. [e] Triphenylphosphane trisulfonate (0.064 mmol). [f] 2,6-Di-O-methyl-β-cyclodextrin (0.032 mmol). [g] *t* = 24 h. [h] Aqueous layer used in Entry 5. [i] Aqueous layer used in Entry 6. [j] Ligand (0.064 mmol). [k] **1b** (0.032 mmol), TPPTS (0.016 mmol).

Treatment of oct-1-ene with a 1:1 mixture of carbon monoxide and hydrogen in water using the TPPTS/[Rh(acac)(CO)₂] complex for 12 h at 100 °C and 4.0 MPa pressure afforded only trace amounts of nonanals (Entry 1). The addition of DMCD to the reaction mixture increased the yield of nonanals to 21 % (Entry 2).^[21] However, when the same reaction was carried out using the **1b**/[Rh(acac)(CO)₂] catalyst (Entry 5), the yield of aldehydes increased to 73 % though the proportion of linear to branched aldehydes was somewhat smaller than that of TPPTS/DMCD. For the case of **1a** (Entries 3 and 4), the catalytic activity was inferior to that of **1b** and resulted in a l:b ratio comparable to that of the TPPTS/DMCD system. The beneficial effect of water-soluble phosphacalix[4]arenes **1a** and **1b** on the yield of aldehydes

can be attributed to an improvement in the mass transfer of the substrate and products between the phases, since it is generally accepted that the biphasic hydroformylation of water-insoluble olefins is limited by the rate of mass transfer.^[3, 6, 9] Thus the (**1a**, **1b**)/[Rh(acac)(CO)₂] complexes function, not only as homogeneous metal catalysts but also as inverse phase-transfer catalysts, that is, they perform a dual functional catalysis.

It is indeed remarkable that the activity and selectivity of the **1b**/[Rh(acac)(CO)₂] catalyst could be retained after being consecutively recycled in the second and third reactions and that the yields are practically identical to that observed with fresh catalyst, as shown in Entries 6 and 7 (Table 1). When a phosphorus to rhodium ratio of 8:1 is employed, no change in the activity is apparent, even though a slight improvement in the linear to branched ratio is observed (Entry 8). On the other hand, addition of TPPTS to the **1b**/[Rh(acac)(CO)₂] catalyst results in a significant enhancement in selectivity but the yield is relatively low (Entry 9). In addition, for the hydroformylation of dec-1-ene, the ligand **1b** was effective and satisfactory, although the formation of isomerization products slightly depressed the measured aldehyde yields (Entry 10).

The novel water-soluble phosphacalix[4]arene–rhodium complexes have acceptable levels of activity, stability, and reusability. This water-soluble catalytic system provides additional options in the field of aqueous organometallic catalysis for synthetic chemistry and process engineering.

Experimental Section

Sulfonation of 6a and 6b: Orthoboric acid (0.927 g, 15.0 mmol) was dissolved in concentrated H₂SO₄ (97%, 18 mL) and the resulting solution was cooled to 0 °C. **6a** or **6b** (1.0 g, 1.0 mmol) was added. The mixture was stirred at room temperature under argon until all solids had dissolved. A solution of oleum (60 wt %, 10 mL) at 0 °C was added dropwise to the solution over a 1 h period, followed by stirring for 24 h at 30 °C. All organic solvents and water employed in the workup of products were degassed by bubbling with argon. After cooling and hydrolysis (water 80 mL), the products were isolated by extraction into toluene/triisooctylamine (70 mL/15 mL) under argon. Further workup was performed according to previously described methods^[18] and **1a** or **1b** was obtained as a cream-colored powder (yield: 83% (**1a**), 88% (**1b**)). **1a**·3 CH₃OH·6 H₂O: ³¹P{¹H} NMR (162 MHz, CD₃OD, external 85% H₃PO₄): δ = −14.1 (s, 72%), −14.8 (s, 28%), 35.3 (vw s, P=O); elemental analyses for C₆₈H₄₉Na₉O₃₄P₂S₁₀·3 CH₃OH·6 H₂O (2203.80): calcd: C 38.70, H 3.34, Na 9.39, P 2.81, S 14.55; found: C 38.26, H 3.43, Na 9.44, P 2.89, S 14.82. **1b**·3 CH₃OH·6 H₂O: ³¹P{¹H} NMR (162 MHz, CD₃OD, external 85% H₃PO₄): δ = −14.3 (s, 41%), −15.0 (s, 59%), 36.4 and 37.2 (vw s, P=O); elemental analyses for C₇₀H₅₂Na₁₀O₃₄P₂S₁₀·3 CH₃OH·6 H₂O (2253.84): calcd: C 38.90, H 3.40, Na 10.20, P 2.75, S 14.22; found: C 39.23, H 3.41, Na 10.50, P 2.74, S 14.30.

Hydroformylation: In a typical experiment, **1a** or **1b** (0.032 mmol) and [Rh(acac)(CO)₂] (0.016 mmol) were dissolved in degassed water (3 mL) under argon. The resulting aqueous solution was filtered through a 0.45 μm PTFE membrane filter and the filtrate was transferred into an autoclave (80 mL), equipped with a glass liner and a magnetic stirring bar. Internal standard (undecane; 0.40 mmol) and oct-1-ene (4.0 mmol) were added. After purging with CO, the autoclave was pressurized to 4.0 MPa with a mixture of CO:H₂ (1:1) and heated to 100 °C with stirring at 800 rpm for 12 h. The autoclave cooled to room temperature and the reaction mixture was extracted with chloroform (5 mL × 3). The combined extracts were dried (Na₂SO₄) and subjected to GC analysis. For recycling experiments, after a reaction time of 12 h per cycle, the autoclave was depressurized and

the contents transferred to a Schlenk flask under argon. After extraction with chloroform, the aqueous catalyst solution was reinjected in the autoclave for the next cycle.

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- [20] **1a** and **1b** were treated with $[\text{Rh}(\text{acac})(\text{CO})_2]$ in CD_3OD , giving rhodium complexes with the phosphacalix[4]arenes acting as ligands. Complexation was indicated by the ^{31}P NMR spectrum, for example, the **1b** $[\text{Rh}(\text{acac})(\text{CO})_2]$ complex showed two doublets at $\delta = 45.2$ ($J(\text{P,Rh}) = 173$ Hz) and 45.7 ($J(\text{P,Rh}) = 174$ Hz).
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$[\text{Mo}(\text{CH}_3)_6]$ and $[\text{Mo}(\text{CH}_3)_7]^{-**}$

Beatrice Roessler and Konrad Seppelt*

More than two decades ago Wilkinson prepared $[\text{W}(\text{CH}_3)_6]$ and $[\text{Re}(\text{CH}_3)_6]$, which at the time were the only neutral hexamethyl transition neutral compounds.^[1,2] Later these compounds gained importance because they are classical examples for d^0 and d^1 complexes containing only σ -binding ligands, and therefore they should be not be octahedral, as predicted by several corresponding theoretical papers.^[3–7] In the meantime the structures of $[\text{Zr}(\text{CH}_3)_6]^{2-}$,^[8] $[\text{W}(\text{CH}_3)_6]$,^[9] $[\text{Re}(\text{CH}_3)_6]$,^[9] $[\text{Nb}(\text{CH}_3)_6]^-$,^[10] $[\text{Ta}(\text{CH}_3)_6]^-$,^[10] $[\text{Ta}(\text{C}_6\text{H}_5)_6]^-$,^[11] and $[\text{Ta}(\text{4-CH}_3\text{C}_6\text{H}_4)_6]^-$ ^[11] have been determined experimentally, and agree fully with the theoretical predictions: The structures are based on a trigonal prism, either regular as in $[\text{Re}(\text{CH}_3)_6]$, $[\text{Ta}(\text{CH}_3)_6]^-$, and $[\text{Zr}(\text{CH}_3)_6]^{2-}$, or more or less distorted trigonal prismatic as in $[\text{W}(\text{CH}_3)_6]$ and $[\text{Nb}(\text{CH}_3)_6]^-$ with retention of the C_{3v} symmetry.

The structure of $[\text{W}(\text{CH}_3)_6]$ has been of special interest because it is strongly C_{3v} -distorted trigonal prismatic, having nonequivalent W–C bonds; that is, three longer ones which have a very narrow angle to each other, and three shorter ones with a larger angle to each other. According to the latest theoretical calculation,^[4] that has also predicted the experimental structure in detail, the C_{3v} distortions should be especially large in the case of $[\text{Mo}(\text{CH}_3)_6]$, $[\text{Re}(\text{CH}_3)_6]^+$, and $[\text{Tc}(\text{CH}_3)_6]^+$. All three molecules or cations, respectively, are presently unknown.

We report here on the preparation of $[\text{Mo}(\text{CH}_3)_6]$ from MoF_6 and $\text{Zn}(\text{CH}_3)_2$, as well as on its structure. This reaction pathway is so far the only one with reasonable yields. Oxidic (MoOCl_4) or starting materials with nonhexavalent Mo centers (MoCl_5) should be avoided. Common methylating agents other than $\text{Zn}(\text{CH}_3)_2$, such as LiCH_3 , reduce MoF_6 . $[\text{Mo}(\text{CH}_3)_6]$, prepared in this way, is an orange-brown crystalline compound at low temperatures, which is volatile in high vacuum, and thermally stable up to about 10°C . It is very sensitive towards oxygen. Proof of its existence and structure stems mainly from a single-crystal X-ray structure determination (Figure 1). Single crystals were obtained by

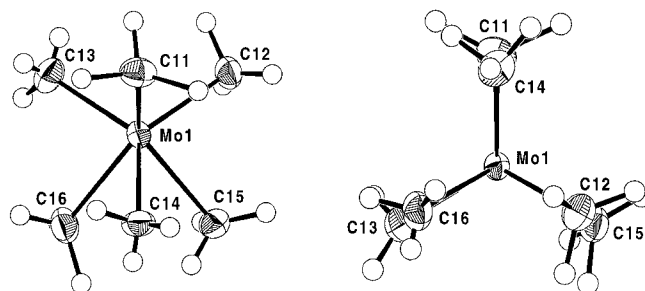


Figure 1. ORTEP representation of $[\text{Mo}(\text{CH}_3)_6]$, molecule I, 50% probability ellipsoids, view perpendicular and along the threefold molecular axis. Because of the smaller angle to the molecular axis of the longer bonded methyl groups these appear closer to the molybdenum atom in the projection on the right-hand side. Distances [pm] and angles $^\circ$ (the corresponding values of $[\text{Mo}(\text{CH}_3)_6]$ II and $[\text{Mo}(\text{CH}_3)_6]$ III are given in parentheses): Mo1–C11 212.6(8) (208.8(6), 213.8(8)), Mo1–C12 210.3(7) (209.6(7), 211.3(5)), Mo1–C13 210.7(6) (211.8(6), 209.5(5)), Mo1–C14 220.0(7) (220.0(6), 216.7(8)), Mo1–C15 217.5(9) (218.8(6), 220.7(5)), Mo1–C16 219.5(6) (220.5(7), 219.7(6)); C11–Mo1–C12 93.6(3) (97.0(3), 96.1(3)), C11–Mo1–C13 93.8(4) (98.9(3), 96.6(3)), C12–Mo1–C13 97.5(3) (96.0(3), 98.2(2)), C14–Mo1–C15 75.2(3) (75.8(2), 75.7(2)), C14–Mo1–C16 76.9(3) (74.7(3), 74.7(3)), C15–Mo1–C16 75.1(3) (75.7(3), 74.2(2)).

recrystallization from acetone at -80°C . The crystal structure is notable for the existence of three crystallographically different, but otherwise essentially similar $[\text{Mo}(\text{CH}_3)_6]$ molecules. As in $[\text{W}(\text{CH}_3)_6]$ and $[\text{Re}(\text{CH}_3)_6]$, the intermolecular interactions can be considered as weak; the shortest Mo–Mo distances are 580 pm.^[9] We concluded from the fact that the three crystallographically different molecules have essentially the same molecular structure that the latter is not influenced by packing effects but rather represents the structure of the free molecule (Table 1). Crystallographically it may be of interest that molecules I and III can be interconverted by a pseudo-inversion center, not however, molecule II with itself. This led to the choice of a noncentrosymmetric space group. Of the 54 different hydrogen atom positions all except one were located in difference Fourier maps and refined. None of

Table 1. Structure of $[\text{Mo}(\text{CH}_3)_6]$ in the crystal, mean (angles are given only between C_{3v} -symmetry equivalent bonds) and calculated values.^[4]

	$[\text{Mo}(\text{CH}_3)_6]$ -I	$[\text{Mo}(\text{CH}_3)_6]$ -II	$[\text{Mo}(\text{CH}_3)_6]$ -III	calcd
Mo–C [pm]	211.2	210.1	211.5	213.6
	219.0	219.7	219.0	220.6
C–Mo–C $^\circ$	94.9	97.3	96.9	97.3
	75.7	75.4	74.5	74.7

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these hydrogen positions gave any indications of agostic interactions.

The C_{3v} distortion of the approximate trigonal-prismatic molecules is clearly visible in Figure 1, and the mean distances and angles agree well with those from the theoretical predictions (Table 1). Also as predicted, bond length differences and angles between differently bonded methyl groups are somewhat larger than in $[\text{W}(\text{CH}_3)_6]$. This difference between the structures of $[\text{Mo}(\text{CH}_3)_6]$ and $[\text{W}(\text{CH}_3)_6]$ can be attributed to the relativistic effect, which in the case of $[\text{W}(\text{CH}_3)_6]$ is particularly strongly pronounced.^[4]

The Raman spectrum of $[\text{Mo}(\text{CH}_3)_6]$ shows four well-separated CH valence vibrations. Under the assumption of local C_{3v} symmetry for each methyl group, two different kinds of methyl groups are indicated, if coupling between methyl groups is neglected. In the ^1H and ^{13}C NMR spectra only one line is found, which indicates nonrigidity of the molecule, resulting in equilibration of the methyl groups. According to calculations a regular trigonal-prismatic structure with six equivalent methyl groups is 39 kJ mol⁻¹ higher in energy.

The seven-coordinate anion $[\text{Mo}(\text{CH}_3)_7]^-$ was prepared by treatment of $[\text{Mo}(\text{CH}_3)_6]$ with excess LiCH_3 . $[\text{Li}(\text{Et}_2\text{O})]^+[\text{Mo}(\text{CH}_3)_7]^-$ is isostructural with $[\text{Li}(\text{Et}_2\text{O})]^+[\text{W}(\text{CH}_3)_7]^-$,^[12] and the anion has accordingly a capped octahedral structure (Figure 2). This geometry is thought to have the smallest interligand repulsion energy for coordination number 7, and should prevail if this principle is structurally determining. However, in the case of main group compounds the pentagonal bipyramid is always found.

Whereas ab initio and density functional theory (DFT) calculations predict the experimentally determined structures very well, a simple explanation for the apparently abnormal structures of $[\text{Mo}(\text{CH}_3)_6]$ and $[\text{W}(\text{CH}_3)_6]$ is lacking, especially for d^0 complexes with exclusively σ -binding ligands in the case of coordination number 6. By applying Pauling's valence bond theory Landis et al. have found that under the assumption of pure sd^n hybridization bond angles of 180° should not exist between the resulting hybrid orbitals. Especially in the case of sd^5 , angles between the hybrid orbitals of 63 and 117° are

favorable.^[7] Thus, four structures can be constructed. One of these has C_{3v} symmetry and is quite similar to the $[\text{Mo}(\text{CH}_3)_6]$ structure, except the larger methyl groups increase the angle of 63° to about 75° for steric reasons. Thus the octahedron on which so much complex chemistry is based is here the most unlikely structure principle. The avoidance of interligand angles of 180° seems to be a general principle. In the case of the coordination number 5 ($[\text{Mo}(\text{CH}_3)_5]$,^[13] $[\text{Ta}(\text{CH}_3)_5]$ ^[12b,c, 13]), the square pyramid is favored; it has likewise no 180° arrangement of ligands in contrast to the trigonal bipyramid $[\text{Sb}(\text{CH}_3)_5]$.^[12b,c] Also the capped octahedron with the coordination number 7 has no such arrangement of ligands, in contrast to the pentagonal bipyramid. Even if in some cases, as in $[\text{Mo}(\text{CH}_3)_7]^-$, the structure is the one with the smallest interligand repulsion, the latter model seems to play a secondary role with the compounds discussed here.

Experimental Section

All experiments were carried out under argon or in vacuum. Diethyl ether and *n*-pentane were dried with Na, acetone with K_2CO_3 , and were degassed in vacuum. $\text{Zn}(\text{CH}_3)_2$ (1M in *n*-heptane) purchased from Aldrich was separated from *n*-heptane by vacuum distillation.

$[\text{Mo}(\text{CH}_3)_6]$: MoF_6 (1.88 g, 8.96 mmol) was dissolved in Et_2O (30 mL). The bordeaux red solution was cooled to -130°C, and $\text{Zn}(\text{CH}_3)_2$ (1.34 g, 14.04 mmol) was added. The solution turned yellow, and colorless ZnF_2 precipitated. The mixture was warmed to -78°C and stirred for 12 h. Et_2O was pumped from the orange-colored solution, and the solid residue was extracted with a little acetone/*n*-pentane. The mixture was warmed to room temperature and sublimed into a liquid-nitrogen-cooled 8 mL glass ampule. Solvents were almost completely removed under vacuum, and the solid was dissolved in acetone. Orange-brown needles crystallized upon cooling from -55°C to -80°C from the dark red solution. These needles were stable up to 10°C, above which temperature the solid turned green; at room temperature sudden decomposition occurred under gas evolution and blackening. The yield was approximately 40%, losses were attributed to the sublimation procedure. Raman spectrum (solid, -70°C): $\tilde{\nu}$ = 3034 (1), 2996 (10), 2942 (12), 2856 (3), 1401 (8), 1205 (10), 1152 (20), 1129 (25), 999 (1), 810 (10), 737 (5), 667 (3), 631 (2), 583 (4), 521 (100), 496 (80), 439 (6), 413 (50), 353 (12), 301 (12), 258 (75), 232 (70), 140 (100) cm⁻¹; ^1H NMR ($[\text{D}_6]$ acetone, -40°C): δ = 1.99; ^{13}C NMR ($[\text{D}_6]$ acetone): δ = 68.07 (broad), $^1J_{\text{C,H}}$ = 126.9 Hz. Crystal structure analysis: A crystal (0.4 × 0.4 × 0.2 mm) was mounted under nitrogen with cooling on a Bruker SMART CCD 1000 M diffractometer; MoK_α irradiation, graphite monochromator, scan width ω of 0–3, 10 s per frame exposure time. A full sphere up to $2\theta = 66^\circ$ was measured with 1800 frames. Data were reduced to the intensities, an empirical absorption correction was achieved by approximation of symmetry-equivalent reflections (Sad abs). Solution and refinement of the structure were performed with the Shelx programs.^[14, 15] $a = 3123.67(8)$, $b = 628.75(1)$, $c = 1302.97(3)$ pm, $\beta = 92.623(2)^\circ$, $V = 2.55636(10)$ nm³, $Z = 12$, space group *Cc*, 14294 measured, 5450 independent reflections, 352 parameters, $R' = 0.0311$, $Rw^2 = 0.0814$.

$[\text{LiO}(\text{C}_2\text{H}_5)_2]^+[\text{Mo}(\text{CH}_3)_7]^-$: MoF_6 (1.09 g, 5.19 mmol) was dissolved in Et_2O (30 mL). The bordeaux red solution was cooled to -130°C and $\text{Zn}(\text{CH}_3)_2$ (1.04 g, 10.89 mmol) was added. The solution turned yellow, and colorless ZnF_2 precipitated. After the mixture had been stirred for 12 h at -78°C, ZnF_2 was filtered off. LiCH_3 (10 mL, 16 mmol; 1.6M

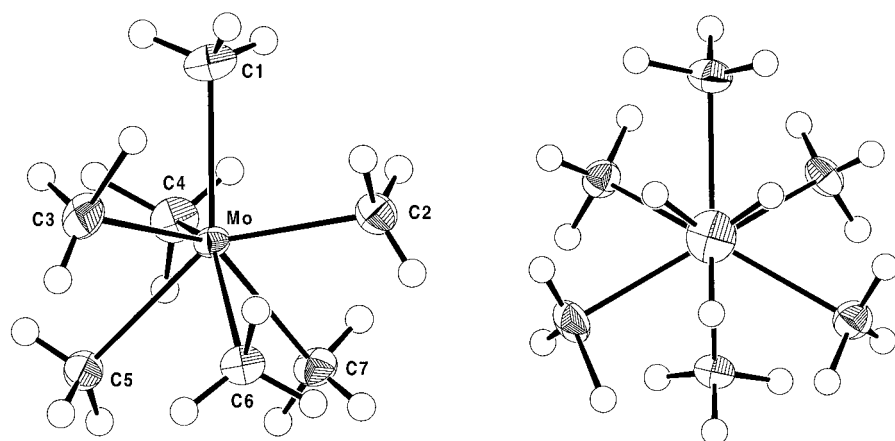


Figure 2. ORTEP representation of the $[\text{Mo}(\text{CH}_3)_7]^-$ ion in $[\text{Li}(\text{Et}_2\text{O})]^+[\text{Mo}(\text{CH}_3)_7]^-$, 50% probability ellipsoids, view perpendicular and along the threefold molecular axis. Distances [pm] and angles [°]: Mo–C1 220.8(3), Mo–C2 216.9(3), Mo–C3 216.8(2), Mo–C4 217.1(3), Mo–C5 229.9(3), Mo–C6 230.1(3), Mo–C7 229.9(2); C1–Mo–C2 81.48(13), C1–Mo–C3 81.70(14), C1–Mo–C4 81.68(14), C1–Mo–C5 132.68(13), C1–Mo–C6 132.28(13), C1–Mo–C7 131.83(13).

solution in Et₂O) was slowly added, the color of the solution turned light red. The reaction mixture was warmed to –15 °C and stirred for 1.5 h. At this temperature the Et₂O was pumped off and the residue was dissolved in a little *n*-pentane. With the help of a Teflon tube the solution was transferred into a 8-mL glass ampule. Upon cooling from –20 °C to –35 °C rubin red plates crystallized. Yield approximately 30%, losses were attributed to the filtration procedure and to the recrystallization. ¹H NMR (*n*-pentane, –20 °C): δ = 1.91; ¹³C NMR: δ = 60.20 (broad), ¹J_{C,H} = 123.4 Hz. Crystal structure analysis: A crystal (0.5 × 0.4 × 0.1 mm³) was mounted under nitrogen with cooling on the CCD diffractometer and measured as described above. Solution and refinement were performed with the Shelx programs.^[14,15] *a* = 694.6(3), *b* = 1278.50(14), *c* = 1733.6(4) pm, *V* = 1.5395(7) nm³, *Z* = 4, space group *Pbc*2₁, 17322 measured, 4603 independent reflections, 222 parameters, *R* = 0.0323, *wR*₂ = 0.0778.

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-135548 ([Mo(CH₃)₆]) and CCDC-135549 ([LiO(C₂H₅)₂]⁺[Mo(CH₃)₇][–]). 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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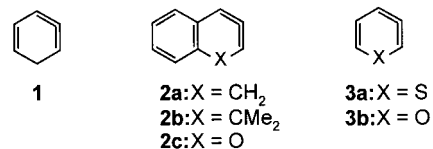
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Synthesis of an Isolable Diphosphaisobenzene and a Stable Cyclic Allene with Six Ring Atoms**

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Dedicated to Professor Manfred Meisel on the occasion of his 60th birthday

The synthesis of unusual, ring-strained isomers of benzene has been attracting increasing interest in the past few years. Besides cyclohexa-1,2,3-triene and cyclohexa-1-en-3-yne,^[1] these species include cyclohexa-1,2,4-triene (**1**), an isobenzene that has been the subject of several theoretical studies.^[2] In 1992, Christl et al. generated **1** for the first time using the Doering–Moore–Skattebøl method and confirmed its existence chemically by means of trapping reactions.^[3] Compound **1** can also be formed by thermolysis of hexa-1,3-dien-5-yne.^[4]

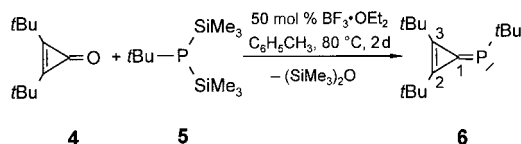


The benzo-condensed isobenzene **2a**,^[3] **2b**,^[5] and the oxygen analogue **2c**^[6] as well as the heteroatom-substituted isobenzene **3a**^[7] have also been generated and trapped. Furthermore, substituted cyclohexa-1,2,4-trienes of the types **1** and **3b** have been discussed as nondetectable intermediates in the [4+2] cycloadditions of enynes and acylacetylenes, respectively, with alkynes.^[8] We now report on the synthesis of the 1*H*-5δ²-diphosphinine **8a**, which is stable at room temperature, and the cyclic allene **10** that can be prepared from it (see Scheme 2).

The starting material for the reactions described here is the previously unknown phosphatriafulvene **6** prepared from **4** and **5** (Scheme 1).^[9] The structure of **6** was deduced from spectroscopic data as well as by comparison with the values reported for other known phosphatriafulvenes^[9] and is not discussed in detail here. When **6** is allowed to react with the kinetically stabilized phosphalkyne **7**^[10] at 80 °C the isobenzene **8a** is obtained. This product is characterized by an

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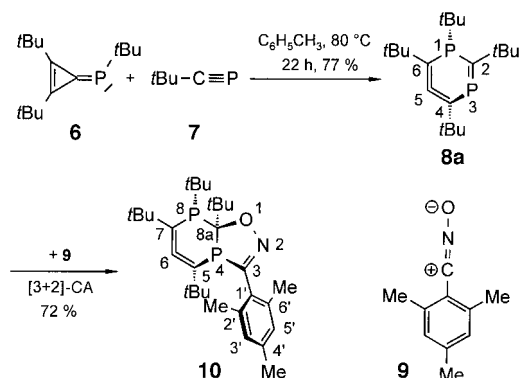
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Scheme 1. Synthesis of **6**.

Table 1. Relative energies of **8**, **11**, and **12** [kcal mol⁻¹].

R	8	11	12
H	49.39	0.00	51.97
Me	43.61	0.00	45.86
<i>t</i> Bu	0.00	4.19	17.87



Scheme 2. Synthesis of **8a** and its further reaction to give **10**. CA cycloaddition.

unexpected thermal stability and was obtained as a red oil in 77% yield by bulb-to-bulb distillation.

The constitution of **8a** can be derived readily from its NMR data. The ³¹P NMR spectrum contains two doublets at $\delta = 351.7$ ($J(\text{P,P}) = 24.5$ Hz; P3) and 52.3 ($J(\text{P,P}) = 24.5$ Hz; P1). The former is in the typical region for the signals of a P–C double bond, while the signal at higher field is split into a multiplet as a consequence of the direct adjacency of a *tert*-butyl group. The ¹³C NMR spectrum provides decisive diagnostic information: the signal at $\delta = 208.1$, which is split into a double doublet by two $J(\text{C,P})$ coupling constants, must be assigned to the carbon atom C2 of the P–C double bond. The two carbon atoms C4 and C6 give signals in the typical region for double bonds and are each in the immediate vicinity of a phosphorus atom. The position of the signal for C5 is typical for a central allene carbon atom.^[11] The prominent IR bands at $\tilde{\nu} = 1865$ and 1846 cm⁻¹ are also in accord with the structure deduced from the NMR spectral data. Two distinct allene bands in a similar region have been discussed for the short-lived cyclohexa-1,2-diene.^[12] As shown by the NMR spectra, the diphosphaisobenzene **8a** is formed highly selectively as a single diastereomer.

For unequivocal confirmation of its isobenzene structure, **8a** was converted to the crystalline adduct **10** by treatment with 2,4,6-trimethylbenzonitrile oxide (**9**); this reaction proceeds chemo-, regio-, and stereoselectively.^[13] Here again, the typical signal at $\delta = 207.1$ for C6 in the ¹³C NMR spectrum and the conspicuous allene bands at $\tilde{\nu} = 1865$ and 1830 cm⁻¹ in the IR spectrum are seen. A single-crystal X-ray structure analysis confirmed not only the constitution but also the

relative configuration of the 5,7,8,8a-tetra-*tert*-butyl-3-(2,4,6-trimethylphenyl)-8a*H*-6*δ*²-[1,3]diphosphinino[1,2-*d*][1,2,4]oxazaphosphole (**10**) and thus also those of **8a**.^[14] To the best of our knowledge, compound **10** is the first stable cyclohexa-1,2-diene with only two heteroatoms in the six-membered ring.^[15]

As expected, the allene unit is bent (155.8° ; Figure 1). The C5–C6 and C6–C7 bond lengths of 1.327 and 1.302 Å, respectively, are in the typical range for cumulenes. The endocyclic dihedral angle as defined by the P4–C5–C6 and the C6–C7–P8 planes of 40.7° deviates widely from the ideal

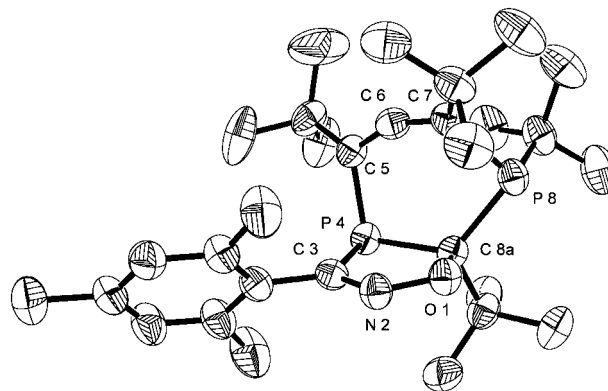
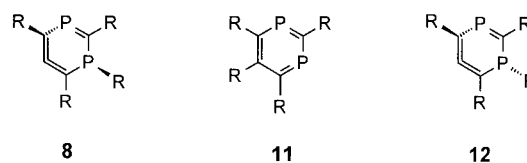


Figure 1. Structure of **10** in the crystal (thermal ellipsoids for 50% probability). Selected bond lengths [Å] and angles [$^\circ$]: P4–C5 1.829(3), C5–C6 1.327(3), C6–C7 1.302(4), C7–P8 1.837(3), P8–C8a 1.953(3), C8a–O1 1.489(3), O1–N2 1.403(3), N2–C3 1.281(3), C3–P4 1.826(2), P4–C8a 1.901(3); P4–C5–C6 109.6(2), C5–C6–C7 155.8(3), C6–C7–P8 110.8(2), C7–P8–C8a 96.37(12), P8–C8a–P4 121.71(14), C8a–P4–C5 104.48(12), P4–C8a–O1 104.73(15), C8a–O1–N2 116.1(2), O1–N2–C3 114.0(2), N2–C3–P4 116.8(2), C3–P4–C8a 87.88(11).

value (90°) and, together with the angle of the allene unit (155.8°), is considerably smaller than the corresponding angles in the first structurally characterized cyclohexa-1,2-diene (64.6° and 166.4° , respectively).^[15] The P8–C8a bond length of 1.953 Å is markedly stretched.^[16]

Calculations on the relative energies^[17] of the isomeric structures **8**, **11**, and **12** reveal that, for small substituents (R = H, Me), the diphosphabenzene **11** is, as expected, the most stable isomer (Table 1). When the *tert*-butyl groups are



considered in the calculations it is found that the isobenzene **8** (**8a**) is more stable than the diphosphabenzene **11** by 4.19 kcal mol⁻¹. The latter is not planar on account of the enormous steric demands of the substituents; this leads to a loss of aromaticity. On the other hand, for **8a** the pyramidalization at P1 as well as the twisting of the six-membered ring through the 1,2-diene unit result in the best possible spatial arrangement of the large substituents. According to the calculations **12** is less stable than the diastereomer **8** and thus also cannot be detected experimentally.

Experimental Section

All reactions were performed under an argon atmosphere in anhydrous solvents.

6: In a pressure Schlenk tube boron trifluoride etherate complex (0.63 mL, 0.71 g, 5 mmol) was added to **4** (3.17 g, 19 mmol)^[18] and **5** (5.5 mL, 4.69 g, 20 mmol)^[19] in toluene (15 mL) and the mixture was stirred at 80 °C for 24 h. After repeated addition of the same amount of boron trifluoride etherate, stirring at 80 °C was continued for further 20 h. The reaction mixture was then allowed to cool and volatile materials were removed at 25 °C/10^{−3} mbar. The resultant yellow solid was taken up in *n*-pentane and the solution filtered through celite. Yield: 3.57 g (79%) pale yellow platelets (from *n*-pentane at −28 °C). M.p. 74 °C. Storage at −28 °C; ³¹P NMR (C₆D₆): δ = 46.5 (dec, ³J(P,H) = 10.5 Hz); ¹³C{¹H} NMR (CDCl₃): δ = 152.2 (d, ²J(C,P) = 31.4 Hz; C2), 154.6 (d, ²J(C,P) = 11.0 Hz; C3), 158.5 (d, ¹J(C,P) = 89.0 Hz; C1); MS (EI, 70 eV): *m/z* (%): 238 (51) [*M*]⁺.

8a: In a pressure Schlenk tube a solution of **6** (328 mg, 0.97 mmol) in toluene (5 mL) was treated with **7** (144 μL, (1 mmol))^[20] and the mixture heated at 80 °C for 22 h. After the mixture was cooled to room temperature the volatile materials were removed at 25 °C/10^{−3} mbar and the crude product purified by bulb-to-bulb distillation (80 °C/10^{−3} mbar). Yield: 254 mg (77%) red oil. ³¹P{¹H} NMR (CDCl₃): δ = 52.3 (d, ²J(P,P) = 24.5 Hz; P1), 351.7 (d, ²J(P,P) = 24.5 Hz; P3); ¹³C{¹H} NMR (CDCl₃): δ = 105.4 (dd, ¹J(C,P) = 32.6 Hz, ³J(C,P) = 3.0 Hz; C4/6), 113.3 (dd, ¹J(C,P) = 59.3 Hz, ³J(C,P) = 2.5 Hz; C4/6), 202.4 (pseudo-t, ²J(C,P) = ²J(C,P) = 3.8 Hz; C5), 208.1 (dd, ¹J(C,P) = 69.5 Hz, ¹J(C,P) = 60.2 Hz; C2); MS (EI, 70 eV): *m/z* (%): 338 (19) [*M*]⁺.

10: Compound **9** (42 mg, 0.26 mmol) in toluene (2 mL) was added by pipette at −78 °C to a solution of **8a** (88 mg, 0.26 mmol) in toluene (2 mL). The mixture was allowed to thaw and stirred for 14 h at room temperature. After removal of volatile materials at 25 °C/10^{−3} mbar, the residue was crystallized from *n*-pentane at −78 °C. Yield: 94 mg (72%) yellowish crystals. M.p. 95 °C. ³¹P{¹H} NMR (CDCl₃): δ = 91.4 (d, ²J(P,P) = 13.5 Hz; P4), 122.5 (d, ²J(P,P) = 13.5 Hz; P8); ¹³C{¹H} NMR (CDCl₃): δ = 107.2 (dd, ¹J(C,P) = 41.8 Hz, ³J(C,P) = 2.4 Hz; C5/7), 110.3 (dd, ¹J(C,P) = 40.2 Hz, ³J(C,P) = 2.4 Hz; C5/7), 127.8 (dd, ¹J(C,P) = 53.8 Hz, ¹J(C,P) = 52.2 Hz; C8a), 159.2 (d, ¹J(C,P) = 40.2 Hz; C3), 207.1 (pseudo-t, ²J(C,P) = ²J(C,P) = 6.6 Hz; C6); MS (CI, isobutene): *m/z*: 500 [*M*+H]⁺.

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Self-Assembled Hydrogen-Bonded Dimeric Capsules with High Kinetic Stability**

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Calix[4]arenes substituted at their wide rim by four urea functions (general formula **3**) exist as hydrogen-bonded dimers^[1, 2] in apolar solvents in the presence of a suitable guest, which is included in the molecular cavity thus formed (Figure 1). Although these capsules^[3] are kinetically stable on

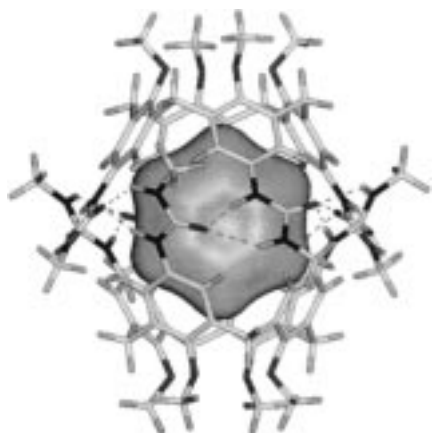


Figure 1. Tetra-urea dimer **3/3** with included benzene.

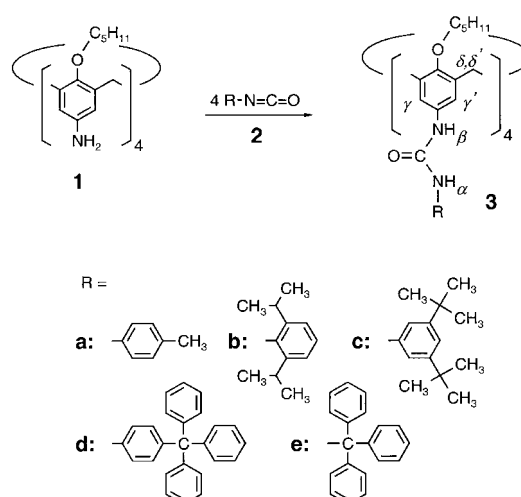
the NMR time scale, their dissociation/recombination occurs within seconds. Rate constants of $k = 0.26 \text{ s}^{-1}$ for the dissociation/recombination process and $k = 0.47 \text{ s}^{-1}$ for the guest (benzene) exchange were determined in benzene by EXSY spectroscopy^[4] for the dimer of a tetra-urea similar to **3a**, but less symmetric due to alternating methyl and pentyl ether groups. We were interested whether the (kinetic) stability of such capsules can be increased by structural modifications. This could be achieved, for instance, by additional attractive forces between the two calixarenes combined in the dimer, or by increasing the energy barrier for the dissociation process by steric hindrance (repulsive forces). We therefore synthesized the sterically crowded tetra-urea derivatives **3b–e** (Scheme 1) and we report herein their ability to form hydrogen-bonded dimers including the first detailed measurements of the rate of their guest exchange.^[5, 6]

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 1. Synthesis of the tetra-urea calixarene **3**.

Compounds **3** were synthesized by reaction of the corresponding isocyanate **2** with the tetraaminocalix[4]arene **1** (Scheme 1). The isocyanates used were commercially available (**2a**, **2b**), or prepared from trityl chloride and potassium cyanate (**2e**),^[7] or from the respective aniline and triphosgene (**2c**, **2d**)^[8] and used in situ. The structure of the tetra-ureas **3** follows unambiguously from their ¹H and ¹³C NMR spectra in [D₆]DMSO where they exist in the monomeric form. It was further confirmed by elemental analysis and by mass spectra.

Homo- and heterodimerization of tetra-ureas **3a–e** was studied by ¹H NMR spectroscopy in [D₆]benzene, a solvent known also to be an excellent guest for the dimer (Table 1). It became apparent that the steric strain produced by R makes

Table 1. Dimerization of tetra-ureas **3a–e**.^[a]

Compound	3a	3b	3c	3d	3e
3a	+	0 ^[b]	50 ^[c]	39 ^[c]	78 ^[b]
3b	–	–	0 ^[b]	0 ^[b]	0
3c	+	–	+	31 ^[c]	0 ^[b]
3d	+	–	+	+	95 ^[b]
3e	+	–	–	+	–

[a] For each pair the formation of dimers is indicated by +. Additionally, the amount of heterodimers present in a 1:1 mixture in [D₆]benzene at a total concentration of $c(\mathbf{3}) = 2.5 \text{ mM}$ is reported in %. [b] Plus one homodimer and one unpaired tetra-urea. [c] Plus two homodimers.

the formation of dimers with all partners impossible for **3b**, while **3e** forms no heterodimers with **3c** and no homodimers. Thus, for example, the ¹H NMR spectrum of **3e** (Figure 2a) shows only very broad signals, while a typical homodimer such as **3a/3a** or **3d/3d** (Figure 2b) shows well-defined, sharp signals among which especially the low-field-shifted NH signal at $\delta = 9.9$ is characteristic for the hydrogen-bonded R-NH groups in the dimer. Remarkably a 1:1 mixture of **3d** and **3e** shows (nearly) exclusively the presence of the heterodimers **3d/3e** (Figure 2c), easily identified by two pairs of doublets for the Ar-CH₂-Ar protons.^[9] Evidently this situation, in which *all* urea groups are “saturated” by intermolecular hydrogen bonds is favored over a situation in which the molecules **3e** are unpaired, while **3d** forms (possibly more perfect) dimers.

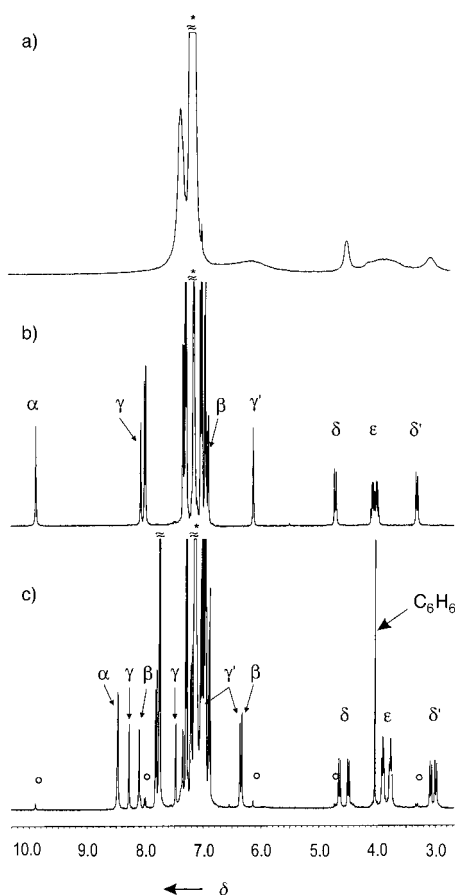
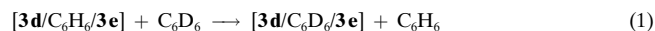


Figure 2. ^1H NMR spectra (400 MHz, $[\text{D}_6]\text{benzene}$, $c(\mathbf{3}) = 2.5 \text{ mM}$, 25°C): a) irregular associate of $\mathbf{3e}$; b) homodimer $\mathbf{3d/3d}$; c) heterodimer $\mathbf{3d/3e}$, prepared in C_6H_6 , about 10 min after dissolution; signals for included benzene and a small amount of $\mathbf{3d/3d}$ ($\circ$) are labeled. Protons of the calixarene skeleton and the amide groups are marked as follows: α/β (NH), γ (ArH), δ (ArCH₂Ar), ϵ (OCH₂); see also Scheme 1.

If a 1:1 mixture of $\mathbf{3d}$ and $\mathbf{3e}$ is dissolved in benzene (ca. 12 h at 35°C), evaporated, and the resulting white powder is dissolved in $[\text{D}_6]\text{benzene}$, the spectrum shown in Figure 2c results, in which the peak at $\delta = 4.03$ belongs to the included benzene. This peak^[10] slowly (!) disappears with time, while the rest of the spectrum remains unchanged. This must be interpreted by an exchange of the nondeuterated guest benzene against $[\text{D}_6]\text{benzene}$ present as solvent in large excess, a process which may be described by Equation (1). In principle the analogous behavior was found for the heterodimers $\mathbf{3a/3e}$.



As Figure 3a shows for the example $[\mathbf{3d}/\text{C}_6\text{H}_6/\mathbf{3e}]$, this disappearance of the guest signal follows first-order kinetics up to conversions of 90%. To our knowledge this is the first clear kinetic analysis of the guest-exchange process in such hydrogen-bonded capsules.^[6] And this guest exchange which most probably is identical with the rate of a dissociation/recombination process^[4] leads to half-life times of $\tau = 130 \text{ min}$ for $[\mathbf{3a}/\text{C}_6\text{H}_6/\mathbf{3e}]$ and $\tau = 60 \text{ h}$ for $[\mathbf{3d}/\text{C}_6\text{H}_6/\mathbf{3e}]$.

Measuring the reaction rate at different temperatures allows one to derive the activation parameters. They are

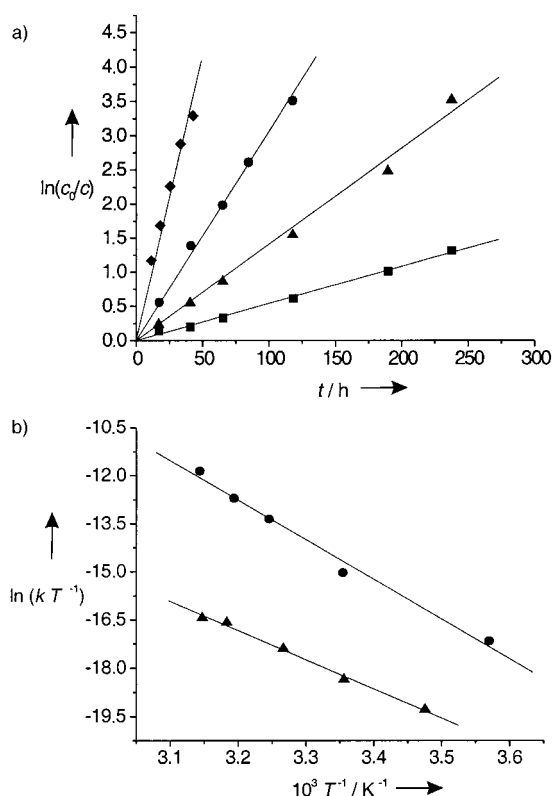


Figure 3. a) First-order plots for the disappearance of the guest signal of $[\mathbf{3d}/\text{C}_6\text{H}_6/\mathbf{3e}]$ in C_6D_6 at 15°C ($\blacksquare$), 25°C ($\blacktriangle$), 33°C ($\bullet$), and 45°C ($\blacklozenge$); b) Eyring plots for $[\mathbf{3a}/\text{C}_6\text{H}_6/\mathbf{3e}]$ ($\bullet$) and $[\mathbf{3d}/\text{C}_6\text{H}_6/\mathbf{3e}]$ ($\blacktriangle$). The points are the average of at least three kinetic runs.

collected in Table 2; Eyring plots are shown in Figure 3b. A higher value for the activation enthalpy $\Delta H^\ddagger$ in $\mathbf{3a/3e}$ is overcompensated in $\mathbf{3d/3e}$ by the lower activation entropy $\Delta S^\ddagger$ which evidently is mainly responsible for the lower

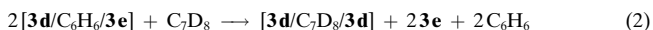
Table 2. Activation parameters for the guest exchange for the heterodimers $\mathbf{3a/3e}$ and $\mathbf{3d/3e}$ in $[\text{D}_6]\text{benzene}$.

Complex	$[\mathbf{3a}/\text{C}_6\text{H}_6/\mathbf{3e}]$	$[\mathbf{3d}/\text{C}_6\text{H}_6/\mathbf{3e}]$
Temp. range $[\text{C}]$	7–45	15–45
R	0.994	0.997
$\Delta H^\ddagger$ $[\text{kJ mol}^{-1}]$	103 (± 6)	75 (± 3)
$\Delta S^\ddagger$ $[\text{J K}^{-1} \text{mol}^{-1}]$	26 (± 21)	–96 (± 10)
$\Delta G^\ddagger$ $[\text{kJ mol}^{-1}]$ ^[a]	95 (± 0.4)	104 (± 0.6)

[a] at 25°C .

exchange rate observed for the latter capsules. This can be understood by less perfect hydrogen bonds and a lower conformational freedom of the residues R in the sterically more strained dimer $\mathbf{3d/3e}$.

If $[\mathbf{3d}/\text{C}_6\text{H}_6/\mathbf{3e}]$ is dissolved in $[\text{D}_8]\text{toluene}$ or $[\text{D}_{10}]\text{p-xylene}$ the signal for the included benzene disappears with a similar rate, leading to $\Delta G^\ddagger = 107$ and $108 \pm 0.5 \text{ kJ mol}^{-1}$, respectively. However, in contrast to $[\text{D}_6]\text{benzene}$ the whole ^1H NMR spectrum changes with the same rate to show finally the spectrum of the homodimer $\mathbf{3d/3d}$, most probably with the solvent included (Figure 4a–c). Evidently the overall process in this case must be formulated by Equation (2).



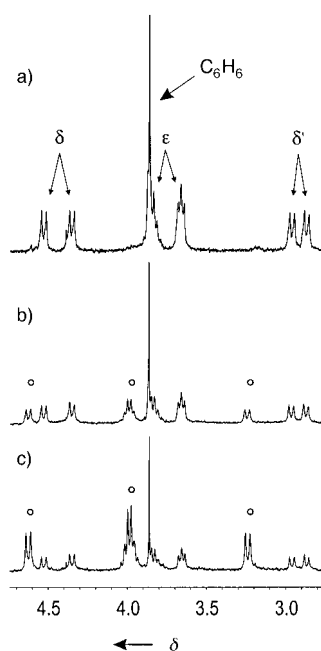


Figure 4. NMR-spectral changes observed for $[3d/C_6H_6/3e]$ in $[D_{10}]p$ -xylene at 25 °C at different times after dissolution; a) 10 min, b) 90 h, and c) 185 h. Not only the guest signal disappears, but also all signals for the heterodimer, while the signals of the homodimer $3d/3d$ (○) appear. For the assignment of protons see Figure 2.

at will by the addition of a hydrogen bond breaking agent.

Clearly the two molecules of dimers like $3d/3e$ are not held together exclusively by a mechanical entanglement of the residues R attached to the urea functions (Figure 5). Hydrogen bonding (and probably guest inclusion^[14]) still play an important role, since the dimer is rapidly destroyed by the addition of DMSO. A comparison of the half-life times for $3a/3a$ (ca. 1 s),^[4] $3a/3e$ (130 min), and $3d/3e$ (60 h) shows, however, that the steric crowding by the residues R plays a very decisive role for the kinetic stability^[15] of these dimers in benzene. This increase by more than five orders of magnitude can hardly be explained in a different way. It should be possible to increase this steric strain and to obtain tetra-urea derivatives which dimerize under drastic conditions (e.g. high temperature, high pressure) to form dimers stable under standard conditions. The chemical modification of “pre-formed” dimers by the subsequent introduction of bulky groups at the residues R would be an alternative strategy.^[16]

Experimental Section

Kinetic studies: Samples for kinetic measurements were prepared by stirring a tetra-urea solution in dichloromethane and methanol (5–10%) with basic aluminum oxide (20-fold excess) for 1.5 h. After filtration and evaporation under reduced pressure, the residue was dried in vacuum for 6 h at 100 °C and finally kept in a desiccator over phosphorus pentoxide and potassium hydroxide. All solvents for kinetic measurements were stored over 4 Å molecular sieves. The kinetic runs were performed at 2–2.5 mM concentration of heterodimers with two pieces of molecular sieves present

This is entirely in agreement with the fact that a mixture of $3d$ and $3e$ does not form heterodimers in toluene or p -xylene.^[11] And this again can be understood by “assuming” that a less favorable guest (toluene/ p -xylene vs. benzene) cannot be included in a sterically more strained capsule like $3d/3e$.^[12] Further measurements extending probably to further dimers will be necessary to establish a complete picture.

Even more remarkable is the behavior of $[3d/C_6H_6/3e]$ in $[D_{12}]$ cyclohexane. After 18 h at 40 °C the signal at $\delta = 4.03$ still corresponds to *one* molecule of included C_6H_6 per heterodimer $3d/3e$, which shows that these capsules are *kinetically stable* under these conditions.^[13] This means that in principle a suitable guest can be “permanently” included, and liberated

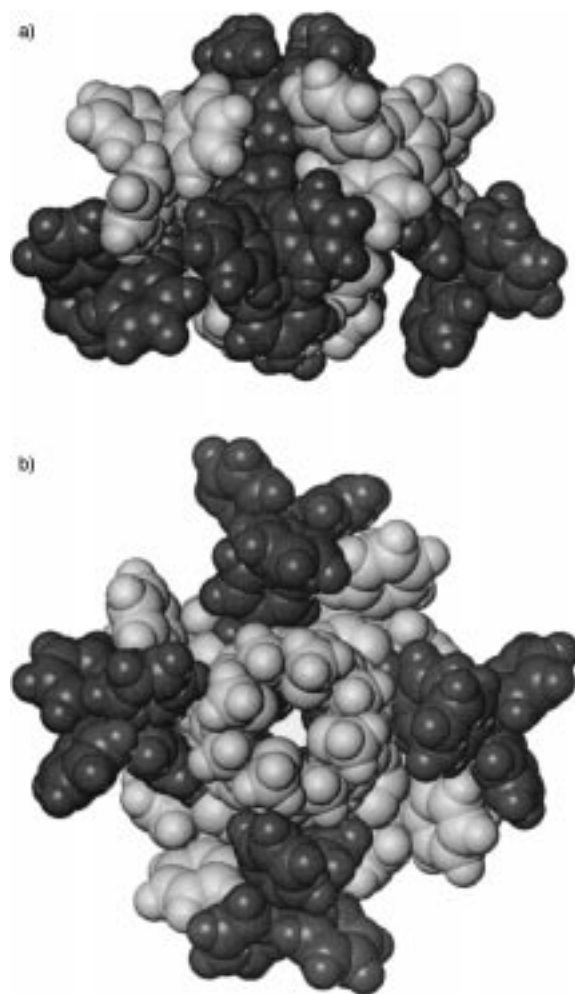


Figure 5. Space-filling representation of the heterodimer $3d$ (dark)/ $3e$ (light) showing the mechanical entanglement of residues R. Methyl ether residues were used for simplicity. a) Side view, b) top view.

directly in the NMR tube. In a typical experiment $3e$ (14.4 mg, 7.5 μ mol) and $3d$ (16.7 mg, 7.5 μ mol) were stirred in benzene (5 mL) (p.a. grade) with molecular sieves for 12 h at 35 °C. A 1 mL portion of the solution was evaporated under reduced pressure, the residual heterodimer was dried in vacuum and then dissolved in $[D_6]$ benzene (0.6 mL). From this solution, kept at constant temperature in a thermostatted bath or in the NMR spectrometer, spectra were recorded in suitable intervals to have 5–10 points over an 80% conversion range.

$[3d/C_6H_6/3e]$: ^1H NMR (400 MHz, $[D_6]$ benzene, 295 K): $\delta = 8.470$ (s, 4H; NH), 8.467 (s, 4H; NH), 8.272 and 6.948 (dd, $^4J(H,H) = 2.4$ Hz, 8H; CH), 8.098 (s, 4H; NH), 7.806 and 7.203 (dd, $^3J(H,H) = 8.8$ Hz, 8H; CH), 7.747 (d, $^3J(H,H) = 8.2$ Hz, 24H; CH), 7.464 and 6.357 (dd, $^4J(H,H) = 2.3$ Hz, 8H; CH), 7.287 (d, $^3J(H,H) = 7.6$ Hz, 24H; CH), 7.024 (t, $^3J(H,H) = 7.6$ Hz, 24H; CH), 6.970 (d, $^3J(H,H) = 7.6$ Hz, 24H; CH), 6.885 (t, $^3J(H,H) = 7.0$ Hz, 12H; CH), 6.324 (s, 4H; NH), 4.636 and 3.070 (dd, $^2J(H,H) = 11.7$ Hz, 8H; Ar-CH₂-Ar), 4.483 and 2.983 (dd, $^2J(H,H) = 11.4$ Hz, 8H; Ar-CH₂-Ar), 4.030 (s, 6H; C_6H_6), 3.891 (t, $^3J(H,H) = 7.6$ Hz, 8H; OCH₂), 3.759 (t, $^3J(H,H) = 7.0$ Hz, 8H; OCH₂), 2.20–2.10 (m, 16H; CH₂), 1.50–1.40 (m, 16H; CH₂), 1.35–1.20 (m, 16H; CH₂), 1.012 (t, $^3J(H,H) = 7.0$ Hz, 12H; CH₃), 0.984 (t, $^3J(H,H) = 7.0$ Hz, 12H; CH₃).

See the Supporting Information for the syntheses and spectroscopic data of $3b-3e$.

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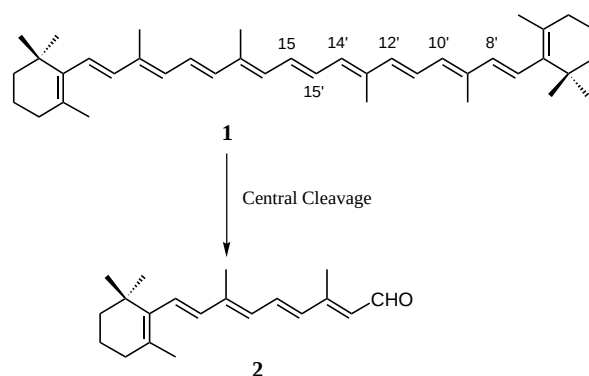
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- [13] If in a control experiment [**3a**/C₆H₆/**3a**] is treated with C₆D₁₂ or C₆H₁₂ under the same conditions, the signal of included C₆H₆ (at δ = 3.88 in C₆D₁₂) disappears completely, being replaced by a signal at δ = –1.44 for included C₆H₁₂ in the latter case.
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A Supramolecular Enzyme Mimic That Catalyzes the 15,15' Double Bond Scission of β,β-Carotene**

Richard R. French, Philipp Holzer, Michele G. Leuenberger, and Wolf-D. Woggon*

Dedicated to Professor Albert Eschenmoser on the occasion of his 75th birthday

The enzymes (carotene dioxygenases, CDOs) that cleave β,β-carotene **1** to provide retinal **2** as a precursor for retinol (vitamin A) are of significance to animal and human nutrition.^[1] To date two modes of cleavage of **1** have been proposed: 1) the more recently discovered excentric cleavage which yields apocarotenals, which can be degraded to **2** by β-oxidation, and 2) the central cleavage of **1** which gives retinal **2** directly (Scheme 1).^[2, 3] The CDO enzymes responsible for



Scheme 1.

catalyzing these reactions have been neither purified nor are their respective co-factors known. Results concerning central cleavage suggest that the enzyme involved places its active site's metal complex directly above the C(15)=C(15') bond.^[4, 5] The fact that this CDO controls the regiospecific cleavage of one C=C bond out of a possible six within the substrate is an intriguing and challenging one.

To mimic such a regiospecific system the following strategy was employed. a) The synthesis of a receptor for **1** for which the binding constant K_a for **1** is orders of magnitude greater than that for retinal **2** was necessary in order to prevent product inhibition. b) The introduction of a reactive metal center which is capable of cleaving *E*-configured, conjugated double bonds to aldehydes. c) The use of a co-

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oxidant which is inert towards **1** in the absence of a catalytic metal center.

We have previously reported on a cyclodextrin-based synthetic receptor for **1** ($K_a = 2.4 \times 10^6 \text{ M}^{-1}$) in which two β -cyclodextrin units are linked through a free-base porphyrin.^[6] As it was anticipated that the binding of **1** to the receptor would be enhanced by an increase in planarity of the porphyrin, as would be the case in the catalytic system, we have synthesized the corresponding porphyrinatozinc(II) complex **3** (Figure 1 a). The binding constant K_a for the binding of

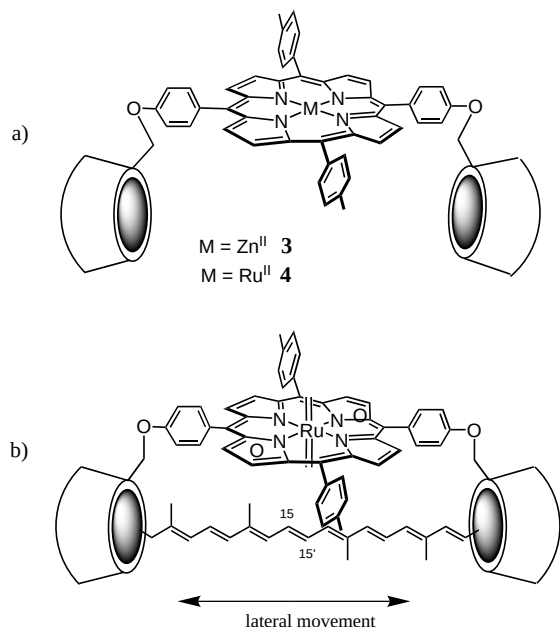
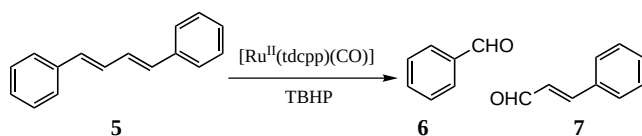


Figure 1. a) Structures of the receptors **3** and **4**. b) Schematic representation of the inclusion complex between **1** and **4**. The double-headed arrow denotes the possible lateral movement of **1** within the binding pocket.

1 to **3** was determined to be $K_a = 8.3 \times 10^6 \text{ M}^{-1}$ by using fluorescence spectroscopy.^[6] This satisfied the first of our strategic criteria for mimicking the biological system as the binding constant for retinal **2** to β -cyclodextrin has been reported to be $3.6 \times 10^3 \text{ M}^{-1}$.^[7]

With regard to the choice of a metalloporphyrin capable of cleaving double bonds, there was only one precedent in the literature: reaction of α -methylstyrene to give acetophenone in the presence of $[\text{Ru}(\text{tdfpp})]$ (tdfpp = tetrakis(2,6-difluorophenyl)porphyrin) and *tert*-butyl hydroperoxide (TBHP).^[8] We have systematically studied the reactivity of *open-face* as well as *face-protected* ruthenium porphyrins towards substrates containing conjugated *E*-configured double bonds in the presence of TBHP. A representative example is the cleavage of *trans,trans*-1,4-diphenyl-1,3-butadiene (**5**) by $\text{Ru}[\text{tdcpp}]$ (tdcpp = tetrakis(2,6-dichlorophenyl)porphyrin)) which gives benzaldehyde (**6**) and cinnamylaldehyde (**7**) (Scheme 2).^[9] Importantly, the first step in the cleavage

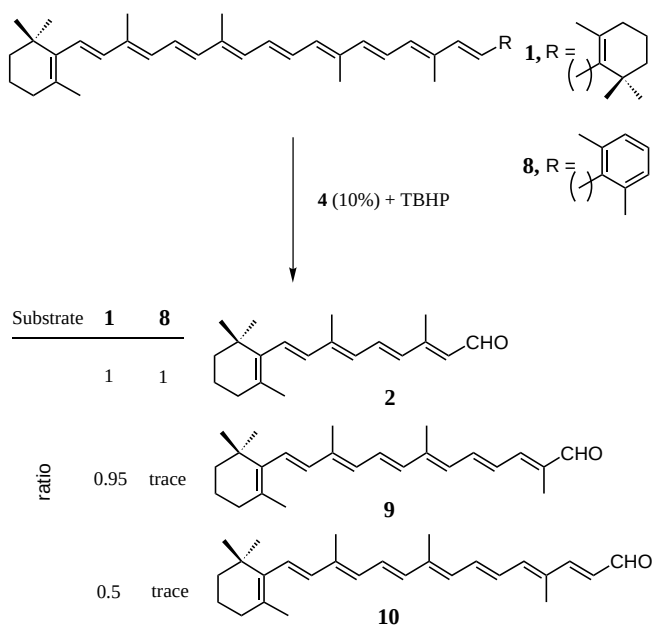


Scheme 2.

of double bonds is epoxide formation, which is followed by TBHP/ruthenium porphyrin mediated fragmentation to yield the products **6** and **7**. The clean reaction of various oxo-Ru porphyrins with the *E*-configured double bonds of **5** and **1** (see below) is novel and is in contrast to the reactivity of oxo-iron porphyrins^[10] and oxo-manganese salene complexes^[11] which exhibit a clear preference for *Z* double bonds. For the latter systems it has been suggested that the olefin approaches the metal oxo double bond in a “side-on” fashion. This interaction is impossible between **5** and $\text{Ru}[\text{tdcpp}](\text{O})_2$ or between **1** and the dioxo complex of **4**. Since we also observed cleavage of *Z*-configured, conjugated olefins by ruthenium porphyrins exhibiting varying degrees of *face-protection*, we conclude that the $\text{Ru}=\text{O}$ group attacks both *E* and *Z* double bonds “head-on”.^[9] Thus, there is no need to invoke different mechanisms for epoxide formation depending on the configuration of the olefin.^[12] Finally, we have also tested the stability of β,β -carotene towards TBHP, and established that no derivatization or degradation took place within 24 h at room temperature. A further control experiment with $[\text{Ru}(\text{tpp})]/\text{TBHP}$ (tpp = tetraphenylporphyrin) and β,β -carotene in dichloromethane gave wholesale degradation of **1**, the complex mixture of products being impossible to characterize.

With the above prerequisites satisfied, the stage was set to employ the supramolecular system **4** (Figure 1 a) to investigate the catalytic cleavage of β,β -carotene **1**.

Dimers **3** and **4** were obtained by the reaction of commercially available 6^A-O-(*p*-tosyl)- β -cyclodextrin^[13] with the corresponding metal porphyrin in the presence of cesium carbonate (DMF, three days, HPLC control),^[14] and the desired products were purified by preparative HPLC. For the catalytic cleavage of β,β -carotene **1**, a biphasic system was established in which **1** is extracted from a 9:1 mixture of hexane and chloroform into a water phase containing the dimer **4** (10 Mol-%) and TBHP (Scheme 3). The reaction products,



Scheme 3. Product ratios for oxidations of **1** and **8** with the catalyst **4**.

released from the receptor, are then extracted into the organic phase, aliquots of which were subjected to HPLC conditions developed for the analysis of carotene dioxygenase enzyme studies.^[15] The reaction products were identified by retention time (co-injection with authentic samples) and by their UV spectra; external calibration curves were used for the quantification. The ratio of reaction products is given in Scheme 3.

It is evident that **1** is not only cleaved at the central double bond but also at C(12')=C(11') to give 12'-apocarotenal **9** and at C(10')=C(9') to give 10'-apocarotenal **10**. The combined yield of aldehydes **2**, **9**, and **10** was 30 %, which compares well with the efficiency of β,β -carotene 15,15' dioxygenase which gives retinal **2** in 20–25 %.^[4] Most interestingly, the double bond in closest proximity to the central one in **1**, C(14')=C(13'), remains untouched. We postulated that this phenomenon is related to interactions between the end-groups of **1** and the cyclodextrin moieties, such that a lateral movement of **1** within the binding pocket exposes only three double bonds to the reactive Ru=O group (Figure 1b). If this hypothesis is true, one would expect a carotenoid with one modified end-group to demonstrate a different selectivity in double-bond cleavage. Accordingly, we investigated the oxidation of synthetic carotenoid **8**,^[16] a substrate of the native enzyme,^[17] under identical conditions. The selectivity for C(15)=C(15') cleavage is almost exclusive when one of the cyclohexene end-groups of β,β -carotene **1** is replaced by an *ortho*-dimethylphenyl group, supporting the relationship between substrate mobility and selectivity. This suggests that stronger hydrophobic interactions between the aromatic end-group of **8** and the β -cyclodextrin cavity are responsible for stabilizing the 1:1 inclusion complex with the central double bond under the reactive ruthenium center.

We have demonstrated the selective cleavage of carotenoids to provide retinal **2** with a supramolecular enzyme mimic which shows an unusual reactivity towards olefins in the presence of TBHP. Work is currently underway to mimic the reactivity and selectivity of the enzymes responsible for excentric cleavage of β,β -carotene **1**.^[18]

Experimental Section

Physical data for **4**: λ_{max} = 414 (100 %), 534 (10 %) 570 (4 %); ¹H NMR (600 MHz, 25 °C, [D₆]DMSO): δ = 8.61 (d, 4H, H-2,8,12,18, J = 4.5 Hz), 8.56 (d, 4H, H-3,7,13,17, J = 4.5 Hz), 8.06 (m, 4H, H-2'',6''), 7.94 (m, 4H, H-3'',5''), 7.58 (m, 4H, H-2',6'), 7.33 (m, 4H, H-3',5'), 5.9–5.6 (br. m, 28H, 2OH), 5.0–4.8 (m, 14H, anomeric H), 4.7–4.4 (m , 12H, 1OH), 3.8–3.25 (m, 84H, β -CD (H-2,3,4,5,6,6')), 2.65 (s, 6H, ArCH₃); MALDI-TOF-MS: m/z : 3007 [M^+], 3024 [M +H₂O]; HPLC (LiChrospher 100 Rp-18 (5 μ m), 250-4) R_t = 9.43 min (20–60 % acetonitrile in 20 min, flow 1.5 mL min⁻¹).

General procedure for cleavage reactions: A 25-mL round-bottomed flask which had been purged with argon and fitted with an egg-shaped magnetic stir bar was charged with a solution of dimer **4** (2.3 mg, 10 Mol-%) in H₂O (1 mL). TBHP (30 μ L of a 70 % solution in water, 30 equiv with respect to **1**) was added. β,β -Carotene **1** (4 mg) was dissolved in hexane/chloroform (9/1; 10 mL) and added to the reaction flask to produce a biphasic system. The reaction system was closed and stirred vigorously to ensure good mixing of the two phases. At different times during the reaction, stirring was stopped to allow phase separation. Aliquots (20 μ L) of the organic phase were taken and subjected to HPLC analysis (LiChrospher 100 Rp-18 5 μ m, length $\times$ ID = 125 mm $\times$ 4.6 mm, 25 °C, 1 mL min⁻¹, gradient: acetonitrile:1 % NH₄OAc_(aq) (1:1) (100 %) $\rightarrow$ acetonitrile:*i*PrOH (1:1) (100 %) in

10 min, then acetonitrile:*i*PrOH (1:1) (100 %) for 5 min, then acetonitrile:*i*PrOH (1:1) (100 %) $\rightarrow$ acetonitrile:1 % NH₄OAc_(aq) (1:1) (100 %) in 2 min). A diode array detector was used for the detection. R_t = 10.39 (**2**), R_t = 12.05 (**9**), R_t = 12.20 min (**10**). In all reactions, carotenoids **1** (R_t = 14.0 min) and **8** (R_t = 15.3 min) were completely consumed after 24 h.

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The Spatial Demand of Dendrimers: Deslipping of Rotaxanes**

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Dendrimers are generally not rigid molecules because of the flexibility of their building blocks,^[1] and this makes it difficult to compare their size with that of voluminous, but rather rigid “conventional” molecules. Recently we described the effect of slight changes in the size of wheels and stoppers

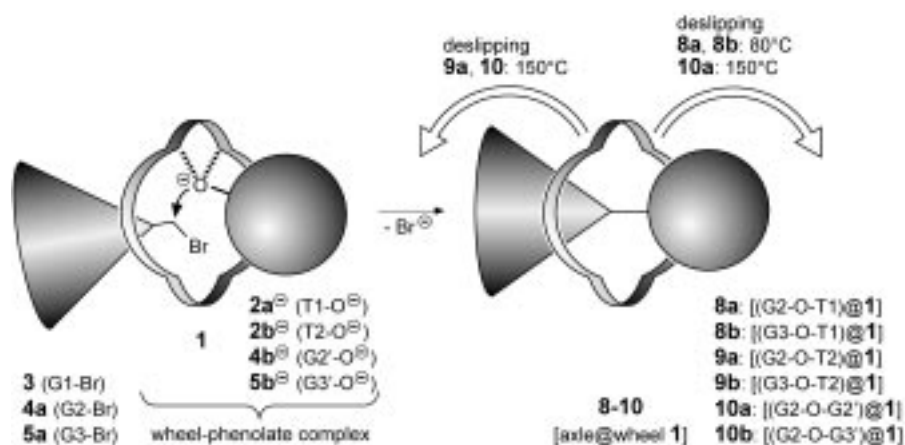
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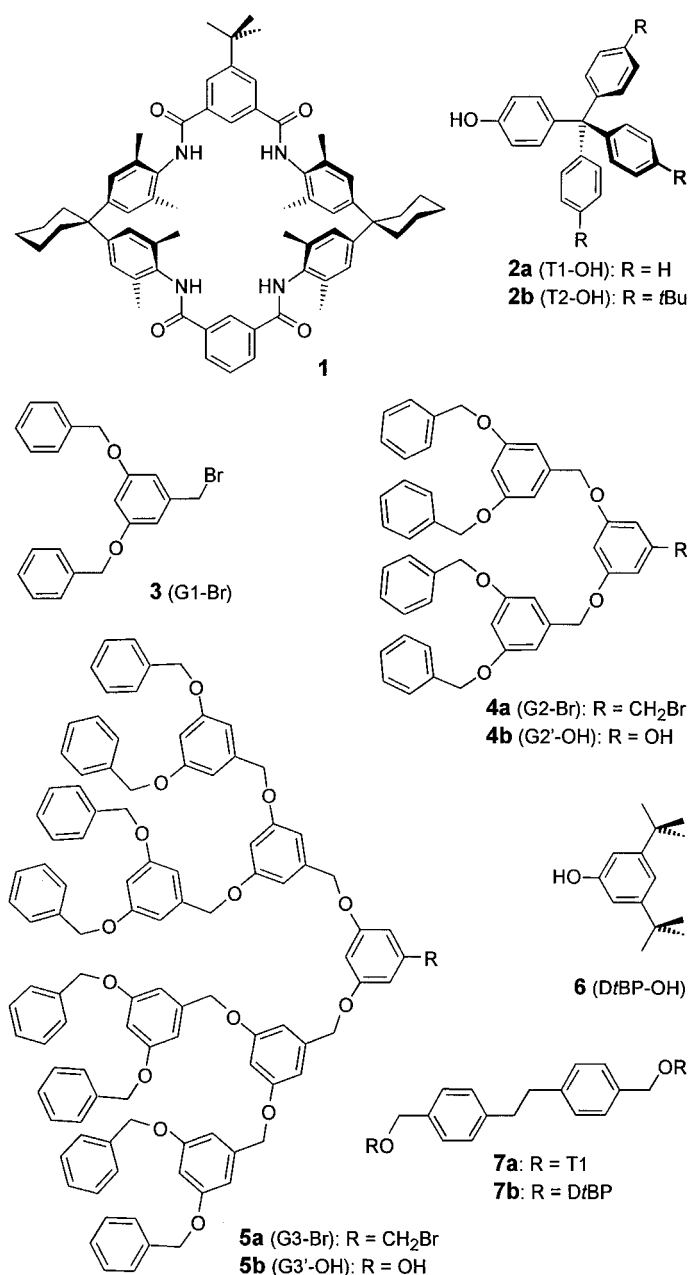
on the deslipping behavior of rotaxanes.^[2–4] This investigation inspired us to compare the effective spatial demand of dendrons such as those of the Fréchet-type^[5] with that of “conventional”, non-dendritic stoppers and thus to derive a sort of size ranking by determination of the stability of the mechanical bonds in rotaxanes.^[6–9]

We used our newly developed trapping procedure for the template synthesis of the new rotaxanes **8–10** (see Scheme 1). This method is based on the complexation of intermediate anionic stopper building blocks by neutral macrocyclic isophthalamides such as **1** and their subsequent reaction with electrophilic stoppers to give rotaxanes with phenyl ether axles.^[10] First, *p*-tritylphenol (**2a**, T1-OH) was treated with the first, second, and third generation dendritic bromides **3**, **4a**, and **5a** (G1-Br, G2-Br, and G3-Br) in the presence of the tetralactam **1**^[11] and K₂CO₃. The rotaxanes **8a** and **8b** with the G2 and G3 stoppers, respectively, were formed (Scheme 1) in yields of 14 and 7%, respectively, while no rotaxane could be isolated with the G1 stopper; only the free axle was obtained. Clearly the first generation (G1) is too small to prevent the (pseudo-) rotaxane that is probably formed as an intermediate from deslipping. The yields of the analogous rotaxanes **9a** and **9b** with the bulkier *tert*-butyl-substituted tritylstopper **2b** (T2-OH)^[12] were 15 and 17%, respectively. In order that the medium-sized G2 and T2 building blocks could be ranked the “doubly dendritic” rotaxane **10b** with G2-O-G3' as the axle had to be prepared so that its deslipping could be compared with that of the G2-O-T2 rotaxane **9a**. Therefore, the previously unknown phenolic dendron **5b** (G3'-OH) was synthesized from 5-acetoxyresorcinol^[13] and G2-Br **4a**.^[14] The reaction of the new nucleophilic dendron **5b** with **4a** in the presence of the macrocycle **1** yielded 1.5% of the rotaxane **10b**. Analogously, 1% of the rotaxane **10a** with the G2-O-G2' axle was obtained from the reaction of **1**, **4a**, and the likewise new G2'-phenol **4b**. The yields of the rotaxanes were considerably lower here than in previously reported trapping syntheses, which were nearly quantitative in some cases,^[10] probably as a result of the steric shielding of the bromomethyl group by the voluminous, flexible dendritic groups and the shielding of the phenolate oxygen atom in the complex with the wheel. Complexation of the dendritic phenolates **4b** and **5b** is possibly also sterically hindered and the effectivity of the template assistance reduced consequently.^[15]

All of the rotaxanes were stable indefinitely at room temperature. However, the spectra of the rotaxanes **8a** and **8b**, the axles of which (G2-O-T1 and G3-O-T1, respectively) each carry one trityl stopper, clearly showed signals of the free components after a few hours at 80 °C. Quantification of the data gave a half-life of eleven hours for **8a** and twelve hours for **8b**, which is not a significant difference considering the accuracy of the method. The rotaxane [7a@1],^[10a] which has a comparatively long bibenzyl central part in the axle, was mechanically more stable with a half-life of 34 h at 80 °C, even



Scheme 1. Illustration of the trapping synthesis of dendritic rotaxanes by the nucleophilic attack of a wheel–phenolate complex on a stopper bromide.



though its wheel has the possibility of slipping over both T1 stoppers. The slower deslipping kinetics is clearly caused by the longer and more flexible axle. The analogous rotaxane [**7b**@**1**] with the smaller 3,5-di-*tert*-butylphenyl (DtBP) stoppers, however, slowly deslipped even at room temperature (ca. 10% in 48 h).^[10a]

In contrast to this, no changes were observed in the spectra of the rotaxanes with the larger *tert*-butyl-substituted trityl stopper (T2) or two dendritic stoppers (G2 or G3) even after many hours at 80 °C. Deslipping experiments were, therefore, carried out at even higher temperatures (150 °C) so that the spatial demands of these three stoppers could be compared.^[16] After a short time signals corresponding to the free components appeared in the NMR spectra of the rotaxanes **9a**, **10a**, and **10b**, which all carry at least one dendron of the second generation on their axles (G2-O-T2, G2-O-G2', and G2-O-G3', respectively). Only the spectra of the G3-O-T2 rotaxane **9b** with a third generation dendron and a substituted trityl stopper showed hardly any changes. Pronounced line broadening and signal overlapping in the spectra of the "doubly dendritic" rotaxanes **10a** and **10b** prevented an exact quantification of the rate of deslipping, but half-lives of about 15–20 h could be estimated. These results lead to the conclusion that the wheel slips over the second generation dendrons in rotaxanes **9a**, **10a**, and **10b** and that this consequently has a lower spatial demand than the substituted trityl group (T2).

Figure 1 shows the space-filling models of the stopper groups used here. They illustrate in particular that the "size" of G2 cannot be estimated intuitively like the two trityl stoppers whereas the deslipping behavior allows a ranking. On the basis of the models it can be said that the third Fréchet generation has the largest spatial demand of all the stoppers used here. Thus the following empirical ranking list of voluminous substituents can be derived from the results: G1 < DtBP < T1 < G2 < T2 < G3.

This comparison of the size of molecules shows that the "rotaxanation" of dendrons and the subsequent deslipping is a suitable method for obtaining a clearer conception of the "dynamic spatial demand" of other types of dendrimers, and to come to an extensive ranking list of different types of wheels and stoppers in the future. This knowledge would be important, for example, for membrane reactors with dendritic catalysts that have to be larger than the pores to prevent them from being washed out with the products.^[17] The surprisingly pronounced dependency of the deslipping kinetics on the length and, probably, the flexibility of the central part of the axle as observed by comparison of rotaxanes **8a** and **8b** with [**7a**@**1**] is currently under investigation and likewise the stability of rotaxanes with dendritic stoppers built from aliphatic units of different length. A comparison of the

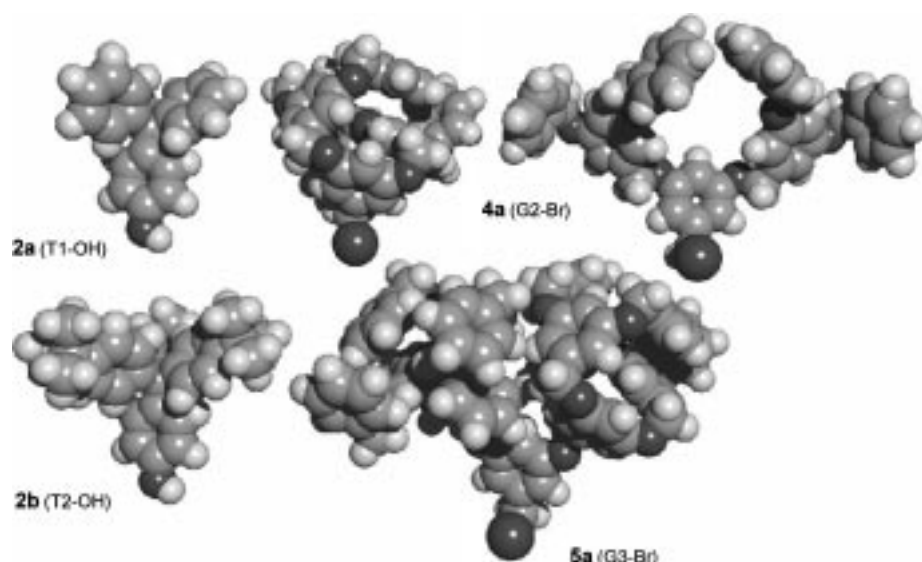


Figure 1. MM2 energy-minimized space-filling models of the stopper units; heteroatoms are shaded dark. The G2 bromide **4a** is shown in a "collapsed" and an (energetically unfavorable) "extended" conformation to illustrate the problem of the size estimation. The models of the dendrons were obtained from arbitrarily chosen starting conformations.

molecular dynamics simulations of the deslipping of dendritic stoppers with those of conventional building blocks would be a useful supplement to the experimental results.

Experimental Section

Synthesis of the phenolic dendrimers G2'-OH (**4b**) and G3'-OH (**5b**): A mixture of 5-acetoxyresorcinol (0.5 mmol), the respective bromides (**3** or **4a**; 1 mmol), dibenzo[18]crown-6 (0.1 mmol), and K₂CO₃ (1 mmol) in acetone (15 mL) was stirred at room temperature for 7 d. The inorganic salts were filtered off and the filtrate evaporated. The residue was then refluxed with NaOMe (1 mmol) in MeOH (15 mL) for 1 d. After removal of the solvent the residue was dissolved in CH₂Cl₂ and extracted with water and the organic phase dried with MgSO₄. Column chromatography with CH₂Cl₂ on silica gel gave about 60% of a colorless solid in both cases. Analytical data of **5b** is given as an example: *R*_f = 0.15 (CH₂Cl₂); ¹H NMR (250 MHz, CDCl₃): δ = 4.89, 4.94, and 5.01 (3s, 4H, 8H, and 16H, respectively, OCH₂), 6.05 (s, 2H, phloroglucinol-H-2/6), 6.21 (s, 1H, phloroglucinol-H-4), 6.53 and 6.63 (2s, 2H and 4H, resorcinol-H2), 6.57 and 6.67 (2s, 4H and 8H, resorcinol-H4/6), 7.3–7.4 (m, 40H, phenyl); ¹³C NMR (62.9 MHz, CDCl₃): δ = 69.84 and 69.98 (OCH₂), 94.74 and 95.40 (phloroglucinol-CH), 101.52 and 106.31 (resorcinol-CH), 127.12, 127.89, and 128.47 (phenyl-CH), 136.69, 139.17, 157.48, 160.03, 160.54 (all C_q); FAB-MS: *m/z*: 1579.5 [MH⁺].

The rotaxanes **8–10** were synthesized in an analogous manner to other rotaxanes with phenylether axles.^[10a] FAB-MS: **4b**: *m/z* = 731.2 [M+H⁺]; **5b**: *m/z* = 1579.5 [M+H⁺]. MALDI-TOF-MS: **8a**: *m/z*: 2045.2 [M+Na⁺]; **8b**: *m/z*: 2895.5 [M+Na⁺]; **9a**: *m/z*: 2213.9 [M+Na⁺], 2230.2 [M+K⁺]; **9b**: *m/z*: 3063.1 [M+Na⁺]; **10b**: *m/z*: 3285.1 [M+Na⁺].

The deslipping experiments were carried out in [D₆]DMSO and followed by NMR spectroscopy by integration of suitable signals of the rotaxanes and the resulting free components.

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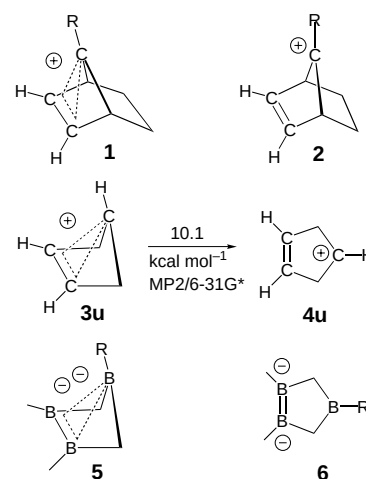
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- [16] To make sure that under these severe conditions the spectral changes were caused by mechanical deslipping and not by chemical decomposition, we exposed the free components of the rotaxanes, that is the tetralactam **1** and the axes, to the same conditions. Indeed, there was a slow color change of the solutions and slight changes in the spectra were observed, however, these processes were significantly slower than the changes observed in the spectra of the rotaxanes.
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Bishomoaromatic 1,2,4-Triboracyclopentane Dianions: Strong Three-Center, Two-Electron Bonds between Three Boron Atoms**

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The three-center, two-electron (3c,2e) bonding of bishomoaromatic cations of type **1**^[1–4] are known to be weakened by R = C₆H₅^[2b, 3a] and displaced by R = *p*-MeOC₆H₄ and R = OH.^[4] Evidently, cations **1** are stabilized by the 3c,2e bonds, whereas cations **2** are stabilized by donor substituents R. According to computational estimates, **1u** (R = H) is more stable than **2u** (R = H) by 15 kcal mol^{−1}.^[2a] The energy difference between the prototypes **3u** and **4u**, neither of which is known experimentally, is only 10.1 kcal mol^{−1}.^[5]



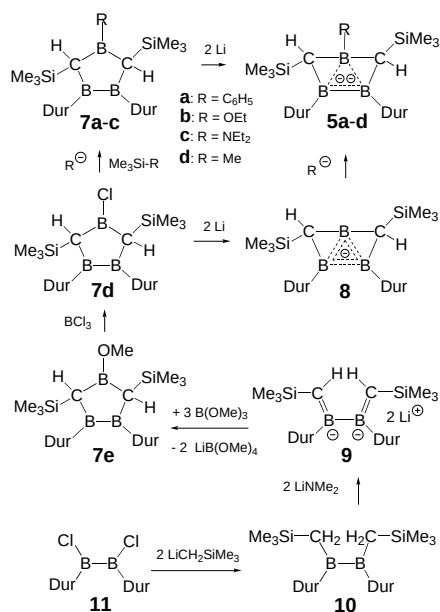
We now report on bishomoaromatic dianions **5** of 1,2,4-triboracyclopentanes that have skeletons isoelectronic to that of **3u**.^[6, 7] The 3c,2e bonds of dianions of type **5** remain intact even in the presence of strong donor substituents like R = NR₂. Hence, the energy difference between **5** and **6** must be larger than the 26 kcal mol^{−1} stabilization afforded to a tricoordinate boron atom by a dialkylamino substituent.^[8] Calculations at the MP2/6-31+G* level^[9] confirm this conclusion.

The dianions **5a–c** (Dur = 2,3,5,6-tetramethylphenyl) are obtained by reduction of **7a–c** with lithium in diethyl ether.

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The reaction of **8** with phenyllithium and methyllithium yields **5a** and **5d**, respectively. Compounds **7a–c** and **8** were obtained from **7d**, which can be synthesized from **11**^[10] via **10**, **9**, and **7e**. The structures of the new compounds are deduced from their ¹¹B, ¹H, and ¹³C NMR spectra (Tables 1 and 2). Similarities of the NMR data with those of the known^[11] isomers with *cis*-trimethylsilyl substituents allows identification of **7d**, **7e**, and **8**. The crystal structures^[12] of **5a**·2Li·2Et₂O and **5b**·2Li·3Et₂O are shown in Figure 1, their relevant spectroscopic and physical data and that of **5c**·2Li·2Et₂O are included in Table 2.

Dianions **5a** and **5b** form contact triple ions with two lithium cations, which, in addition, are coordinated to diethyl ether molecules. Li1 is η^2 -coordinated to the B2–B3 σ bond and to the *ipso*- and *ortho*-C atoms of the duryl substituents.^[13] Li2 in **5a** exhibits a remarkably short distance to B1 (211 pm) as well as contacts to C1 and C2 (230 pm).

The five-membered rings of **5a–c** feature distortions characteristic of two-electron bishomoaromatics:^[3] short transannular distances (e.g. between B1 and B2,3) as well as

Table 1. Selected physical and spectroscopic properties of **5a–c**, **7a–e**, and **8–10**.

5a: yellow solid, yield 98%; ¹H NMR (500 MHz, C₆D₆, 25 °C): δ = 7.92 (d, 2H, Ph-*o*-H), 7.20 (m, 2H, Ph-*m*-H), 7.04 (t, 1H, Ph-*p*-H), 6.71, 6.68 (each s, each 1H, Dur-H), 2.93, 2.82, 2.45, 2.22, 2.18, 2.12, 2.08 (each s, total of 24H, Dur-CH₃), 2.64 (br., 8H, Et₂O), 0.59 (br., 12H, Et₂O), 0.46, 0.15 (each s, each 9H, SiMe₃), 0.02, –0.43 (each s, each 1H, BCH); ¹³C NMR (125 MHz, C₆D₆, 25 °C): δ = 156.2 (s, Ph-*i*-C), 152.2, 151.7 (each s, Dur-*i*-C), 139.5, 138.6, 138.2, 137.1, 133.8, 133.7, 133.5, 133.2 (each s, Dur-*o*- and *m*-C), 136.0 (d, Ph-*o*-C), 129.62, 129.57 (each d, Dur-*p*-C), 126.8 (d, Ph-*m*-C), 123.7 (d, Ph-*p*-C), 65.1 (t, Et₂O), 22.4, 22.1, 21.3, 21.0, 20.9, 20.8 (each q, Dur-CH₃), 18.0 (d, ¹J(C,H) = 111 Hz, BCH), 14.0 (q, Et₂O), 4.3, 3.8 (each q, SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 25 °C): see Table 2

5b: orange-red solid, yield 97%; ¹H NMR (500 MHz, C₆D₆, 25 °C): δ = 6.70, 6.65 (each s, each 1H, Dur-H), 3.95 (q, 2H, OEt), 2.79, 2.68, 2.64, 2.21, 2.15 (each s, total of 24H, Dur-CH₃), 2.70 (br., 8H, Et₂O), 1.22 (t, 3H, OEt), 0.64 (br., 12H, Et₂O), 0.45, 0.14 (each s, each 9H, SiMe₃), –0.07, –0.98 (each s, each 1H, BCH); ¹³C NMR (125 MHz, C₆D₆, 25 °C): δ = 155.1, 152.6 (each s, *i*-C), 139.2, 136.9, 136.2, 133.5, 132.8, 132.4 (each s, *o*- and *m*-C), 128.9, 128.8 (each d, *p*-C), 65.5 (t, Et₂O), 61.4 (t, OEt), 24.0, 21.3, 21.1, 20.9, 20.5 (each q, Dur-CH₃), 18.7 (q, OEt), 18.0 (d, ¹J(C,H) = 107 Hz, BCH), 14.2 (q, Et₂O), 12.1 (d, ¹J(C,H) = 113 Hz, BCH), 3.8, 3.7 (each q, SiMe₃); ¹¹B NMR (160 MHz, C₆D₆, 25 °C): see Table 2

5c: orange-red solid, yield 95%; ¹H NMR (500 MHz, [D₁₀]Et₂O, –30 °C): δ = 6.65 (s, 2H, Dur-H), 3.38 (q, Et₂O), 2.68, 2.54, 2.50, 2.49, 2.12, 2.11, 2.09 (each s, total of 24H, Dur-CH₃), 1.13 (t, Et₂O), 0.14, –0.31 (each s, each 9H, SiMe₃), BCH and NEt₂ not observed; ¹³C NMR (125 MHz, [D₁₀]Et₂O, –30 °C): δ = 153.0, 152.2 (each s, *i*-C), 140.5, 137.3, 136.8, 134.8, 133.6, 133.5, 133.1 (each s, *o*- and *m*-C), 129.14, 129.10 (each d, *p*-C), 66.2 (t, Et₂O), 51.5, 49.0 (t, NEt₂), 23.1, 22.4, 21.3, 21.2, 21.1, 20.9, 20.7, 20.0 (each q, Dur-CH₃), 18.2, 17.2 (q, NEt₂), 15.6 (q, Et₂O), 4.3, 3.7 (each q, SiMe₃), BCH not observed; ¹¹B NMR (160 MHz, C₆D₆, 25 °C): see Table 2

7a: yellow solid, m.p. 98 °C, yield 99%; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.76 (m, 2H, Ph-H), 7.53 (m, 3H, Ph-H), 6.98 (s, 2H, Dur-H), 3.98 (s, 2H, BCH), 2.25 (s, 12H, Dur-CH₃), 2.1 (br. s, 12H, Dur-CH₃), –0.08 (s, 18H, SiMe₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 149.5 (br. s, Dur-*i*-C), 146.2 (br. s, Ph-*i*-C), 133.0, 132.5 (each s, Dur-*o*- and *m*-C), 131.7 (d, Ph-*m*-C), 130.7 (d, Dur-*p*-C), 129.9 (d, Ph-*p*-C), 127.5 (d, Ph-*o*-C), 65.0 (d, ¹J(C,H) = 108 Hz, BCH), 20.9, 19.6 (each q, Dur-CH₃), 3.0 (q, SiMe₃); ¹¹B NMR (96 MHz, CDCl₃, 25 °C): δ = 101, 82 (2:1)

7b: yellow oil, yield 99%; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 6.86 (s, 2H, Dur-H), 4.20 (m, 2H, OEt), 2.80 (s, 2H, BCH), 2.25, 2.20 (each s, each 12H, Dur-CH₃), 1.43 (t, 3H, OEt), 0.12 (s, 18H, SiMe₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 149.5 (br. s, *i*-C), 132.8, 131.1 (each br. s, *o*- and *m*-C), 130.2 (d, *p*-C), 62.9 (t, OEt), 53.3 (d, ¹J(C,H) = 101 Hz, BCH), 20.4,

19.7, 19.0 (each br. q, Dur-CH₃), 17.6 (q, OEt), 2.7 (q, SiMe₃); ¹¹B NMR (96 MHz, CDCl₃, 25 °C): δ = 96, 53 (2:1)

7c: yellow solid, m.p. 128 °C, yield 98%; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 6.91 (s, 2H, Dur-H), 3.51, 3.01 (each q, each 2H, NEt₂), 3.01 (s, 2H, BCH), ca. 2.2 (br. s, 24H, Dur-CH₃), 1.19 (t, 6H, NEt₂), 0.02 (s, 18H, SiMe₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 149.8 (br. s, *i*-C), 133.3, 133.1 (each s, *o*- and *m*-C), 130.9 (d, *p*-C), 52.5 (d, ¹J(C,H) = 107 Hz, BCH), 42.9 (t, NEt₂), 21.6, 19.8 (each q, Dur-CH₃), 15.8 (q, NEt₂), 3.5 (q, SiMe₃); ¹¹B NMR (96 MHz, CDCl₃, 25 °C): δ = 97, 49 (2:1)

7d: yellow solid, m.p. 133 °C, yield 75%; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 6.85 (s, 2H, Dur-H), 3.37 (s, 2H, BCH), 2.12 (s, 12H, Dur-CH₃), ca. 1.9 (br. s, 12H, Dur-CH₃), 0.13 (s, 18H, SiMe₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 148.4 (br. s, *i*-C), 133.1, 131.8 (each s, *o*- and *m*-C), 130.8 (d, *p*-C), 63.8 (d, ¹J(C,H) = 111 Hz, BCH), 20.6, 19.4 (each q, Dur-CH₃), 2.6 (q, SiMe₃); ¹¹B NMR (96 MHz, CDCl₃, 25 °C): δ = 97, 74 (2:1)

7e: yellow oil, yield 99%; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 6.82 (s, 2H, Dur-H), 3.89 (s, 3H, OMe), 2.82 (s, 2H, BCH), 2.16 to 1.58 (br. s, total of 24H, Dur-CH₃), 0.01 (s, 18H, SiMe₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 149.5 (br. s, *i*-C), 132.8, 131.3 (each s, *o*- and *m*-C), 130.2 (d, *p*-C), 54.7 (q, OMe), 53.2 (d, ¹J(C,H) = 104 Hz, BCH), 20.3, 19.2 (each q, Dur-CH₃), 2.6 (q, SiMe₃); ¹¹B NMR (96 MHz, CDCl₃, 25 °C): δ = 97, 53 (2:1)

8: yellowish solid, yield 59%; ¹H NMR (500 MHz, [D₈]THF, –80 °C): δ = 6.34 (s, 2H, Dur-H), 3.35 (Et₂O), 2.10, 1.80, 1.63 (each s, total of 24H, Dur-CH₃), 1.11 (Et₂O), 0.05 (s, 2H, BCH), –0.28 (s, 18H, SiMe₃); ¹³C NMR (125 MHz, [D₈]THF, –80 °C): δ = 153.6 (br. s, *i*-C), 132.8, 135.0, 134.5, 130.6, 130.1 (each s, *o*- and *m*-C), 126.9 (d, *p*-C), 66.8 (Et₂O), 21.4, 20.2 (each q, Dur-CH₃), 2.9 (d, ¹J(C,H) = 129 Hz, BCH), 2.2 (q, SiMe₃); ¹¹B NMR (96 MHz, Et₂O, 25 °C): δ = 24, 20 (2:1)

9: colorless solid, m.p. 118 °C, yield 85%; ¹H NMR (300 MHz, C₆D₆, 25 °C): δ = 6.67 (s, 2H, Dur-H), 3.25 (q, 8H, Et₂O), 3.24 (s, 2H, BCH), 2.23, 2.16 (each s, each 12H, Dur-CH₃), 1.01 (t, 12H, Et₂O), 0.08 (s, 18H, SiMe₃); ¹³C NMR (75 MHz, C₆D₆, 25 °C): δ = 155.7 (br. s, *i*-C), 132.2, 131.4 (each s, *o*- and *m*-C), 128.0 (d, *p*-C), 83.7 (d, ¹J(C,H) = 90 Hz, BCH), 66.1 (t, Et₂O), 22.2, 20.6 (each q, Dur-CH₃), 3.2 (q, SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 25 °C): δ = 51

10: greenish, fluorescent solid, m.p. 134 °C, yield 98%; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 6.80 (s, 2H, Dur-H), 2.16, 1.90 (each s, each 12H, Dur-CH₃), 1.79 (s, 4H, BCH₂), 0.06 (s, 18H, SiMe₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 149.6 (br. s, *i*-C), 133.0, 129.5 (each s, *o*- and *m*-C), 129.3 (d, *p*-C), 28.6 (t, ¹J(C,H) = 113 Hz, BCH₂), 20.3, 19.3 (each q, Dur-CH₃), 1.7 (q, SiMe₃); ¹¹B NMR (96 MHz, CDCl₃, 25 °C): δ = 97

Table 2. Selected distances [pm] and interplanar angles [°] of **5a**·2Li·2Et₂O, **5b**·2Li·3Et₂O, and **5c**·2Li·2Et₂O (crystal structures) as well as of model compounds **5u**-R (R = H, Me, Ph, OH, NH₂) (//MP2/6-31+G*); ¹¹B NMR chemical shifts [ppm] are also given.

	B1...B2	B1...B3	B2-B3	C1-B2-B3-C2/ C1-B1-C2 ^[a]	δ(B1)	δ(B2), δ(B3)
5a ·2Li·2Et ₂ O	185.7(6)	184.1(6)	163.7(6)	80.0(4)	−20	15, 18
5u -Ph ^[b]	185.8	185.8	166.4	82.4	−35.6	20.8
5b ·2Li·3Et ₂ O	186.5(4)	187.8(4)	163.0(4)	82.7(3)	−2	13, 15
5u -OH ^[b]	184.7	184.7	165.3	81.8	−7.1	20.5
5c ·2Li·2Et ₂ O	192.7(6)	190.8(5)	165.0(6)	85.1(4)	−4	7, 21
5u -NH ₂ ^[b]	183.6	183.6	165.5	80.2	−17.2	21.6, 19.7
5d					−21	13, 16
5u -Me ^[b]	184.6	184.6	165.4	81.4	−28.5	20.0
5u -H ^[b]	184.8	184.8	165.5	81.7	−47.8	9.2

[a] Interplanar angle. [b] NMR chemical shifts were computed at GIAO-SCF/6-311+G**//MP2(fc)/6-31+G*.

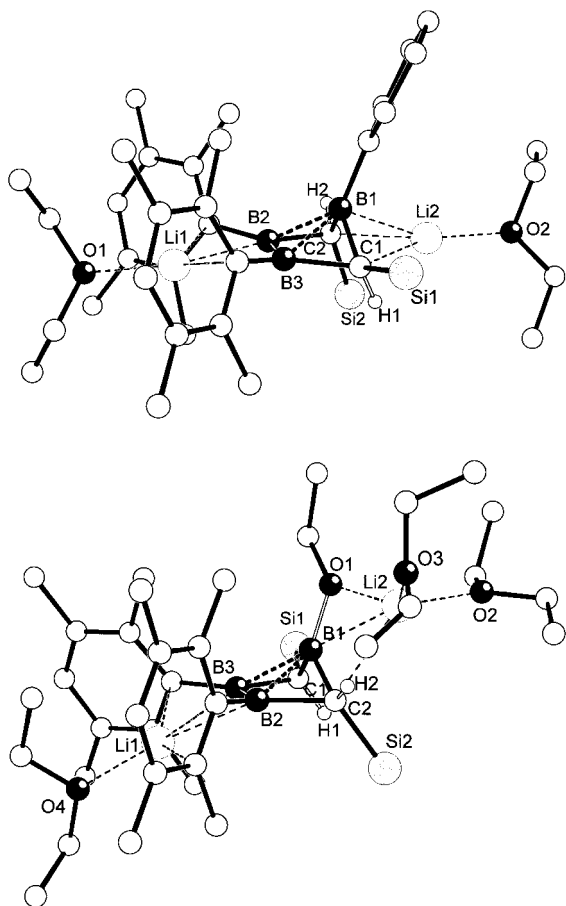
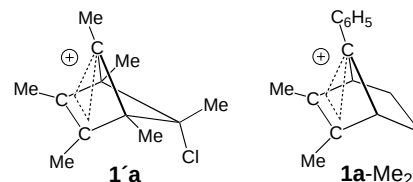


Figure 1. Structures of **5a**·2Li·2Et₂O (top) and **5b**·2Li·3Et₂O (bottom) in the crystal, the methyl substituents at Si1 and Si2 as well as most of the H atoms are omitted for clarity. Selected bond lengths (in addition to those in Table 2) [pm] and bond angles [°]. **5a**: B1-C1 165.1(5), B1-C2 163.6(5), C1-B3 162.3(5), C2-B2 163.3(5); C1-B1-C2 110.1(3), B1-C2-B2 69.2(2), C2-B2-B3 108.9(3), B2-B3-C1 109.0(3), B3-C1-B1 68.4(2); **5b**: B1-C1 161.4(4), B1-C2 162.7(4), C1-B3 164.1(4), C2-B2 164.4(4); C1-B1-C2 113.7(2), B1-C2-B2 69.5(2), C2-B2-B3 109.3(2), B2-B3-C1 109.1(2), B3-C1-B1 70.5(2).

small interplanar angles (here between the C1-B3-B2-C2 and C1-B1-C2 planes). The experimental data are compared to values computed for the model compounds **5u**-R (R = H, Me, Ph, OH, NH₂) in Table 2.

The strong donors OEt, OH, NEt₂, and NH₂ distort bishomoaromatics of type **5** to a small extent (Table 2). For

the bishomoaromatic cations of type **1**, even the relatively weak phenyl donor substituent at C7 leads to a considerable elongation of the transannular C-C distance from 172.1 pm^[14] in **1u** (R = H) to 190.1 pm in **1a** (R = C₆H₅). The interplanar angle also is increased (from 81.3 to 93.6°, //MP2(fc)/6-31G*),^[2b] Similar geometries are found in the X-ray structures of **1'a**^[3b] and **1a**-Me₂.^[3a]

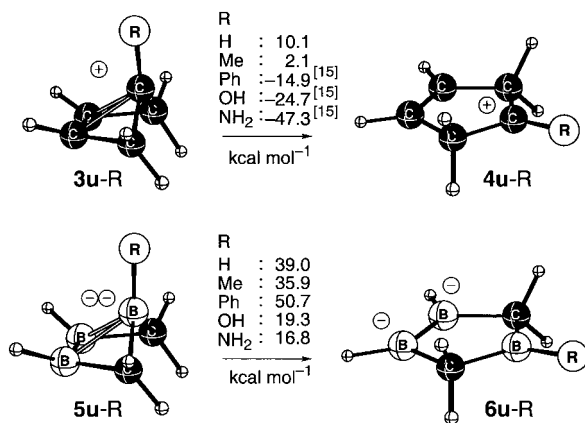


The monocyclic cation **3u**-Me (with a transannular distance of 182.1 pm) is only 2.1 kcalmol^{−1} higher in energy than the classical 4-methyl-4-cyclopentenyl cation, **4u**-Me, and no local minima of the **3u** type could be localized when effective π- or n-donors like phenyl or OH and NH₂ were present. These structures must be much less stable than the corresponding classical cations **4u**-Ph, **4u**-OH, and **4u**-NH₂.^[15]

Likewise, strong donors influence the NMR chemical shifts of the pentacoordinate boron atoms of dianions **5** (Table 2) to a lesser extent than the shifts of the pentacoordinate C atoms of **1**. Replacing R = Me in the nonclassical **1** by OH gives the classical **2b** (R = OH), as indicated by the deshielding of C7 by 153 ppm (δ¹³C = 72 → 225). An analogous exchange of substituents in the dianions **5** (**5d** → **5b**) leads to a ¹¹B deshielding of only 19 ppm.^[16, 17]

The ineffectiveness of the donor substituents is expressed most impressively in the geometries characterizing the 3c,2e bonds of the bishomoaromatics **5a**–**c**: these parameters, like those in **5u**-Ph, **5u**-OH, and **5u**-NH₂, are almost identical (Table 2).

Hence, the 3c,2e bonding in bishomoaromatic dianions **5** is much stronger than those of the isoelectronic cations of type **1**. A quantitative measure for the 3c,2e bond strengths is given by the computed energy differences between bishomoaromatic **5u**-R and classic **6u**-R. At the MP2/6-31+G* + 0.89 ZPE(HF/6-31G*) level **5u**-H is more stable than **6u**-H by 39.0 kcalmol^{−1}; this is about 30 kcalmol^{−1} greater than the difference between the isoelectronic **3u** and **4u**. The difference between nonclassical and classical forms is only about



10 kcal mol⁻¹ smaller (29.6 kcal mol⁻¹) for the monoanionic prototypes which result from protonating the B–B bond in dianions of type **5**.^[18]

In conclusion, both the statement, based on results for homoaromatic cations and neutral compounds, that “the very existence of homoaromaticity is a matter of a few kcal mol⁻¹”^[19] as well as the one that anionic homoaromaticity is “either quite insignificant or nonexistent altogether”^[20] are not valid any longer.

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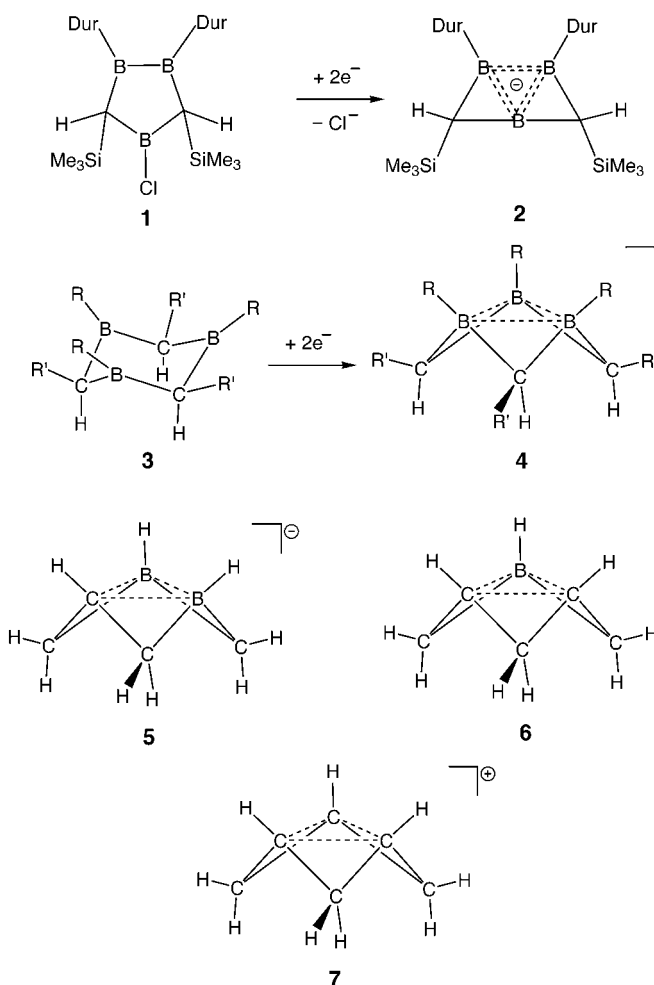
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Trishomoaromatic Dianions of 1,3,5-Triboracyclohexanes**

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Dedicated to Professor Dirk Walther on the occasion of his 60th birthday

Reductions of boron-containing heterocycles in donor solvents by alkaline metals lead to aromatic anions.^[1] A remarkable example was obtained by Berndt et al.^[2] from the organoborane **1** (Scheme 1): the monoanion **2** is both



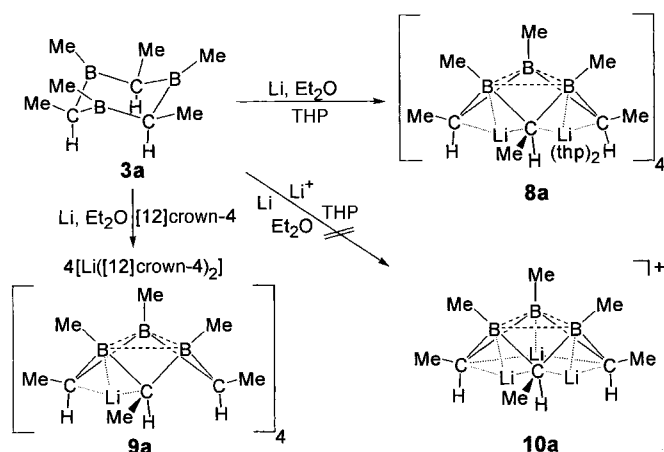
Scheme 1. Dur = 2,3,5,6-Tetramethylphenyl.

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bishomo- and doubly aromatic, because it possesses two three-center, two-electron bonds, one with π and the other with σ symmetry (dashed B_3 triangles). The three empty p orbitals of the related trifunctional Lewis acidic 1,3,5-triboracyclohexanes **3**^[3] should also accept two electrons and form the trishomoaromatic dianions **4**, which are isoelectronic with the trishomocyclopropenyl cations.^[4] We report here on the unusual structure of reduced **3a** ($R = R' = Me$) together with computational results on the stabilization and nucleus-independent chemical shifts (NICS)^[5] of the isoelectronic, all-hydrogen-substituted trishomoaromatic set **4–7** ($R = R' = H$; Scheme 1).

While **3a** reacted with Li powder at 0 °C in both Et_2O and THF (Scheme 2) to give yellow-orange solutions after filtration, only amorphous residues resulted after solvent removal.



Scheme 2. Synthesis of **8a** and **9a**.

In $[D_8]THF$ solution, the reduction product obtained initially exhibited two broad ^1H NMR signals at $\delta = -3.2$ and -3.4 , which were assigned to methine protons. Three B-Me and two C-Me signals indicated the presence of a mixture of isomers with axial/equatorial orientations of the C-Me substituents, as has been found for $(MeCH)_3(CIB)_3$, the precursor of **3a**.^[3] The ^{11}B NMR signal of these products at $\delta = -29.2$ was at extremely high fields (**3a**: $\delta = 84.3$) and indicated multiple connectivities at the boron atoms. IGLO calculations^[5, 6] of the ^{11}B NMR shift of the C_{3v} model compound $[(CH_2)_3(BH)_3Li_3]^+$ (Figure 1) gave $\delta = -31.8$, in very good agreement with the experimental value, as well as NICS values^[5] of $\delta = -28.5$ at the center of all the C and B atoms and $\delta = -42.3$ at the center of the three boron atoms. These

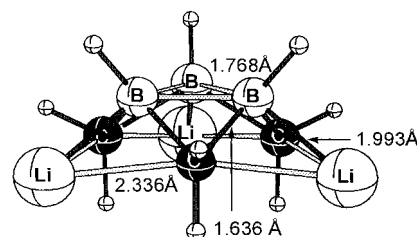


Figure 1. Structure of $[(CH_2)_3(BH)_3Li_3]^+$ (C_{3v}) optimized at the B3LYP/6-311+G** density functional level.

data indicate pronounced homoaromatic character (see below).

Crystals were obtained by adding tetrahydropyran (THP) or the crown ether [12]crown-4 to the THF solutions after reduction. Surprisingly, the X-ray structure analyses revealed tetrameric aggregates for both **8a** and **9a**. While disorder of the THP ligands severely reduced the quality of the X-ray analysis of **8a**, the structure of **9a** was ligand-free and refined well^[7] (Figure 2). The low solubility of both these crystals precluded spectroscopic characterization. Even the reduction of **3a** in the presence of LiCl (in the hope that $[(\text{MeCH})_3(\text{MeB})_3\text{Li}_3]^+$, **10a**, might form) failed to give a monomeric product and to prevent aggregation.

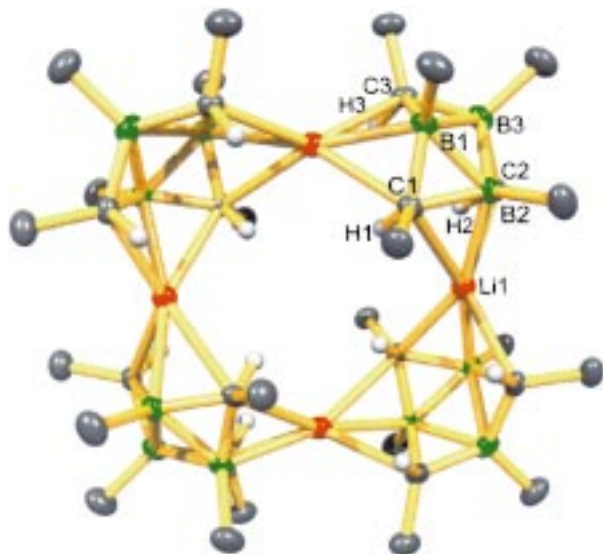


Figure 2. Molecular structure of **9a** in the crystal. Selected distances [Å] and angles [°]: B1–B2 1.825(5), B1–B3 1.851(5), B2–B3 1.848(5), Li1–C1 2.456(6), Li1'–C1 2.354(6), Li1'–C3 2.285(6), Li1–C2 2.247(6), Li1'–B1 2.239(6), Li1–B1 2.251(6); B2–B1–B3 60.4(2), B1–B2–B3 60.5(2), B1–B3–B2 59.1(2), B1–C1–B2 68.6(2), B2–C2–B3 70.0(2), B1–C3–B3 69.8(3).

The four $(\text{MeCH})_3(\text{MeB})_3\text{Li}$ units in the ringlike arrangement of **9a** are connected by Lewis acidic Li centers. The transannular boron–boron distances in the C_3B_3 ring are short and differ somewhat (1.825(5) Å, when both B atoms coordinate to Li atoms, as well as 1.851(5) and 1.848(5) Å, when only one B coordinates to Li). The $\text{Li} \cdots \text{B}$ contacts are long (2.239(6), 2.251(6) Å), the B–C bond lengths are normal for a single bond (between 1.603(5) and 1.632(4) Å). Each C_3B_3 unit has three axial C–H and three equatorial C–Me groups.

Comprehensive computations on the various possible minima of monomeric $[(\text{CH}_2)_3(\text{BH})_3\text{Li}_3]^+$, $(\text{CH}_2)_3(\text{BH})_3\text{Li}_2$, and $[(\text{CH}_2)_3(\text{BH})_3\text{Li}]^-$ reveal that the B_3 face is preferred over the C_2B face attachment of Li in all cases. The lithium bonding is predominantly electrostatic, but minor covalent interactions between the Li^+ centers and nearby H, B, and C atoms are present. The C_2B face coordination observed experimentally for **8a** and **9a** may be attributed to the combined effects of the sterically active methyl groups at the B_3 face and to the electrostatic energetic advantages on the tetrameric association.

Most surprising is the remarkable homoaromatic stabilization energy^[8] of the $[(\text{CH}_2)_3(\text{BH})_3]^{2-}$ dianion (**4**, $\text{R} = \text{R}' = \text{H}$), which is larger than all three of the isoelectronic counterparts **5–7**. Stabilization energies, evaluated by two different methods, are given in Table 1.

Table 1. Stabilization energies [kcal mol^{−1}] (//B3LYP/6-311 + G**) and NICS values (PW91/IGLO III)^[4b] for the trishomoaromatic systems **4–7** ($\text{R} = \text{R}' = \text{H}$).

Trishomoaromatic system	Isodesmic reaction ^[a]	Difference to open form ^[b]	NICS(0)	NICS(rc)
$[(\text{CH}_2)_3(\text{BH})_3]^{2-}$ 4	−41.05	−32.35	−35.4	−22.5
$[(\text{CH}_2)_3(\text{CH})(\text{BH})_2]^-$ 5	−19.63	−16.11	−37.1	−21.4
$[(\text{CH}_2)_3(\text{CH})_2(\text{BH})]$ 6	+5.55	+6.63	−34.8	−16.7
$[(\text{CH}_2)_3(\text{CH})_3]^+$ 7	−8.73	−12.54	−46.4	−22.7

[a] The isoelectronic equations involve cyclohexane and **4–7** as product pairs. The reactions are valid for the cyclohexyl cation (for **7**) and boracyclohexane (for **4–6**) as well as for bicyclo[3.1.0]hexane (for **6** and **7**) and its 1-(B^-) (for **5**) and 1,5-(B^-)₂ (for **4**) counterparts. [b] Energy differences between **4–7** and their chair-form conformers which lack 3c,2e bonding (see ref. [5f] for a prior use of this method).

The NICS(0) values, based on total NMR shieldings, and the NICS(rc; 3c,2e) ring current (rc) contributions (see Table 1) are computed at the centers of the ring 1,3,5-atoms with Malkin's implementation^[5b] of Kutzelnigg's IGLO program.^[6] IGLO provides a detailed breakdown of the total shieldings in terms of all the localized orbital contributions.

Of greatest interest are the diatropic effects due to the cyclic electron delocalization (i.e., the magnetic evaluation of the 3c,2e “aromatic” bonding given by NICS(rc)). These values are augmented by the local diatropic shielding contributions of nearby C–C, C–H, and B–H bonds. Hence, the NICS(0) values are displaced further upfield. (The local induced circulations of the sigma C–C bonds in benzene, in contrast, are paratropic and reduce the NICS(0) value to about −10.) The benzene NICS (rc, i.e. π value), which is about −22 at the ring center, is quite similar to the 3c,2e data above.

Our results show that the reaction of **3a** with lithium leads to the trishomoaromatic compounds **8a** and **9a** as tetrameric aggregates. The expected monomeric dianion **4a** ($\text{R} = \text{R}' = \text{Me}$) and the cation **10a** as electronic analogues to the trishomocyclopropenylum cation **7**^[4] could not be isolated. Alternatively the monomeric unit **10a** with two donor molecules at each of the three Li centers may be described as a *hypho* cluster with 26 skeleton electrons.^[9]

Experimental Section

To a suspension of freshly purified lithium powder (50 mg, 350 mmol) in diethyl ether (20 mL), hexamethyl-1,3,5-triboracyclohexane (**3a**; 200 mg, 1.23 mmol) was added at 0 °C. The reaction mixture was allowed to warm to 20 °C while stirring overnight. Separation of excess alkaline metal by using a glass filter (G III porosity) led to a clear yellow-orange solution, which was reduced to 2 mL by vacuum evaporation. For crystallization [12]crown-4 (0.2 mL) was added to yield **9a** (12 mg; 2.9 %).

NMR data of the initial reduction product: ¹H NMR (200 MHz, [D₈]THF): δ = −3.42 (q, ca. 2 H, ³J(H,H) = 3 Hz, CH_{ax}), −3.23 (m, br., ca. 1 H, CH_{ax}), −0.59 (s, br., 9 H, BCH_3), −0.52 (s, br., 6 H, BCH_3), −0.45 (s, br., 3 H, BCH_3), 1.23 (d, 6 H, ³J(H,H) = 3 Hz, CCH_3), 1.35 (d, 12 H, ³J(H,H) = 3 Hz,

CCH₃); ¹³C NMR (50 MHz, [D₈]THF): δ = 38.6 (CCH₃), 39.1 (CCH₃); ¹¹B NMR (64 MHz, [D₈]THF): δ = -29.2.

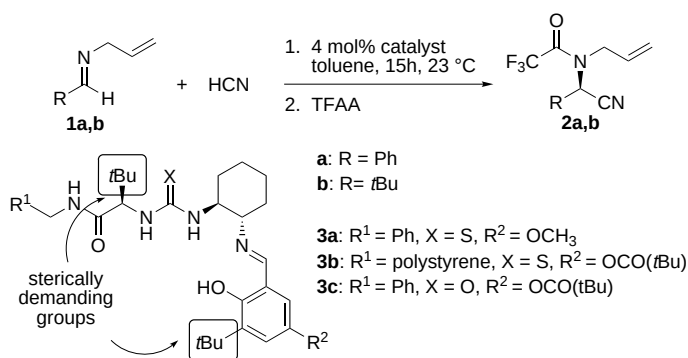
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- [7] Crystal Structures: **8a**: monoclinic, spacegroup *C2/c*, *a* = 31.846(11), *b* = 16.305(11), *c* = 23.787(14) Å, β = 112.91(4)°, *Z* = 4. Because of the poor quality of the crystals (few observed reflections, disorder of the THP ligands) no accurate bond lengths and angles could be obtained. **9a**: C₃₆H₈₄B₁₂Li₄·4C₁₆H₃₂LiO₈ tetragonal, space group *P4₃/n*, *a* = 20.156(11), *c* = 14.937(8) Å, *V* = 6068(6) Å³, *Z* = 2. Data were collected with a four-circle diffractometer (MoKα radiation, ω scan, -70°C). A total of 5341 independent reflections were collected (θ_{max} = 25°), solution of the structure with direct methods (SHELXS 86), structure refinement with all reflections versus *F*² (SHELXL 97), non-hydrogen atoms anisotropic (364 parameters), *R*1 = 0.059, *wR*2 = 0.173. 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-133326 (**9a**). 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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A General Catalyst for the Asymmetric Strecker Reaction**

Matthew S. Sigman, Petr Vachal, and Eric N. Jacobsen*

α -Amino acid derivatives are broadly useful chiral building blocks, with especially important applications in complex natural product and combinatorial syntheses. Substantial progress has been made toward the development of efficient methods for the preparation of these compounds, with a growing emphasis on the identification of enantioselective catalytic approaches with practical potential.^[1, 2] One of the most attractive strategies amenable to asymmetric catalysis is the addition of hydrogen cyanide to imines (the Strecker reaction, Scheme 1),^[3] and promising enantioselective variants of this reaction have been uncovered very recently.^[4] Here we report new catalysts for the Strecker reaction that display high enantioselectivity and broad substrate scope for both aromatic and aliphatic imines. These catalysts can be used either in solution or covalently linked to polystyrene resin, with the latter retaining full reactivity and enantioselectivity after repeated recycling.



Scheme 1. Asymmetric Strecker reaction with catalysts **3**.

The discovery and optimization of catalysts for the asymmetric Strecker reaction was approached by screening parallel synthetic libraries of resin-bound catalyst candidates and validating the most enantioselective library members by the preparation of soluble analogues.^[5] In previous work,^[4c] simple Schiff base libraries with the general structure shown in Scheme 1 were identified as effective catalysts for the asymmetric hydrocyanation of aromatic imine **1a**. The key elements responsible for high enantioselectivity were the presence of bulky substituents at both the amino acid position and at the 3-position of the salicylimine moiety, with **3a**

emerging from the preliminary screens as an enantioselective catalyst with promising generality (Scheme 1). On the basis of these encouraging results, we have constructed a new optimization library of 70 compounds incorporating seven amino acids with large α -substituents and ten new salicylaldehyde derivatives. Each library member was evaluated for enantioselectivity in the Strecker reaction of aliphatic imine **1b** at 23 °C, and the 5-pivaloyl-substituted Schiff base **3b** proved to be the superior catalyst.^[6, 7]

A soluble analogue of **3b** was prepared (**3c**) and evaluated.^[8] At –78 °C, 2 mol % of **3c** catalyzed the formation of the Strecker adduct **2b** in 75% yield (isolated product) and 95% *ee*. This constitutes a substantial improvement over results obtained with catalyst **3a** (85% *ee*).^[4c] Benzaldimine **1a** also underwent hydrocyanation with improved enantioselectivity (95% *ee* with catalyst **3c** vs. 91% *ee* with **3a**).

The scope of the asymmetric Strecker reaction catalyzed by **3c** proved to be remarkably broad (Table 1). Aryl imines

Table 1. Asymmetric catalytic Strecker reactions with catalyst **3c**.

Entry		Imine 1	R ¹	Yield [%]	<i>ee</i> [%] ^[a]
		R			
1	a	C ₆ H ₅	allyl	74	95
2	b	<i>tert</i> -butyl	allyl	75	95 (91)
3	c	<i>p</i> -OCH ₃ C ₆ H ₄	allyl	98	95
4	d	<i>m</i> -OCH ₃ C ₆ H ₄	allyl	99	93
5	e	<i>o</i> -OCH ₃ C ₆ H ₄	allyl	93	77
6	f	<i>p</i> -CH ₃ C ₆ H ₄	allyl	99	95
7	g	<i>m</i> -CH ₃ C ₆ H ₄	allyl	97	96
8	h	<i>o</i> -CH ₃ C ₆ H ₄	allyl	96	95
9	i	<i>p</i> -BrC ₆ H ₄	allyl	89	89
10	j	<i>m</i> -BrC ₆ H ₄	allyl	87	90
11	k	<i>o</i> -BrC ₆ H ₄	allyl	88 ^[b]	95
12	l	<i>p</i> -(CH ₃) ₃ CC ₆ H ₄	allyl	89	97
13	m	<i>tert</i> -butyl	benzyl	88	96 (93)
14	n	cyclohexyl	benzyl	85	87
15	o	cyclohexyl	allyl	88	86
16	p	1-cyclohexenyl	benzyl	90	91 (87)
17	q	(CH ₃) ₃ CCH ₂	benzyl	85	90 (87)
18	r	CH ₃ (CH ₂) ₄	benzyl	69	78
19	s	(CH ₃) ₂ CH	benzyl	74	79
20	t	cyclopropyl	benzyl	89	91
21	u	cyclooctyl	allyl	65	90

[a] Values of *ee* in parentheses were obtained with resin-bound catalyst **3b**.

[b] Reaction time was 36 h.

(entries 1, 3–12) are excellent substrates, undergoing hydrocyanation in generally high enantioselectivities and yields. The bromo-substituted products **2i–k** are particularly versatile intermediates, as these can be elaborated further by using cross-coupling or Heck reactions, thereby providing access to a wide variety of arylglycine derivatives. While all of the aryl imine substrates **1a, c–l** exist predominantly or exclusively as the *E* isomers, this does not appear to be a requirement for high enantioselectivity. The cyclic *Z*-imine 3,4-dihydroisoquinoline (**1v**) underwent hydrocyanation with **3c** in 91% *ee*,

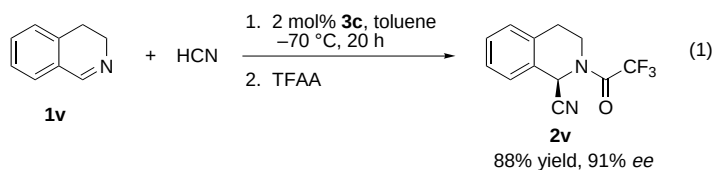
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with the same sense of stereoselection with respect to the benzylic center as the acyclic *E*-imines [Eq. (1)].^[9]

Catalyst **3c** also proved very effective for the hydrocyanation of a variety of aliphatic substrates (Table 1, entries 2, 13–20). Either *N*-benzyl or allyl imines could be used with no significant differences in the results obtained (entries 2 and 13, and 14 and 15). The size of the aliphatic group appears to dictate the level of enantioselectivity with these substrates, with the largest groups affording the highest *ee* values (e.g., entry 12). Given the results described above for 3,4-dihydroisoquinoline (**1v**), it appears unlikely that the lower *ee* values obtained with unhindered imines are due to the increased amount of *Z* isomer present in these substrates.



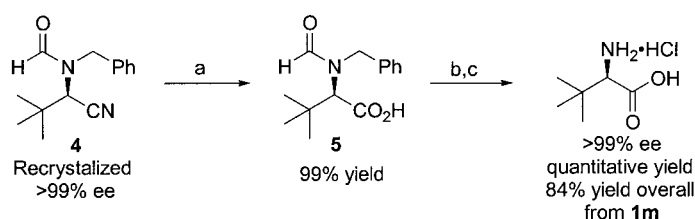
In general, the soluble catalyst **3c** effected hydrocyanation of imines with 2–4% higher *ee* values than the resin-bound analogue **3b** (Table 1, entries 2 and 13, 16 and 17). On the other hand, while all of the reactions summarized in Table 1 led to quantitative product formation with no detectable by-products, some losses were incurred upon product isolation as a result of the need to separate the catalyst chromatographically. In that respect, the polymer supported catalyst **3b**—which is easily removed from the reaction mixtures by simple filtration—holds practical advantages compared to the solution-phase analogue, despite the slightly lower enantioselectivity it displays. To assess the practical potential of the resin-bound catalyst, the Strecker reaction of pivalaldehyde **1m** was examined under preparative conditions. Clean hydrocyanation of **1m** was observed with only a slight reduction in enantioselectivity (96% to 93% *ee*) by using **3b** (Table 1, entry 13). The product was isolated in nearly quantitative yield after catalyst removal by filtration, and no loss of catalyst reactivity or product enantioselectivity was observed after ten catalyst recycles (Table 2).

As noted above, one of the most important applications of the asymmetric Strecker reaction is toward the synthesis of enantiomerically enriched amino acids. We selected *D*-*tert*-leucine as a target because of its considerable utility as a chiral building block and its high current commercial cost (>\$100 g⁻¹). Attempts to hydrolyze the amino nitrile product of the Strecker reaction of **1m** required fairly harsh conditions (concentrated acid, >90 °C) and resulted in considerable decomposition. This problem was circumvented by first protecting the amino nitrile as the formamide **4**, and this allowed facile recrystallization to give enantiomerically pure material in 85% overall yield. Complete and clean hydrolysis of **4** and deformylation was accomplished in one pot (Scheme 2) by using concentrated HCl at 70 °C, although some racemization was observed (99% *ee* to 93% *ee*). In contrast, selective hydrolysis of the nitrile to the acid **5** with concentrated sulfuric acid at 45 °C for 20 h occurs with no

Table 2. Preparative Strecker reactions with resin-bound catalyst **3b**.^[a]

Cycle ^[b]	Yield [%] ^[c]	<i>ee</i> [%]
1	97	92
2	98	93
3	98	93
4	97	93
5	97	92
6	96	93
7	98	93
8	97	93
9	98	93
10	98	93

[a] Either HCN or equimolar quantities of TMSCN (TMS = trimethylsilyl) and MeOH were employed with identical results (1.3 equiv). The scale of the reaction was 1.07 g (6.1 mmol) in all cases. [b] Catalyst was removed by filtration from the previous reaction mixture and rinsed with toluene prior to reuse. [c] Yield of isolated **2** bearing no detectable impurities as determined by ¹H NMR spectroscopy.



Scheme 2. Hydrolysis and deformylation of **4**. a) 65% (w/v) H₂SO₄, 45 °C, 20 h; b) HCl (conc.), 70 °C, 12 h; c) H₂, Pd/C, MeOH.

racemization. Deformylation was then effected in quantitative yield by using concentrated HCl to yield the benzyl-protected amino acid; removal of the benzyl group with Pd/C under 1 atm of H₂ gas afforded *tert*-leucine in >99% *ee* and 84% overall yield from imine **1m**.

In summary, the asymmetric Strecker reaction catalyzed by nonmetal catalysts **3b** and **3c** provides direct access to a diverse range of unnatural aliphatic and aromatic substituted amino acid precursors in high enantiomeric excess. The catalysts are easy to prepare in solution or on solid phase. The use of the resin-bound catalyst **3b** allows Strecker product purification by simple filtration and solvent removal, and the catalyst can be reused indefinitely without loss of either activity or enantioselectivity. Preliminary kinetic experiments indicate that the reaction follows Michaelis–Menten kinetics consistent with reversible binding of imine followed by rate-limiting addition of HCN. Consistent with the notion that these catalysts are enzyme-like, all structural components of **3c** have been shown to be vital for both reactivity and enantioselectivity and thus appear to function cooperatively. Experiments to ascertain the precise mechanism of catalysis and the application of this catalyst class to other types of enantioselective reactions of imines and related electrophiles are currently under investigation.

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- [9] The stereochemical assignment is based on comparison of CD spectra of **2v** with those of compounds **2f**, **g**, **i**, and **p** (see Supporting Information).

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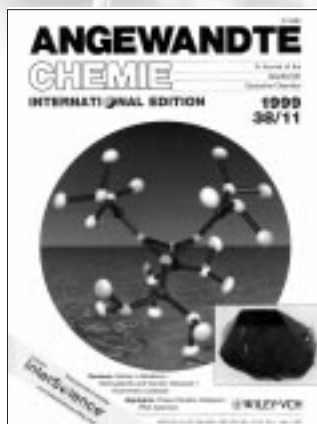
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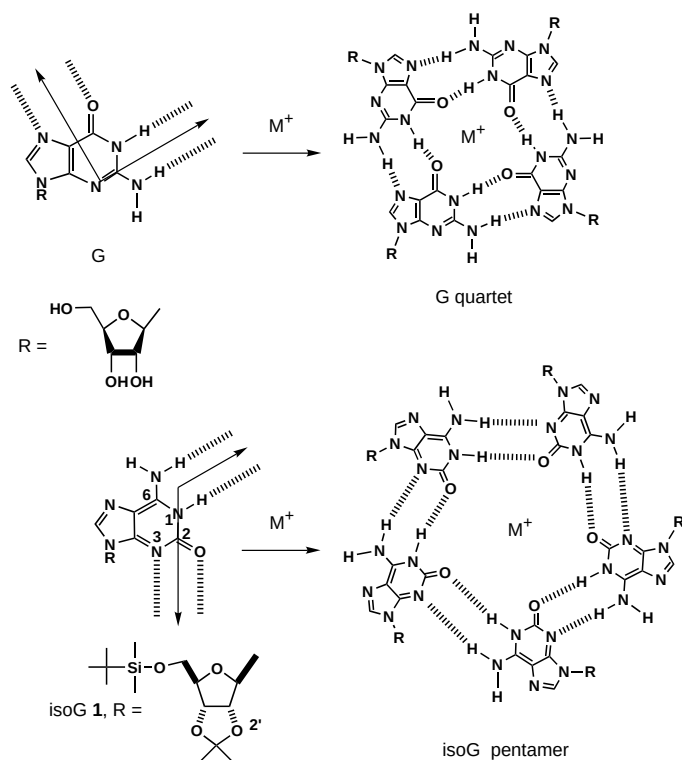
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Binding Cesium Ions with Nucleosides: Templated Self-Assembly of Isoguanosine Pentamers**

Mangmang Cai, Allison L. Marlow, James C. Fetting, Daniele Fabris, Tamara J. Haverlock, Bruce A. Moyer, and Jeffery T. Davis*

Guanosine (G) derivatives self-associate in the presence of metal ions to give the hydrogen-bonded G quartet (Scheme 1).^[1] The G quartet, the cavity of which is surrounded by four oxygen atoms, binds cations with a selectivity



Scheme 1. Aggregation of guanosine and isoguanosine in the presence of metal ions.

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of $K^+ > Na^+, Rb^+ \gg Cs^+, Li^+$.^[1] Isoguanosine (isoG), a guanosine isomer with transposed carbonyl and amino groups, also self-associates in the presence of cations. Poly(isoguanic acid) aggregates more strongly than four-stranded poly(G),^[2] and oligonucleotides containing 2'-deoxy-isoG^[3, 4] or 7-deaza-2'-deoxy-isoG^[5] form tetraplexes in the presence of Na^+ and K^+ .

While exploring the self-association of lipophilic nucleosides,^[6] we discovered that 5'-*tert*-butyldimethylsilyl-2',3'-*O*-isopropylidene-substituted isoG **1** forms a hydrogen-bonded complex with Cs^+ .^[7] This isoG derivative extracts cesium salts from water into $CHCl_3$ with an affinity and selectivity rivaling that of covalent macrocycles.^[7] Given the potential for using a Cs^+ -selective ionophore to bind the fission product $^{137}Cs^+$,^[8] we sought to characterize the complex formed by **1** and Cs^+ .^[9]

We recently proposed that, in addition to a tetramer, isoG can form a hydrogen-bonded pentamer in a cation-templated process.^[10] Subsequent biochemical and computational studies support this proposal, as oligonucleotides containing 2'-deoxy-isoG form stable Cs^+ pentaplexes.^[11, 12] Chaput and Switzer proposed that the relative orientation of the hydrogen-bond donor and acceptor groups (see arrows in Scheme 1) favors formation of a planar cyclic pentamer.^[11] Here we present evidence from both solid-state and solution studies that **1** coordinates to Cs^+ to give the complex $(1)_{10} \cdot Cs^+$, which contains two hydrogen-bonded isoG pentamers.

Tracer distribution experiments with radioactive $^{137}Cs^+$ showed that a 10 mM solution of **1** in $CHCl_3$ extracts cesium chloride, nitrate, and perchlorate from water. Figure 1 shows

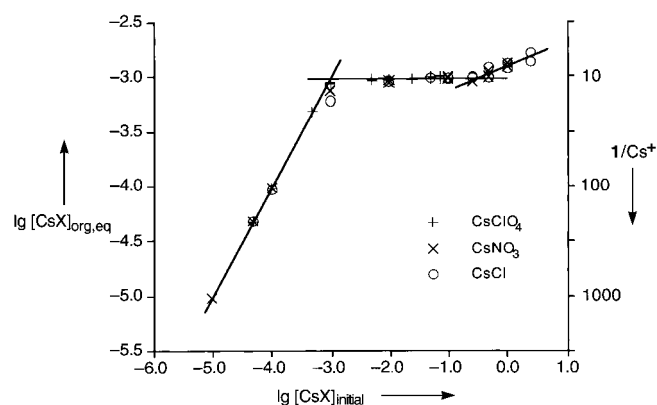


Figure 1. Cesium distribution measurements. A lg/lg plot of the Cs^+ ion concentration [M] extracted into $CHCl_3$ by **1** versus the initial concentration of cesium salt [M] in the aqueous phase. The ligand concentration in $CHCl_3$ was $[1] = 10$ mM. The aqueous solutions of $CsCl$, $CsNO_3$, and $CsClO_4$ contained a radioactive ^{137}Cs ion tracer for precise Cs^+ analysis.

an equivalence point and a plateau consistent with the 10:1 composition of $(1)_{10} \cdot Cs^+$. At initial concentrations of less than 1 mM ($lg[CsX]_{initial} < -3$) the cesium salts are almost quantitatively extracted ($> 96.4\%$ for Cl^- , $> 99.2\%$ for NO_3^- , and $> 99.6\%$ for ClO_4^-). The efficiency of cesium salt extraction by **1** is unprecedented for a neutral cation receptor.^[13]

The X-ray structure unambiguously showed that **1** forms a pentameric macrocycle when templated by Cs^+ .^[14] Single crystals were obtained from CH_3CN containing **1** (300 mM) and $Cs^+Ph_4B^-$ (30 mM). The asymmetric unit, with over 750

non-hydrogen atoms, includes twenty molecules of **1** that make up two independent $(\mathbf{1})_{10} \cdot \text{Cs}^+ \text{Ph}_4\text{B}^-$ units, as well as 37 acetonitrile and 1.5 water molecules. A top view (Figure 2A) of the structure shows two C_5 -symmetric pentamers stacked in a tail-to-tail orientation such that the purine rings directly overlap.^[15] The virtual D_5 symmetry of the $(\mathbf{1})_{10} \cdot \text{Cs}^+$ moiety renders all ten isoG molecules chemically equivalent. The 12-coordinate Cs^+ ion (there are two apical CH_3CN molecules) is nestled within a cage formed by 10 isoG carbonyl oxygen atoms (Figure 2B). A side view (Figure 2C) shows the two planar isoG pentamers, separated by 3.3 Å, sandwiching the Cs^+ ion.

Each isoG pentamer has 15 hydrogen bonds. The self-association of IsoG **1** is mediated by intermolecular $\text{N1-H} \cdots \text{O2}$ and $\text{N6-H} \cdots \text{N3}$ hydrogen bonds (av $d_{\text{N1-O2}} = 2.73$ Å, $\theta_{\text{N1-H} \cdots \text{O2}} = 173^\circ$; $d_{\text{N6-N3}} = 2.87$ Å, $\theta_{\text{N6-H} \cdots \text{N3}} = 170^\circ$; for the numbering scheme see Scheme 1). Sugar–base hydrogen bonds between adjacent monomers also promote self-association of **1**.^[6] The amino group forms hydrogen bonds with $\text{O2}'$ of the ribose residue of the neighboring molecule (av $d_{\text{N6-H} \cdots \text{O2}'} = 2.82$ Å, $\theta_{\text{N6-H} \cdots \text{O2}'} = 139^\circ$). In isoG, the ribose and the hydrogen-bond acceptors (O2 and N3) are located together on the lower edge of the purine residue. In contrast, sugar–base hydrogen bonds are not possible in the G quartet, since the hydrogen-bond acceptors (O6 and N7) and the sugar residue are on opposite sides of the heterocycle.

The $(\mathbf{1})_{10} \cdot \text{Cs}^+$ complex is stable in solution. Electrospray mass spectra of $(\mathbf{1})_{10} \cdot \text{Cs}^+ \text{Ph}_4\text{B}^-$ in CHCl_3 showed a predominant peak at m/z 4509.4, consistent with the molecular ion

(calcd 4508.6 Da). Formation of $(\mathbf{1})_{10} \cdot \text{Cs}^+ \text{Ph}_4\text{B}^-$ in CD_3CN was also monitored by ^{133}Cs NMR spectroscopy. At 25°C , isoG-complexed Cs^+ ($\delta = -54.4$) and solvated Cs^+ ($\delta = 8.1$) were in fast exchange ($k_{\text{ex}}(\text{Cs}^+) > 10^5 \text{ s}^{-1}$) and gave a single, population-averaged NMR signal. Titration gave a sharp end point when ten equivalents of **1** were added for each equivalent of $\text{Cs}^+ \text{Ph}_4\text{B}^-$ (Figure 3), and this indicates that $(\mathbf{1})_{10} \cdot \text{Cs}^+$ is thermodynamically stable ($K_a > 10^5 \text{ M}^{-1}$) but kinetically labile.

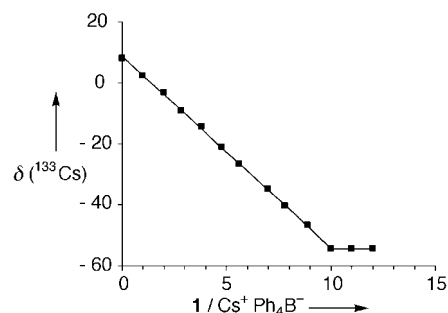


Figure 3. ^{133}Cs NMR (65.6 MHz) chemical shift as a function of the molar ratio of $\mathbf{1}/\text{Cs}^+ \text{Ph}_4\text{B}^-$ in CD_3CN at 25°C . The salt concentration was held constant at $[\text{Cs}^+ \text{Ph}_4\text{B}^-] = 10 \text{ mM}$, while the ligand concentration was varied between $[\mathbf{1}] = 0$ and 120 mM .

The unique structure of $(\mathbf{1})_{10} \cdot \text{Cs}^+$ illustrates the power of noncovalent synthesis;^[16] combining isoG and Cs^+ results in 30 hydrogen bonds and 10 ion–dipole bonds. Furthermore, self-assembly gives a potentially useful supramolecule from a simple monomer. The structure also provides a basis for the next challenge: tuning the dynamics of this Cs^+ ionophore. The relatively rapid Cs^+ exchange by $(\mathbf{1})_{10} \cdot \text{Cs}^+$ in CD_3CN bodes well for using self-assembled ionophores as reversible cation receptors. In particular, **1** may find use in demanding separations of radioactive $^{137}\text{Cs}^+$ in a variety of nuclear applications.

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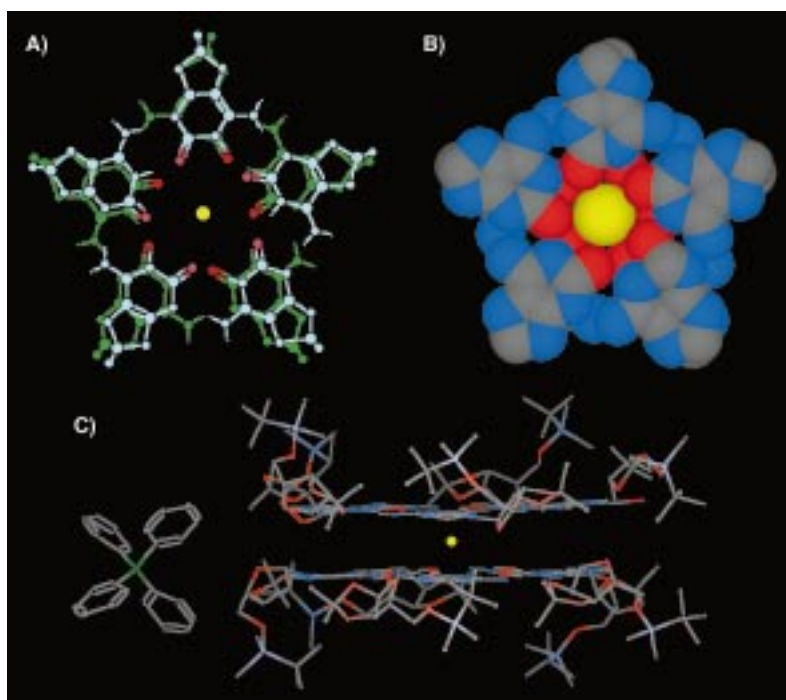


Figure 2. A) A top view of the X-ray crystal structure of $(\mathbf{1})_{10} \cdot \text{Cs}^+ \text{Ph}_4\text{B}^-$. The sugar residues are omitted for clarity. One isoG pentamer is blue, and the other is green. B) Space-filling top view. The Cs^+ ion is yellow, O atoms are red, N atoms are blue, and C atoms are gray. The Cs^+ ion is bound to 10 carbonyl O atoms (av $d_{\text{Cs-O}} = 3.40$ Å). C) Side view of $(\mathbf{1})_{10} \cdot \text{Cs}^+ \text{Ph}_4\text{B}^-$. Some of the atoms on the 5' side chain of the ribose residue are omitted for clarity. This view shows the stacking of the two planar isoG pentamers. The Ph_4B^- anion is remote from the encapsulated Cs^+ ion.

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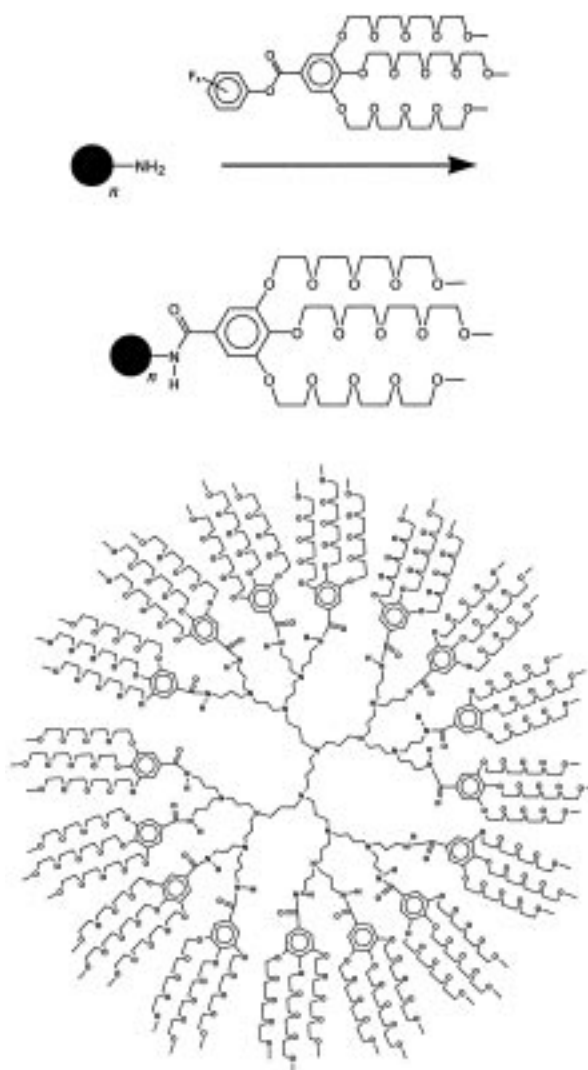
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The Localization of Guests in Water-Soluble Oligoethyleneoxy-Modified Poly(propylene imine) Dendrimers**

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The highly branched, three-dimensional geometry of dendritic macromolecules^[1] makes these new molecular architec-

tures ideal container molecules.^[2] It has been suggested that these molecules could be used in a number of applications including those related to the controlled release of pharmaceuticals.^[3, 4] Several host–guest systems have already been developed, for example, dendritic hosts with unimolecular (inverted) micellar structures,^[5] the “dendritic box”,^[6] crown ether dendrimers,^[7] and cyclophane dendrimers.^[8] A restricted number of guests, such as rose bengal, can be encapsulated in the “dendritic box”, (a fifth generation poly(propylene imine) dendrimer modified with a dense shell of amino acids)^[6] and released by simple chemical modification of the shell.^[6c] Dynamic hosts in organic media^[9a] or supercritical CO₂^[9b] are based on hydrophobically modified poly(propylene imine) dendrimers and have proved to be efficient extractants of aqueous solutes. Recently, more attention has been focussed on water-soluble dendritic systems,^[10] but their host–guest properties have not been addressed so far. Herein we present poly(propylene imine) dendrimers modified with 3,4,5-tris(tetraethyleneoxy)benzoyl units, which have a basic interior of tertiary amines and a hydrophilic periphery (Scheme 1). Titrations and small angle X-ray scattering



Scheme 1. Top: Synthesis of oligoethyleneoxy-functionalized poly(propylene imine) dendrimers; *n* = 4: **1**; *n* = 16: **2**; *n* = 32: **3**, and *n* = 64: **4**. Bottom: Schematic structure of host **2**.

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(SAXS) experiments show that unique interactions lead to the preferential location of guests in the core of these novel, unimolecular water-soluble dendritic hosts.

Four different generations of oligoethyleneoxy-functionalized poly(propylene imine) dendrimers (DAB-*dendr*-(NHCO-EG)_n, where EG represents the 3,4,5-tris(tetraethyleneoxy)-benzoyl unit and with $n = 4$: **1**, $n = 16$: **2**, $n = 32$: **3**, and $n = 64$: **4**) have been synthesized by reaction of the corresponding pentafluorophenyl ester with the amine-functionalized poly(propylene imine) dendrimers. Dendrimers **1–4** and all intermediates have been characterized by ¹H NMR, ¹³C NMR, and IR spectroscopy as well as by mass spectrometry (ESI or MALDI-TOF). The functionalized dendrimers are monodisperse compounds, for example, a single peak is observed at $m/z = 13243$ in the mass spectrum of the third generation dendrimer **2**, which corresponds to the correct mass. The defects that are observed in the fourth and fifth generation can be attributed to defects already present in the amine-functionalized poly(propylene imine) dendrimers,^[11] and are not a result of incomplete modification of the dendrimer end groups.

The host–guest properties of these dendritic structures were studied in buffered aqueous media at pH 7 using two anionic, water-soluble xanthene dyes as guest molecules (**I**: 4,5,6,7-tetrachlorofluorescein, **II**: rose bengal). Titration of a stock solution of **4** to a solution of guests **I** or **II** yielded a

bathochromic shift in the wavelength of the maximum absorption (λ_{max}) in both cases, which is indicative of an interaction (complexation) between the dendrimer host and the xanthene guest. This complexation was studied by plotting the ratio of the absorptions corresponding to the complexed and free guest against the guest–host ratio (GHratio; Figure 1).^[12] The complexation of guest **II** with the dendritic host is much stronger than for guest **I**, with association constants K_a of $(5.0 \pm 0.04) \times 10^5 \text{ M}^{-1}$ and $(3.0 \pm 0.4) \times 10^4 \text{ M}^{-1}$, respectively. Upon titration of **I** with **4** the absorption at the λ_{max} of the free dye decreases and there is an isosbestic point over the whole titration range, which is indicative of an equilibrium existing between the complexed and free dye. The single isosbestic point indicates that the λ_{max} of the complexed dye is independent of the number of dyes complexed. More information can be obtained from the titration of **II** with **4** (Figure 1, bottom right) where three different regimes and two inflection points (marked by arrows) at GHratios of 1 ± 0.5 and 40 ± 5 can be distinguished. Moreover, the UV spectra not only reveal complexation of the guest, but also the effect of dye–dye interactions inside a single host. Between $0 < \text{GHratio} < 1$ a strong complexation of the guest takes place and a constant absorption spectrum is obtained (regime A). Between $1 < \text{GHratio} < 40$ all the guests are strongly complexed, but as a result of dye–dye interactions of the guest within one host molecule a decrease in the ratio A_{563}/A_{547} is

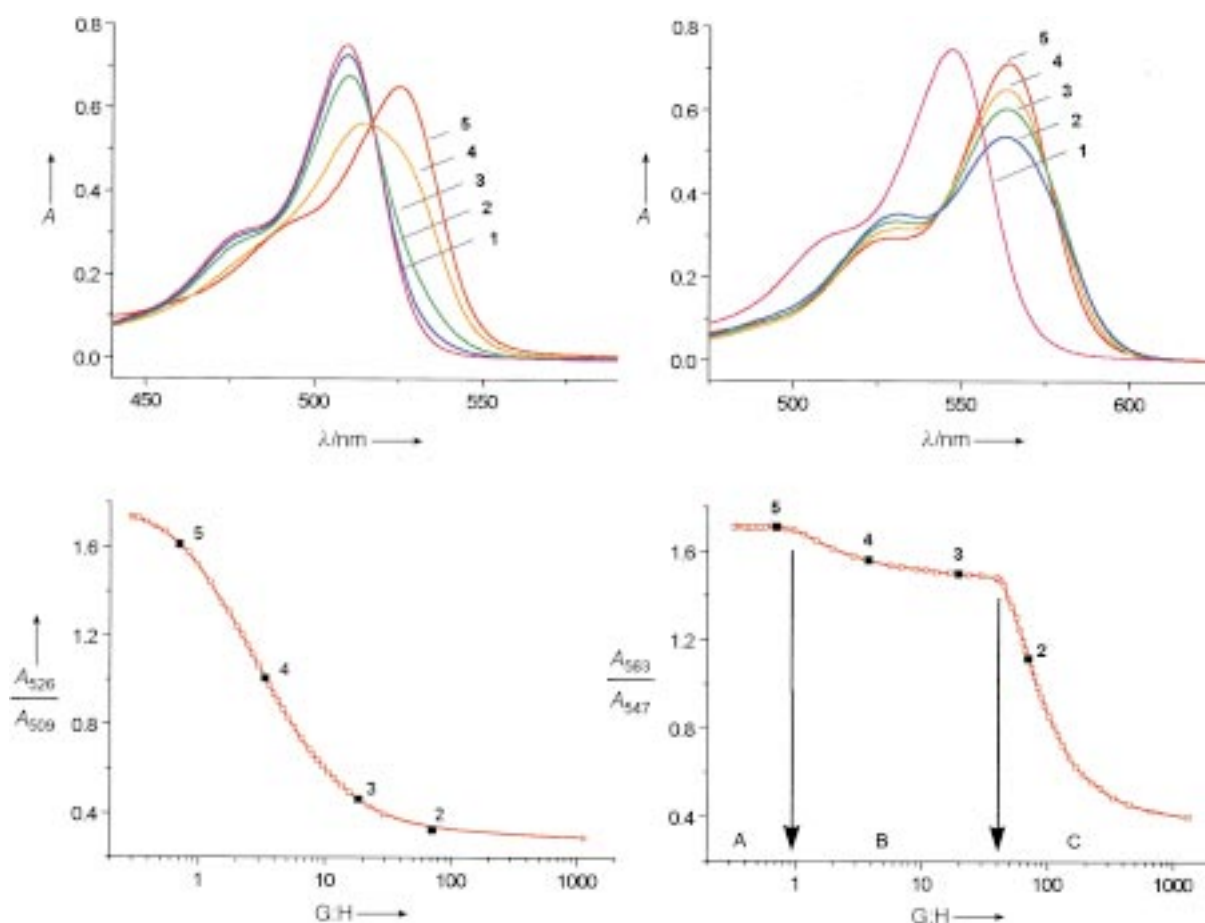


Figure 1. Top: UV/Vis spectra obtained from the titration of guest **I** (left) and **II** (right) with **4**. Typical UV/Vis spectra are marked from 1 to 5. Bottom: Ratio of the absorption of the complexed dye to the free dye as a function of the GHratio for guest **I** (left) and guest **II** (right). Numbers 2–5 are used to refer to the UV/vis spectra. Number 1 at infinite GHratio is omitted.

observed (regime B). Finally, for a GHratio > 40 an excess of guest is present in equilibrium with complexed guest molecules (regime C).

The association between the host and guest described above is explained by acid–base interactions between the acidic functionality of the guest and the tertiary amine groups of the dendritic host, similar to previously reported host–guest systems^[9a, 13] This argument is also supported by the association behavior of **I** being strongly pH dependent. The smaller pH-dependence of **II** suggests, however, that it is not only electrostatic interactions, but also the higher hydrophobicity of **II**^[12] that plays an important role in the association process. The stability of the system is demonstrated by an ultrafiltration technique, in which a membrane with a molecular weight cut-off of approximately 10 kDa was used. We were able to distinguish between host–guest complexes formed with hosts **1** (3 kDa) and **4** (53 kDa). In the case of host **4**, all the guest molecules are retained in the filtration cell, which is indicative of the high molecular weight of the host and the strong host–guest association. This result is in contrast to a host–guest complex of **1**, which passes through the membrane.

The structure of dendrimer **4** in different solutions has been analyzed by SAXS measurements.^[14] The oligoethyleneoxy-functionalized dendrimers are soluble in toluene, dichloromethane, tetrahydrofuran, acetonitrile, ethylene glycol monomethyl ether, ethanol, and aqueous media. Interactions between the dendrimers in dilute solutions are negligible and they reveal maximum dimensions of 5.1–5.6 nm.^[15] Consequently, measurements have been performed on dilute solutions (concentrations approximately 10 mg mL^{−1}) of host **4** and guest **II** at different GHratios. In all cases the SAXS intensity at low scattering vector q is described using the Guinier approximation and displayed in Figure 2 (top).

This plot reveals three features: 1) the forward scattering intensity $I_h(q \rightarrow 0)$ obtained by extrapolation and the invariant Q_h were derived in order to calculate the particle volume without absolute scaling of q [Eq. (1)].

$$V_h = \frac{2\pi^2 I_h(0)}{Q_h} \quad (1)$$

This equation yields $V_h = 8.5 \times 10^{-26} \text{ m}^3$ and the molar mass of the host $M_h = V\rho N_A$ is therefore 51.5 kDa when a density of 1000 kg m^{−3} is assumed, whereas the actual molar mass is 53.5 kDa as measured by MALDI-TOF mass spectrometry. This result confirms that the SAXS pattern reflects the scattering from individual macromolecules. Additional scattering data, scaled to absolute intensities, are given in the Supplementary Information; 2) an increase in the forward scattering intensity $I(q \rightarrow 0)$ with increasing amounts of dye molecules in the dendrimer, which not only reflects the change in molecular weight of the complex from addition of the guest molecules (1 kD) to the dendritic host (53 kD), but also a change in contrast $\Delta\rho$, since the guest molecules with chlorine and iodine atoms add a substantial amount of electrons to the system; 3) a change in the slope of the Guinier plots, which reveals a significant decrease in the radius of gyration (R_g^*) of the complex upon addition of the guest molecules (•—•). If the dyes were uniformly distributed

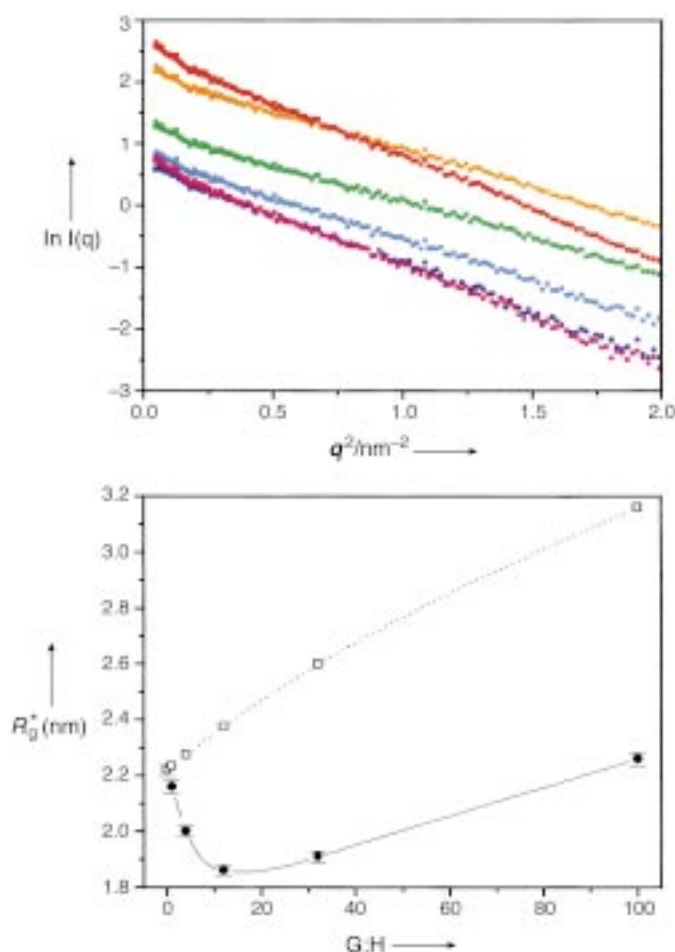


Figure 2. Top: Guinier plots for complexes of **4** and **II** for different GHratios; purple: no guest, dark blue: 1 guest, Light blue: 4 guests, green: 12 guests, yellow: 32 guests, red: 100 guests. Bottom: Radius of gyration of complexes (R_g^*) of **4** and **II** as a function of the GHratio (•—•). Expected radius of gyration of complex is included, and assumes a homogeneous distribution of guests (·····).

within the dendrimer molecules, a slight increase would be expected in both the radius of gyration of the complex (·····) and the maximum dimensions as a result of the increase in the total molecular weight. In the present systems, however, the maximum dimensions are essentially unchanged, whereas the radius of gyration (Figure 2, bottom) decreases with an increasing number of guest molecules (up to a ratio of 12:1). Since the latter reflects the second moment of the (electron) density distribution $\rho^*(r)$ within the complex, and not $\rho(r)$ of the dendritic host, this in fact indicates that the dye molecules are preferentially accumulated in the central region of the dendritic hosts. If more guests are complexed to the dendritic hosts, the outer regions fill up and an increase in the R_g is observed. Surprisingly, with an excess of guest, that is, a GHratio of 100, the R_g equals that of the unloaded host (Figure 3).

In summary, we conclude that a new host–guest system has been developed and the interactions in aqueous media have been studied by UV/Vis titrations. A typical property of dendrimers, namely their retention in membranes as a result of their nanometer dimensions, has been shown by ultrafiltration. As there is no aggregation the SAXS measurements

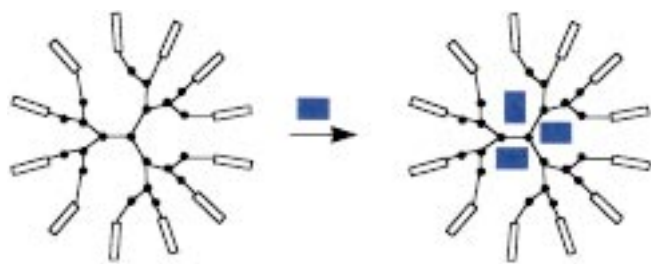


Figure 3. Schematic representation of the preferential location of dye molecules in the dendrimer as the concentration of the dye is increased.

provide strong evidence for the preferential location of the guests in the interior of the dendrimer.

Experimental Section

A more extended description of the compounds, synthesis, and characterization are presented in the Supplementary Information. Moreover, experimental details and additional SAXS data are included in this section. Only a typical procedure for the synthesis of oligoethyleneoxy-modified poly(propylene imine) dendrimers is described here.

2: The pentafluorophenyl ester of 3,4,5-tris(tetraethyleneglycol)benzoic acid (8.82 g, 9.72×10^{-3} mol, 1.025 equiv per NH_2) was added to a solution of DAB-dendr- $(\text{NH}_2)_{16}$ (1.00 g, 5.93×10^{-4} mol) in CH_2Cl_2 (10 mL). After stirring the mixture overnight it was extracted with 0.1 M NaOH and excess active ester was removed by chromatography on biobeads (BioRad, SX1) to yield pure **2** (6.28 g, 80%) as a viscous oil. Purity was confirmed by TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5, $R_f = 0$). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.96$ (s, 16H, NHCO), 7.16 (s, 32H, Ar-H), 4.16–4.00 (96H, Ar- OCH_2), 3.80–3.45 (672H, OCH_2), 3.42 (32H, CH_2NHCO), 3.38 (144H, OCH_3), 2.60–2.30 (84H, NCH_2), 1.80–1.40 (60H, NCH_2CH_2); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 167.2$ (NHCO), 152.3 (Ar-C3,C5), 140.8 (Ar-C4), 129.7 (Ar-C1), 106.7 (Ar-C2,C6), 72.6/72.1/70.8/70.7/69.8/69.0 (OCH_2), 59.0 (OCH_3), 52.4–51.8 (NCH_2), 38.9 (CH_2NHCO), 27.5 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{NHCO}$); MALDI-TOF-MS: calcd. for $\text{C}_{632}\text{H}_{1136}\text{N}_{30}\text{O}_{256}$: 13251.9; found: 13243 $[M+H]^+$.

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Crystal Engineering of Metalloporphyrin Zeolite Analogues**

Yael Diskin-Posner, Sanjay Dahal, and Israel Goldberg*

Molecular self-assembly has emerged in recent years as an attractive approach to the fabrication of new materials.^[1] This process involves the spontaneous aggregation of small molecular building blocks in solution that recognize each other through multiple molecular recognition sites to form extended architectures (while overcoming solvation forces and negative entropy effects), and it can be particularly effective in the design of nanoporous solids. However, such formula-

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tions have enjoyed a limited success thus far, mostly as a result of the softness of the intermolecular bond, which has left open the formidable task of synthesizing stable, three-dimensional supramolecular frameworks with open voids that can be readily accessed by other species. However, a few recent successes in the construction of structurally robust porous organic crystals,^[2] based on well established principles of the supramolecular design in solids^[3] provide an encouraging indication that development of stable porous molecular solids with structural and functional resemblance to the naturally occurring inorganic zeolites could be feasible. The ability to organize molecular building blocks into desired supramolecular architectures through cooperative noncovalent forces requires identification of effective synthons with suitable geometries and adequate enthalpic driving forces.

In this context, several functionalized tetraarylmetalloporphyrin molecules were shown to self-assemble in different ways to yield hydrogen-bonded columns,^[4] hydrogen-bonded networks with large interporphyrin voids,^[5] coordination polymers propagated by coordination of the lateral substituents of a given porphyrin entity to the metal center of a similar unit,^[6] and multiporphyrin arrays sustained by external transition metal centers^[7] or by bidentate ligands that can bridge axially between adjacent metalloporphyrin cores.^[5a, 8] Most of these materials are composed of one- or two-dimensional porphyrin aggregates, and only a small number of them yielded porous crystalline architectures.^[5c, 6c, 7a] Particularly notable here is the tetra(4-carboxyphenyl)zinc porphyrin moiety [$\text{Zn}^{\text{II}}(\text{tcpp})$], which was used by us in the formation of a unique, and remarkably stable, molecular sieve structure with nanosized (1.5 nm wide) channels.^[5c]

Herein we report on the successful crystal engineering of a novel uniquely structured multiporphyrin assembly based on interlinked arrays of [$\text{Zn}^{\text{II}}(\text{tcpp})$] and 4,4'-bipyridyl (bpy) ligands by using a simple preparative procedure, and without resorting to external transition metal auxiliaries. The crystal structure of the constructed material represents an open three-dimensional framework in which the individual metalloporphyrin units are cross-linked both axially as well as equatorially by ion-pairing interactions, metal–ligand coordination, and hydrogen bonding. Its lattice is thus fully sustained by specific intermolecular interactions, and not by virtue of van der Waals forces as is commonly observed in molecular crystals,^[9] and thus provides a striking resemblance to the architecture of common zeolites.

The key feature to this successful formulation turned out to be the use of

an alkali metal salt of mono-deprotonated tetracarboxylic acid, rather than of the neutral metalloporphyrin molecule. This compound allows tessellation of the commonly observed layered organization of the tcpp units not only by means of the soft hydrogen-bonding interactions,^[5b,c] but also by more effective ion-pairing forces. Recent literature related to inorganic materials indicated that carboxylic derivatives may assemble as binuclear di-potassium or di-sodium (carboxyl/carboxylate)_{6–8} aggregates in the presence of alkali cations,^[10] but this interesting observation has not been further explored as yet in the context of deliberate synthesis of supramolecular systems. To confirm the occurrence of this synthon in the much bulkier tcpp system we initially prepared and structurally analyzed crystals of a potassium salt of [$\text{Cu}^{\text{II}}(\text{tcpp})$] (**1**, see Experimental Section for detailed composition). The templating of the anionic porphyrin arrays by potassium ions leads to the formation of the binuclear $\{\text{K}^+_{2}(-\text{COO}^-)_2(-\text{COOH})_6\}$ unit (Figure 1). With no axial coordination to the porphyrin metal center (Cu^{II} has four-coordination preference) this structure consists of continuous columns of offset-stacked [$\text{Cu}^{\text{II}}(\text{tcpp})$] species with an interporphyrin distance of 3.87 Å, which is in line with the strong tendency of the tetraphenylporphyrin units to stack in a face-parallel fashion.^[11]

The characterization of the templating effect of alkali metal cations on the self-assembly of the tcpp units led to the next series of experiments in which the [$\text{Cu}^{\text{II}}(\text{tcpp})$] moieties were

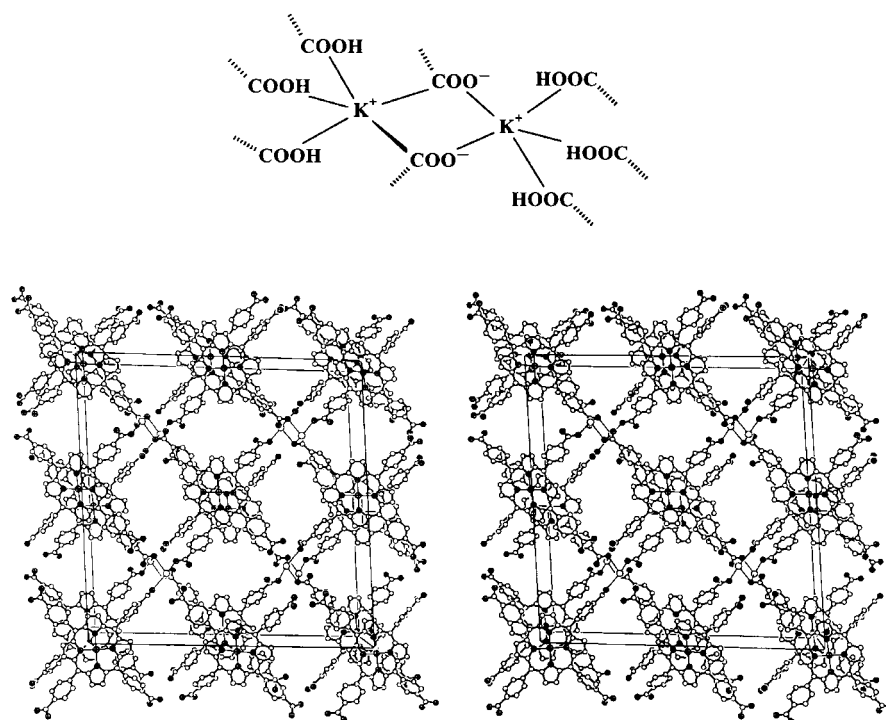


Figure 1. The structure of the binuclear $\{\text{K}^+_{2}(-\text{COO}^-)_2(-\text{COOH})_6\}$ unit dominant in **1** and the stereoview, approximately down the *b* axis, of its columnar crystal structure. The columns composed of stacked [$\text{Cu}(\text{tcpp})$][−] units are interconnected to each other through the potassium ions as well as by hydrogen bonding between the carboxylic acid groups, which yields an open architecture. Interporphyrin channels propagate along the *b* axis of the unit cell and are partly occupied by disordered nitrobenzene molecules (not shown for clarity). Every alkali metal cation is coordinated at 2.72–2.78 Å to three of the oxygen atoms (dark circles) of the carboxylic acid groups and at 2.87–3.11 Å to three other carboxylic acid groups, as well as to an additional molecule of water at 2.67 Å (not shown). The distance between the two potassium nuclei (large open circles) is 4.33 Å.

replaced by the corresponding $[\text{Zn}^{\text{II}}(\text{tcpp})]$ and $[\text{Mn}^{\text{III}}(\text{tcpp})] \cdot \text{ClO}_4$ analogues, which have an added capacity to coordinate ligands in the axial, as well as the equatorial, direction. These experiments were carried out in the presence of linear bidentate ligands (for example, bpy) in an attempt to induce axial coordination between the porphyrin species, and thus extend the supramolecular interaction in three dimensions. Single crystals suitable for a detailed structural characterization could only be obtained for the zinc derivative **2** (see Experimental Section for a detailed composition) from a reaction of $[\text{Zn}^{\text{II}}(\text{tcpp})]$ with bpy in a hot solution of methanol and ethyl benzoate in the presence of sodium chloride. Formation of the final product under such conditions is associated with proton transfer from one of the carboxy groups to the chloride anion and expulsion of hydrochloric acid. Analysis of the resulting material reveals an unprecedented zeolite-like architecture, which is perforated by wide channels in two perpendicular directions (Figure 2). This

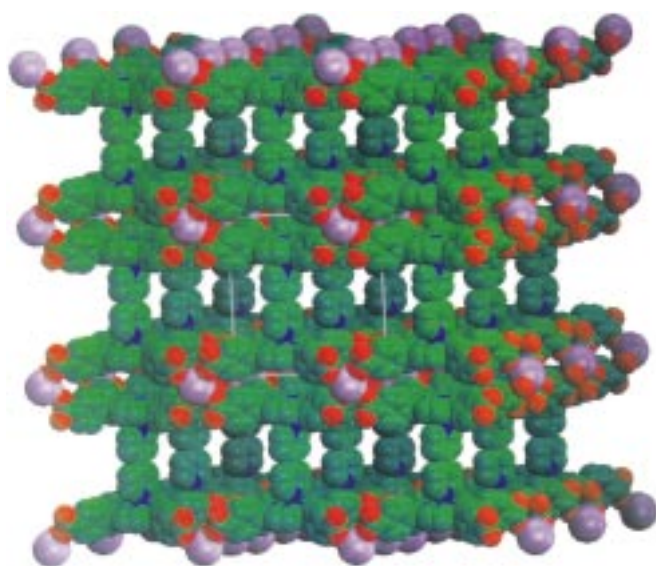


Figure 2. Space-filling (CPK) representation of the open zeolite-like supramolecular framework in **2**. It consists of sodium-tessellated metal-porphyrin bilayers extending parallel to the *ab* plane of the crystal, which are bridged by bipyridyl ligands along the *c* direction. The open galleries accessible to other molecules propagate between the bipyridyl pillars in directions parallel to the porphyrin bilayers. Na: violet, N: blue, O: red, C: green (Zn is hidden).

fascinating supramolecular assembly represents an open, single-framework three-dimensional polymer. It can be best described as composed of layers of $[\text{Zn}^{\text{II}}(\text{tcpp})]^-$, which are held together by hydrogen bonds as well as by charge interactions and lie parallel to the *ab* plane of the crystal (Figure 3a). The sodium counter ions also provide the electrostatic force which combines two such layers back-to-back into a closely packed $[\text{Zn}^{\text{II}}(\text{tcpp})]^- \cdot \text{Na}^+$ bilayer (Figure 3b,c). Each interaction site involves a binuclear $\{\text{Na}^+_2(-\text{COO}^-)_2(-\text{COOH})_6\}$ unit with $\text{Na} \cdots \text{O}$ and $\text{Na} \cdots \text{Na}$ distances of 2.33–2.41 and 3.589 Å, respectively. The zinc ions, having a strong affinity for a five-coordinate environment, deviate outward (by 0.25 Å with respect to the plane of the respective porphyrin core) from the bilayer in opposite

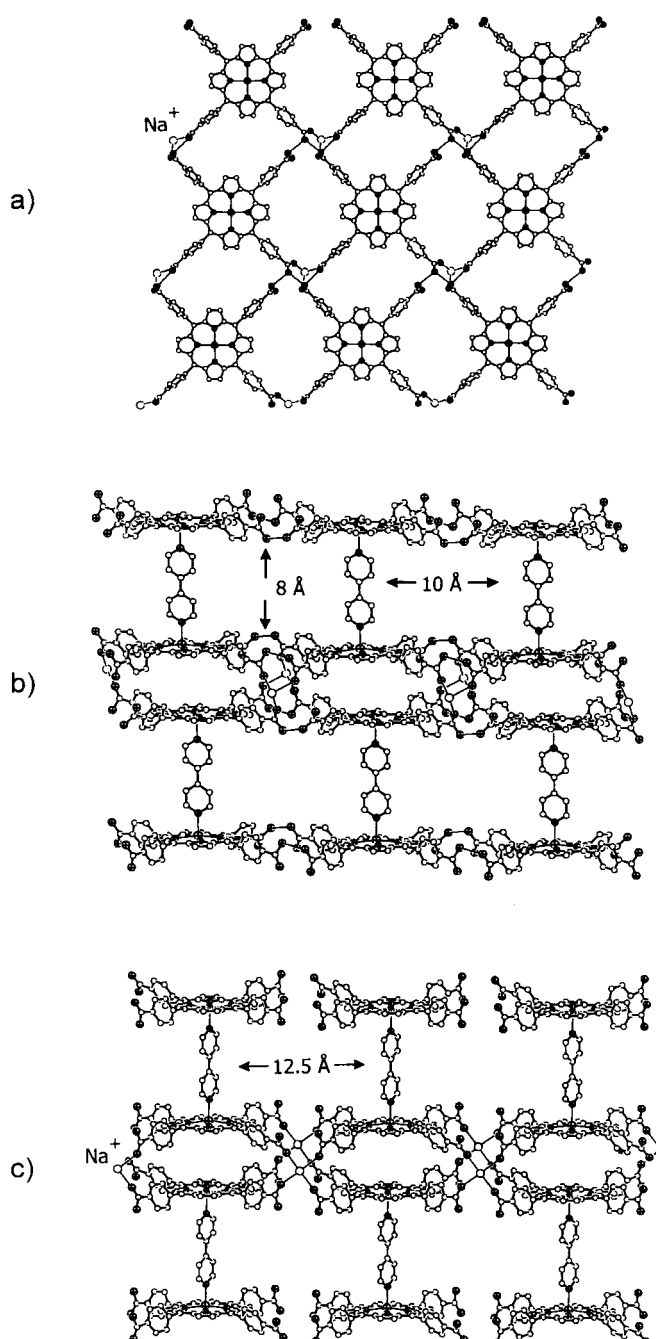


Figure 3. Detailed illustration of crystal structure **2**. a) Molecular organization in a single metal-porphyrin network, marking the hydrogen bonding (between dark circles denoting O atoms) and $\text{Na}^+ \cdots \text{O}$ (Na^+ is represented by the large open circles) interactions between adjacent units. Molecules of ethyl benzoate, which protrude into the interporphyrin voids in these layers, are not shown for clarity. Sections through the crystal: b) in the *ac* plane (*a* axis is horizontal) and c) the *bc* plane (*b* axis is horizontal), illustrating the three-dimensional supramolecular coordination scheme between the constituent entities. The distances between the van der Waals surfaces of the lattice framework are indicated, which define the approximate open space available in this lattice for the intercalation of other compounds. All aromatic hydrogen atoms (not shown for clarity) were accounted for in these estimations.

directions and provide an additional binding site. This arrangement allows successively displaced bilayers to be linked together axially (the average spacing between the inner porphyrin cores of two adjacent bilayers is 11.85 Å) by the bpy

ligands ($\text{Zn} \cdots \text{N}_{\text{py}} = 2.147 \text{ \AA}$) along the c axis of the crystal (Figure 3). The ethyl benzoate solvent is located in a disordered manner within the small interporphyrin cavities of each layer (as observed in related metalloporphyrin β -molecular networks)^[5a,b] and completes the octahedral coordination sphere around each sodium cation with its carbonyl oxygen atom ($\text{Na} \cdots \text{O}(\text{solvent}) = 2.43 \text{ \AA}$).

The crystal lattice of this material is perforated by wide-open channels which propagate between the bpy pillars in different directions parallel to the plane of the porphyrin bilayers. The distances between the van der Waals surfaces of these pillars are rather large, approximately $10.0 \text{ \AA}$ along the a axis and $12.5 \text{ \AA}$ along the b axis, while the corresponding height of the open space is about $8 \text{ \AA}$ (Figures 2 and 3). Yet, in spite of the fact that the $[\text{Zn}^{\text{II}}(\text{tcpp})]^- \cdot \text{Na}^+ \cdot \text{bpy} \cdot \text{ethyl benzoate}$ lattice occupies only 42% of the crystal volume (34% when the ethyl benzoate solvent coordinating to the Na^+ ions is excluded as well), the presence of no other species intercalated between the porphyrin bilayers could be identified from the diffraction data. Only very diffuse residual electron density observed in the open galleries provided evidence for their partial occupation by disordered solvent (see below). The structural refinement of this lattice alone converged at a relatively low (for such "hollow", yet crystalline systems) $R1$ value of 13.6%, which confirmed with a high degree of certainty the validity of this determination. The very loose crystal packing is also reflected in the rotational disorder of the two pyridyl rings about the main axis of the bpy molecule, as well as in the relatively large thermal displacement parameters of other atoms positioned along the channel walls. Thermogravimetric analysis (TGA/DTA) of these crystals indicated a major weight loss (32%) between 50 and 150°C , and a more moderate and monotonic weight reduction of about 13.5% on further heating from 150 to 400°C . Intercalation of approximately 32 volatile molecules of methanol (or a corresponding combination of methanol and water) into the crystal lattice per unit cell can be deduced from the weight loss at the first stage where there is no apparent phase transition or damage to the crystal morphology. The second part of this process is attributed to the loss of the high-boiling ethyl benzoate solvent, followed by sublimation of the bridging bpy ligands and slow decarboxylation, phase transition (at 305°C), and conversion of the crystalline lattice to a dark amorphous powder. After subtraction of the disordered and diffused solvent contribution to the diffraction pattern, the crystallographic refinement converged with a reasonable precision at a considerably lower $R1$ value of 7.6%, without any major distortion of the supramolecular porphyrin–bipyridyl lattice being observed. The stability of this lattice, as well as its dynamic properties related to the intercalation and exchange of other compounds, are the subject of further investigations.

The supramolecular synthesis of molecular sieve materials based on effective synthons with intermolecular interaction capabilities is an exciting challenge in molecular chemistry. The ability to generate low-density, stable crystalline solids consisting of a single-framework three-dimensional lattice, in which 50% or more of the crystal volume is an open space that is accessible to other sizeable molecules provides a

promising perspective for new robust molecular solids and zeolite mimics with interesting and useful properties (although such lattices are not yet sufficiently robust at high temperatures and often loose crystallinity when completely empty). Other recently developed designs of open lattices that may exhibit catalytic properties are based on the formulation of binuclear Cu_2 and Mo_2 polycarboxylate assemblies of related metalloporphyrin building blocks in which access to the porphyrin metal center is not blocked by a bridging ligand. The ordered array of open channels in this kind of structures will permit a low resistance to the diffusion of the potential reactant molecules to the active metal sites located within the channels.

Experimental Section

Tetra(4-carboxyphenyl)porphyrin was prepared by standard procedures.^[12] The products were obtained by treating stoichiometric amounts of either $[\text{Cu}^{\text{II}}(\text{tcpp})]$ and KClO_4 in a mixture of methanol and nitrobenzene (for **1**) or $[\text{Zn}^{\text{II}}(\text{tcpp})]$, NaCl , and bpy (for **2**) in a mixture of methanol and ethyl benzoate (similar experiments with $[\text{Mn}^{\text{III}}(\text{tcpp})] \cdot \text{ClO}_4$ led to crystals with very high mosaicity), followed by preparative crystallization. The diffraction data for **1** and **2** were collected on a Nonius KappaCCD diffractometer at 115 K to minimize thermal motion and evaluated by standard crystallographic techniques.

Crystal data for **1**: $[\{\text{C}_{48}\text{H}_{27}\text{N}_4\text{O}_8\text{Cu}\}]^- \cdot \text{K}^+ \cdot 2\text{H}_2\text{O} \cdot \text{C}_6\text{H}_5\text{NO}_2$, $M_r = 1049.5$, monoclinic, space group $I2/a$ (No. 15), $a = 34.922(1)$, $b = 8.790(1)$, $c = 33.245(1) \text{ \AA}$, $\beta = 93.84(1)^\circ$, $V = 10182.2 \text{ \AA}^3$, $Z = 8$, $\rho_{\text{calc}} = 1.369 \text{ g cm}^{-3}$, $2\theta_{\text{max}} = 51.5^\circ$, 9391 unique reflections. Final $R1 = 0.119$ for 5684 reflections with $F > 4\sigma(F)$, $R1 = 0.189$, $wR2 = 0.328$, and $\text{GOF} = 1.007$ for all data, with the nitrobenzene and one molecule of water being severely disordered in the lattice (the nitrobenzene exhibits a twofold orientational disorder about the normal to its plane). When the contribution of the disordered solvent (located in the voids of the interporphyrin channel of the lattice) to the diffraction pattern is subtracted from the observed data by the "Squeeze" method,^[13] the final $R1 = 0.079$ for 5428 reflections with $F > 4\sigma(F)$, $R1 = 0.144$, $wR2 = 0.206$, and $\text{GOF} = 1.051$ for all data.

Crystal data for **2**: $[\{\text{C}_{48}\text{H}_{27}\text{N}_4\text{O}_8\text{Zn}\}]^- \cdot \text{Na}^+ \cdot \frac{1}{2}(\text{C}_{10}\text{H}_8\text{N}_2) \cdot \text{C}_9\text{H}_{10}\text{O}_2 \cdot (\text{CH}_3\text{OH})_x$, triclinic, space group $P\bar{1}$ (No. 2—based on intensity statistics), $a = 16.315(1)$, $b = 17.405(1)$, $c = 18.410(1) \text{ \AA}$, $\alpha = 89.59(1)$, $\beta = 84.33(1)$, $\gamma = 82.52(1)^\circ$, $V = 5157.8 \text{ \AA}^3$, $Z = 2$, $2\theta_{\text{max}} = 51.3^\circ$, 19005 unique reflections. For $x = 16$ (based on TGA), $M_r = 1617.0$, $\rho_{\text{calc}} = 1.041 \text{ g cm}^{-3}$, $\rho_{\text{meas}} \approx 1.0 \text{ g cm}^{-3}$. This crystallographic refinement (excluding the lattice-diffused methanol solvent) converged at $R1 = 0.136$ for 15037 reflections with $F > 4\sigma(F)$, $R1 = 0.161$, and $wR2 = 0.380$ for all data. After subtracting the contribution of all disordered solvent (ethyl benzoate as well as methanol) to the diffraction pattern from the observed data by "Squeeze",^[13] the final $R1 = 0.076$ for 14500 reflections with $F > 4\sigma(F)$, $R1 = 0.093$, $wR2 = 0.231$, and $\text{GoF} = 1.100$ for all data; values of min/max residual electron density: $0.89/-0.63 \text{ e \AA}^{-3}$. This crystal structure was also analyzed in the space group $P1$ to ensure that the apparent structural disorder is not an artifact of selecting a wrong space group. This analysis revealed similar disorder features in the structural model and high correlation coefficients between equivalent atomic parameters. In all the calculations the hydrogen atoms attached to carbon atoms were placed in calculated positions and added as fixed contributions to the structure factors. Different distributions of the carbon–oxygen bond lengths provided a clear discrimination between the carboxylic and carboxylate groups in the tcpp moieties.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-137545 and -137546. 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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Charge Separation in a Molecular Triad Consisting of an Iridium(III) – bis-terpy Central Core and Porphyrins as Terminal Electron Donor and Acceptor Groups**

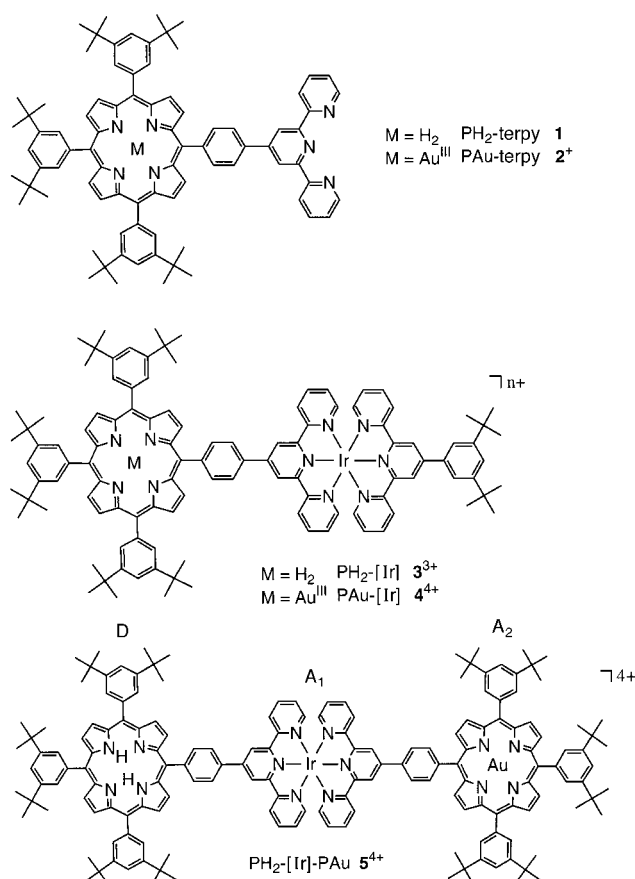
Isabelle M. Dixon, Jean-Paul Collin,*
Jean-Pierre Sauvage,* Francesco Barigelletti, and
Lucia Flamigni*

Synthetic multiporphyrin systems represent interesting mimics of the natural photosynthetic reaction centers in green plants^[1a] and bacteria.^[1b] In photosynthetic bacteria, one of the key reactions is electron transfer from the singlet excited state of the primary donor (special pair of bacteriochlorophylls, P) to a tetrapyrrolic unit (accessory bacteriochlorophyll, B), which is followed by another ultrafast electron transfer to a secondary acceptor (bacteriopheophytin, H). This three-component natural device (triad) is extremely efficient and has triggered the synthesis and study of many triads, designed to function in a similar way.^[2]

Until now most of these systems relied on covalent bonds. Recently, alternative strategies were proposed for constructing multiporphyrin assemblies, mostly based on hydrogen bonds,^[3a] mechanical bonds,^[3b] or coordination bonds.^[3c] In particular, ruthenium(II) bis-terpy (terpy = 2,2':6',2''-terpyridine) has been used as a central complex^[4] that 1) gathers together the various electro- and photoactive groups to be incorporated in the triad, and 2) provides a central electroactive species that participates in the multistep electron-transfer process. This latter function can be complicated by energy-transfer processes, due to the presence of a relatively low lying (ca. 1.9 eV) triplet metal-to-ligand charge transfer (³MLCT) state located on the [Ru(terpy)₂]²⁺ core.^[5] To circumvent these potential difficulties we looked for an alternative metal, and iridium(III) appeared to be particularly well suited. The [Ir(terpy)₂]³⁺ unit forms the central complex (A₁) of the present triad (Scheme 1), in which a free-base porphyrin (PH₂) is the primary electron donor (D), and a gold(III) porphyrin (PAu) the secondary electron acceptor (A₂). In the natural photosynthetic reaction center, D, A₁, and A₂ are P, B, and H, respectively. It is noteworthy that the three-component assembly PH₂–[Ir]–PAu (**5**⁴⁺) has a linear arrangement with very little flexibility and hence good control over the geometry of the ensemble. Given the properties of

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Scheme 1. Components of the triad PH_2 -[Ir]-PAu **5⁴⁺**.

the independent D, A₁, and A₂, the present triad is expected to undergo the sequence of reactions (1)–(3).



The complex $[Ir(terpy)_2]^{3+}$ was described by Demas et al. in 1990.^[6] Recently, we reported an efficient synthetic procedure for making related complexes, including asymmetrical compounds containing two different terpy ligands.^[7] A detailed electrochemical, spectroscopic, and photochemical study clearly showed that 1) $[Ir(terpy)_2]^{3+}$ is a potentially interesting electron relay (Ir^{III}/Ir^{II} : $E^0 \approx -0.7$ V vs. SCE in CH_3CN ; “ Ir^{II} ” is in fact an iridium(III)-stabilized radical anion localized on the terpy ligand), 2) no low-lying excited states (< 2.5 eV) are present, and 3) the excited state populated by light absorption (mostly of ligand-centered character) is photochemically very promising, especially for complexes of 4'-substituted terpy: it is long lived (> 1 μs at 298 K in CH_3CN), strongly luminescent, and expected to display a very strong electron-accepting character. To the best of our knowledge, this family of compounds represents the first series of multicomponent iridium(III) complexes of the polyimine type. In fact, it is likely that the expected synthetic difficulties had discouraged other groups from using such complexes.

The synthesis of Ir^{III} complexes containing two different terpy ligands is a key reaction. As in our previous work,^[7] we developed a two-step procedure. The most difficult reaction is the coordination of the second terpy ligand. It is carried out under harsh conditions over a short period of time. The use of robust tetraarylporphyrins is essential, since etioporphyrins would not resist the brutal conditions necessary for the complexation of the second ligand.

The unsymmetrical porphyrin **1** (see Scheme 1) can be prepared by Adler's procedure,^[4] but we instead chose a Suzuki coupling procedure between a porphyrin bearing a boronic ester (prepared by the method of Lindsey et al.^[8]) and 4'-bromo-terpy.^[9] Metalation of **1** with gold(III) to afford **2⁺** (Scheme 1) was achieved under the usual conditions.^[10] Diads **3³⁺** and **4⁴⁺** and triad **5⁴⁺** were obtained from the terpy-porphyrin conjugate **1** after appropriate metalation reactions of its coordination sites. Their synthesis and characterization will be reported elsewhere. For the sake of clarity, the names of the compounds are used in the discussion instead of formula numbers.

In the diads and the triad, the presence of phenylene spacers should ensure a certain degree of electronic insulation of the components. Therefore, the redox potentials are expected to remain unchanged on going from individual components to the diads and the triad. In the free-base diad PH_2 -[Ir], the oxidation of the porphyrin occurs at +0.96 V, and the reduction of the terpy ligands at −0.78 and −0.94 V. In the gold diad PAu -[Ir], the reduction of the porphyrin occurs at −0.59 and −1.11 V, while the reduction of the terpy ligands occurs at −0.75 and −0.91 V.

The absorption spectra of the diads and the triad are in good agreement with the sum of the absorption spectra of the components PH_2 , [Ir] (standing for the relevant model $[Ir(4'$ -tolylterpy)₂]³⁺) and PAu (acetonitrile solutions). This is again indicative of the absence of strong coupling between the different units of the structure.

At 298 K, the luminescence intensity of the free-base porphyrin ($\lambda_{exc} = 592$ nm) is strongly quenched in acetonitrile solutions of PH_2 -[Ir] and of PH_2 -[Ir]-PAu. Time-resolved emission measurements indicate that the lifetime of the singlet free base is reduced from 8.3 ns to 30 ps in PH_2 -[Ir] and PH_2 -[Ir]-PAu. Such quenching does not occur in a butyronitrile glass at 77 K, where the lifetime of the model porphyrin (11 ns) is maintained in both arrays (Table 1). These obser-

Table 1. Emission properties and energy levels of the excited states.^[a]

	298 K			77 K		
	λ_{max} [nm]	τ [ns]	Φ_{fluor}	λ_{max} [nm]	τ [μs]	E [eV] ^[b]
PH_2 ^[c]	652	8.3	0.15 ^[d]	647	0.011	1.92
				840 ^[d]	6000 ^[d]	1.47 ^[d]
PAu ^[e]				710	10; 100	1.75
PH_2 -[Ir] ^[c]	652	0.03	0.002	648	0.012	1.91
PAu -[Ir] ^[e]				705	16; 100	1.76
PH_2 -[Ir]-Au ^[c]	652	0.03	0.001	650	0.011	1.91
				706 ^[e]	20; 150 ^[e]	1.75 ^[e]

[a] In CH_3CN at 298 K, except for PH_2 ($CH_3CN/BuCN$ 2/1); in $BuCN$ at 77 K.

[b] Energy levels from the emission maxima at 77 K. [c] Excitation at 592 nm for steady-state and at 532 nm for time-resolved experiments. [d] From ref. [11].

[e] Excitation at 405 nm for steady-state and 532 nm for time-resolved experiments.

vations support a quenching of the excited state of PH_2 by electron transfer. Table 1 lists the luminescence properties at 298 K and 77 K for the arrays and the pertinent models.

Transient absorbance measurements at ambient temperature ($\lambda_{\text{exc}} = 532 \text{ nm}$) on acetonitrile solutions of $\text{PH}_2\text{-[Ir]-PAu}$ and PAu-[Ir] allowed the detection of the triplet state of the gold porphyrin, which is formed with a yield of unity (calculated on the basis of the photons absorbed by this unit only) and has a lifetime of 1.4 ns, both typical of the model PAu. This indicates that the energy absorbed at 532 nm by the free-base moiety in the triad is not funneled to the triplet state of the gold porphyrin and that the triplet state of the gold porphyrin that is directly formed by irradiation at 532 nm is not quenched.

In the absence of any detectable photoproduct and excluding the possibility of an external heavy atom effect, which would be active also at 77 K in a glass, the quenching of the free base porphyrin singlet in $\text{PH}_2\text{-[Ir]}$ and in $\text{PH}_2\text{-[Ir]-PAu}$, which occurs with a rate of $k = 3.3 \times 10^{10} \text{ s}^{-1}$, must be ascribed to electron and/or energy transfer occurring with 100% efficiency.

In the case of $\text{PH}_2\text{-[Ir]}$, on the basis of the electrochemical and spectroscopic data, electron transfer from the porphyrin to the metal complex can be expected. This is in fact the only thermodynamically allowed process, with $\Delta G \approx -0.2 \text{ eV}$. A transient absorption experiment with selective excitation of the PH_2 unit of $\text{PH}_2\text{-[Ir]}$ ($\lambda_{\text{exc}} = 532 \text{ nm}$) allowed the product of the electron transfer process, namely, the charge-separated state $\text{PH}_2^+\text{-[Ir]}^-$, to be detected (Figure 1). This spectrum, the

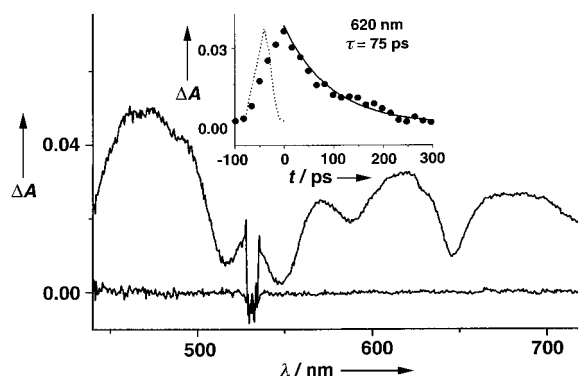


Figure 1. Transient absorption changes detected in a solution of $\text{PH}_2\text{-[Ir]}$ in acetonitrile after a laser pulse (35 ps FWHM, $\lambda = 532 \text{ nm}$). In the inset the decay of the absorbance at 620 nm is shown with the fitted decay function and the laser profile (---). A = absorption.

main features of which are in agreement with those of the free-base porphyrin cation,^[2, 4] decays with a lifetime of $(75 \pm 5) \text{ ps}$ that is identical over the whole spectral range. The PH_2 -localized triplet, measured with a nanosecond flash-photolysis apparatus ($\lambda_{\text{exc}} = 532 \text{ nm}$), had a lifetime of 8 μs and a yield of 0.1. Therefore the decay of the charge-separated state $\text{PH}_2^+\text{-[Ir]}^-$ occurs essentially by charge recombination to give the ground state.

A schematic energy level diagram for $\text{PH}_2\text{-[Ir]-PAu}$, drawn by using the excited state energies (Table 1) and the electrochemical data, is shown in Figure 2. In the triad, the decay of

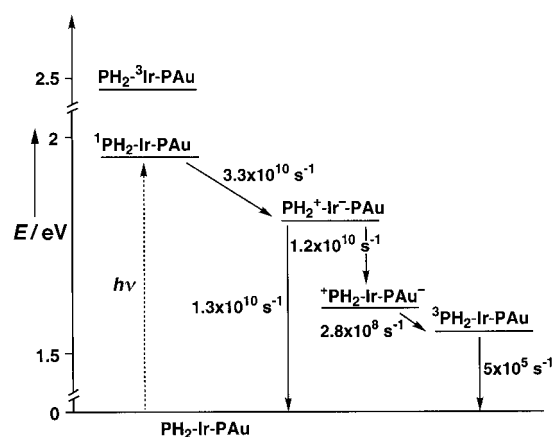


Figure 2. Schematic energy level diagram for the processes taking place in $\text{PH}_2\text{-[Ir]-PAu}$.

the excited singlet state of the free-base porphyrin is identical to that detected in $\text{PH}_2\text{-[Ir]}$. Hence, the same process that for the diad was assigned to an electron transfer from the porphyrin excited state to the iridium complex is assumed to also occur in $\text{PH}_2\text{-[Ir]-PAu}$ at the same rate ($3.3 \times 10^{10} \text{ s}^{-1}$). Selective excitation of the free-base porphyrin moiety at 598 nm yields a transient state very similar to $\text{PH}_2^+\text{-[Ir]}^-$, which we assign to $\text{PH}_2^+\text{-[Ir]}^-\text{-PAu}$ (Figure 3). The time

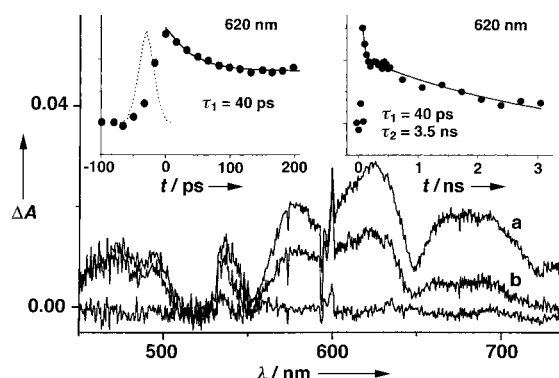


Figure 3. Transient absorption changes detected in a solution of $\text{PH}_2\text{-[Ir]-PAu}$ in acetonitrile after excitation (35 ps FWHM, $\lambda = 598 \text{ nm}$) at the end of the pulse (a) and 140 ps after the end of the pulse (b). In the insets the decay at 620 nm in two different time ranges is shown with the fitted functions. The laser profile is also plotted (---). A = absorption.

evolution of this species, which decays with a lifetime of $(40 \pm 5) \text{ ps}$ that is shorter than in the diad, leads to a longer-lived species with a rather broad and featureless spectrum. We identify the latter, which has a lifetime of $(3.5 \pm 0.3) \text{ ns}$, as the fully charge-separated state, $\text{PH}_2^+\text{-[Ir]}^-\text{-PAu}^-$, formed by a secondary electron-transfer step from the reduced Ir(III) complex to the easily reducible gold porphyrin unit ($\Delta G \approx -0.2 \text{ eV}$). This assignment is in agreement with previous reports on similar charge-separated states.^[4]

By comparing the lifetime of the $\text{PH}_2^+\text{-[Ir]}^-$ state in the diad (75 ps) to the lifetime of the $\text{PH}_2^+\text{-[Ir]}^-\text{-PAu}$ state in the triad (40 ps), a rate for the secondary electron transfer ($\text{PH}_2^+\text{-[Ir]}^-\text{-PAu} \rightarrow \text{PH}_2^+\text{-[Ir]}^-\text{-PAu}^-$) of $1.2 \times 10^{10} \text{ s}^{-1}$ and an efficiency of approximately 50% can be derived. The triplet localized on

the free-base porphyrin was examined in a nanosecond flash-photolysis experiment ($\lambda_{\text{exc}} = 532 \text{ nm}$). This revealed a lifetime of 2 μs and a yield of 0.6, calculated on the basis of the photons absorbed by the PH_2 unit. The calculated yield allows us to establish that the $\text{PH}_2^+[\text{Ir}]\text{-PAu}^-$ state, formed by a two-step mechanism from the excited-state singlet of the free base, is essentially deactivated through the triplet state. The presence of this low-lying triplet state clearly facilitates charge recombination. It is expected that longer-lived charge-separated states can be obtained with other metalated porphyrins that do not display such low-lying triplet states.

The present system utilizes an iridium(III) complex as electron relay and central core. This species is particularly well suited to the construction of multicomponent assemblies that can undergo charge separation, as demonstrated, in particular, by the behavior of the triad $\text{PH}_2\text{-}[\text{Ir}]\text{-PAu}$. The fully charge-separated state is formed with a quantum efficiency of 0.5, and recombination is 50 times slower than in the corresponding diad $\text{PH}_2\text{-}[\text{Ir}]$.

Experimental Section

Cyclic voltammetry was carried out in MeCN solution with Bu_4NPF_6 as supporting electrolyte, a Pt working electrode, a Pt counterelectrode, and a saturated calomel electrode (SCE) as reference. The typical sweep rate was 200 mV s^{-1} , and the window used was from -1.4 to $+1.3 \text{ V}$. All waves were irreversible. Absorption spectra were recorded with a Perkin-Elmer Lambda 9 spectrophotometer. Uncorrected emission spectra were detected by a Spex Fluorolog II spectrofluorimeter, equipped with a phosphorimeter accessory (1934 D). The time-resolved luminescence apparatus was based on an Nd:YAG laser (35 ps FWHM = full width at half maximum) and a Streak Camera. The standard iterative reconvolution procedure with the laser profile was used to measure emission lifetimes shorter than 90 ps. Transient absorbance in the picosecond range was measured with a pump and probe system based on the same laser and an OMA detector. Time zero for these experiments was set at the end of the laser pulse, calibrated by a 3,3'-diethyloxadiorbocyanine iodide (DODCI , $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_2\text{I}$) solution in methanol.^[11] and decay analysis was performed after the end of the laser pulse. Under these conditions deconvolution of the signal with the laser profile was unnecessary. For excitation at 598 nm, the second harmonic (532 nm) was Raman-shifted by a cell containing perdeuterated cyclohexane. The PH_2 triplet yields and lifetimes were determined by a laser flash photolysis apparatus with a Nd:YAG laser (20 ns pulse). Triplet yields were measured in oxygen-free solutions with the models PAu and PH_2 as reference, only the photons absorbed by the examined unit were taken into account, and calculations were performed on the basis of the molar absorption coefficients. The error for quantum yield determinations was 20% and that for lifetime determinations 10%, unless otherwise specified. Further details on the experimental setup, solvents, sample preparation and experimental procedures can be found elsewhere.^[5, 11, 12]

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A Hermaphrodite Molecule: Quantitative Copper(II)-Directed Formation of a Doubly Threaded Assembly from a Ring Attached to a String**

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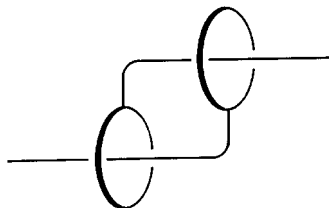
Whereas catenanes, rotaxanes, and knots were regarded as laboratory curiosities only 15 years ago,^[1] they are now relatively common molecules^[2, 3] with a fast growing number of uses regarding electron transfer,^[4] polymers,^[5] and controlled molecular motions. The last-mentioned field of research is particularly active and has recently produced

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several examples of so-called molecular machines and motors.^[6] To extend the number of working parts of future machines, topologies other than simple catenanes and rotaxanes are needed. In particular, one-dimensional molecular assemblies that can undergo stretching and contraction under the action of an external signal might contain the doubly threaded topology represented in Scheme 1.



Scheme 1. A molecular assembly with a doubly threaded topology.

Such a doubly threaded topology was recently obtained by Stoddart et al. in the solid state by dimerization of a self-complementary monomer, whereas in solution single-threading processes led to the formation of various pseudo-oligomeric rotaxane topologies.^[7, 8] We now report that, by using copper(I) as a gathering and threading center, it is possible to generate the doubly threaded species shown schematically in Figure 1, both in solution and in the solid state. In such a dinuclear dimer each organic unit is a self-complementary monomer of a chelating ring attached to a coordinating stick. Due to the structural features of the ring-and-stick ligand **1**,^[9] the complexation reaction that affords the doubly threaded copper(I) complex **2**²⁺ can be regarded as a double plugging-in process between the female (ring) and the male (coordinating stick) components; thus, the organic ligand has a hermaphroditic character.

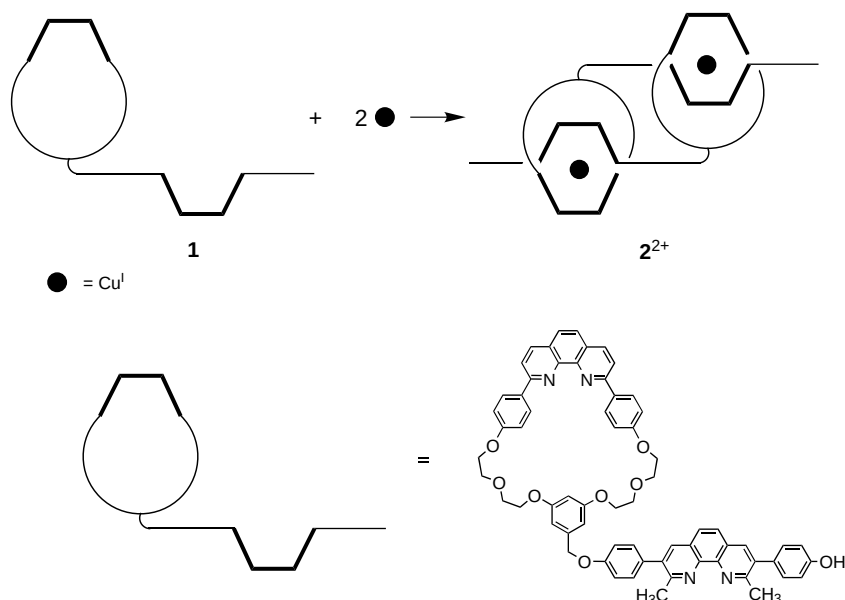


Figure 1. Schematic representation of the double-threading process induced by Cu^I (black dots) between two hermaphrodite ligands, each containing a chelating ring and a coordinating stick (the bidentate 1,10-phenanthroline units are represented by bold lines) and chemical structure of the ligand **1**.

The CPK model strongly suggested that **1** was not able to form an intramolecular tail-biting complex. The rigid rod consisting of 3,8-diaryl-1,10-phenanthroline is too stiff and connected to the ring by too short a linker for **1** to fold up so as to allow a self-threading process, comparable to what was observed in previously reported organic systems.^[10] In fact, the dimerization shown in Figure 1 occurred quantitatively in solution when **1** was treated with a stoichiometric amount of [Cu(CH₃CN)₄]PF₆ in CH₃CN/CH₂Cl₂ at room temperature. Interestingly, ¹H NMR studies and thin-layer chromatography clearly showed that the initial kinetic mixture of copper(I) complexes obtained immediately after addition of the copper(I) salt to **1** re-equilibrates. The various cyclic or linear oligomers initially present in the reaction mixture besides **2**²⁺ are spontaneously converted to the thermodynamically more stable dimer **2**²⁺ in quantitative yield over a period of 48 h at room temperature.^[11] The pronounced upfield shift observed for the aromatic protons H_o and H_m (Figure 2) and the various interfragment interactions revealed by 2D-ROESY NMR experiments (e.g., between CH₃ and H_o, H_m and H_{o'}, H_m and H_{m'}, -OCH₂- and H_{4'}, H_m and H_{m'}) are clear evidence for the threading of the rigid linear stick of one ligand through the macrocycle of the other. The dimeric nature of **2**²⁺ was unambiguously supported by high-resolution mass spectrometry (ESI-MS). The spectrum of the single product obtained is that expected for **2**²⁺: it not only contains the molecular ion peak at *m/z* 2310.3 (calcd 2310.3), but also displays an intense, well-resolved peak at *m/z* 1082.7 (calcd for *M*/2: 1082.7) characteristic of a doubly charged species.

The dimer **2**²⁺ was isolated as deep red crystals of its PF₆⁻ salt. X-ray quality crystals were grown from acetone/diethyl ether by diffusion. The molecular structure of the dinuclear dimer **2**²⁺, which possesses only a single C₂ axis, is shown in Figure 3.^[12] The complex contains two identical symmetry-related subunits, each consisting of one macrocycle, one linear 3,8-diaryl-1,10-phenanthroline rod, and one copper ion. The most striking feature of the structure is its linear extended arrangement, which results in a distance between the two terminal phenolic oxygen atoms of 36.3 Å. The two copper atoms are 18.3 Å apart and occupy similar environments. The coordination tetrahedron around each copper atom appears to be distorted, with two wide angles, one opening towards the outside of the molecule (N1-Cu-N3 125.6°) and the other towards the second copper ion of the complex (N2-Cu-N4 137.3°). The N-Cu distances range from 2.035 to 2.076 Å and are thus close to the values found in copper(I) complexes of related ligands.^[13]

In conclusion, a new transition metal directed assembly and double-threading process has been shown to take place quantitatively in solution. Interestingly, the two threaded sticks are disposed antiparallel to one another, opening the door to

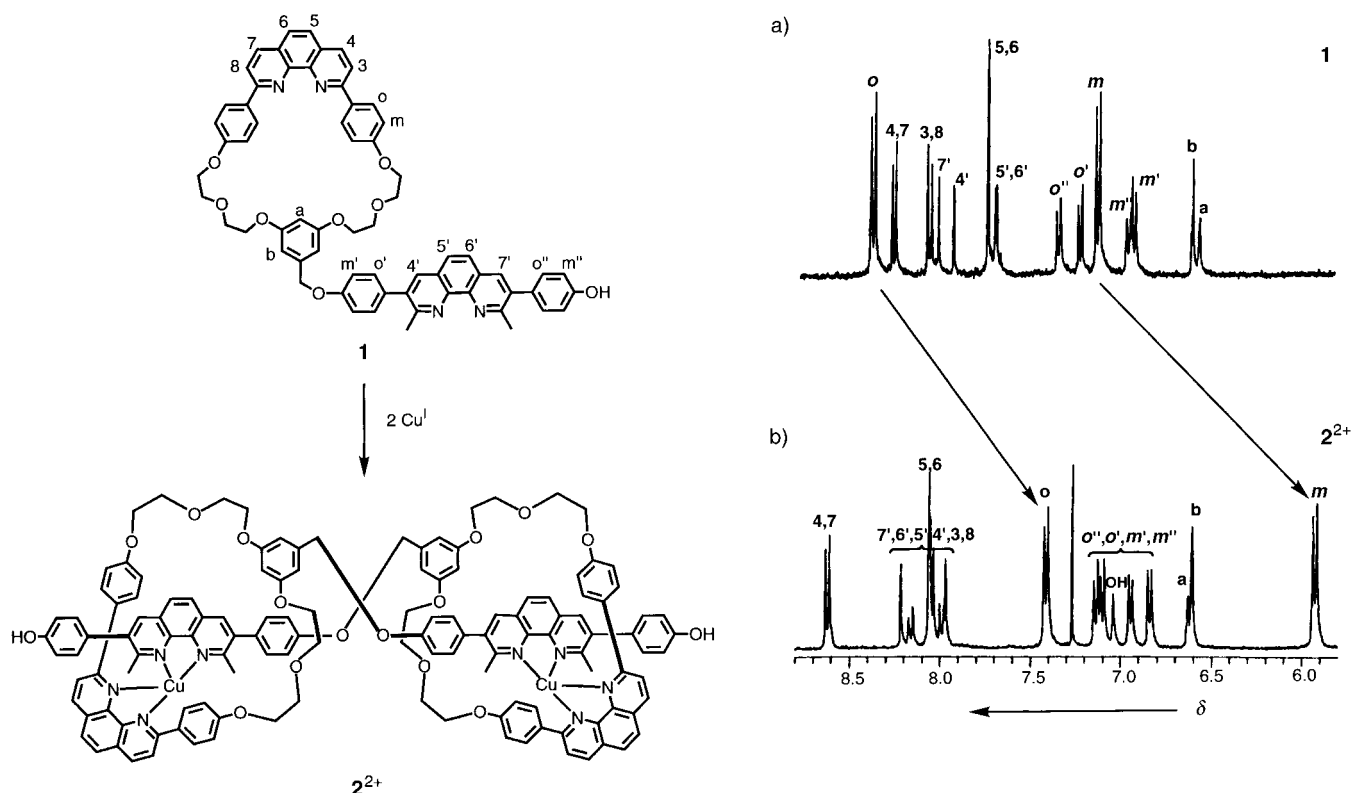


Figure 2. ^1H NMR spectra (400 MHz) of a) the free ligand **1** (in $\text{CD}_2\text{Cl}_2/\text{CD}_3\text{CN}$) and b) the doubly threaded dinuclear copper(I) dimer **2**²⁺ (in CD_2Cl_2).

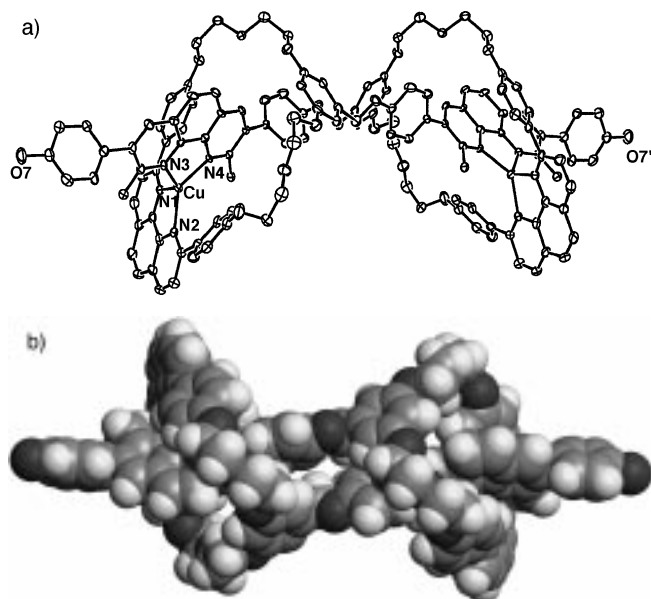


Figure 3. Crystal structure of the dicopper(I) dimer **2**²⁺. a) ORTEP plot showing the numbering scheme adopted. b) Space-filling representation; the C_2 axis is shown perpendicular to the plane.

new one-dimensional multicomponent molecular systems and devices.

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- 7.75 (s, 1H, H₅), 7.76 (s, 1H, H₆), 7.80 (s, 2H, H_{5,6}), 7.99 (s, 1H, H₄), 8.07 (s, 1H, H₇), 8.12 (d, *J* = 8.3 Hz, 2H, H_{3,8}), 8.31 (d, *J* = 8.3 Hz, 2H, H_{4,7}), 8.43 (d, *J* = 8.8 Hz, 4H, H₀); FAB-MS: *m/z* calcd for C₆₅H₅₅N₄O₈⁺: 1019.4; found: 1019.5.
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- [12] X-ray crystallography for ²⁺. Deep red single crystals of ²⁺ · 2PF₆[−] · 2CH₃OH were obtained as described above. C₆₇H₆₁O₁₀N₄PF₆Cu, *M*_r = 1290.76, monoclinic, *a* = 25.543(1), *b* = 20.870(1), *c* = 27.869(1) Å, β = 116.96(2)°, *V* = 13242(2) Å³, space group C2/c, *Z* = 4, ρ_{calcd} = 1.295 g cm^{−3}, μ = 4.296 mm^{−1}. Data were collected at −100 °C on a Nonius Kappa CCD diffractometer by using the standard data-collection procedures (2.5 < θ < 30°) and graphite-monochromated MoKα radiation (λ = 0.71073 Å) on a crystal of dimensions 0.30 × 0.30 × 0.20 mm³. 21 423 data collected; 7329 with *I* > 3σ(*I*). The structure was solved by direct methods. The diffraction power of the crystals was very poor, and the data of four samples were collected with the same results. It was therefore not possible to fully resolve the disorder of one of the PF₆[−] ions and to locate all solvent molecules, even by refining on *F*² and using all data with *I* > 2σ(*I*). Nevertheless, the core of the molecule is correct and refines normally. Final results: *R* = 0.142, *R*_w = 0.193. 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-135902. 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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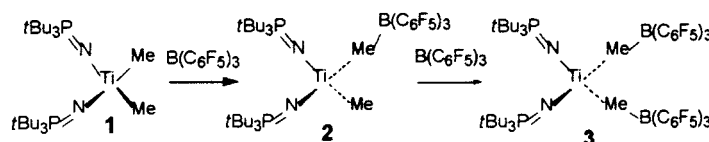
Synthesis and Structure of the Dicationic Bisborate Adduct [(*t*Bu₃PN)₂Ti{μ-MeB(C₆F₅)₃}]²⁺

Frédéric Guérin and Douglas W. Stephan*

Complexes of nitrogen-based ligands have been the focus of much attention in the quest for new olefin polymerization catalysts. For example, Brookhart and co-workers^[1–4] and Gibson and co-workers^[5, 6] have recently reported unprecedented Fe- and Cr-based polymerization catalysts containing

Schiff-base ligands, while McConville and co-workers^[7, 8] observed living olefin polymerization using a Ti–amide catalyst. Recently, we described titanium compounds containing phosphanimide ligands of the form [CpTi(NPR₃)Me₂] (R = *t*Bu, *i*Pr, Cy; Cp = C₅H₅) and [(*t*Bu₃PN)₂TiMe₂] (**1**).^[9, 10] These species are catalyst precursors for olefin polymerization, and in fact **1** is highly active under both laboratory screening (1 atm, 25 °C) and commercially relevant (103 bar, 160 °C) polymerization conditions. The interaction of the precursors with Lewis acid activators is of fundamental importance. Marks,^[11–15] Jordan,^[16–18] and Bochmann^[19] and their groups have elucidated the interaction of metallocenes with Lewis acid activators. The analogous chemistry of non-metallocene catalysts with Lewis acids has drawn lesser attention. Herein, we describe reactions of **1** with the Lewis acid B(C₆F₅)₃. In the reaction with excess borane B(C₆F₅)₃, a bis-borate zwitterionic species is obtained.

We have previously described the stoichiometric reaction of **1** with B(C₆F₅)₃ which generates the zwitterionic species [(*t*Bu₃PN)₂TiMe(μ-Me)B(C₆F₅)₃] (**2**) (Scheme 1).^[9] This isolated species is an active catalyst for ethylene polymerization.^[9] While single-component catalysts are of interest, in situ



Scheme 1. Generation of **2** and **3** through reaction of **1** with B(C₆F₅)₃.

generation of catalysts by the combination of precursor complex and co-catalyst is a more common practice. In the generation of **2** in situ for ethylene polymerization experiments, we noted that the order of addition of the reagents had a dramatic effect on the activity. Initially, **2** was generated by adding **1** to a solution of B(C₆F₅)₃ at 25 °C under an ethylene atmosphere. This led to poor activity and thus to only a small amount of polyethylene (PE; < 50 g of PE per mmol per hour). In contrast, addition of B(C₆F₅)₃ to a solution of **1** gave significantly increased catalyst activity^[20] (265 g PE mmol^{−1} h^{−1}).

In probing these observations, we examined the reaction of **1** in the presence of excess B(C₆F₅)₃ in CH₂Cl₂ under an N₂ atmosphere. Upon addition of **1**, a yellow crystalline product **3** was formed immediately, which was isolated in 95 % yield. ¹H, ¹³C, ¹⁹F, ¹¹B, and ³¹P NMR spectroscopic data confirmed the presence of the B and Ti moieties. The observation of a distinct ³¹P chemical shift indicated that this new product **3** was not the 1:1 zwitterionic species **2**. Moreover, the presence of a single, temperature-invariant, Ti–methyl environment suggested the formation of a bis-B(C₆F₅)₃ adduct.

Crystals of **3** · 2CH₂Cl₂ were isolated from CH₂Cl₂. A crystallographic study^[21] confirmed that [(*t*Bu₃PN)₂Ti{μ-MeB(C₆F₅)₃}]₂ (**3**), an unprecedented di-zwitterionic species, sits on a position with crystallographically imposed twofold symmetry (Figure 1). The pseudo-tetrahedral coordination sphere about Ti comprises the nitrogen atoms of the

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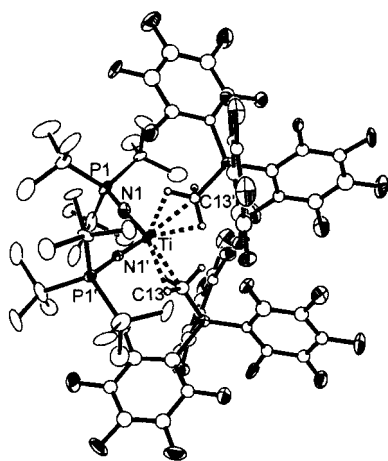


Figure 1. ORTEP drawing of **3** (30% thermal ellipsoids are shown). All hydrogen atoms except those of the B-bound methyl groups are omitted for clarity.

phosphanimide ligands and the carbon atoms of the two methyl groups of the two borate anions (Figure 2). The

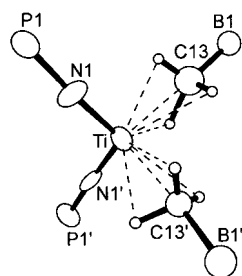


Figure 2. Molecular structure of the core of **3**. Selected bond lengths [Å] and angles [°]: Ti–N1 1.757(5), Ti–C13 2.333(7), P1–N1 1.628(5); N1–Ti–N2 115.4(3), N1–Ti–C13 109.1(2), C13–Ti–C13' 104.6(4), P1–N1–Ti 176.3(3), B1–C13–Ti 175.0(5).

seen in the zwitterionic species $[\text{CpTi}(\text{NPrBu}_3)\text{Me}\{\mu\text{-MeB}(\text{C}_6\text{F}_5)_3\}]$ (**4**).^[10] The Ti–C distance in **3** is 2.333(7) Å, which compares to the longer Ti–C(borate) distance of 2.404(4) Å in **4**, and the Zr–C(borate) distances of 2.549(3) and 2.667(5) Å in $[(\text{C}_5\text{H}_3\text{Me}_2)_2\text{ZrMe}\{\mu\text{-MeB}(\text{C}_6\text{F}_5)_3\}]$ (**5**)^[12] and $[(\text{C}_5\text{H}_3(\text{SiMe}_3)_2)_2\text{ZrMe}\{\mu\text{-MeB}(\text{C}_6\text{F}_5)_3\}]$ (**6**),^[19] respectively. The nearly linear Ti–C–B angle in **3** (Ti–C–B_{av} 175.0(5)°) is significantly larger than the corresponding M–C–B angles in **4–6** of 167.2(3)°, 161.8(2)°, and 170.5(3)°, respectively. The positions of the hydrogen atoms of the B-bound methyl groups in **3** were located and refined. For the methyl group, two of the three protons were slightly closer to the metal center than the third, reminiscent of the M–methyl interactions in **4–6**. The range of the Ti–H distances in **3** (2.201–2.351 Å; Figure 2) is comparable to that of the Ti–H distances in the related zwitterionic species **4** (2.197–2.435 Å).^[10] The close approach of the methyl group to the Ti center reflects the formal +2 charge at Ti in **3**. While donor–^[22–26] or metal–arene-stabilized^[27] dicationic complexes are known, **3** repre-

sents an unprecedented example of a zwitterionic dicationic complex.

The gross structural features of **3** support the view that phosphanimide ligands provide a sterically protective shell, which is remote from the metal center. While it may be postulated that a bisphosphanimide metal fragment provides a steric analogy to a metallocene, the more remote nature of the steric demands in phosphanimide ligands appears to permit greater access to the metal coordination sphere. This proposition is supported by the close approach of the borate anions to Ti in **3**. Moreover, this view is consistent with our observation that the complexes $[\text{Cp}_2\text{ZrMe}_2]$, $[\text{Cp}_2\text{TiMe}_2]$, $[\text{CpTi}(\text{NPrBu}_3)\text{Me}_2]$, and $[(\text{C}_5\text{H}_4\text{SiMe}_2\text{NtBu})\text{TiMe}_2]$ fail to react with more than one equivalent of $\text{B}(\text{C}_6\text{F}_5)_3$. Presumably, steric congestion closer to the metal center precludes reactivity, although these species are expected to be more nucleophilic than **1**.

Compound **3** exhibits negligible polymerization activity when placed in solution under an atmosphere of ethylene. In addition, **3** is stable with respect to comproportionation, undergoing no reaction with added **1**. This stability of **3** is not surprising given the steric crowding and the formal +2 charge at the Ti center and is consistent with the observed dependence of catalytic activity on the order of addition of **1** and $\text{B}(\text{C}_6\text{F}_5)_3$. Moreover, these observations demonstrate that while $\text{B}(\text{C}_6\text{F}_5)_3$ activates **1** to generate the active catalyst **2**, excess $\text{B}(\text{C}_6\text{F}_5)_3$ acts to poison **2** affording the inactive compound **3**. This is the first such evidence of this duality for $\text{B}(\text{C}_6\text{F}_5)_3$.

In conclusion, the reaction of **1** with an excess of the Lewis acid $\text{B}(\text{C}_6\text{F}_5)_3$ yields the first bis-borate-zwitterionic species **3**. The isolation and characterization of **3** clearly defines a deactivation pathway for the active catalyst **2** in the presence of excess $\text{B}(\text{C}_6\text{F}_5)_3$. Moreover, this work demonstrates the importance of the order of addition for the pre-catalyst and activator as this is the first evidence, to our knowledge, that $\text{B}(\text{C}_6\text{F}_5)_3$ may act as a catalyst poison.

Experimental Section

3: A solution of complex **1** (0.200 g, 0.392 mmol) in CH_2Cl_2 (2 mL) was added to a solution of $\text{B}(\text{C}_6\text{F}_5)_3$ (0.421 g, 0.822 mmol) in the same solvent (2 mL). The solution turned bright yellow within seconds, and was stirred for 30 min at room temperature. The solvent was removed under vacuum to yield light yellow **3** (0.570 g, 0.371 mmol, 95%). ^1H NMR (CD_2Cl_2 , 25 °C): δ = 1.52 (d, $^3J_{\text{PH}}$ = 14.6 Hz, 52 H; PCMe_3), 0.49 (s, 6 H; MeB); $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 25 °C): δ = 150.4, 147.3, 139.1, 135.2, 39.9 ($^1J_{\text{PC}}$ = 39.0 Hz), 29.9 (br), 29.5; $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 25 °C): δ = 60.57; $^{11}\text{B}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 25 °C): δ = –15.22; $^{19}\text{F}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 25 °C): δ = –55.80 (d, $^3J_{\text{FF}}$ = 22.0 Hz), –87.87 (d, $^3J_{\text{FF}}$ = 20.6 Hz), –90.44 (d, $^3J_{\text{FF}}$ = 21.0 Hz); elemental analysis (%) calcd for $\text{C}_{62}\text{H}_{60}\text{B}_2\text{F}_{30}\text{N}_2\text{P}_2\text{Ti}$: C 47.06; H 3.82; N 1.77; found: C 46.86, H 3.69, N 1.73.

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- [21] Crystal structure analysis of **3**: monoclinic, space group *C2/c*, *a* = 23.417(9), *b* = 14.776(6), *c* = 22.678(8) Å, β = 109.98(3)°, *V* = 7374.2(49) Å³, *Z* = 4, ρ_{calc} = 1.535, μ = 0.421, 5661 reflections, 486 parameters, *R* = 0.0823, *Rw* = 0.1827, GOF = 1.002. Diffraction experiments were performed on a Siemens SMART System CCD diffractometer, and the structure was solved with the SHELX-TL software 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-134941. 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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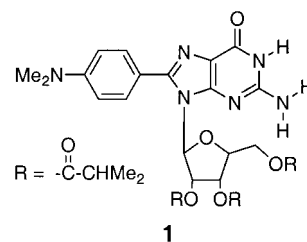
A G-Quartet Formed in the Absence of a Templating Metal Cation: A New 8-(*N,N*-dimethylaniline)guanosine Derivative**

Jonathan L. Sessler,* Muhunthan Sathiosatham, Katherine Doerr, Vincent Lynch, and Khalil A. Abboud

Dedicated to Professor Jean-Marie Lehn on the occasion of his 60th birthday

Self-assembly is one of the more intriguing subfields within the general area of molecular recognition. Indeed, quite a number of natural and unnatural molecules form ordered supramolecular ensembles by self-assembly.^[1] Notable among these is guanosine, a compound known to self-assemble into dimeric,^[2] tetrameric,^[3] ribbonlike,^[4] and helical structures^[5] as the result of Watson–Crick and Hoogsteen base-pairing interactions. The tetrameric forms of guanosine, known also as G-quartets, have drawn considerable attention over the past three decades. They have been implicated in a variety of biological functions^[6] and have seen application in a range of nonbiological areas such as ionophores^[7] and phase-transfer catalysts.^[8] X-ray analyses of crystals obtained from aqueous solutions of 5'- and 3'-guanosine monophosphate revealed that the constituent bases adopt a tetrameric planar arrangement, which then stacks in a helical fashion with other tetramers to form columnar aggregates.^[9]

Currently, it is believed that templating alkali metal cations such as Na⁺ and K⁺ are needed to stabilize the formation of G-quartets.^[10] The need for such cations to stabilize self-assembled and higher order aggregates formed from lipophilic deoxyguanosine derivatives in chlorinated organic solvents (that is, G-quartet model systems) has also been explicitly noted.^[4,7] Indeed, in the absence of alkali metal cations these compounds were found to adopt a ribbonlike structure (but not G-quartets) in both chloroform solution^[4a] and in the solid state.^[4b] Here, we report the synthesis of the new (*N,N*-dimethylaniline)guanosine derivative **1** that forms a G-quartet in the absence of alkali metal

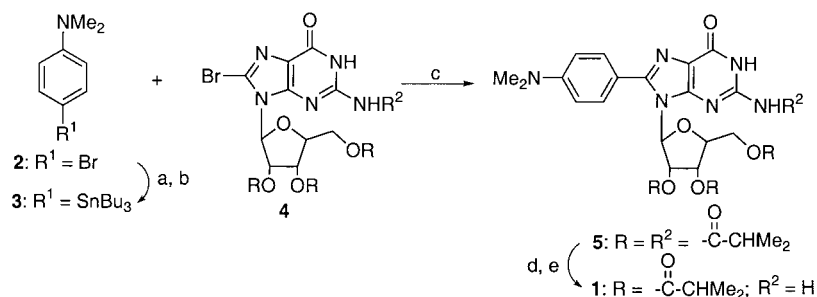


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Scheme 1. Synthesis of guanosine derivative **1**. a) BuLi, THF, -78°C ; b) $n\text{Bu}_3\text{SnCl}$, $-78^\circ\text{C} \rightarrow \text{room temperature}$, 90%; c) $[\text{Pd}(\text{PPh}_3)_4]$, toluene, reflux, 95%; d) NH_3 , MeOH, CH_2Cl_2 ; e) $(\text{Me}_2\text{CHCO})_2\text{O}$, DMAP, TEA, MeCN, 50%. DMAP = 4-dimethylaminopyridine, TEA = triethylamine.

cations in both chlorinated organic solvents and in the solid state.

Scheme 1 outlines the synthesis of **1**. Briefly, *N,N*-dimethyl-4-(tri-*n*-butylstannyl)aniline (**3**) was synthesized from commercially available 4-bromo-*N,N*-dimethylaniline (**2**) by treatment with BuLi in THF at -78°C , followed by tri-*n*-butylstannyl chloride. Coupling of this tin derivative with the 8-bromoguanosine derivative **4**^[11] under Stille cross-coupling conditions afforded N-protected **5** which was converted to **1** by using standard deprotection and protection procedures.^[11]

Crystals of **1**^[12] were obtained by slow evaporation of a solution of **1** in acetonitrile/isopropyl alcohol. An X-ray crystallographic analysis of **1** revealed that it forms H-bonded head-to-tail^[10a] tetramers in the absence of an alkali metal cation template (Figure 1). Each individual tetramer (see Figure 2 for a schematic representation) possesses C_4 symmetry along the *c* axis and has all four guanine bases within an essentially planar array. The protected ribose subunits occupy the space above this plane and adopt *syn* conformations with

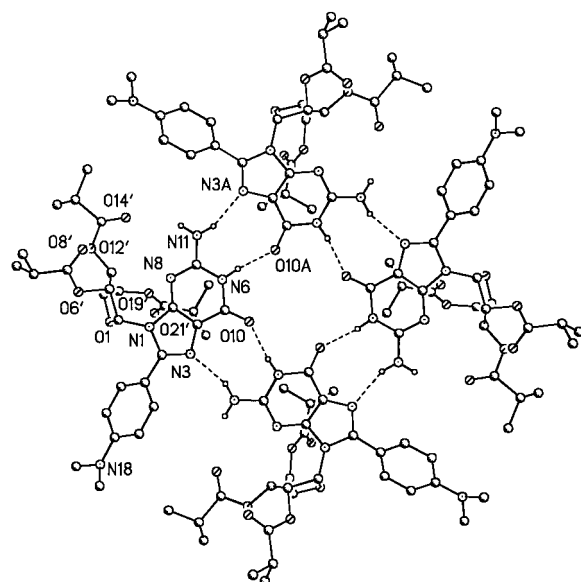


Figure 1. Ball-and-stick representation of the tetrameric arrangement of molecules of **1** in the solid state. The geometry of the hydrogen bonding interaction is: $\text{N11} \cdots \text{H11b} \cdots \text{N3A}$ (related by $y, 1-x, z$), $\text{N} \cdots \text{N}$ 2.927(2) Å, $\text{N} \cdots \text{H}$ 2.107(2) Å, $\text{N} \cdots \text{H} \cdots \text{N}$ 159.1(1)°; $\text{N6} \cdots \text{H6} \cdots \text{O10A}$ (related by $y, 1-x, z$), $\text{N} \cdots \text{O}$ 2.778(2) Å, $\text{H} \cdots \text{O}$ 1.92(3) Å, $\text{N} \cdots \text{H} \cdots \text{O}$ 172(2) Å.

respect to the relevant N9–C1' glycosidic bonds. Such an all-*syn* arrangement presumably reflects either a) unfavorable steric interactions between the isobutryl protecting group and the dimethylaniline moiety that would exist in the *anti* conformation,^[13] or b) the possibility of hydrogen bond formation between the C5' isobutryl carbonyl group and the (N2)H*, or c) some combination of these two effects.

The various guanosine and deoxyguanosine derivatives soluble in organic solvents whose self-assembly properties were studied previously all lack the aryl substituent present in **1**. They thus adopt an *anti* conformation both in sol-

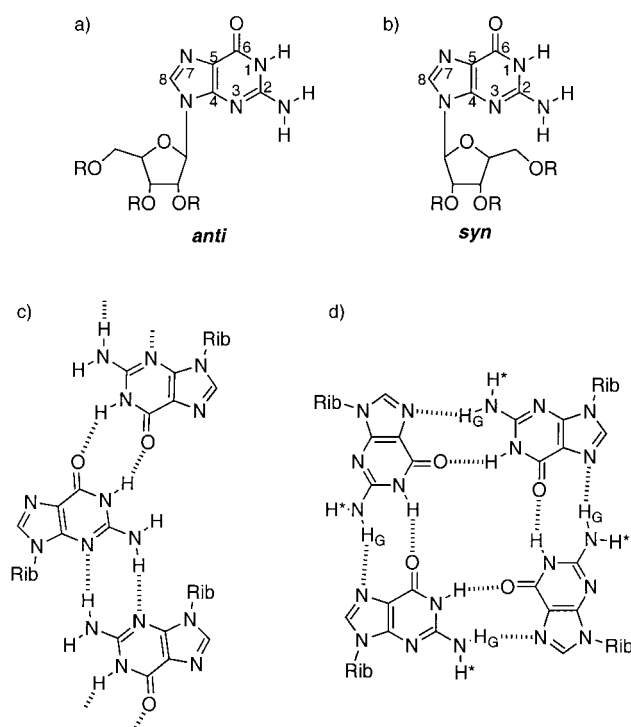


Figure 2. Schematic representations of *anti* (a) and *syn* conformers of guanosines (b) that can arise as the result of rotation about the purine–ribose bond. c) Truncated view of the ribbonlike structures observed for lipophilic guanosine derivatives that are capable of adopting an *anti* conformation. d) Idealized view of G-quartet-like tetramer formed from **1** both in solution in dichloromethane and in the solid state (the *p*-NMe₂C₆H₄ substituent at C8' has been omitted for clarity). This structure displays a *syn* arrangement of the ribose (Rib) and purine subunits. H_G and H* indicate the amino protons that are, and are not, participating in G-quartet formation, respectively.

ution and in the solid state. They also self-assemble in the form of ribbonlike structures rather than G-quartets in the absence of K⁺ or other templating cations.^[4] By contrast **1**, presumably as a consequence of adopting a *syn* conformation, self-assembles to form a cyclic tetramer. In the *syn* conformation, one of the faces on the guanosine subunit is blocked (Figure 2). Apparently, this prevents the formation of ribbonlike supramolecular structures as is seen in the case of compounds that are capable of adopting an *anti* conformation.

The putative formation of a G-quartet-like structure from **1** was studied in organic solutions by ¹H NMR spectroscopy. In

[D₆]DMSO, where intermolecular H-bonding interactions are minimized,^[14] no significant self-assembly was observed at room temperature (as indicated by the presence of NH₂ and (N1)H signals at δ = 6.40 and 10.80, respectively; Figure 3a). By contrast the ¹H NMR spectrum of a 58 mM solution of **1** in CD₂Cl₂ at room temperature showed evidence for self-assembly. Under these conditions a broad signal, exchangeable with D₂O, is observed between δ = 7.0 and 7.8 (Figure 3b). While such a signal, assigned on the basis of integration to (N2)H_G, is consistent with the formation of a tetramer that is in fast equilibrium with other self-assembled species (dimers, trimers, oligomers, etc.), it could also indicate the incomplete formation of the proposed G-quartet-like ensemble. We currently favor the first of these interpretations since re-recording the spectrum at -30°C produces well-defined spectral patterns that are considered consistent with the formation of a G-quartet (Figure 3c). In particular, new exchangeable signals at δ = 9.81 and 5.15, ascribed to (N2)H_G and (N2)H*, respectively, are observed that are coincident, in terms of chemical shift, with those of previously described guanine-derived tetramers that are stabilized by alkali metal cations.^[7, 15] Furthermore, the fact that under these low-temperature conditions only a single signal is seen for each of the (N3)H_G and (N3)H* protons leads us to suggest that, in contrast to other G-quartets,^[7, 15] only one of two possible *syn/anti* ribose conformers, presumably *syn*, is present in solution.

To probe more fully the solution-phase characteristics of **1**, the number-averaged molecular weight of putative aggre-

gate(s) in dichloroethane was estimated at 40°C by using vapor-pressure osmometry (VPO).^[16] These studies, carried out at initial concentrations^[17] of 28, 42, 57, and 71 mM (in **1**), revealed an averaged molecular weight of 2170 ± 150 amu, that is, close to the molecular weight expected for a tetramer of **1** (2448 amu). We thus conclude that the tetrameric form, although subject to exchange, constitutes the predominant species in solution as well as in the solid state.

We have shown that G-quartets can be stabilized in the absence of a templating alkali metal cation. This leads us to suggest that this kind of structural motif may be more fundamental in its origin and easier to form than previously assumed.

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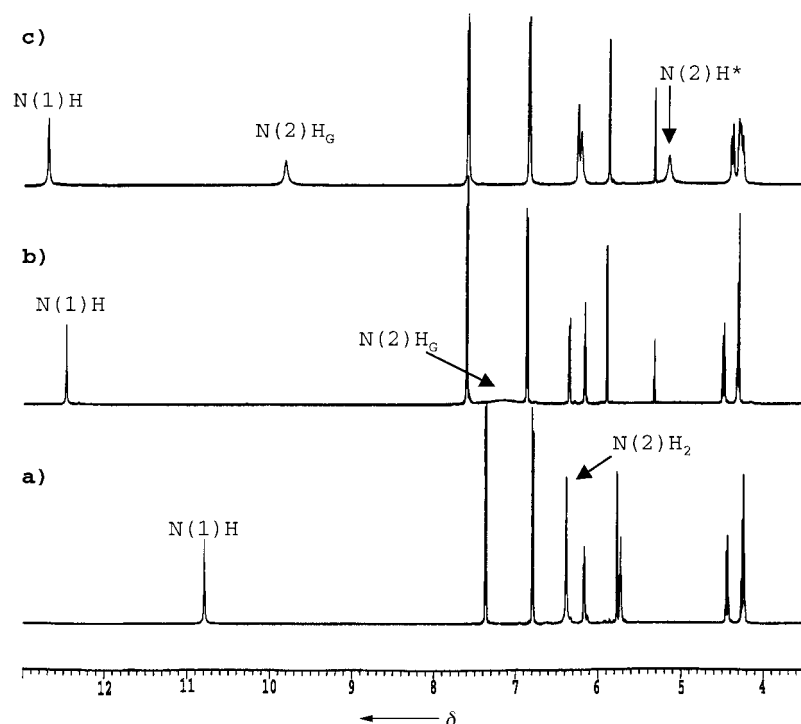


Figure 3. Portion of the proton NMR spectrum of **1** showing changes consistent with the formation of a G-quartet: a) 70 mM solution of **1** in [D₆]DMSO at room temperature; b) 58 mM solution of **1** in CD₂Cl₂ at room temperature; c) 58 mM solution of **1** in CD₂Cl₂ at -30°C . The signals ascribed to (N1)H are observed at δ = 10.80, 12.47, and 12.70 in the case of spectra a), b), and c), respectively. By contrast, the (N2)H₂ signal observed at δ = 6.40 in [D₆]DMSO at room temperature appears in the form of two signals at δ = 5.15 and 9.81 when the spectrum is recorded at -30°C in CD₂Cl₂. See text for further discussion. For definitions of H_G and H* see caption to Figure 2.

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- [12] X-ray crystal data for **1**: Thin colorless needles were grown from a CH₃CN/*i*PrOH mixture (1:1 ratio). C₃₀H₄₀N₆O₈ · ½ CH₃CN, tetragonal, *I*4, *Z* = 4, *a* = 28.3035(11), *c* = 8.2683(5) Å, *V* = 6623.6(5) Å³, ρ_{calcd} = 1.27 g cm⁻³, *F*(000) = 2696. A total of 23013 reflections were measured, 7585 unique (*R*_{int} = 0.029), on a Siemens SMART PLATFORM equipped with a CCD area detector using graphite-monochromated MoK α radiation (λ = 0.71073 Å) at -100°C . The structure was refined on *F*² to an *R*_w = 0.107, with a conventional *R* = 0.0455 (5821 reflections with *F*_o > 4[σ (*F*_o)]), GOF = 1.21 for 437 refined parameters. The tetramer resides around the crystallographic fourfold rotation axis. A molecule of acetonitrile resides between layers of tetramers, spaced 8.2 Å apart, and is disordered along the fourfold rotation axis. 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-134040. 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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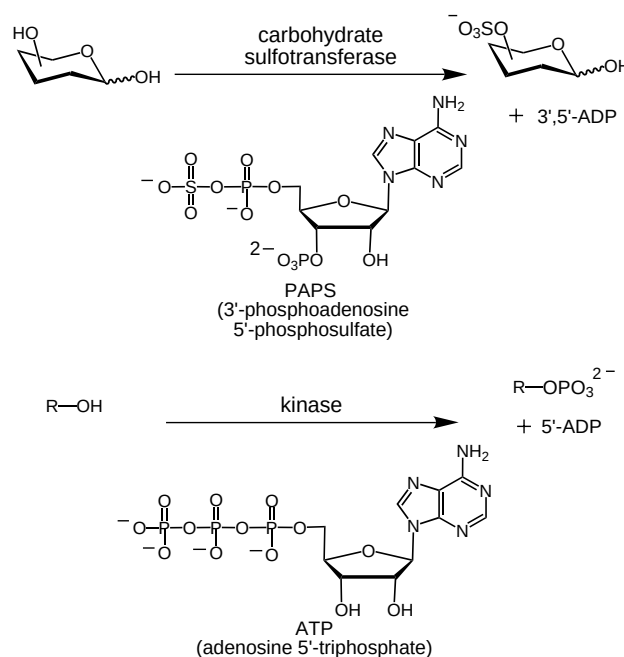
Discovery of Carbohydrate Sulfotransferase Inhibitors from a Kinase-Directed Library**

Joshua I. Armstrong, Adam R. Portley, Young-Tae Chang, David M. Nierengarten, Brian N. Cook, Kendra G. Bowman, Anthony Bishop, Nathanael S. Gray, Kevan M. Shokat, Peter G. Schultz, and Carolyn R. Bertozzi*

Carbohydrate sulfotransferases have recently emerged as an important and relatively unexplored class of therapeutic targets.^[1] For example, the seminal discovery that sulfated sialyl Lewis^x mediates the adhesion of leukocytes to inflamed

endothelium established carbohydrate sulfotransferases as potential targets for anti-inflammatory therapy.^[2] Ongoing genome sequencing projects have uncovered numerous carbohydrate sulfotransferase genes in the past few years.^[1, 3] It is now apparent that carbohydrate sulfotransferases comprise a large family of enzymes with overlapping tissue distribution and substrate specificities. To deconvolute the precise role of each sulfotransferase gene product and elucidate its contribution to normal and pathological processes, cell-permeable and highly specific small-molecule antagonists need to be identified. Surprisingly, no inhibitor of a carbohydrate sulfotransferase has been reported to date. At present, the limited structural and mechanistic information about this class of enzymes impedes rational approaches to inhibitor design. To identify lead inhibitors of carbohydrate sulfotransferases, we therefore adopted a strategy that involved the screening of small-molecule libraries.

To narrow our search, we focused on the similarities between the substrates utilized by sulfotransferases and kinases, a widely studied family of enzymes for which diverse and potent inhibitors are available.^[4] Carbohydrate sulfotransferases catalyze the transfer of a sulfonyl group from the universal sulfate donor 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to a hydroxy (or amino) group of the acceptor oligosaccharide (Scheme 1).



Scheme 1. Reactions catalyzed by carbohydrate sulfotransferases and kinases.

Kinases catalyze a similar anionic group transfer reaction using adenosine 5'-triphosphate (ATP) as a phosphoryl donor. Thus, both enzyme classes recognize adenosine-based substrates, PAPS and ATP. Furthermore, the hydrophobic adenine binding pockets of the recently crystallized estrogen sulfotransferase,^[5] and heparin N-sulfotransferase^[6] are similar to those of several kinases. On the basis of these parallels, we chose to screen a panel of previously reported kinase-

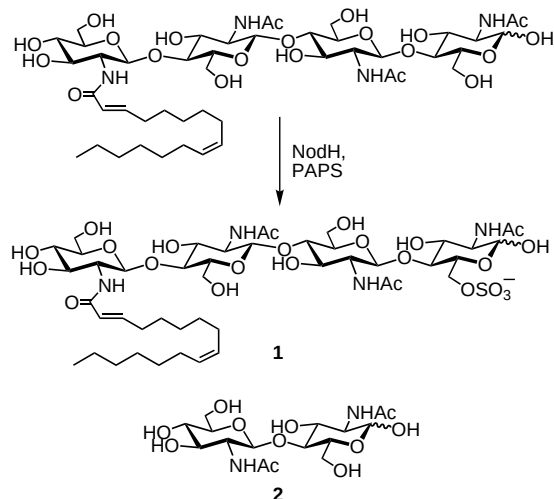
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directed inhibitors that are competitive with ATP for cross-reactivity with carbohydrate sulfotransferases. Here we report the discovery of the first carbohydrate sulfotransferase inhibitors from a kinase-directed library.

We selected the well-characterized GlcNAc-6-sulfotransferase NodH from *Rhizobium meliloti* as an initial enzymatic target.^[7] NodH is involved in the biosynthesis of the sulfated nodulation factor **1** (Scheme 2) which induces root nodulation in the symbiotic host plant alfalfa.^[8] NodH can also utilize the simple disaccharide chitobiose (**2**) as a substrate.^[9]



Scheme 2. The NodH sulfotransferase catalyzes the sulfonation of a lipochitooligosaccharide, but can use chitobiose (**2**) as a substrate.

We developed a medium-throughput radiolabel transfer assay similar to that of Bourdineaud et al.^[10] that involves thin-layer chromatography separation of the product, ³⁵S-labeled 6-sulfo-chitobiose from excess substrate, and ³⁵S-labeled PAPS. Using this assay we measured a K_M value for PAPS of $4.3 (\pm 0.3) \mu\text{M}$ and a K_I value for the product 3',5'-ADP of $1.36 (\pm 0.08) \mu\text{M}$ (data not shown).

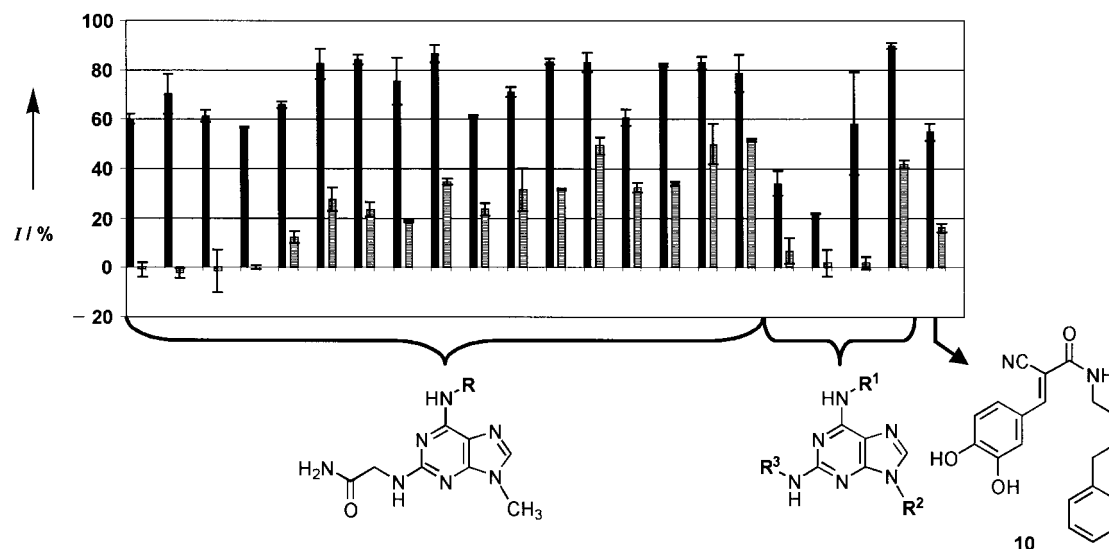
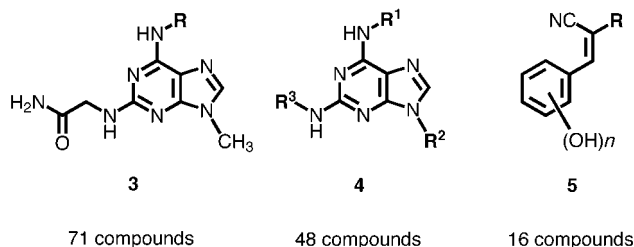


Figure 2. Inhibitor rescreen at 50 μM . I = Inhibition; black bars: 50 μM inhibitor, 2.4 μM PAPS; gray bars: 50 μM inhibitor, 8.04 μM PAPS.

Our initial inhibitor screen included 139 compounds comprising selected structures from purine libraries (**3** and **4**),^[4b, 11] as well as commercially available protein kinase inhibitors (16 tyrphostins (**5**) and four representatives from other kinase-inhibitor families) (Figure 1). One set of purines

Kinase inhibitor panels:



Other commercially available kinase inhibitors:

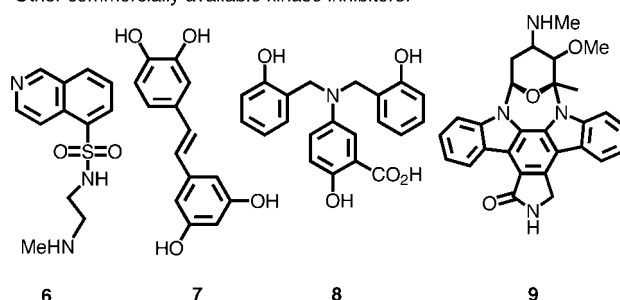


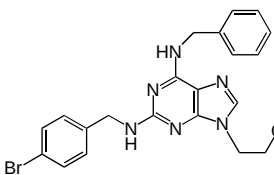
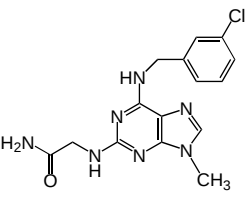
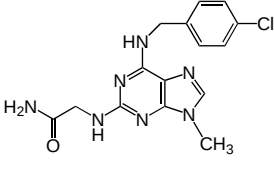
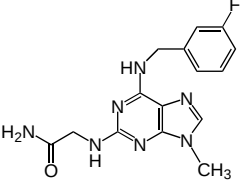
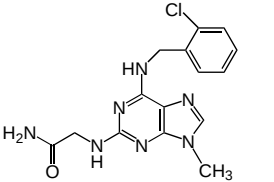
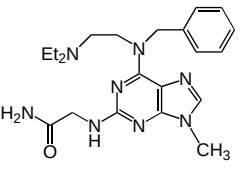
Figure 1. Initial inhibitor panel.

(**3**) possessed conserved N9-methyl and N2-carboxamide groups, but varied in structure at N6. The second set of purines (**4**) contained diverse substituents at all three positions. These libraries were originally directed toward cyclin-dependent kinases (CDKs).^[4b, 11]

Enzyme assays in the presence of the test compounds (200 μM) identified several purine analogues and one tyrphostin analogue (compound **10**, Figure 2) as lead inhibitors;

these compounds displayed over 80 % inhibition of enzyme activity. To assess the relative inhibitory activity more accurately, we next rescreened the chosen compounds under more stringent conditions (Figure 2). Even at 50 μM , several compounds still displayed high levels of inhibition. As expected for a PAPS-competitive inhibitor, the inhibitory potency was highly dependent on the concentration of PAPS used in the assay. Increasing the concentration of PAPS from 2.4 to 8.0 μM (0.5 to 2 times the K_M) triggered a dramatic decrease in the inhibitory activity of most compounds. However, several of the purine analogues still maintained modest activity under these conditions. We chose the most potent six purines and determined their IC_{50} values (Table 1).

Table 1. IC_{50} [μM] values against NodH sulfotransferase.^[a]

Inhibitor	IC_{50}	Inhibitor	IC_{50}
	20		40
	40		35
	25		40

[a] Serial dilutions of each inhibitor were tested in the presence of 2.4 μM PAPS, 5 mM chitobiose, and 1 μU NodH.

These ranged from 20 to 40 μM —modest yet impressive activity considering the limited pool of compounds initially screened. Interestingly, five of the six most potent inhibitors were derived from the same purine class (**3**) and possessed benzylic substituents at N6. This preliminary structure–activity information will form the basis for future sulfotransferase-directed libraries.

Selectivity has been difficult to achieve with kinase inhibitors that are competitive with ATP since all kinases possess an ATP binding pocket. Therefore, we were concerned with the selectivity of our lead compounds against other carbohydrate sulfotransferases, particularly GlcNAc-6-O-sulfotransferases. When evaluated against a GlcNAc-6-sulfotransferase expressed in human high endothelial venules^[3a] and a widely expressed keratan sulfate sulfotransferase,^[12] none of the six purines showed measurable inhibitory activity at 200 μM , indicating that these modest inhibitors are selective among these sulfotransferases (data not shown).

As the library above comprises known kinase inhibitors, a major concern is the possible cross-reactivity of the identified “hits” with kinases. We tested the compounds for inhibitory activity against two serine/threonine kinases, p38/MAP kinase, and cyclin-dependent kinase 2 (CDK2), the original target of the library we had screened.^[4b, 13] Against the former, the compounds displayed IC_{50} values greater than 60 μM . However, not surprisingly, they were more active against CDK2, with IC_{50} values in the range of 15 to 40 μM . Our next goal is to explore structural modifications that enhance potency against the sulfotransferases while simultaneously reducing kinase inhibitory activity.

Experimental section

Purine analogues were prepared as previously described.^[14] All other kinase inhibitors were purchased from Calbiochem (La Jolla, CA).

Preparation of [^{35}S]PAPS: Carrier-free [^{35}S]PAPS was synthesized in vitro using a procedure similar to that described by Long and co-workers.^[15] Carrier-free [^{35}S]Na₂SO₄ (0.2 mCi) was incubated for 24 h with 0.12 U ATP sulfurylase (Sigma), 8.3 U inorganic pyrophosphatase (Sigma), and 210 mg APS Kinase in buffer A (50 mM Tris-HCl pH 8.0, 30 mM KCl, 5 mM MgCl₂, 1 mM EDTA, 1 mM DTT, 10 % glycerol) containing 30 mM ATP. The incorporation of ^{35}S into [^{35}S]PAPS was quantified by TLC on PEI-cellulose plates (eluting with 0.9 M LiCl) followed by phosphorimaging analysis (Model 445 SI, Molecular Dynamics). The reaction yield typically exceeded 90 % based on [^{35}S]Na₂SO₄.

NodH sulfotransferase assay: Inhibitors were screened at 200 μM with 1 μU NodH (Calbiochem) 2.4 μM [^{35}S]PAPS (1.0 μCi) and 5 mM *N,N'*-diacetylchitobiose (Calbiochem) in buffer A. After preincubation of the enzyme and inhibitors for 20 min at room temperature, the enzymatic reaction was initiated by addition of [^{35}S]PAPS and, after 6 min at room temperature, terminated by dilution with MeOH (120 μL). A 25- μL aliquot of each reaction was spotted on Whatman LKTLC plates and eluted with 6:3:2 BuOH:EtOH:H₂O. The plates were dried and analyzed by phosphorimaging. For IC_{50} determinations, serial dilutions of the inhibitors were prepared and tested in the presence of 2.4 μM [^{35}S]PAPS (1.0 μCi) and 5 mM *N,N'*-diacetylchitobiose in buffer A (100 μL total volume). Aliquots (5 μL) were removed and diluted with MeOH (30 μL) after 3, 6, 9, and 12 min. Reaction rates were determined by calculating the incorporation of radioactive sulfate into *N,N'*-diacetylchitobiose-6-OSO₃ over time.

Supporting information contains a full list of compounds from libraries **3–5** as well as kinetic data for K_m and K_i measurements (6 pages).

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Facile and Clean Oxidation of Alcohols in Water Using Hypervalent Iodine(III) Reagents**

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Tomohiro Maegawa, and Yasuyuki Kita*

Oxidation of alcohols to carbonyl compounds is a pivotal reaction in organic chemistry and numerous methods using a variety of reagents and conditions have been developed. Recent demand for eco-conscious chemical processes has encouraged the development of several clean and practical oxidation reactions,^[1] and awaits further development of high-yielding, clean, safe, and economical methods for the oxidation of alcohols. Hypervalent iodine reagents have been used extensively in organic syntheses as a result of their low toxicity, ready availability, and easy handling.^[2] For example,

the highly utilized pentavalent iodine reagents such as Dess–Martin periodinane (DMP)^[3] and *o*-iodoxybenzoic acid (IBX)^[4] oxidize alcohols mildly and efficiently to carbonyl compounds in high yields in organic solvents such as CH₂Cl₂, DMSO, and acetone. However, despite their utility, iodine(V) reagents are potentially explosive, cannot be stocked, and the generated iodine(III) species are usually not utilized (only iodine(V) species can be used for the oxidation of alcohols). Therefore, a facile and efficient use of the readily available and relatively stable iodine(III) reagents in place of iodine(V) reagents has been long desired. In contrast to oxidations with iodine(V)-based reagents, only a few examples of the oxidation of alcohols using iodine(III) reagents have been described.^[5] Existing methods are limited to organic solvents and usually involve activation of Ru or Yb catalysts^[5a,b] or of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)^[5c] by an iodine(III) co-oxidant. As an exception, readily oxidizable benzylic alcohol derivatives do not require catalysts.^[6, 13a] We have been studying the activation of hypervalent iodine reagents using several additives and solvents,^[7] and report herein an efficient oxidation of alcohols using iodosobenzene (PhI=O) with an inexpensive inorganic salt, KBr, in water under neutral conditions. This method was extended to an environmentally benign polymer-supported (diacetoxyiodo)benzene (PSDIB) oxidation procedure.

Various aqueous oxidation reactions have been developed since economic and environmental concerns encourage the use of water as a reaction medium.^[8] Very recently we have achieved a novel catalytic activation of PhI=O using a cationic surfactant, cetyltrimethylammonium bromide (CTAB), under neutral conditions. Its low solubility in water and in most organic solvents normally limits the reactivity of PhI=O, however, our micellar and reversed micellar systems have expanded the choice of solvents (from nonpolar solvents to water) for hypervalent iodine oxidation.^[9] In this study we first examined the oxidation of alcohols using PhI=O–CTAB in water, by the CTAB-catalyzed (20 mol %) oxidation of 2-octanol (**1e**) in water to give 2-octanone (**2e**) in 67 % yield. Thus, we re-examined the activation of PhI=O in this reaction with a variety of additives including alkali metal salts. The addition of bromide salts such as NaBr, KBr, and LiBr was found to activate PhI=O remarkably to give **2e** in good yields (94 % yield (KBr)), while salts other than bromide (NaX: X = F, Cl, I, HSO₄, BF₄, HCO₃, ClO₄, OAc, NO₃) did not catalyze the reaction effectively.^[10] We therefore chose KBr, the most economical alkali metal bromide, for further studies. The oxidation of activated alcohols such as benzylic or allylic alcohols proceeds quantitatively just by activating PhI=O with a small amount of water (10 equiv.), and without addition of KBr (Table 1, entries 1–3). With benzyl alcohol (**1a**), the reaction rate is enhanced remarkably by adding a catalytic amount of KBr. In contrast, a catalytic amount of KBr is indispensable for the oxidation of saturated primary and secondary alcohols. This PhI=O–KBr system is applicable to the oxidation of a variety of primary and secondary alcohols bearing functional groups such as ether, ester, sulfonamide, and azido groups (see Table 1). Oxidation of primary alcohol **1k** only yields carboxylic acid **2k** (52 % yield) and none of the corresponding aldehyde when using 1.1 equivalents of PhI=O.

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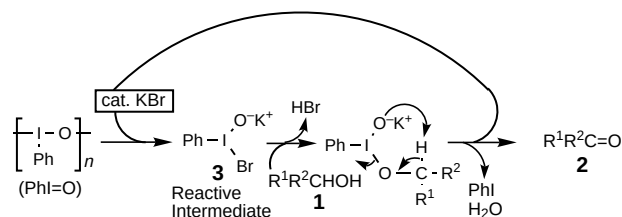
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Table 1. Oxidation of alcohols **1** with $\text{PhI}=\text{O}-\text{KBr}$ in H_2O .

Entry	Substrate	Product	KBr [equiv.]	Time [h]	Yield [%] ^[a]
1	$\text{Ph}-\text{CH}_2\text{OH}$ 1a	PhCO_2H 2a	none	30	quant. ^[b]
2	$\text{C}_6\text{H}_5\text{OH}$ 1b	$\text{C}_6\text{H}_5\text{O}$ 2b	none	6	78(94) ^[c, d]
3	$\text{C}_6\text{H}_4\text{OH}$ 1c	$\text{C}_6\text{H}_4\text{O}$ 2c	none	24	87
4	1c	2c	0.2	2	quant.
5	$\text{PhCH}(\text{OH})\text{Et}$ 1d	PhCOEt 2d	1.0	4	quant. ^[d]
6	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1e	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ 2e	none	48	trace
7	1e	2e	0.2	24	94 ^[d]
8	1e	2e	1.0	8	98 ^[d]
9	$\text{PhCOOCH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1f	$\text{PhCOOCH}_2\text{CH}_2\text{CH}_2\text{O}$ 2f	1.0	4	quant.
10	$\text{C}_6\text{H}_{11}\text{OH}$ 1g	$\text{C}_6\text{H}_{11}\text{O}$ 2g	1.0	3	quant. ^[d]
11	$\text{TsNCH}_2\text{CH}_2\text{OH}$ 1h	$\text{TsNCH}_2\text{CH}_2\text{O}$ 2h	1.0	24	86
12	L-menthol 1i	L-menthone 2i	1.0	7	quant. ^[d]
13	3 β -cholestanol 1j	5 α -cholestan-3-one 2j	1.0	4	quant.
14	$\text{PhCH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1k	$\text{PhCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ 2k	none	48	trace
15	1k	2k	0.2	2	92 ^[b]
16	$\text{BnOCH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1l	$\text{BnOCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ 2l	0.2	2	76 ^[b]
17	$\text{EtO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1m	$\text{EtO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ 2m	0.2	2	92 ^[b]
18	$\text{N}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1n	$\text{N}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ 2n	0.2	2	90 ^[b]

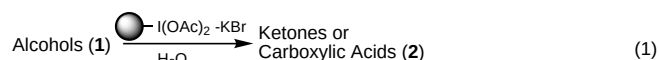
[a] Yields of isolated products unless otherwise noted. [b] 2.2 equiv. $\text{PhI}=\text{O}$ was used. [c] Yield in parenthesis is based on the consumed starting material. [d] Yields were determined by GC.

A plausible mechanism for the catalytic activation of $\text{PhI}=\text{O}$ with KBr is depicted in Scheme 1. Polymeric iodoso-benzene is initially depolymerized by the addition of KBr to form a highly reactive intermediate **3**, which reacts with alcohols **1** to yield the corresponding carboxylic acids or ketones with regeneration of KBr. Although another mechanism mediated by Br^+ may be possible, **3** is more likely to be the reactive species since only a trace amount of **2e** was obtained even with an excess of either aqueous H_2O_2 or aqueous NaOCl in the presence of KBr. Thus, the activation of $\text{PhI}=\text{O}$ with KBr involving **3** is very different from the mechanism involving transition metals or TEMPO, since in

Scheme 1. Catalytic activation of $\text{PhI}=\text{O}$ with KBr.

the latter cases, the metal oxide or *N*-oxoammonium salt works as the reactive species.

Next, we modified this system to develop a practical and clean procedure for the oxidation of alcohols using a polymer-supported hypervalent iodine(III) reagent. Solid and polymer-supported reagents have applications in combinatorial chemistry, and the use of such operationally simple and environmentally benign reagents is becoming more and more important in the pharmaceutical and agrochemical industries. Several polymer-bound oxidants have been reported,^[11] and polymer-supported hypervalent iodine reagents should be a welcome addition as a result of their versatility, low toxicity, and high yields. Recently, Togo et al.^[12] and Ley et al.^[13] demonstrated that PSDIB [see Eq. (1)]^[14] shows similar reactivity to (diacetoxyiodo)benzene and utilized it in organic solvents as a replacement for previously reported iodine(III) reagents. A method for the oxidation of alcohols using DMP with a thiosulfate resin was recently reported by Parlow et al.,^[15] but, this required an excess amount of reagent. We re-examined the oxidation using PSDIB in water. The oxidation of saturated secondary alcohols using 1.1 equivalents of PSDIB and 0.2 equivalents of KBr proceeded in water at room temperature in a few hours to give the corresponding carbonyl compounds **2** in excellent yields, while the addition of 1.0 equivalents of NaHCO_3 was necessary for primary alcohol **1k**^[16] (Table 2). Furthermore, the iodinated resin could be regenerated and recycled successfully. We also unexpectedly found that water is a suitable solvent for PSDIB-induced oxidation, and that PSDIB is considerably

Table 2. Oxidation of alcohols **1** with PSDIB–KBr in H_2O [Eq. (1)].

Entry	Substrate	Product	KBr [equiv.]	Time [h]	Yield [%] ^[a]
1	1a	2a	0.2	24	quant. ^[c]
2	1d	2d	0.2	4	quant. ^[b]
3	1e	2e	0.2	7	quant. ^[b]
4	1i	2i	0.2	20	86 ^[b]
5	1k	2k	1.0	24	90 ^[c, d]

[a] Yields of isolated products unless otherwise noted. [b] Yields were determined by GC. [c] 2.5 equiv. PSDIB was used. [d] In the presence of

stable in water.^[17] Since both water and Br^- are indispensable for the reaction progression, this reaction might also be proceeding via a reactive intermediate similar to **3**, being formed by ligand exchange of diacetate.^[18]

The positive features of the present method are summarized as follows: 1) ease of operation; 2) facile recycling of the polymer-supported iodine(III) reagent; the recovered resin (polyiodostyrene) is easily reoxidized with peracetic acid (30% H_2O_2 and Ac_2O)^[14] and can be used repeatedly without loss of activity; 3) excellent yields; 4) environmental consciousness: no organic solvent is used in the reaction and only a small amount is needed in the workup.

In summary, we have achieved a clean and efficient oxidation of alcohols using $\text{PhI}=\text{O}$ or PSDIB with KBr in water. The present procedure will provide a facile and environmentally benign method for the catalytic activation

of a variety of sluggishly reactive and/or sparsely soluble hypervalent iodine reagents in water under neutral conditions. Further studies on the application of this system are now in progress.

Experimental Section

Method A (for primary alcohols): $\text{PhI}=\text{O}$ (0.44 mmol; Tokyo Chemical Industry Co., Ltd.) was added at room temperature to a stirred mixture of **1** (0.20 mmol) and KBr (0.04 mmol) in water (1.0 mL), and the mixture was stirred for 2 h. The resulting mixture was extracted with AcOEt , washed with brine, dried over Na_2SO_4 , evaporated in vacuo, and the residue was purified by column chromatography ($\text{EtOAc}/n\text{-hexane}$) to give pure **2**. Intermolecular esterification through nucleophilic attack on the initially formed aldehyde also proceeds under the conditions of Method B.

Method B (for secondary alcohols): Water (2.0 mmol) was added dropwise to a stirred mixture of **1** (0.2 mmol), $\text{PhI}=\text{O}$ (0.22 mmol), and KBr (0.2 mmol). The mixture was stirred or sonicated for several hours while checking the reaction progress by gas or thin-layer chromatography. After completion, $n\text{-hexane}$ was added to the mixture, and then filtered. Evaporation of the solvent under vacuum afforded a crude product that was further purified by column chromatography ($\text{Et}_2\text{O}/n\text{-hexane}$) to give pure **2**.

Method C (for the oxidation with PSDIB): PSDIB (22 mmol), used without any pretreatment, was added at room temperature to a stirred suspension of **1** (20 mmol) and KBr (14 mmol) in water (40 mL), and the mixture was then sonicated for several hours. The resulting mixture was filtered and the residue containing **2** was washed with water to remove KBr , then extracted with $n\text{-hexane}$ or MeOH , and the filtrate was evaporated to give **2**. The product was purified by column chromatography, when necessary.

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- [17] Even after stirring PSDIB in water for 4 d, the addition of **1e** and KBr to this suspension gave **2e** in 68% yield.
- [18] **2e** was obtained only in 8% yield, when the reaction was performed with PSDIB in CH_2Cl_2 (containing 4-Å molecular sieves) in the presence of 20 mol% NEt_4Br as a bromide ion source. However, addition of a catalytic amount of water to the above mentioned mixture enhanced the yield of **2e** to 51%.

Total Synthesis of (+)-Concanamycin F**

Ian Paterson,* Victoria A. Doughty,
Malcolm D. McLeod, and Thomas Trieselmann

The concanamycin group of macrolides, first isolated from a culture of *Streptomyces diastatochromogenes* Sp. S45 by Kinashi and co-workers and typified by concanamycin A (**1**, Figure 1)^[1a–d] and its aglycone, concanamycin F (**2**),^[1e,f] exhibit potent inhibition of vacuolar (H^+) ATPase activity.^[2] The

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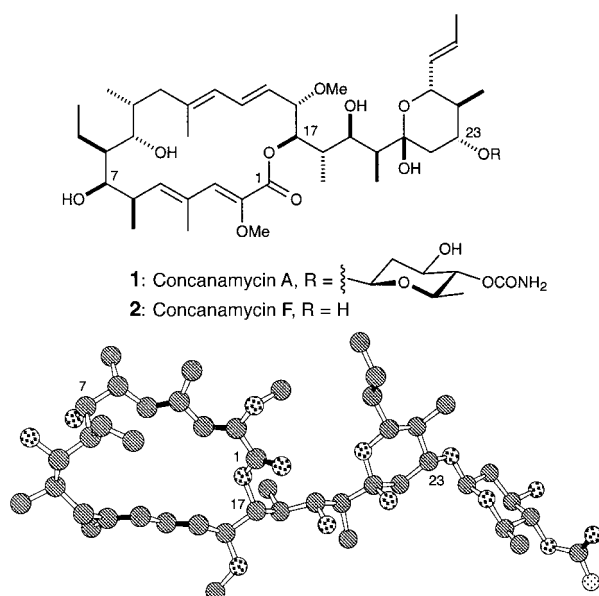
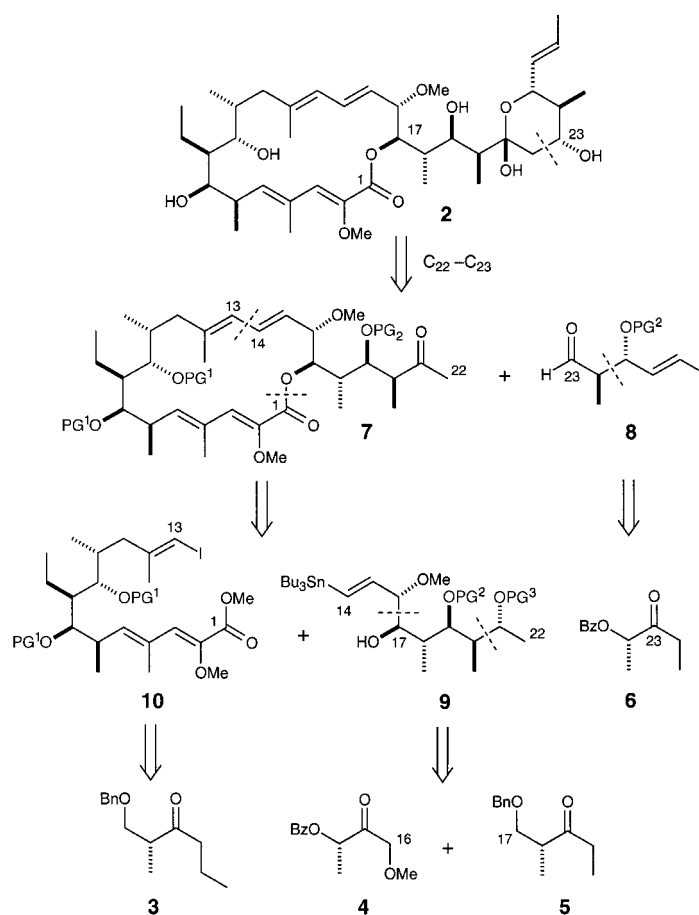


Figure 1. Structures of concanamycins A and F (concanolide A).

(ability of the concanamycins to disrupt cellular acidification leads to a diverse range of biological activity, including antiviral^[3a] and immunosuppressant activity^[3b] as well as the attenuation of resistance in MDR tumor cell lines.^[3c] Recently, this general class of bioactive macrolides, which include the bafilomycins, has served as a template for the design of novel therapeutic agents for the treatment of osteoporosis by selectively targeting the proton ATPase responsible for bone resorption.^[3d,e]

The concanamycins are characterized by a densely functionalized 18-membered macrolactone incorporating a poly-oxygenated side chain at C₁₇. The side chain itself contains a six-membered hemiacetal which is both acid- and base-labile. The structural complexity of these macrolides and their significant biological activity have attracted considerable synthetic attention. A total synthesis of concanamycin F (**2**) has been described recently by the Toshima group,^[4a,b] and syntheses of the simpler 16-membered macrolides bafilomycin A₁^[5a-c] and hygrolidin^[5d] have also been achieved. We now report an expedient, highly stereocontrolled synthesis^[6] of concanamycin F (26 steps, 5.3% overall yield) by the application of *anti*-selective aldol reactions of chiral ketones **3–6** (Scheme 1) developed in our laboratory,^[7] and by employing a C₂₂–C₂₃ coupling strategy for introducing the side chain. The careful selection of protecting groups proved imperative both for achieving macrocyclization and facilitating the use of mild deprotection conditions, thus enabling the survival of the sensitive side chain.

Central to our synthetic planning^[6a, 8] was the late installation of the C₁₇ side chain by the stereocontrolled aldol coupling of methyl ketone **7** with aldehyde **8**, thus affording a protected version of concanamycin F and potentially providing access to novel glycoside analogues. The majority of the stereochemistry and oxygenation in the two components selected for construction of the macrocyclic ketone **7**, that is the stannane **9** and the iodide **10**, would then be introduced using boron-mediated aldol reactions.^[8] Previously, we had



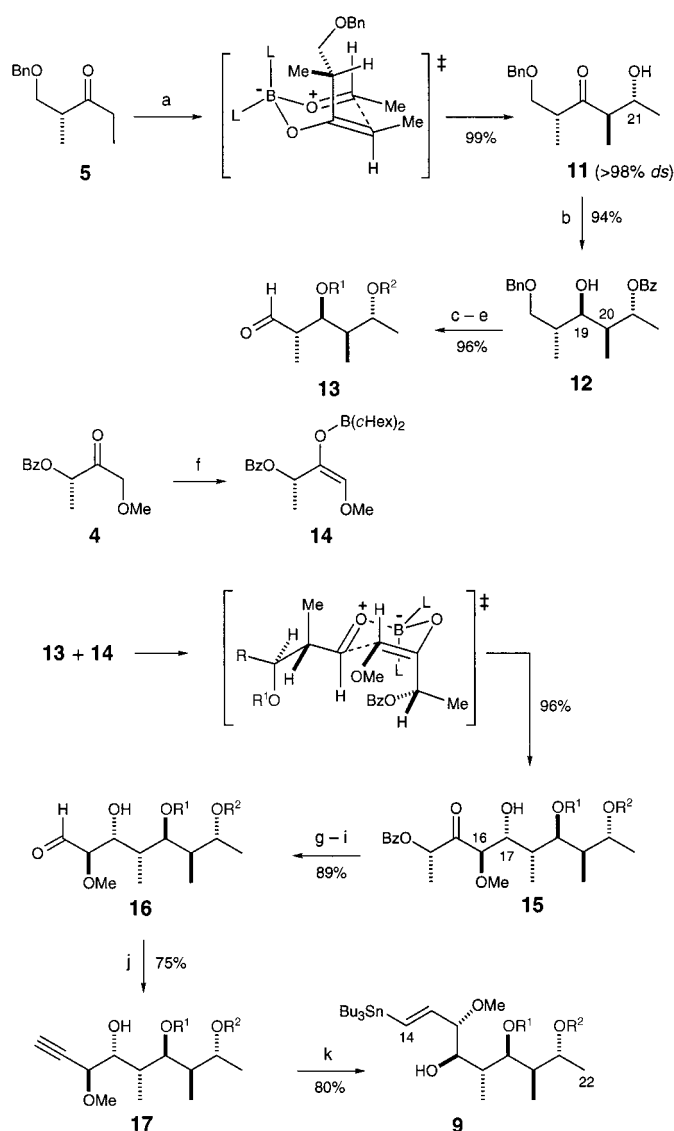
Scheme 1. Retrosynthetic analysis. Bn = benzyl, Bz = benzoyl, PG = protecting group.

shown that an *anti*-aldol reaction between ketone **3** and methacrolein and in situ reduction of the intermediate boron aldolate gave access to a key intermediate which was elaborated into iodide **10**.^[6b]

A synthesis of the vinylstannane partner **9**, which contains six contiguous stereocenters, was now required. Achieving efficient macrocyclization (by lactonization or intramolecular sp²–sp² coupling), followed by C₂₂–C₂₃ aldol coupling (**7** + **8**) and global deprotection, were identified as further critical issues for completion of the total synthesis.

The synthesis of the C₁₄–C₂₂ stannane subunit **9** (Scheme 2) started out with a (cHex)₂BCl-mediated boron aldol reaction^[7a,b] of ethyl ketone **5** with acetaldehyde, which gave the *anti*-adduct **11** in 99% yield (>98% *ds*). The temporary introduction of the C₂₁-hydroxy group enabled access to the desired C₁₉–C₂₀ *syn* relationship by employing a 1,3-*anti* hydroxy-directed reduction. Thus, an Evans–Tishchenko reduction^[9] of **11** (SmI₂, PhCHO) generated the ester **12** as the sole product (94%). A three-step sequence of: 1) silylation to generate the diethylisopropylsilyl (DEIPS) ether; 2) hydrogenolysis of the benzyl ether (Pd(OH)₂); and 3) Swern oxidation gave **13** in 96% overall yield.

The novel (*S*)-lactate-derived ketone **4**^[10] was employed for the chain extension of **13** and introduction of the oxygen-bearing stereocenters at C₁₆ and C₁₇. Enolization of **4** ((cHex)₂BCl, Et₃N, Et₂O) generated the (*E*)-enol borinate



Scheme 2. Synthesis of the C₁₄–C₂₂ subunit (**9**). a) (cHex)₂BCl, Et₃N, Et₂O, 0 °C, 2 h; MeCHO, Et₂O, –78 → –20 °C, 16 h; H₂O₂, MeOH, pH 7 buffer, 0 °C, 1 h; b) PhCHO, SmI₂, THF, –10 °C, 1 h; c) DEIPSCl, imidazole, DMF, 20 °C, 16 h; d) Pd(OH)₂, H₂, 20 °C, 3 h; e) DMSO, (COCl)₂, CH₂Cl₂, Et₃N, –78 → 0 °C, 30 min; f) (cHex)₂BCl, Et₃N, Et₂O, 0 °C, 3 h; **13**, Et₂O, –78 → –20 °C, 16 h; H₂O₂, MeOH, pH 7 buffer, 0 °C, 1 h; g) NaBH₄, MeOH, 20 °C, 30 min; h) K₂CO₃, MeOH, 20 °C, 30 min; i) Pb(OAc)₄, Na₂CO₃, CH₂Cl₂, 20 °C, 10 min; j) MeCOC(=N₂)PO(OMe)₂, K₂CO₃, MeOH, 20 °C, 16 h; k) [PdCl₂(PPh₃)₂], Bu₃SnH, CH₂Cl₂, 20 °C, 10 min. R¹ = DEIPS (≡ PG² in Scheme 1), R² = Bz (≡ PG³ in scheme 1). cHex = cyclohexyl, DEIPSCl = diethylisopropylsilyl chloride, DMSO = dimethyl sulfoxide.

14 which on addition to aldehyde **13** gave solely the *anti*- α -methoxy- β -hydroxy ketone **15** (96 %), where the dominant enolate π -facial bias is matched with the (weak) Felkin–Anh preference of the aldehyde component.^[7c] Compound **15** was then transformed into the β -hydroxy aldehyde **16** in 89 % overall yield by: 1) ketone reduction (NaBH₄); 2) chemoselective hydrolysis (K₂CO₃, MeOH) of the benzoate proximate to the C₁₅–OH; and 3) glycol cleavage (Pb(OAc)₄).

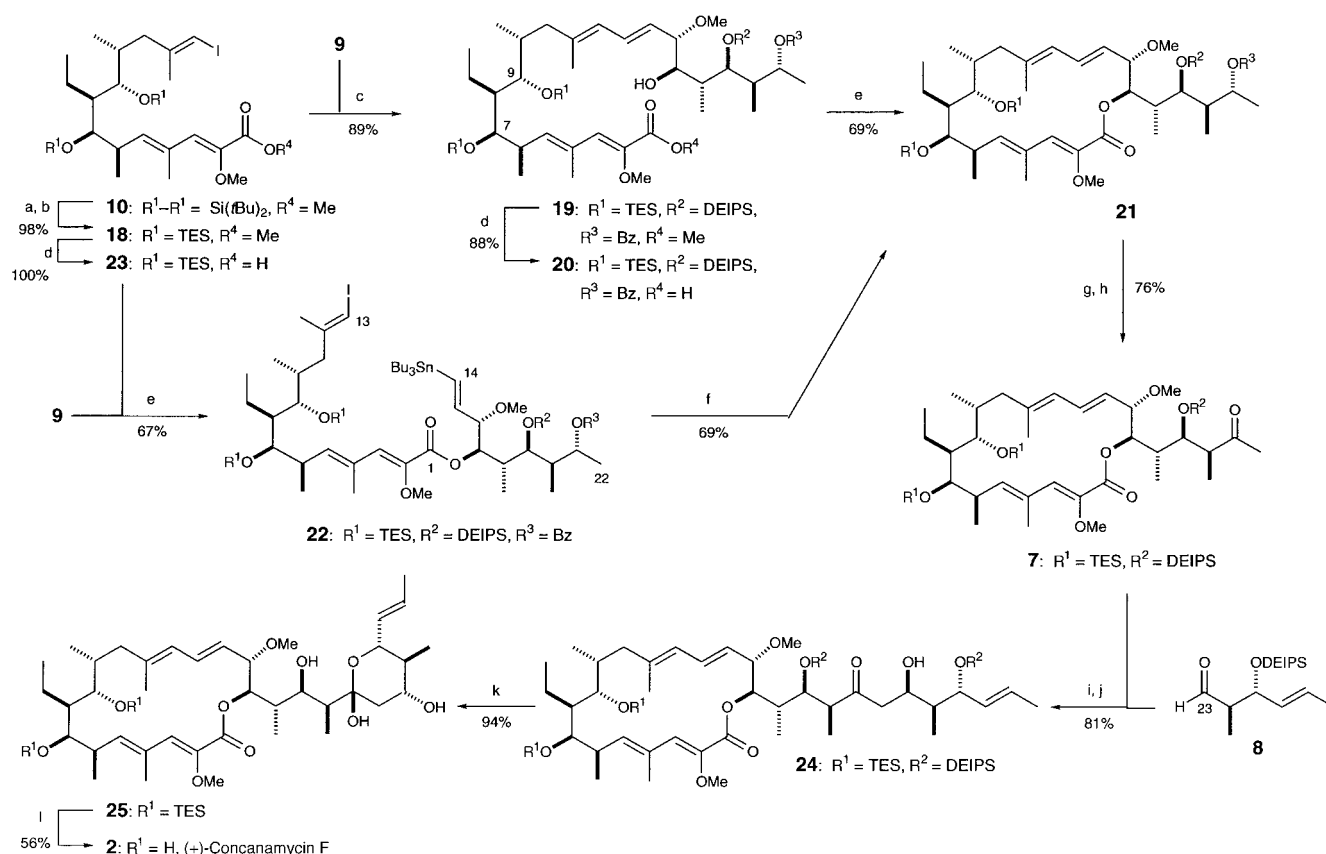
Elaboration into the (*E*)-alkenylstannane **9** was then addressed. After obtaining unsatisfactory yields for Takai

olefination^[11] on this sensitive, highly oxygenated aldehyde, the desired transformation was achieved by using the Ohira–Bestmann alkylation protocol^[12] (75 %) and subsequent Pd-catalyzed *syn*-hydrostannation^[13] of the terminal alkyne **17** to give **9** in 80 % yield. This efficient 11-step sequence provided the C₁₄–C₂₂ subunit **9** in 46 % yield with essentially complete control in the introduction of the six stereogenic centers.

At this point, it proved necessary to replace the cyclic silylene protection of the C_{7,9}-diol in the vinyl iodide **10** (Scheme 3) with the corresponding bis-triethylsilyl (TES) ether **18**. The C₁₃–C₁₄ coupling between stannane **9** and iodide **18** to give diene **19** was achieved in 89 % yield under mild conditions (NMP, 20 °C, 1 h) using copper(I) thiophene-2-carboxylate (CuTC), a new Cu^I reagent introduced by Liebeskind et al.^[14] to promote Stille-type coupling reactions in the absence of Pd catalysis.^[15] Notably, this is the first application of this new procedure for the construction of the characteristic diene unit found in the concanamycins and bafilomycins.

Selective cleavage of the methyl ester in the presence of the benzoate was then performed by nucleophilic displacement with KOSiMe₃,^[16] providing the secoacid derivative **20** (88 %) in readiness for macrolactonization. Cyclization to the 18-membered macrolide **21** proceeded in 69 % yield under modified Yamaguchi conditions (2,4,6-Cl₃(C₆H₂)COCl, Et₃N, 4-DMAP, PhMe).^[17] The use of acyclic protecting groups was crucial to the success of this reaction.^[18] We initially prepared the corresponding secoacid derivatives **20** (R¹–R¹ = Si(*t*Bu)₂, R² = DEIPS or H, R³ = Bz, R⁴ = H) with silylene protection of the C_{7,9}-diol, by a similar sequence from **10** itself. These protected derivatives could not be macrolactonized under Yamaguchi or other, more forcing, conditions, presumably due to their inability to access the required conformation. The 18-membered macrolactone could also be generated in 64 % yield by an intramolecular Stille coupling performed on **22**,^[18] which was obtained by hydrolysis of **18** (100 %) and esterification of the derived acid **23** with **9** (67 %). In contrast to the above intermolecular process, this cyclization succeeded under Pd catalysis,^[19] as also shown by Toshima et al.,^[5b] whereas attempted Cu^I catalysis with CuTC led to protodestannylation of **22**. Next, reductive cleavage of the benzoate in the presence of the lactone carbonyl group was achieved selectively by treatment of **21** with DIBAL, which after tetrapropylammonium perruthenate (TPAP) oxidation^[20] of the resulting C₂₁-alcohol provided the macrocyclic methyl ketone **7** in 76 % yield.

Introduction of the remainder of the concanamycin side chain was best achieved using a carefully optimized Mukaiyama aldol coupling,^[21] which relied on Felkin–Anh induction from the aldehyde component **8** (prepared from ketone **6**^[6a]). The preformed silyl enol ether from **7** (LiHMDS, Me₃SiCl, Et₃N) was combined in CH₂Cl₂ with aldehyde **8**, in the presence of CaH₂,^[22] and treated with BF₃·OEt₂ at –100 °C for 5 min. This provided the required aldol adduct **24** as the sole isomer in 81 % yield. Finally, successful removal of the silyl protecting groups necessitated stepwise treatment with TASF^[23] to give the hemiacetal **25** (94 %), followed by acidic hydrolysis (TsOH, aq. MeCN) of the remaining TES ethers.



Scheme 3. Subunit coupling and total synthesis of (+)-concanamycin F (**2**). a) $\text{HF} \cdot \text{Et}_3\text{N}$, THF, 20°C , 7 d; b) TESOTf , 2,6-lutidine, CH_2Cl_2 , $-78 \rightarrow 0^\circ\text{C}$, 10 min; c) CuTC , NMP, 20°C , 1 h; d) KOTMS , Et_2O , 20°C , 30 min; e) Et_3N , 2,4,6- $\text{Cl}_3(\text{C}_6\text{H}_2)\text{COCl}$, 4-DMAP, PhMe, 20°C , 18 h; f) $[\text{Pd}_2(\text{dba})_3]$, Ph_3As , $i\text{Pr}_2\text{NEt}$, DMF, THF, 60°C , 16 h; g) DIBAL , CH_2Cl_2 , -78°C , 1 min; h) TPAP, NMO, 4 Å mol. sieves, CH_2Cl_2 , 20°C , 2 h; i) Me_3SiCl , Et_3N , THF, -78°C ; LiHMDS , 10 min; j) $\text{BF}_3 \cdot \text{OEt}_2$, CaH_2 , CH_2Cl_2 , -100°C , 5 min; k) TASF , DMF, 20°C , 1 h; l) TsOH , MeCN, H_2O , 0°C , 3 h. TESOTf = triethylsilyl triflate, CuTC = copper(II) thiophene-2-carboxylate, NMP = 1-methyl-2-pyrrolidinone, KOTMS = potassium trimethylsilanolate, 4-DMAP = 4-*N,N*-dimethylamino-pyridine, dba = dibenzylideneacetone, DMF = *N,N*-dimethylformamide, DIBAL = diisobutylaluminum hydride, TPAP = tetrapropylammonium perruthenate, NMO = 4-methyl-morpholine-*N*-oxide, LiHMDS = lithium hexamethyldisilazide, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TsOH = *para*-toluenesulfonic acid.

This gave a 56% yield of concanamycin F (**2**) ($[\alpha]_D^{20} = +10.6$ ($c = 0.32$, CHCl_3)), which had identical physical and spectroscopic data to material derived^[1f] from concanamycin A ($[\alpha]_D^{20} = +11.0$ ($c = 0.3$, CHCl_3)).

In summary, we have completed an expedient synthesis of concanamycin F (26 steps longest linear sequence from **3** in 5.3% overall yield with >85% overall diastereoselectivity). This work demonstrates the power of substrate-based aldol stereocontrol using the ketone building blocks **3–6** and the utility of the Liebeskind Cu^I -promoted protocol for the Stillé-type coupling of complex, polyoxygenated fragments (as in **9** + **18** → **19**). Moreover, the synthesis of novel concanamycin macrolides having modified biological activity should now be feasible.

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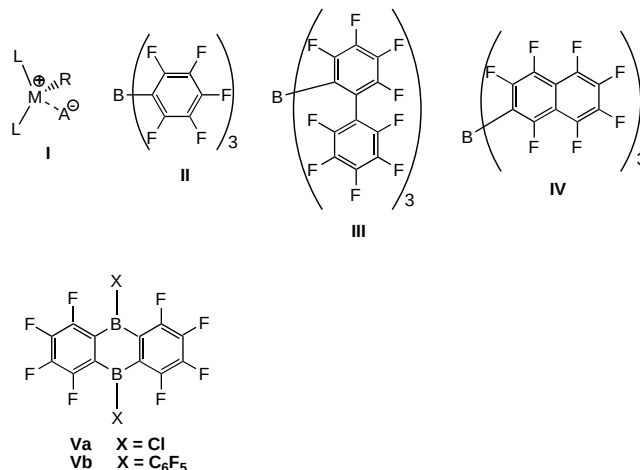
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Organo-Lewis Acid Cocatalysts in Single-Site Olefin Polymerization—A Highly Acidic Perfluorodiboraanthracene**

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For early transition metal single-site homogeneous olefin polymerization catalysts **I**^[1], organo-Lewis acids such as alumoxanes and tris(perfluoroaryl)boranes (e.g., **II–IV**)^[2] play a key role both in catalyst activation and in mechanistic understanding. For example, growing evidence indicates that the cation–anion pairing, as modulated by the steric and electronic characteristics of the cocatalyst/counter anion (A[−] in **I**)^[2, 3] can have a profound influence on polymerization and chain-transfer rates, enchainment stereochemistry, and catalyst stability.^[2–4] With the goal of further modifying fluoroarylborane architecture to enhance Lewis acidity (multiple electron-deficient centers, conjugative negative-charge



delocalization, open structure), we focused on the perfluorodiboraanthracene skeleton **V**^[5] for which calculations at the B3LYP/6-31++G** level indicate **Vb** to have about 10 kcal mol^{−1} greater affinity for CH₃[−] than does B(C₆F₅)₃.^[6] We communicate here the synthesis, characterization, and unusual properties of **Vb**, including significantly enhanced Lewis acidity and cocatalytic olefin polymerization activity.^[7]

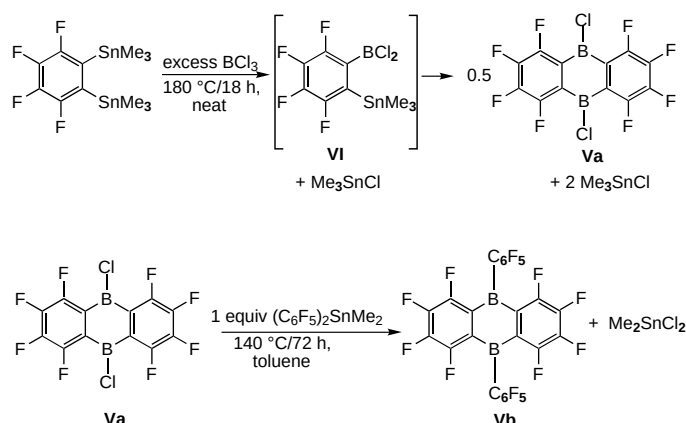
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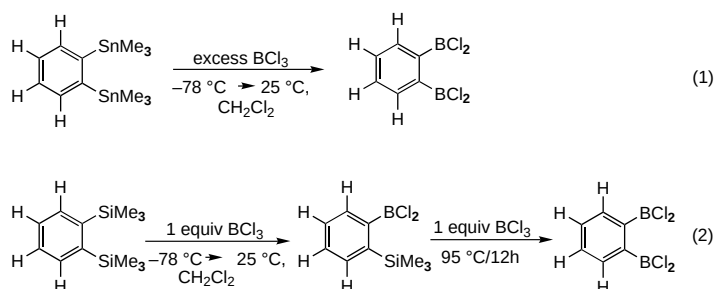
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Parent dichlorodiboraanthracene **Va** was prepared by reaction of 1,2- $\text{C}_6\text{F}_4(\text{SnMe}_3)_2$ [8] with BCl_3 (Scheme 1). Mono-substituted 1,2- $\text{C}_6\text{F}_4(\text{SnMe}_3)\text{BCl}_2$ (**VI**) is formed initially, and



Scheme 1. Synthesis of diboraanthracenes **Va** and **Vb**.

subsequent heating affords **Va** in high yield. No ^{19}F NMR signals for 1,2- $\text{C}_6\text{F}_4(\text{BCl}_2)_2$ were detected at any time during the reaction. In marked contrast, nonfluorinated 1,2- $\text{C}_6\text{H}_4(\text{SnMe}_3)_2$ is reported to undergo rapid metalloid metathesis with BCl_3 at 25 °C to yield 1,2- $\text{C}_6\text{H}_4(\text{BCl}_2)_2$ [Eq. (1)], and both $\text{C}_6\text{H}_4(\text{SiMe}_3)\text{BCl}_2$ and 1,2- $\text{C}_6\text{H}_4(\text{BCl}_2)_2$ are readily accessible from 1,2- $\text{C}_6\text{H}_4(\text{SiMe}_3)_2$ [Eq. (2)].^[10] In the present



case, the decreased nucleophilicity of the perfluoroaryl compound **VI** relative to the C_6H_4 analogue apparently disfavors the second electrophilic aromatic substitution/metalloid metathesis step relative to coupling to yield **Va**.

Reaction of **Va** with one equivalent of $(\text{C}_6\text{F}_5)_2\text{SnMe}_2$ yields the diboraanthracene **Vb** as a pale yellow, air-sensitive crystalline solid (Scheme 1). The reaction requires prolonged heating but is very clean; the crude reaction mixture contains **Vb** in 95% or greater purity. For selective B–Cl/B– C_6F_5 metathesis, $(\text{C}_6\text{F}_5)_2\text{SnMe}_2$ appears to be a general, mild reagent that effects little or no competing alkyl exchange.^[11] In contrast, reaction of **Va** with two equivalents of LiC_6F_5 in pentane or diethyl ether affords a complex mixture of products, while reaction with two equivalents of $\text{C}_6\text{F}_5\text{SnR}_3$ ($\text{R} = \text{Me}, n\text{Bu}$) results in clean alkyl/chloride exchange, in preference to the desired Cl/ C_6F_5 exchange.

Compound **Vb** was characterized by standard spectroscopic and analytical techniques (see Experimental Section) and by X-ray diffraction. The ^{19}F NMR spectrum reveals signifi-

cant upfield displacements of the *o*-, *m*-, and *p*- C_6F_5 signals versus $\text{B}(\text{C}_6\text{F}_5)_3$ ($\Delta\delta = -5, -2, -10$, respectively), while the C_6F_4 signals are shifted considerably downfield of those of **Va** ($\Delta\delta = +5, +5$) and $\text{B}(\text{C}_6\text{F}_5)_3$. These data therefore suggest minimal π conjugative interaction of the C_6F_5 rings in **Vb** with the $(\text{C}_6\text{F}_4\text{B})_2$ π system, which is rather electron-deficient.

In the solid-state structure of **Vb** (Figure 1),^[12] the $(\text{C}_6\text{F}_4\text{B})_2$ skeleton is planar, with an average atomic deviation from the mean plane of 0.013 Å. The C_6F_4 rings are bent slightly out of

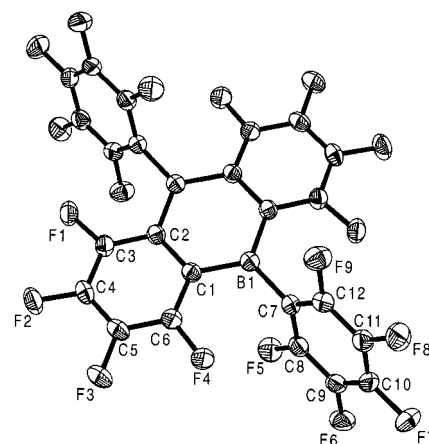
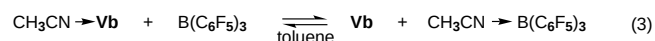


Figure 1. ORTEP diagram of **Vb** (50% probability thermal ellipsoids). Selected bond lengths [Å] and angles [°] for one of the crystallographically independent molecules of **Vb** (corresponding distances/angles for the other molecule are very similar): B1–C1 1.554(2), C1–C2 1.435(2), B1–C2A 1.560(2), B1–C7 1.583(2), C2–C3 1.388(2), C3–C4 1.392(2), C4–C5 1.365(2), C5–C6 1.392(2), C1–C6 1.389(2); B1–C1–C2 120.2(1), C1–B1–C2A 119.6(2), C1–C2–B1A 120.1(1), C1–B1–C7 120.5(1), C2A–B1–C7 119.8(1).

the central B_2C_4 plane, with an average inter-ring dihedral angle of 0.6°. As expected from steric considerations, the C_6F_5 rings are twisted out of the diboraanthracene plane; the crystallographically independent $(\text{C}_6\text{F}_4\text{B})_2/\text{C}_6\text{F}_5$ twist angles are both 75°. All bond lengths and angles (Figure 1, caption) are within normal ranges for fluoroarylboranes^[2], with the exception of a significant lengthening of the C1–C2 bond to 1.435(2) Å. While this may in part reflect withdrawal of π -bonding electron density from the C_6F_4 units by the electron-deficient boron centers, note that some elongation at this position is typically observed in anthracenes.^[13]

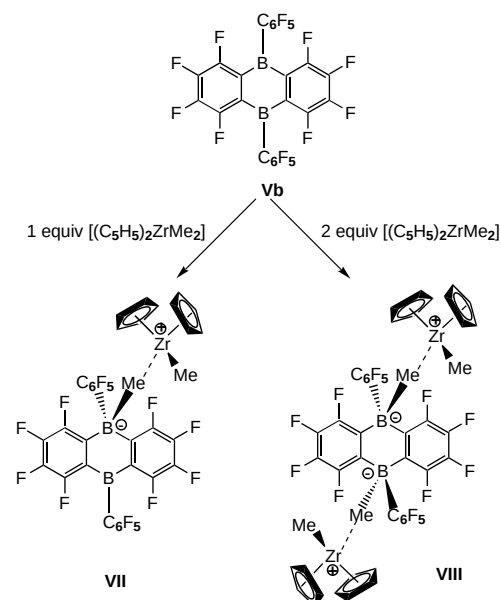
In regard to the Lewis acidity of **Vb**, equilibration studies with $\text{CH}_3\text{CN} \cdot \text{B}(\text{C}_6\text{F}_5)_3$ ^[2c] over a temperature range of 67 K in $[\text{D}_8]\text{toluene}$ followed by van't Hoff analysis of the ^{19}F NMR data yield $\Delta H = +1.4(2) \text{ kcal mol}^{-1}$ and $\Delta S = -5.3(1) \text{ J K}^{-1} \text{ mol}^{-1}$ for reaction (3). These data indicate that



Vb is a stronger Lewis acid than $\text{B}(\text{C}_6\text{F}_5)_3$ with respect to acetonitrile, while the negative ΔS suggests loss of degrees of freedom, consistent with greater steric congestion in $\text{CH}_3\text{CN} \cdot \text{B}(\text{C}_6\text{F}_5)_3$. The perfluorodiboraanthracene **Vb** is the strongest organo-Lewis acid synthesized to date, and the magnitude of the enthalpy of reaction with acetonitrile decreases in

the order **Vb** $[-18.5(2)] > \text{IV}$ $[-17.8(2)]^{[2c]} > \text{B}(\text{C}_6\text{F}_5)_3$ $[-17.1(9)]^{[2a]} > \text{III}$ $[-11.5(3) \text{ kcal mol}^{-1}]^{[2a]}$

Reaction of **Vb** with metallocene dimethyl complexes such as $[(\text{C}_5\text{H}_5)_2\text{ZrMe}_2]$ proceeds with clean, instantaneous methyl anion abstraction to generate catalytically active (vide infra) cation–anion pairs (Scheme 2). Reaction with one equivalent



Scheme 2. Reaction of **Vb** with 1.0 and 2.0 equiv $[(\text{C}_5\text{H}_5)_2\text{ZrMe}_2]$ in CD_2Cl_2 at 25°C . The “*trans*” isomer of **VIII** is shown. The NMR data do not allow an unambiguous differentiation between *cis* and *trans* (C_{2v} vs C_{2h}) isomers, however steric considerations would appear to favor the “*trans*” isomer.

of $[(\text{C}_5\text{H}_5)_2\text{ZrMe}_2]$ on an NMR-tube scale resulted in **VII**—the first mixed borane/borate metallocene catalyst. The ^1H and ^{19}F NMR data (see Experimental Section) indicate a static, unsymmetrical structure with an anionic BMe group. At 25°C the spectrum^[14] indicates that both BMe/B and ZrMe/BMe interchanges^[2d,e] are slow on the NMR time scale, and distinct pairs of magnetically inequivalent C_6F_5 *ortho*- and *meta*- ^{19}F nuclei indicate restricted rotation about the B– C_6F_5 bond. Reaction of **Vb** with two equivalents of $[(\text{C}_5\text{H}_5)_2\text{ZrMe}_2]$

results in instantaneous formation of symmetrical bis-borate **VIII** (see Scheme 2; both C_{2v} and C_{2h} idealized structures are possible). This is the first example of a bis-anion in cationic metallocene catalysis and demonstrates that borane/borate **VII** is sufficiently Lewis acidic to abstract a zirconocene methanide group. Again, room-temperature ^1H and ^{19}F NMR data (see Experimental Section) indicate a static structure, with slow ZrMe/BMe interchange and hindered rotation of the (now magnetically equivalent) C_6F_5 rings. The above transformations are accompanied by ^{19}F NMR chemical shift displacements consistent with the aforementioned ability of the $(\text{C}_6\text{F}_5\text{B})_2$ framework to effectively disperse negative charge (Figure 2), with major upfield shifts in these signals and smaller shifts in the C_6F_5 signals relative to $\text{B}(\text{C}_6\text{F}_5)_3 \rightarrow \text{CH}_3\text{B}(\text{C}_6\text{F}_5)_3^-$.

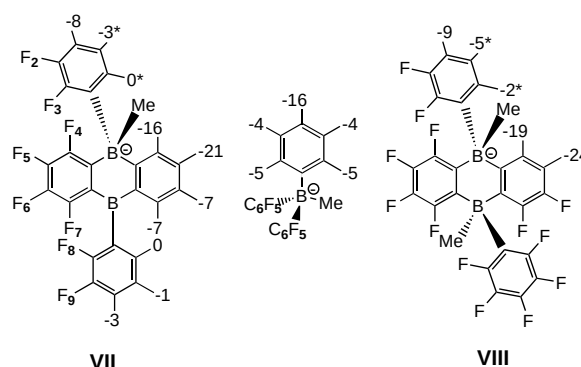


Figure 2. ^{19}F NMR chemical shift displacements for $\text{B}(\text{C}_6\text{F}_5)_3$ and **Vb** upon methyl anion abstraction from $[(\text{C}_5\text{H}_5)_2\text{ZrMe}_2]$. All values at 25°C in CD_2Cl_2 . Data for **VII** are assigned under the assumption that fluoroarylborate ^{19}F signals are shifted further upfield than fluoroarylborane signals. The asterisks denote chemical shifts that are the averaged values for the two magnetically non-equivalent sites.

The cocatalytic characteristics of **Vb** for ethylene and propylene polymerization were examined by using previously described batch-reactor methods.^[2b,e] Activating $[(\text{C}_5\text{H}_5)_2\text{ZrMe}_2]$, $[(\text{Me}_5\text{C}_5)_2\text{ZrMe}_2]$, or $[(\text{Me}_2\text{Si})\text{Me}_4\text{C}_5]$ – $(t\text{BuN})\text{TiMe}_2$ with **Vb** leads to extremely active catalysts (Table 1). In general, catalysts derived from **Vb** exhibit significantly higher polymerization activities than the

Table 1. Comparative olefin polymerization data for catalysts activated by $\text{B}(\text{C}_6\text{F}_5)_3$ and **Vb**.

Entry	Catalyst	Monomer ^[a]	$\mu\text{mol Cat.}^{[b]}$	Conditions $[\text{C}, \text{s}]^{[c]}$	Polymer yield [g]	Activity ^[d,e]	$10^{-3} M_w^{[f]}$	M_w/M_n
1 ^[g]	$[(\text{C}_5\text{H}_5)_2\text{ZrMe}]^+\text{MeB}(\text{C}_6\text{F}_5)_3^-$	E	15	25, 60	1.0	4.0×10^6	124	2.03
2	$[(\text{C}_5\text{H}_5)_2\text{ZrMe}]^+\text{Me}[\text{C}_6\text{F}_4\text{B}(\text{C}_6\text{F}_5)]_2^-$	E	7.5	20, 30	0.28	4.5×10^6	218	2.12
3 ^[g]	$[(\text{C}_5\text{Me}_5)_2\text{ZrMe}]^+\text{MeB}(\text{C}_6\text{F}_5)_3^-$	E	15	25, 60	0.80	3.2×10^6	136	2.54
4	$[(\text{C}_5\text{Me}_5)_2\text{ZrMe}]^+\text{Me}[\text{C}_6\text{F}_4\text{B}(\text{C}_6\text{F}_5)]_2^-$	E	7.7	20, 16	0.56	1.6×10^7	135	2.34
5	$[(\text{C}_5\text{Me}_5)_2\text{ZrMe}]^+_2\text{Me}_2[\text{C}_6\text{F}_4\text{B}(\text{C}_6\text{F}_5)]_2^{2-}$	E	16	20, 17	0.92	1.3×10^7	118	2.00
6 ^[g]	$[(\text{Me}_2\text{Si})\text{Me}_4\text{C}_5](t\text{BuN})\text{TiMe}]^+\text{MeB}(\text{C}_6\text{F}_5)_3^-$	E	15	25, 600	0.20	8.0×10^4	1058	9.54
7	$[(\text{Me}_2\text{Si})\text{Me}_4\text{C}_5](t\text{BuN})\text{TiMe}]^+\text{Me}[\text{C}_6\text{F}_4\text{B}(\text{C}_6\text{F}_5)]_2^-$	E	10	25, 40	0.04	3.6×10^5		
8	$[(\text{Me}_2\text{Si})\text{Me}_4\text{C}_5](t\text{BuN})\text{TiMe}]^+\text{Me}[\text{C}_6\text{F}_4\text{B}(\text{C}_6\text{F}_5)]_2^-$	E	7.9	65, 22	0.50	1.0×10^7	169	2.14
9 ^[h]	$[(\text{Me}_2\text{Si})\text{Me}_4\text{C}_5](t\text{BuN})\text{TiMe}]^+\text{MeB}(\text{C}_6\text{F}_5)_3^-$	E/O	2.0	140, 900	131	7.7×10^7		
10 ^[h]	$[(\text{Me}_2\text{Si})\text{Me}_4\text{C}_5](t\text{BuN})\text{TiMe}]^+\text{Me}[\text{C}_6\text{F}_4\text{B}(\text{C}_6\text{F}_5)]_2^-$	E/O	2.0	140, 900	262	1.5×10^8		
11	$[(\text{Me}_2\text{Si})\text{Me}_4\text{C}_5](t\text{BuN})\text{TiMe}]^+\text{MeB}(\text{C}_6\text{F}_5)_3^-$	P	6.0	70, 600	11	1.0×10^5	175	2.10
12	$[(\text{Me}_2\text{Si})\text{Me}_4\text{C}_5](t\text{BuN})\text{TiMe}]^+\text{Me}[\text{C}_6\text{F}_4\text{B}(\text{C}_6\text{F}_5)]_2^-$	P	0.75	70, 600	216	2.0×10^6	182	2.14

[a] E = ethylene, E/O = ethylene + 1-octene, P = propylene. [b] Based on moles of metallocene added. [c] Polymerization temperature, reaction time. [d] Entries 1–10: (g polymer)/(mol cationic metallocene) $^{-1}$ (atm) $^{-1}$ (h) $^{-1}$. [e] Entries 11 and 12: (g polymer)/(g Ti) $^{-1}$ (h) $^{-1}$. [f] By gel-permeation chromatography relative to polystyrene standards. [g] Data from ref. [2g]. [h] Large-scale reactor procedure of ref. [2c].

B(C₆F₅)₃-based analogues (cf. entries 3 and 4, 6 and 7, and 11 and 12). Note also that using a zirconocene:**Vb** ratio of 2:1, which presumably generates a dianionic cocatalyst, has only minor effects on polymerization activity, polymer molecular weight, and product polydispersity (entries 4 and 5).

These results demonstrate the substantial and efficacious differences in organo-Lewis acid characteristics and in those of derived metallocene ion pairs that can be effected by manipulation of fluoroarylborane cocatalyst architecture. These include enhanced Lewis acidity, significant olefin polymerization activity enhancements over B(C₆F₅)₃, and the first examples of effective dianionic metallocene cocatalysts.

Experimental Section

All manipulations of air-sensitive materials were performed as described elsewhere^[2b-d] with rigorous exclusion of oxygen and moisture in flamed Schlenk-type glassware on a dual-manifold Schlenk line or interfaced to a high-vacuum line (10⁻⁶ Torr), or in a N₂-filled Vacuum Atmospheres glove box with a high-capacity recirculator (<1 ppm O₂). All solvents for high-vacuum line manipulations were stored in vacuo over Na/K alloy in Teflon-valved bulbs.

Va: An excess of BCl₃ (5.0 g, 44 mmol) was condensed into a thick-walled tube fitted with a J. Young valve and containing 1,2-C₆F₄(SnMe₃)₂^[8] (5.3 g, 11.1 mmol) at -196 °C. The flask was next evacuated to 0.05 Torr, and the valve closed. The reaction mixture was then heated at 180 °C for 18 h. [Caution: Heating this closed system results in a pressure build-up. In addition to evacuating the system prior to heating, the reaction tube was enclosed in a steel pipe behind a blast shield.] After cooling the reaction mixture to room temperature, excess BCl₃ was removed under dynamic vacuum, and a slightly moist, beige solid was obtained. The product was extracted with pentane (3 × 20 mL), leaving behind about 65% of the Me₃SnCl by-product. The remaining Me₃SnCl was removed by sublimation at 40 °C/10⁻⁵ Torr. The product was then sublimed at 90 °C/10⁻⁵ Torr, affording **Va** as a yellow solid (1.15 g, 53% yield). ¹⁹F NMR (282 MHz, C₆D₆): δ = -122.7 (m, 4F), -143.9 (m, 4F); ¹³C NMR (75 MHz, CDCl₃): δ = 152.6 (d, ¹J_{CF} = 262 Hz), 144.6 (d, ¹J_{CF} = 260 Hz), 122.8 (br, BC); MS (EI, 8.7 eV): m/z (%): 392 (16), 391 (18), 390 (67), 389 (M⁺, 47), 388 (100), 387 (51), 342 (21), 318 (22), 304 (28), 250 (25), 201 (30); analysis calcd for C₁₂F₈B₂Cl₂: C 37.1, H 0.0; found: C 38.2, H 0.3.

Vb: A thick-walled tube fitted with a J. Young valve was charged with **Va** (0.265 g, 0.68 mmol) and (C₆F₅)₂SnMe₂ (0.33 g, 0.68 mmol). The flask was cooled to -78 °C, toluene (20 mL) was condensed in, and the valve was closed. The reaction mixture was heated to 140 °C for 72 h to give a bright yellow solution. After the mixture was cooled to room temperature, the solvent was removed under dynamic vacuum. The Me₂SnCl₂ by-product was also removed under dynamic vacuum (10⁻⁵ Torr/12 h). The crude product was then crystallized twice from toluene (10 mL, slow cooling to -78 °C) to give **Vb** as a light yellow crystalline solid (0.35 g, 80% yield). ¹⁹F NMR ([D₈]toluene): δ = -118.2 (br, 4F, o-C₆F₄), -133.9 (dd, ³J_{FF} = 25.1, ⁴J_{FF} = 7.9 Hz, 4F, o-C₆F₅), -138.9 (m, 4F, m-C₆F₄), -152.1 (t, ³J_{FF} = 21 Hz, 2F, p-C₆F₅), -161.4 (ddd, ³J_{FF} = 22, ³J_{FF} = 22, ⁵J_{FF} = 7 Hz, 4F, m-C₆F₅); ¹³C NMR (CDCl₃): δ = 156.1 (d, ¹J_{CF} = 267 Hz), 145.9 (d, ¹J_{CF} = 265 Hz), 144.3 (d, ¹J_{CF} = 241 Hz), 141.6 (d, ¹J_{CF} = 265 Hz), 137.6 (d, ¹J_{CF} = 253 Hz), 128.3 (br), 123.7 (br); analysis calcd for C₂₄F₁₈B₂: C 44.22, H 0.00; found: C 42.61, H 0.52. This compound consistently proved difficult to combust, despite attempts with X-ray quality crystals.

In situ generation of **VII**: ¹⁹F NMR: (CD₂Cl₂, 25 °C): δ = -123.1 (br, 2F, F7; see Figure 2 for assignments), -132.4 (m, 3F, F3 + F4 or F8), -134.0 (br, 2F, F4 or F8), -134.8 (br, 1F, F3), -145.0 (br, 2F, F6), -155.4 (t, ³J_{FF} = 21 Hz, 1F, F10), -158.9 (m, 2F, F5), -160.0 (m, 1F, F1), -161.8 (br, 1F, F2), -162.5 (br, 1F, F2), -164.1 (br, t, ³J_{FF} = 21 Hz, 2F, F9); ¹H NMR: (CD₂Cl₂, 25 °C): δ = 6.34 (s, 10H), 0.66 (s, 3H), 0.17 (br, 3H).

In situ generation of **VIII**: ¹⁹F NMR: (CD₂Cl₂, 25 °C): δ = -132.7 (br, 2F, o-C₆F₅), -134.7 (br, 4F, o-C₆F₄), -136.4 (br, 2F, o-C₆F₅), -161.6 (t, ³J_{FF} = 20 Hz, 2F, p-C₆F₅), -162.6 (d, ³J_{FF} = 19 Hz, 4F, m-C₆F₄), -164.4 (br, 2F, m-

C₆F₅), -165.4 (br, 2F, m-C₆F₅); ¹H NMR: (CD₂Cl₂, 25 °C): δ = 6.22 (s, 10H), 0.69 (s, 3H), 0.19 (br, 3H); a slight excess of [(C₅H₅)₂ZrMe₂] was present in this sample, and signals attributable to this compound were also detected.

Polymerization experiments: Table 1, entries 1–8: Experiments were carried out^[2b] on a high-vacuum line (10⁻⁶ Torr) in 100 mL toluene at 1.0 atm ethylene pressure. Activities given in Table 1 are the average of two trials; reproducibility was within ±5%. The experiments of entries 9 and 10 in Table 1 were carried out in a stirred 2.0-L Parr reactor charged with 740 g Isopar-E mixed alkanes solvent and 118 g of 1-octene comonomer.^[2c] Hydrogen (25 psi) was added to control polymer molecular weight. The reactor was heated to 140 °C and saturated with ethylene at 500 psi. Next, with rapid stirring, 2.0 μmol catalyst/cocatalyst mixture was injected into the reactor as a 0.0050 M solution, and the conditions maintained for 15 min with ethylene on demand. The experiments of entries 11 and 12 in Table 1 were carried out^[2c] in a stirred 2.0-L autoclave reactor charged with 640 g Isopar-E mixed alkanes solvent and 216 g propylene. Hydrogen (26 psi) was added to control polymer molecular weight. The reactor was heated to 70 °C, and a 0.0050 M catalyst/cocatalyst solution in toluene was injected into the reactor with rapid stirring. Polymerization conditions were maintained for 10 min. In these polymerization experiments, 1,2-C₆H₄F₂ was used as the solvent for the catalyst solutions, by mixing the metallocene complex and borane, then allowing the resulting solution to stand for 5 min.

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- [11] See also R. D. Chambers, T. Chivers, *J. Chem. Soc.* **1965**, 3933–3939.
- [12] Crystallographic data for **Vb**: $C_{24}F_{18}B_2 \cdot 2C_7H_8$; monoclinic, space group $P2_1/c$; $a = 22.855(2)$, $b = 10.865(1)$, $c = 13.750(1)$ Å, $\beta = 99.689(1)^\circ$, $V = 3366(1)$ Å³, $Z = 4$; $\rho_{\text{calcd}} = 1.650$ g cm⁻³; $\mu = 1.65$ cm⁻¹; $T = -120^\circ\text{C}$. The structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in idealized positions and not refined. The final cycle of full-matrix least-squares refinement was based on 8069 observed reflections ($I > 2.00\sigma(I)$) and 523 variable parameters and converged (largest parameter shift was 0.087 times its esd) with unweighted and weighted agreement factors of $R = 0.042$ and $R_w = 0.118$. For clarity of the crystallographic discussion, note that there are two half molecules in the asymmetric unit, and consequently there are two independent bond lengths and angles for each bond length/angle of **Vb**. 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-135514. 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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- [14] Because of limited solubility of **VII** in [D₆]benzene and [D₈]toluene, NMR spectra were recorded in CD₂Cl₂, in which at room temperature and below, the complexes are sufficiently stable for adequate spectroscopy.

Photocontrol of Triple-Helix Formation by Using Azobenzene-Bearing Oligo(thymidine)**

Hiroyuki Asanuma, Xingguo Liang, Takayuki Yoshida, Akira Yamazawa, and Makoto Komiyama*

Triple-helix formation by oligonucleotides is one of the most promising methods for sequence-specific recognition of DNA double helices.^[1] Various applications (for example, regulation of gene expression and cell growth) have already been demonstrated.^[2] However, little is known on the regulation of triple-helix formation by external signals. If triple helices can be formed at will (as triggered by a signal), the scope of their applications would be extended.

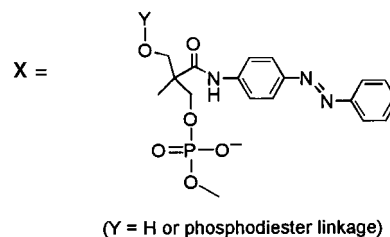
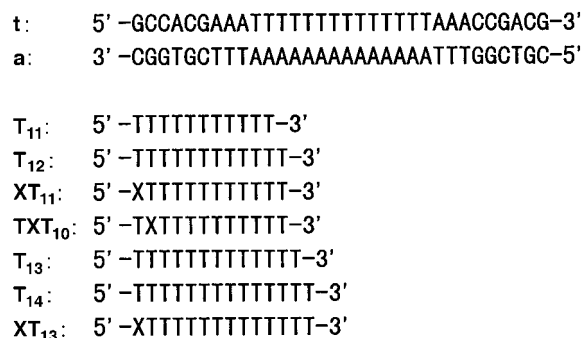
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Previously, it was shown that intercalating agents stabilize triple helices when tethered to oligonucleotides.^[1b, d, h, 2a] Furthermore, formation of DNA double helices was regulated by photoisomerization of the azobenzene-tethered oligonucleotides.^[3, 4] These findings have prompted us to study on photoregulation of triple-helix formation. Here, we show modified oligo(thymidine) (oligo(T)) species, which carry an azobenzene at the appropriate position, form stable triple helices with oligo(T)/oligo(dA) double helices (oligo(dA) = oligo(deoxyadenosine)). More importantly, these triple helices can be formed and dissociated repeatedly by photo-induced *cis-trans* isomerization of the azobenzene.

The double helix [**t/a**] is formed from two complementary 32-mer oligonucleotides, and involves a T₁₄ and dA₁₄ block (from the **t** and **a**, respectively) (Scheme 1).^[5] Its melting temperature (T_m) is 73.0 °C at pH 7.0 ([MgCl₂] = 0.1 M; other



Scheme 1. The oligonucleotides used in this study; **X** denotes the residue carrying an azobenzene moiety in the side chain. The configuration of the N=N bond in **X** is noted.

conditions are presented in the Experimental Section). With addition of oligonucleotide **T**₁₃ to the [**t/a**] double helix, the melting curve for the system is double-sigmoidal, corresponding to the formation of the [**T**₁₃/**t/a**] triple helix ($T_m = 18.0^\circ\text{C}$). When the modified oligonucleotide **XT**₁₃ is used in place of **T**₁₃, a double-sigmoidal curve is also obtained (Figure 1). Here, the azobenzene mostly (90 %) takes its *trans*-form with respect to the stereochemistry of the N=N bond, as indicated by the reversed-phase HPLC analysis. The T_m for the [*trans*-**XT**₁₃/**t/a**] triple helix is 26.0 °C. This T_m value is higher than that of either [**T**₁₃/**t/a**] or [**T**₁₄/**t/a**] triple helices (Table 1). The *trans*-azobenzene moiety stabilizes the triple helix, at least in this case, to a greater extent than thymine.

Upon irradiating the [*trans*-**XT**₁₃/**t/a**] solution with light ($300 < \lambda < 400$ nm), the azobenzene in **XT**₁₃ isomerized to the *cis*-form. Concurrently, the melting curve for the [*cis*-**XT**₁₃/**t/a**] triple helix (see Figure 1) notably shifts towards lower temperatures with respect to the [*trans*-**XT**₁₃/**t/a**]

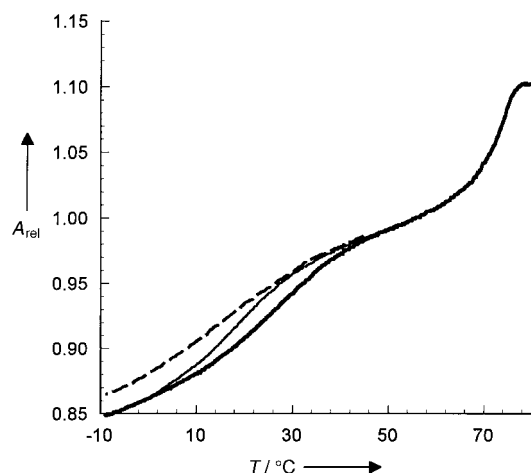


Figure 1. Melting curves (cooling profiles) for the triple-helix formation between the [t/a] double helix and *trans*-**XT**₁₃ (—), *cis*-**XT**₁₃ (---), or **T**₁₃ (····). The *T*_m values obtained from these curves are listed in Table 1. The heating profiles superimpose almost perfectly on the cooling ones. The conditions are described in the Experimental Section.

Table 1. The melting temperatures (*T*_m) of triple helices between the [t/a] duplex and the modified oligonucleotides. Where the azobenzene moiety **X** is present, its configuration is noted.

Oligonucleotide	<i>T</i> _m [°C]		Change in <i>T</i> _m [°C] on <i>trans</i> → <i>cis</i> isomerization
	<i>trans</i> - X	<i>cis</i> - X	
XT ₁₃ ^[a]	26.0	12.7	− 13.3
T ₁₄	22.5		
T ₁₃	18.0		
XT ₁₁ ^[b]	29.1	14.3	− 14.8
TX ₁₀	15.8	6.6	− 9.2
T ₁₂	26.8		
T ₁₁	20.6		

[a] [MgCl₂] = 0.1 M. [b] [MgCl₂] = 0.4 M.

curve. The *T*_m value is 12.7 °C, which is by 13.3 °C lower than that of [trans-**XT**₁₃/t/a] (Table 1). The stability, as measured by *T*_m values, of the triple helix formed with the [t/a] double helix is as follows: *trans*-**XT**₁₃ > **T**₁₄ > **T**₁₃ > *cis*-**XT**₁₃. When the *cis*-azobenzene moiety is isomerized to the *trans*-form by irradiating with visible light ($\lambda > 400$ nm), the melting curve is almost superimposed with that before the UV irradiation. Thus the triple-helix formation is reversibly modulated by the photoirradiation. Similar results were obtained for the triple-helix formation with **XT**₁₁. The *T*_m decreases in the following order: *trans*-**XT**₁₁ > **T**₁₂ > **T**₁₁ > *cis*-**XT**₁₁ (Table 1). The difference in *T*_m between [trans-**XT**₁₁/t/a] and [cis-**XT**₁₁/t/a] is 14.8 °C.

When *trans*-**XT**₁₃ forms a triple helix with [t/a], circular dichroism (CD) is explicitly induced (the solid line in Figure 2A). The azobenzene is incorporated in the chiral environment of the double helix. As expected, no CD is induced at temperatures higher than the *T*_m (the dotted line). The induced CD around 360 nm (the π - π^* transition of azobenzene) is negative and rather weak, showing that the long axis of the azobenzene

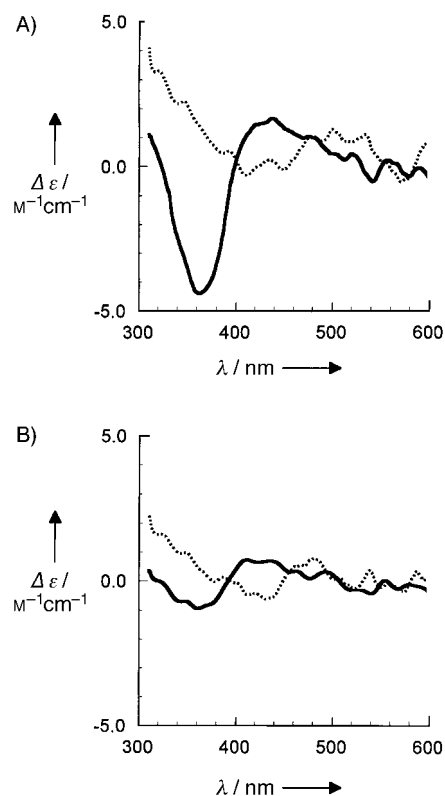


Figure 2. The CD spectra of the solutions containing the [t/a] duplex and either *trans*-**XT**₁₃ (A) or *cis*-**XT**₁₃ (B) at 0 °C (—) and 45 °C (---). The concentrations of the oligonucleotides **t**, **a**, and **XT**₁₃ are 5.5, 5.0, and 6.0 μM, respectively, and [MgCl₂] = 0.1 M.

(which is parallel to the transition moment) is almost parallel to the plane of the A-T base pairs.^[6] If the transition moment were to be parallel to the helical axis, the induced CD should be positive and much more intense.^[7] This indicates strongly that the *trans*-azobenzene moiety intercalates into the [t/a] and stabilizes the triple helix. The absorption band of the *trans*-azobenzene shows a bathochromic shift, consistent with the triple-helix formation (Figure 3A).^[8] Upon formation of [cis-**XT**₁₃/t/a], however, the induced CD is much weaker (the solid line in Figure 2B). Whereas *trans*-azobenzene is planar, *cis*-azobenzene is nonplanar,^[9] and rather than intercalation into the [t/a], it destabilizes the triple helix by steric repulsion.

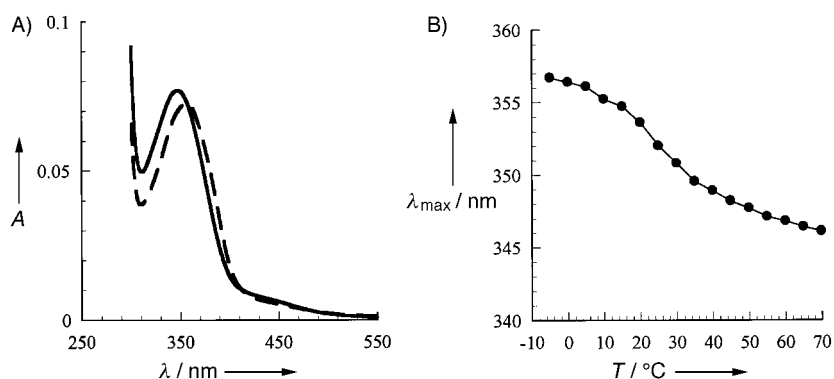


Figure 3. A) Bathochromic shift of $\lambda_{\max}$ for the formation of the *trans*-[**XT**₁₃/t/a] triple helix. Spectra were measured at 70 °C (—) (above *T*_m) and at 0 °C (---) (below *T*_m). B) Plot of $\lambda_{\max}$ of the *trans*-[**XT**₁₃/t/a] system as a function of temperature.

Triple-helix formation is also photoregulated when an azobenzene is included within the oligo(T) block. As shown in Table 1, [*trans*-**TX**T₁₀/t/a] is more stable than [*cis*-**TX**T₁₀/t/a] ($\Delta T_m = 9.2^\circ\text{C}$). In this case, however, the triple helices (even of the *trans*-isomer) are less stable than either [T₁₁/t/a] or [T₁₂/t/a]. The intercalation of the *trans*-azobenzene to form the triple helix is less efficient here, mainly because it accompanies partial breakdown of the adjacent Hoogsteen-type base-pairs.

Experimental Section

The modified oligonucleotides (**XT**₁₃, **XT**₁₁, and **TX**T₁₀) were synthesized as described in ref. [3a]. The ratio of the *trans* to the *cis*-isomer in the reaction mixtures was determined by reversed-phase HPLC. In order to isomerize the azobenzene, the solutions were irradiated for 30 min by light from a 150 W xenon lamp through an appropriate filter (UV-D36C and L-42 filters from Asahi Technoglass Corporation for the *trans*→*cis* and *cis*→*trans* isomerization, respectively). The T_m value was determined from the maximum in the first derivative of the melting curve. The absorbance at 280 nm, which is the isosbestic point of the *trans*- and the *cis*-azobenzene, was monitored at pH 7.0 (10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl] ethanesulfonic acid (HEPES) buffer) on a JASCO model V-530 spectrophotometer equipped with a programmable temperature controller. The temperature ramp was $1.0^\circ\text{C min}^{-1}$. The concentrations of t, a, and the modified oligo(T) were 2.2, 2.0, and 2.4 μM , respectively.^[10] In the T_m measurement of the *cis* isomer, intermittent UV irradiation was used in order to suppress the thermal *cis*→*trans* isomerization. The fraction of the *cis* isomer was kept almost constant (at 70%) throughout the measurement.

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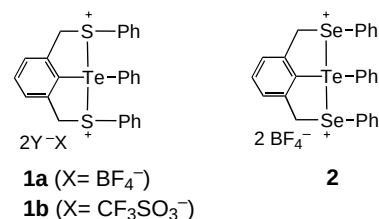
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- [5] The modified oligonucleotides **XT**₁₃, **XT**₁₁, and **TX**T₁₀ were used as mixtures of the two diastereomers with respect to the chirality of the X residue. The attempts to separate these two diastereomers by HPLC have been unsuccessful.
- [6] Nordén et al. concretely correlated the sign and magnitude of the CD, induced on the binding of small molecules to DNA, to the manner of the binding: a) M. Kubista, B. Åkerman, B. Nordén, *J. Phys. Chem.* **1988**, *92*, 2352–2356; b) R. Lyng, A. Rodger, B. Nordén, *Biopolymers* **1992**, *32*, 1201–1214; c) P. Pradhan, B. Jernström, A. Seidel, B. Nordén, A. Gräslund, *Biochemistry* **1998**, *37*, 4664–4673.

- [7] The rotatory strength of the [*trans*-**XT**₁₃/t/a] triple helix was determined to be -0.15 Debye–Bohr magnetons (DBM). This is in marked contrast with the large positive values for the well-known groove binders dibutylproflavine (+1.77 DBM) and netropsin (+1.31 DBM) (data from ref. [6]).
- [8] The middle point of the λ_{max} versus T plot is 25°C (Figure 3B), which is identical with the T_m of the triple helix, within experimental error.
- [9] J. M. Robertson, *J. Chem. Soc.* **1939**, 232–236.
- [10] The t:a ratio was kept at 1:1 in order to ensure that there exists no free a, which should form a duplex with the modified oligo(T) and perturb the T_m measurement.

Synthesis of Dicationic Telluranes by Remote Oxidation through a π -Conjugated System**

Katsutoshi Kobayashi, Soichi Sato, Ernst Horn, and Naomichi Furukawa*

Recently, we synthesized a sulfanyl-substituted tellurium cation as a bis-tetrafluoroborate (**1a**) and a bis-trifluoromethanesulfonate salt (**1b**) and the analogous selenyl-substituted tellurium cation as bis-tetrafluoroborate salt (**2**) by the reaction of tellurides or telluroxides having heteroatoms at



the 2,6-positions of the benzene ring with oxidizing agents such as NOBF₄ and NOPF₆, or with (CF₃SO₂)₂O. In these reactions, the tellurium atom should be directly oxidized by the oxidizing agent to form the corresponding dicationic tellurane.^[1] Furthermore, we have reported on remote oxygen migration between sulfur atoms in the monooxide of 1,4-bis(methylsulfanyl)benzene in the presence of CF₃CO₂H. This reaction is proposed to proceed not via a quinoid-type intermediate but via the bis(dithia dication) dimer.^[2]

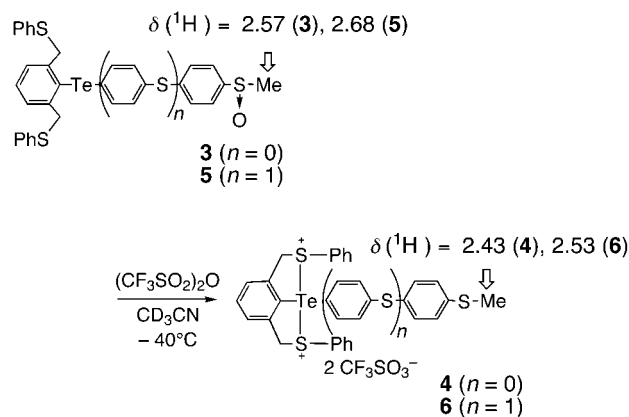
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On the basis of these results, we treated the tellurides with a sulfinyl substituent at the 4-position of the tellurophenyl ring with $(\text{CF}_3\text{SO}_2)_2\text{O}$ with the aim of obtaining the corresponding dicationic telluranes. Apparently, deoxygenation of the sulfinyl group is promoted by the telluride group and the (phenylsulfonyl)methyl groups in 2,6-position by the concerted donation of electrons. We propose that this process involves a novel remote oxidation reaction with electron transfer through π -conjugated bonds, similar to the domino effect. Here we report the synthesis of dicationic telluranes and the reaction mechanisms of these novel remote oxidation reactions.

The telluride **3** was prepared by the oxidation of the dicationic tellurane derived from 2,6-bis[(phenylsulfonyl)methyl]phenyl 4-(methylsulfonyl)phenyl telluride with *m*-chloroperbenzoic acid (*m*-CPBA) and then reduction of the dicationic part with PhSH.^[3] Treatment of **3** with 1.2 equivalents of $(\text{CF}_3\text{SO}_2)_2\text{O}$ ($\text{ Tf}_2\text{O}$) at -40°C in CD_3CN readily afforded the corresponding stable dicationic tellurane **4** (Scheme 1). In the ^1H NMR spectrum of **4**, the benzylic



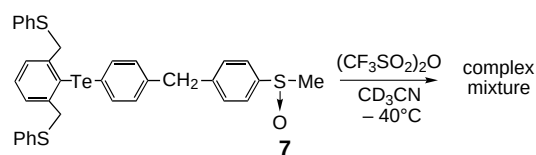
Scheme 1. Reaction of **3** or **5** with $\text{ Tf}_2\text{O}$.

methylene protons give rise to two sets of AB quartet signals at $\delta = 4.42, 5.26$ ($J = 18$ Hz) and $4.90, 5.24$ ($J = 17$ Hz) in a 1:1 ratio. These signals were assigned to the asymmetric bicyclic form of the dicationic tellurane. These results demonstrate that the two sulfur atoms are directly coordinated to the central tellurium atom. The ^1H NMR signal of the methyl protons is shifted upfield from $\delta = 2.57$ to 2.43 on adding $\text{ Tf}_2\text{O}$. This indicates that the sulfur atom of the methylsulfonyl substituent is reduced to form a methylsulfanyl substituent. The ^{125}Te chemical shift of **4** is $\delta = 1343$, which is similar to that of the corresponding dicationic tellurane **1b** ($\delta = 1331$) without a *p*-sulfonylmethyl group. The dicationic tellurane **4** was characterized by elemental and spectroscopic (EI-MS; ^1H , ^{13}C , and ^{125}Te NMR) analyses, and the structure was determined by X-ray crystallographic analysis.^[4]

The telluride **5**, which has an extended π -conjugated system, was prepared similarly to **3** and treated with $\text{ Tf}_2\text{O}$ to give the corresponding dicationic tellurane **6** with a methylsulfanyl substituent (Scheme 1). The structure of this dicationic tellurane was assigned by EI-MS and ^1H , ^{13}C , and ^{125}Te NMR spectroscopy. The ^1H NMR spectrum of **6** also shows two sets of AB quartet signals that are shifted downfield

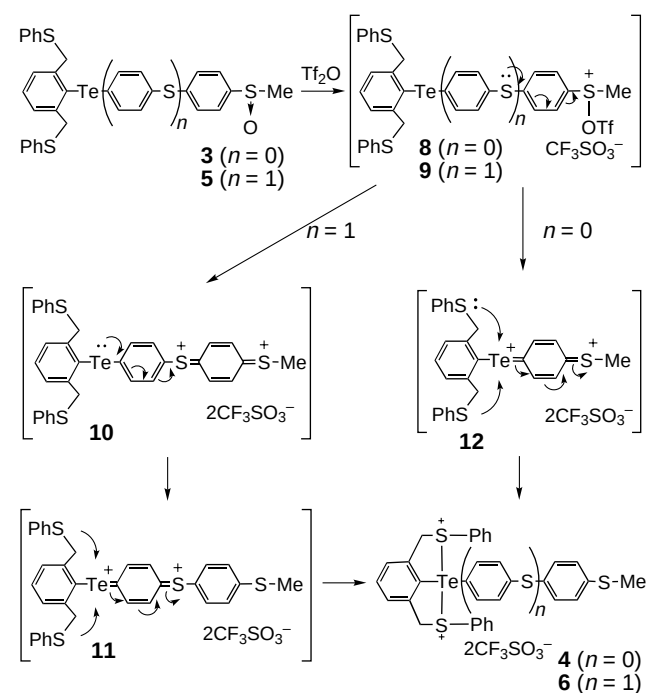
relative to those of **5**. The ^{125}Te NMR signal of **6** was observed at $\delta = 1339.7$.

To determine the mechanism of this type of reaction, the telluride **7**, without a π -conjugated system between the tellurium atom and the sulfinyl substituent, was treated with



$\text{ Tf}_2\text{O}$. This reaction gave only a complex mixture, and no dicationic tellurane was observed. This result supports the notion that the π -conjugated system is necessary to transfer electrons from the tellurium atom to the sulfur atom of the sulfinyl group and also rules out intermolecular electron transfer between two molecules of the telluride.

On the basis of this result, the reaction is considered to proceed by the mechanism shown in Scheme 2. In the case of **3**, the formation of the intermediate sulfonium salt **8** may be



Scheme 2. Proposed mechanism for the reaction of **3** or **5** with $\text{ Tf}_2\text{O}$.

followed by reaction with $\text{ Tf}_2\text{O}$, and the corresponding dicationic compound **4** could be produced by the conformational change of the two (phenylsulfonyl)methyl groups via the dicationic quinoid-type compound **12** as an intermediate or a transition state, formed by electron transfer from the tellurium atom to the sulfur atom of the methylsulfonyl group. The reaction proceeds too rapidly to observe **8** or **12** by NMR spectroscopy.

A similar mechanism is predicted for the reaction of the telluride **5** with $\text{ Tf}_2\text{O}$. As shown in Scheme 2, electron transfer

occurs from the tellurium atom to the sulfur atom of the methylsulfinyl group by means of intramolecular π -conjugation between the benzene rings and the sulfur atom. This sulfur atom is important in connecting the π -conjugated system on the tellurium atom with the sulfur atom of the methylsulfinyl group.

In summary, we have found a new remote oxidation reaction through π -conjugated bonds for the formation of dicationic telluranes.

Experimental Section

4: Te_2O (4 μL , 0.024 mol) was added to a solution of **3** (14 mg, 0.02 mol) in dry CH_3CN at -40°C under an argon atmosphere. The resulting solution was stirred for 12 h at room temperature, and the solvent was then evaporated to give **4** (15 mg, 86%) as the residue. M.p. $118-123^\circ\text{C}$ (decomp); ^1H NMR (270 MHz, CD_3CN): $\delta = 2.43$ (s, 3H), 4.42, 5.26 (AB q, $J = 18$ Hz, 2H), 4.90, 5.24 (AB q, $J = 17$ Hz, 2H), 6.86–8.23 (m, 17H, Ar-H); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 14.5$, 39.1, 39.9, 124.2, 124.9, 127.6, 128.7, 130.0, 131.0, 131.5, 132.2, 132.3, 132.8, 132.9, 134.8, 136.2, 147.5, 147.9, 150.5; ^{125}Te NMR (126 MHz, CD_3CN , 25°C): $\delta = 1343.2$ (relative to Me_2Te); EI-MS: m/z : 574 [$M^+ - 2\text{TfO}^-$]; elemental analysis calcd for $\text{C}_{29}\text{H}_{24}\text{F}_6\text{O}_6\text{S}_5\text{Te}$: C 40.02, H 2.78; found: C 39.79, H 2.99.

6: M.p. $145-150^\circ\text{C}$ (decomp); ^1H NMR (400 MHz, CD_3CN): $\delta = 2.53$ (s, 3H), 4.45, 5.15 (AB q, $J = 18$ Hz, 2H), 5.03, 5.22 (AB q, $J = 17$ Hz, 2H), 6.81–8.16 (m, 21H, ArH); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 15.0$, 39.5, 40.3, 120.1, 122.3, 123.3, 124.6, 125.3, 127.7, 128.3, 129.0, 130.3, 131.0, 131.6, 132.1, 132.5, 132.8, 132.9, 135.3, 136.2, 136.5, 143.2, 147.7, 148.1, 150.0; ^{125}Te NMR (126 MHz, CD_3CN): $\delta = 1339.7$ (relative to Me_2Te); FAB-MS: m/z : 831 [$M^+ - \text{TfO}^-$].

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- [3] Since 2,6-bis[(phenylsulfonyl)methyl]phenyl 4-(methylsulfonyl)phenyl telluride has four chalcogen atoms which are susceptible to oxidation, it is difficult to selectively oxidize the S atom of the methylsulfonyl group. Therefore, the compound was initially converted to the corresponding dicationic tellurane, which was then treated with *m*-CPBA to oxidize the sulfur atom of the methylsulfonyl group. The telluride **3** was obtained by reduction of the dicationic tellurane with two equivalents of thiophenol.
- [4] X-ray structure analysis of **4**: Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Te1–S1 2.637(1), Te1–S2 2.730(1), S1–Te1–S2 160.60(3). Crystal data: $\text{C}_{29}\text{H}_{26}\text{F}_6\text{O}_7\text{S}_5\text{Te}$, crystal dimensions $0.75 \times 0.30 \times 0.25$ mm, triclinic, space group $P\bar{1}$ (no. 2), $a = 10.822(3)$, $b = 16.531(3)$, $c = 10.187(2)$ $\text{\AA}$, $\alpha = 99.65(1)$, $\beta = 103.81(2)$, $\gamma = 92.63(2)^\circ$, $V = 1737.7(7)$ $\text{\AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.70$ g cm^{-3} , $2\theta_{\text{max}} = 60.0^\circ$. Rigaku AFC-7R four-circle diffractometer, $\text{MoK}\alpha$ radiation, $\lambda = 0.71069$ $\text{\AA}$, $\omega/2\theta$ scan mode, $T = 296$ K, 11 109 measured reflections, Lorentzian and polarization corrections, absorption coefficient 12.3 cm^{-1} , semiempirical absorption correction (ψ scans; transmission factors 0.93–1.00), structure solution with direct methods, program package *teXsan*(1992), full-matrix least-squares refinement on F , 7190 observed reflections ($I > 3.0\sigma(I)$), 440 parameters, hydrogen atoms included but not refined, $R = 0.041$, $R_w = 0.053$, residual electron density 1.07 $\text{e \AA}^{-3}$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-136391. 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).

Pyrone-Like Structures as Novel Oxygen-Based Organic Superbases**

Dimas Suárez, J. Angel Menéndez, Enrique Fuente, and Miguel A. Montes-Morán*

The concept of strong organic basicity is generally associated with proton sponge compounds.^[1] An unexpectedly high $\text{p}K_a$ value was reported for the parent compound of this class, 1,8-bis(dimethylamino)naphthalene (DMAN) by Alder et al. more than 30 years ago.^[2] This high thermodynamic basicity arises from the interaction of basic groups in close proximity to each other. In contrast, the hydrophobic shielding of the basic centers in DMAN derivatives results in a weak nucleophilic character and low rates of proton transfer,^[3] attributes which ultimately will decide the utilization of the organic superbases as proton scavengers in chemical and biochemical processes.^[4]

The term “pyrone-like structures” (as used in this communication) was originally adopted by Voll and Boehm^[5] to define a type of oxygen-containing functionality capable of acting as a basic center on carbon surfaces.^[6] According to their definition^[5] these pyrone-like compounds are combinations of non-neighbouring carbonyl and ether oxygen atoms at the edges of a graphene layer. Thus, this generic designation would include not only γ -pyrone derivatives but also structures where the two oxygen atoms are located in different rings. Although there are no reported data, within our knowledge, for these latter pyrone-like systems, we have recently demonstrated using ab initio calculations that they show a broad spectrum of base strength (around 12 $\text{p}K_a$ units).^[7]

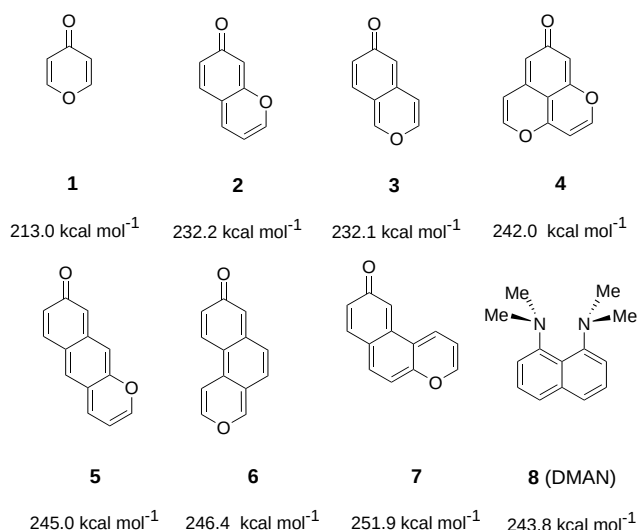
Herein we report a systematic ab initio study of the gas-phase proton affinities (PAs) of mono- and polycyclic pyrone-like structures **1–7**. The structural and energetic results for compounds **1–7** will be compared with those of the prototypical proton sponge DMAN **8**, and thus support the title proposal of pyrone-like structures as organic superbases. In addition, some specific aspects justify the novelty of and interest shown in the comparison of these relatively simple organic compounds with conventional proton sponges. First, the proton acceptor atom corresponds to a neutral carbonyl oxygen atom in contrast to the predominance of amine and imine functionalities in the nitrogenated superbases. Second-

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ly, both the polarity of the pyrone-like compounds and the easy access of solvent to their basic center may facilitate either an acceptable solubility or fast kinetics for proton transfer from and to the carbonyl functionality. Finally, the important control of resonance stabilization on the PAs of **1–7** supports a clear structure–basicity correlation for these and other pyrone-like structures of potential interest.

The corresponding gas-phase PAs for structures **1–8** were calculated at the MP2/6-311 + G(2d,2p)//MP2/6-31G(d) level of theory. The simplest pyrone-like structure, γ -pyrone (**1**), has a PA of 213.0 kcal mol⁻¹, a value around 9–14 kcal mol⁻¹ below typical PAs for weak nitrogen bases such as pyridine (PA = 222.3 kcal mol⁻¹), or trimethylamine (PA = 226.8 kcal mol⁻¹).^[8] The PAs of these latter bases are taken here as an experimental reference because of the lack of data concerning the gas-phase basicity of γ -pyrone (or α -pyrone) compounds. Nevertheless, to further calibrate the methodology to be used in the determination of PAs for the rest of systems studied, we also calculated the PA of **1** with the G2(MP2,SVP) method.^[9] The resultant G2(MP2,SVP) value is 213.0 kcal mol⁻¹, which matches perfectly the PA of **1** estimated at the MP2/6-311 + G(2d,2p)//MP2/6-31G(d) level.

The PA values for the possible pyrone-like structures with two fused rings, **2** and **3**, are 232.2 and 232.1 kcal mol⁻¹, respectively, which are around 10 kcal mol⁻¹ above the experimental value for pyridine.^[8] We also note from these values that the exact position of the ether oxygen atom has a very weak influence on the PA for the pyrone-like structures with two fused rings. Hence, our calculations predict that the gas-phase PA of **2** and **3** are reinforced by around 19 kcal mol⁻¹ with respect to **1**. This large increment of the PA can be well understood in terms of the stability conferred to the protonated system by conjugation throughout the ether ring and the aromaticity of the resultant phenolic ring. A similar argument has been recently employed to explain the high basicity predicted for quinodiimine compounds.^[10] Interestingly, the reported increase in the PA per quinoid ring (≈ 20 kcal mol⁻¹)^[10] remains very close to the difference between the PA values of **1** and the pyrone-like molecules **2** and **3** (≈ 19 kcal mol⁻¹). It is also worth noting that the stabilization of the protonated form by aromatization is

significantly more important than the contribution of the strain energy to the basicity of conventional proton sponges (4–14 kcal mol⁻¹).^[11] However, the formation of the intramolecular hydrogen bond in DMAN derivatives stabilizes the protonated species better by contributing 24 kcal mol⁻¹ or more.^[11]

It is clear from the PA calculations for structures **1–3** that the larger the conjugation gained upon protonation of pyrone-like structures the greater their PA and pK_a values, which eventually reaches the commonly accepted ranges of superbases (PA ≈ 240 kcal mol⁻¹). To further explore this possibility we considered four hypothetical superbases with three fused rings corresponding to the pyrone-like structures **4–7**. Structure **4**, which represents the enlargement of **2** by addition of a second ether ring, has a PA of 242.0 kcal mol⁻¹, which is about 29 and 10 kcal mol⁻¹ larger than those for **1** and **2**, respectively. However, when pyrone-like structures are grown by the appropriate insertion of sp² carbon atoms, a more important stabilization of the protonated forms results, with the calculated PA values for structures **5–7** being 245.0, 246.4, and 251.9 kcal mol⁻¹. Therefore the pyrone-like structures **4–6**, and especially **7**, should be considered as organic superbases in the gas phase.

Structure **7** is the pyrone-like structure with the largest PA reported in this work (Figure 1). From a comparison of the

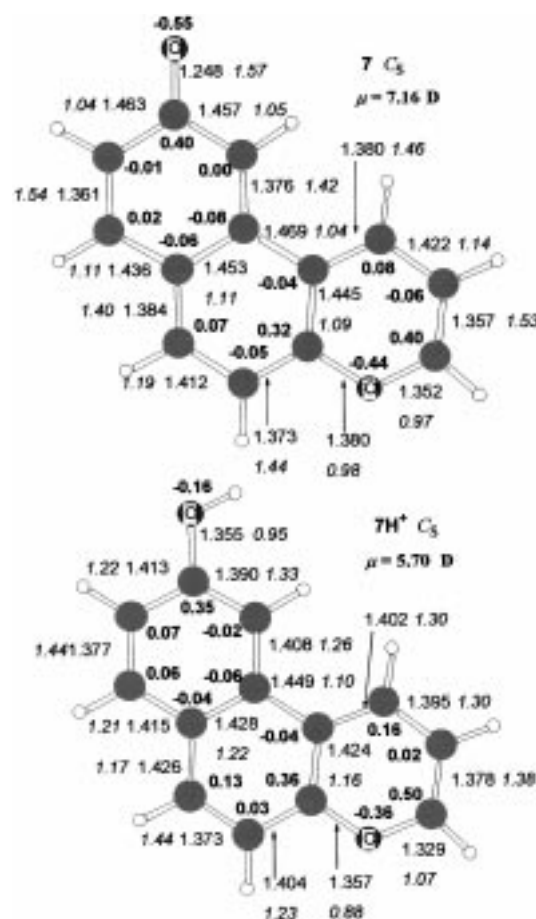
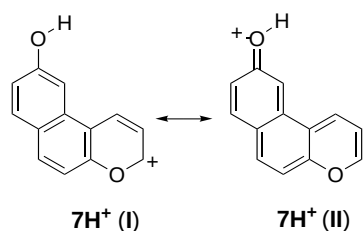


Figure 1. MP2/6-31G(d)-optimized structures for the neutral and protonated forms of the pyrone-like structure **7**. Distances are given in Ångströms. Mayer bond orders and NPA atomic charges are shown in italic and bold characters, respectively. The dipole moment calculated by MP2/6-31G(d) is given in Debyes.

geometrical data and Mayer bond orders between **7** and the protonated form **7H⁺** we confirm that a certain aromatization of the all-carbon rings is induced upon protonation, which renders C–C distances in **7H⁺** lying within the range 1.36–1.45 Å (bond orders 1.44–1.10). Inspection of the corresponding changes in the charges in **7H⁺** by Natural Population Analysis reveals that 38% and 34% of the positive charge are delocalized throughout the ether ring and the hydroxyl groups, respectively. Thus, the nature of **7H⁺** can be better described in terms of the two resonance structures **7H⁺** (I) and **7H⁺** (II), with structure **7H⁺** (I) being the predominant one.



For comparative purposes, we briefly discuss our calculations on the most prototypical proton sponge, DMAN (Figure 2). The calculated gas-phase PA for DMAN is 243.8 kcal mol⁻¹, 8.1 kcal mol⁻¹ below that of **7**, and compares very well with the experimental value of 241.9 kcal mol⁻¹.^[8] Similarly, the MP2/6-31G(d) geometrical data (see Figure 2) for the most stable conformers of DMAN and DMAN-H⁺ with C₂ and C_s symmetry, respectively, are in good agreement with recent experimental results.^[12] As discussed in previous work,^[11, 12] various electronic and structural changes occur when DMAN accepts a proton. Most remarkably, the naphthalene ring becomes completely planar (although the corresponding C–C distances and bond orders suffer slight variations) and the proton is located asymmetrically between the N atoms with equilibrium distances of 1.108 and 1.561 Å, thus forming a short and strong N–H...N hydrogen bond.

In summary, the comparative analysis of the theoretical results for the pyrone-like structure **7** and DMAN clearly supports the prediction of pyrone-like structures as organic superbases. We expect that the theoretical results reported in this work will stimulate further work aimed at the synthesis of pyrone-like structures. This new type of reagents might expand the possibilities in the design of more specific oxygen-based superbases.

Experimental Section

Stable structures were fully optimized at the HF/6-31G(d) and MP2/6-31G(d) levels of theory^[13] and characterized by calculating their HF/6-31G(d) frequencies. Proton affinities in the gas phase were obtained by combining MP2/6-311 + G(2d,2p)//MP2/6-31G(d) electronic energies and the corresponding HF/6-31G(d) thermal corrections at standard conditions. All the calculations were performed using the Gaussian 94 series of programs.^[14]

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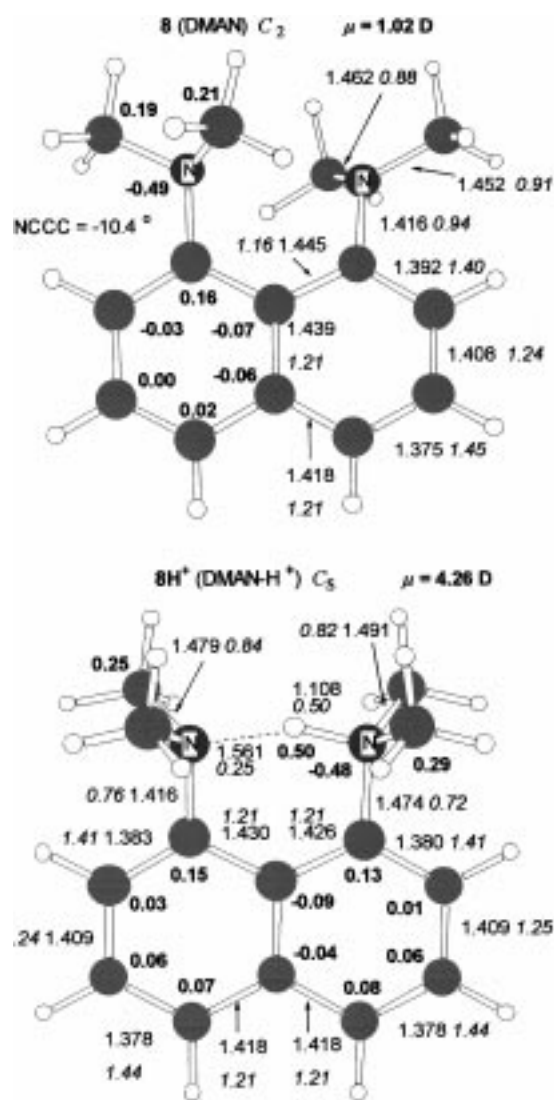


Figure 2. MP2/6-31G(d)-optimized structures for the neutral and protonated forms of DMAN. Distances are given in Ångströms. Mayer bond orders and NPA atomic charges are also shown in italic and bold characters, respectively. The dipole moment calculated by MP2/6-31G(d) is given in Debyes.

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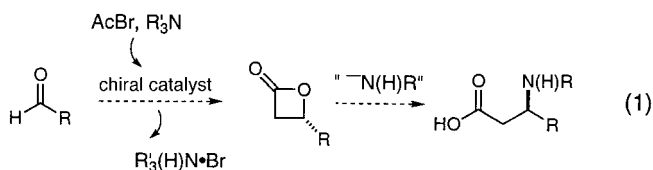
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Enantioselective β -Amino Acid Synthesis Based on Catalyzed Asymmetric Acyl Halide–Aldehyde Cyclocondensation Reactions**

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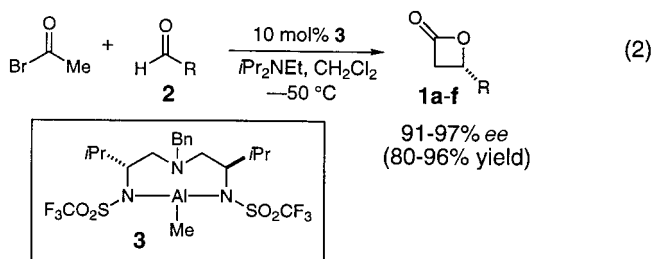
Optically active β -amino acids have become increasingly prevalent features in small-molecule chemotherapeutic agents^[1] and are integral components of peptidic materials that have unique structural properties.^[2] As a result, efficient and economical preparation of enantiomerically enriched β -

amino acids has become the focus of numerous synthesis studies.^[3,4] The amine-mediated S_N2 ring opening of β -lactones presents an especially attractive and straightforward entry to compounds that contain β -amino carbonyl functionalities [Eq. (1)].^[5,6] However, the evolution of this strategy as

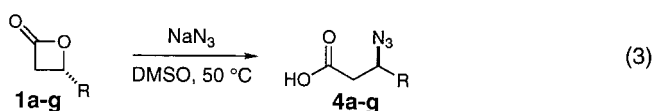


a general asymmetric synthesis of β -amino acids has been limited by the availability of the requisite optically active β -lactone electrophiles.^[7] Herein we describe the union of catalytic asymmetric acyl halide–aldehyde cyclocondensation reactions with azide- or sulfonamide-anion-mediated ring opening of the derived enantiomerically enriched β -lactones as an economical and efficient asymmetric synthesis of N-protected β -amino acids.

Catalyzed enantioselective acyl halide–aldehyde cyclocondensation (AAC) reactions have recently been reported to provide convenient access to β -lactones with high enantiomeric purities [Eq. (2)].^[8] We envisioned that integrating the



catalytic asymmetric AAC reaction technology with the reactivity of nitrogen-based nucleophiles toward β -lactones would represent a general asymmetric synthesis of β -amino acid derivatives. Thus, a series of enantiomerically enriched β -lactones **1** were prepared by the asymmetric cyclocondensation of acetyl bromide and a variety of aldehyde electrophiles **2** catalyzed by the Al^{III} triamine complex **3** (Table 1). Based on pioneering observations by the groups of Vederas and Seebach,^[5a–c] azide ion was evaluated initially as a suitable nucleophile for effecting the desired S_N2 mode of 2-oxetanone ring opening. Reacting the optically active β -lactones **1a–f** with sodium azide (2.0 equiv) in DMSO (50 °C) promoted efficient S_N2 lactone ring opening to directly afford the β -azido acids **4a–f** in 78–95 % yield [Eq. (3)].^[9] Azide-induced



ring opening was insensitive to the structure of the lactone alkyl substituent; lactones bearing aliphatic unbranched, alkoxy-substituted, α -branched,^[10] and β -branched alkyl sub-

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

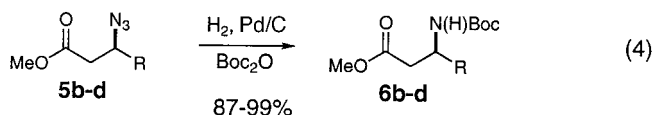
Table 1. Asymmetric catalyzed AAC and azide-mediated ring-opening reactions.

Entry	Aldehyde 2 (R)	ee [%] (1) ^[a] (Yield [%])	Yield [%] (4) ^[b] (Config.)	ee [%] (4)
1	a (BnOCH ₂)	91 (88)	94 (R)	92 ^[c]
2	b (PhCH ₂ CH ₂)	97 (96)	95 (S)	93 ^[c]
3	c (Me ₂ CHCH ₂)	95 (95)	95 (S)	97 ^[d]
4	d (CH ₃ CH ₂ CH ₂)	96 (95)	78 (S)	
5	e (CH ₃ (CH ₂) ₃)	97 (80)	83 (S)	
6	f (CH ₂ CH(CH ₂) ₈)	94 (96)	87 (S)	
7	g (cC ₆ H ₁₁)	99 (48) ^[e]	93 (R)	

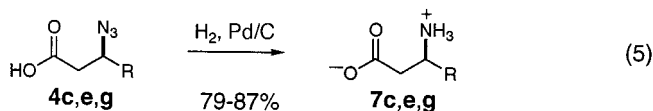
[a] Lactones **1** were prepared and assayed by using the procedures described in ref. [8a] (except lactone **1g**). [b] Reported yields are for compounds obtained from the acid–base extractive workup of the azide ring-opening reactions. [c] Enantiomer ratio determined by chiral-phase HPLC (Chiralcel OD-H column) of the corresponding methyl ester. [d] Enantiomer ratio determined by chiral-phase HPLC (Chiralcel OD-H column) of the corresponding benzyl ester. [e] Lactone **1g** was obtained by the resolution procedure described in ref. [10a].

stituents are subject to efficient lactone ring opening with the anticipated inversion of configuration (Table 1).^[11] Product isolation and purification was facilitated by acid–base partitioning of the β -azido acid reaction products; the β -azido acids typically emerge from the extractive workup in >95 % purity.^[12]

The optically active β -azido acids **4** can be further derivatized or protected to correctly format the carboxylic acid and amino functions for subsequent transformations. Upon converting the azido acids **4b–d** to the corresponding methyl esters **5b–d** (CH₂N₂, Et₂O), transforming the azide residue to the carbamate-protected amine was achieved by catalyzed hydrogenolysis of the β -azido esters **5b–d** in the presence of di-*tert*-butyl dicarbonate (Boc₂O) to afford the *N*-Boc-protected β -amino acid derivatives **6b–d** in 87–99 % yield [Eq. (4)].^[13] The free β -amino acid salts **7c, e, g** were

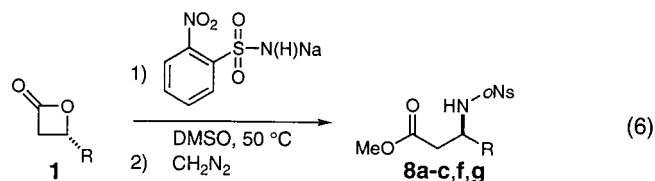


obtained in 79–87 % yield by Pd⁰-catalyzed hydrogenolysis of the β -azido acids **4c, e, g** [Eq. (5)]. Note that the optically active β -azido acids emerge from the lactone ring-opening reaction appropriately derivatized for direct coupling at the carboxylate terminus, while the acid protection–azide reduction sequence formats the resulting β -amino esters for amide-bond construction at the nitrogen terminus.



In anticipation of the demands that multistep synthesis applications might place on the β -amino acid derivatives emerging from this procedure, we were interested in developing methods for directly installing the protected β -amine

function in the correct oxidation state. Ring opening of optically active β -lactones with stabilized amine anions would afford an asymmetric synthesis of β -amino acids in which the nitrogen function would be directly introduced bearing an electron-withdrawing protecting group. Sulfonamide anions were expected to possess the correct electronic properties to allow S_N2 β -lactone ring opening to predominate relative to the alternative ring-opening pathway involving nucleophilic attack at the lactone carbonyl group.^[14] Accordingly, the anion derived from *o*-nitrobenzenesulfonamide was selected as a suitable nitrogen nucleophile based on the utility of nosylate (*o*-nitrobenzenesulfonyl, *o*Ns) groups as easily removable nitrogen protecting groups [Eq. (6)].^[15] Reacting the enan-



tiomerically enriched β -lactones **1a–c, f** with the sodium salt of *o*-nitrobenzenesulfonamide in DMSO (50 °C) afforded the *N*-protected β -amino acids **8a–c, f** in good yields (64–83 %) accompanied by little (≤ 10 %) to none of the imide product arising from carbonyl addition (Table 2).^[16] Steric bulk

Table 2. Sulfonamide-anion-mediated lactone ring opening.

Entry	Lactone 1 (R)	Yield [%] (8) ^[a] (Config.)	ee [%] (8) ^[b] (ee [%] (1))
1	a (BnOCH ₂)	64 (R)	
2	b (PhCH ₂ CH ₂)	72 (S)	≥ 95 (97)
3	c (Me ₂ CHCH ₂)	74 (S)	93 (95)
4	f (CH ₂ CH(CH ₂) ₈)	83 (S)	
5	g (cC ₆ H ₁₁)	43 (R) ^[c]	≥ 95 (99)

[a] Reported values are for chromatographically purified compounds. [b] Enantiomer ratios determined by ¹H NMR analysis of corresponding (*S*)- α -methoxyphenylacetamides; see ref. [16]. [c] 38 % of regioisomer formed.

adjacent to the electrophilic carbon atom, however, alters the regioselectivity of nucleophilic addition to the β -lactones; sulfonamide anion addition to the cyclohexyl-substituted lactone **1g** suffers from significant competition between the S_N2 and carbonyl addition pathways (Table 2, entry 5).^[17] In this regard, the azide-mediated ring-opening reactions that do not exhibit substrate-dependent regioselectivity represent attractive complements to sulfonamide anion addition reactions. Since *o*-nitrobenzenesulfonyl-protected nitrogen functionalities are conveniently unmasked with thiolate ion, this procedure constitutes a convenient two-step synthesis of versatile *N*-protected β -amino acids.^[18]

The asymmetric AAC–amine ring-opening sequence provides an operationally simple and economical enantioselective synthesis of β -amino acid derivatives. The availability of either enantiomer of the cyclocondensation catalyst **3** affords convenient access to β -amino acids in either enantiomeric series.

Experimental Section

General procedure for S_N2 addition of NaN₃ to β -lactones **1**: To a solution of NaN₃ (72 mg, 2.0 mmol, 2.0 equiv) in anhydrous DMSO (3.4 mL) at 50 °C was added β -lactone **1** (176 mg, 1.0 mmol, final concentration 0.3 M) by syringe. The resulting homogeneous solution was stirred until all the lactone had been consumed as monitored by TLC (ca. 6 h). After the reaction mixture had been cooled to ambient temperature, saturated aqueous NaHCO₃ (3 mL) was added. The resulting heterogeneous mixture was triturated with water until all the precipitated salts dissolved. The resulting mixture was extracted with ethyl acetate (2 $\times$ 5 mL) and the aqueous layer was separated and acidified with 1 M HCl. The acidic aqueous layer was extracted with ethyl acetate (3 $\times$ 5 mL) and the combined organic portions were washed with water (2 $\times$ 5 mL) and brine (2 $\times$ 5 mL). The organic portion was dried (Na₂SO₄) and evaporated in vacuo to afford the β -azido acid **4**.

General procedure for S_N2 addition of *o*-nitrobenzenesulfonamide (monosodium salt) to β -lactones **1**: To a suspension of *o*-nitrobenzenesulfonamide (monosodium salt; 700 mg, 3.13 mmol, 2.0 equiv) and activated powdered 4 Å molecular sieves (200 mg) in anhydrous DMSO (5.2 mL, in lactone) at 50 °C was added β -lactone **1** (200 mg, 1.56 mmol, final concentration 0.3 M) by syringe. The resulting suspension was stirred until all the lactone had been consumed as monitored by TLC (ca. 5 h). After the reaction mixture had been cooled to ambient temperature, 1 M aqueous HCl (5 mL) was added and the resulting mixture was extracted with ethyl acetate (3 $\times$ 5 mL). The combined organic extracts were washed with water (2 $\times$ 5 mL) and brine (2 $\times$ 5 mL). The organic layer was separated, dried (Na₂SO₄), and concentrated in vacuo to afford a yellow solid. The solid was triturated with chloroform and the insoluble material (*o*-nitrobenzenesulfonamide) removed by filtration. The filtrate was concentrated in vacuo to afford the crude β -sulfonamido acid. The crude acid was dissolved in ethyl acetate and a solution of CH₂N₂ in diethyl ether was added until a yellow color persisted. Glacial acetic acid was added to decolorize the reaction mixture and the volatiles were evaporated in vacuo to afford the β -sulfonamido ester **8** as a yellow oil that was purified by column chromatography (hexanes/ethyl acetate, 65:35).

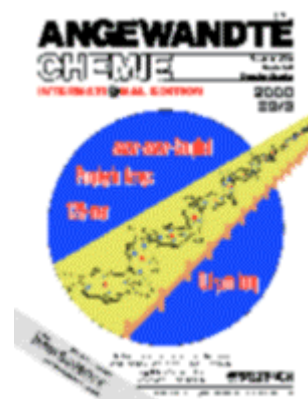
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- [12] To verify that lactone ring opening was proceeding with rigorous inversion of configuration, the enantiomeric purities of azides **4a–c** were determined by chiral-phase HPLC (Chiralcel OD-H column) of the methyl esters derived from **4a** and **4b**, and the benzyl ester derived from **4c**.
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- [16] The enantiomeric purities of the β -sulfonamido esters **8b, c, g** were determined by integrating representative signals in the ¹H NMR spectrum of the corresponding (*S*)- α -methoxyphenylacetamides. The diastereomeric (*S*)- α -methoxyphenylacetamides were prepared from **8** by sulfonamide deprotection (PhSH, K₂CO₃, DMF) followed by coupling the derived β -amino ester with (*S*)- α -methoxyphenylacetic acid (dicyclohexyl carbodiimide, 5 mol % 4-(dimethylamino)pyridine).
- [17] Attempts to introduce carbamate-protected nitrogen residues by addition of benzylcarbamate- or *tert*-butylcarbamate-derived anions afforded β -hydroxy imide products derived from predominant carbonyl addition.
- [18] Sulfonamide deprotection (PhSH, K₂CO₃, DMF) of representative β -sulfonamido esters **8** proceeded in 80–90% yield.

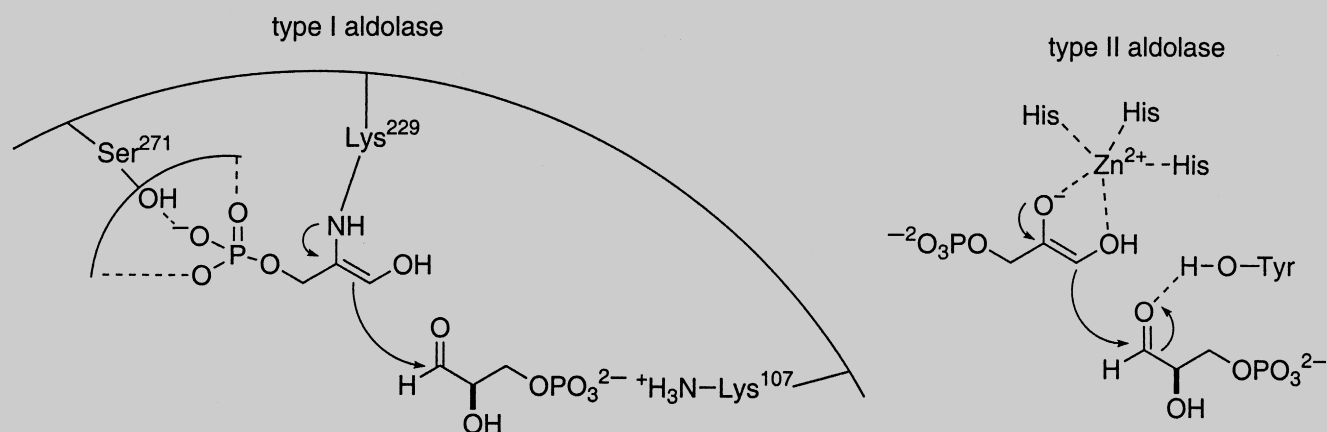
Cover Picture

Naoki Aratani, Atsuhiko Osuka, Yong Hee Kim, Dae Hong Jeong, Dongho Kim

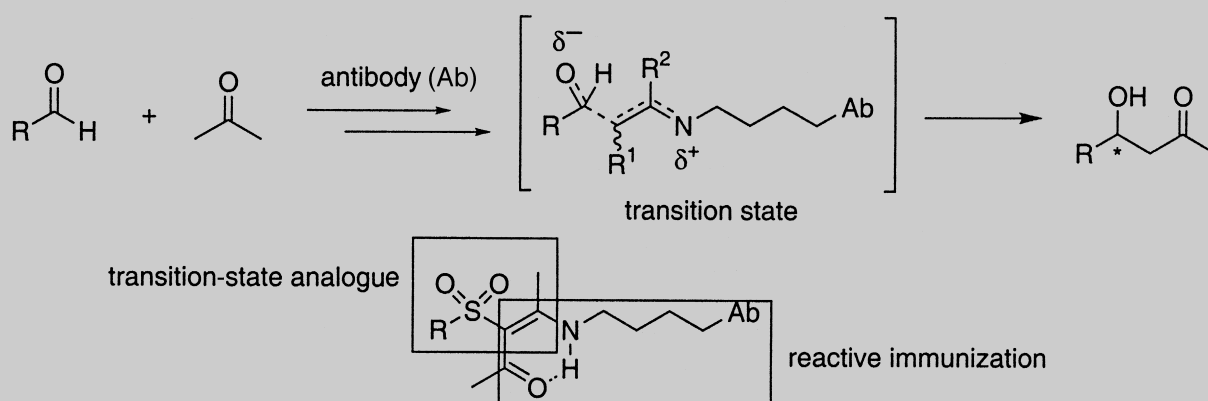
The cover picture shows a schematic representation of a supramolecular rod composed of *meso-meso*-coupled porphyrins. The Ag^I-promoted *meso-meso*-coupling of Zn^{II} 5,15-diarylporphyrins enabled regularly arranged arrays with 2-128 porphyrins to be assembled. An examination of the absorption spectra of these rods show that they all exhibit split Soret bands as a result of exciton coupling. As the number of porphyrins increases the low-energy Soret band is shifted to longer wavelength while the high-energy Soret band stays at nearly the same wavelength, which results in a progressive increase in the splitting energy. A study of the fluorescence spectra of the arrays shows the S₁ states are delocalized over 6-8 porphyrin units. The 128mer at 0.1-μm long is the longest monodisperse, rodlike molecule so far known, and should, together with the smaller arrays, have the potential for application as light-harvesting wires. Further details are reported by A. Osuka et al. on p. 1458 ff.



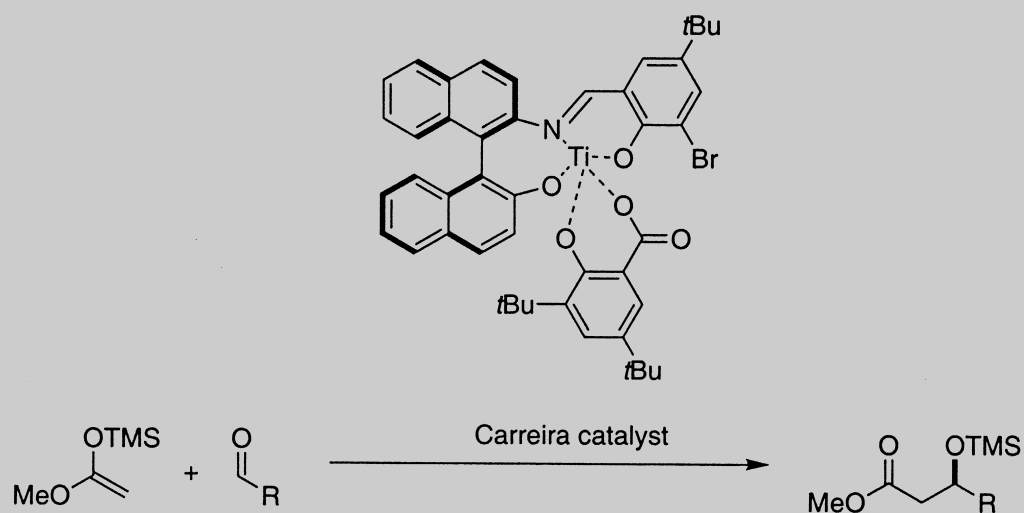
Aldolase-catalyzed reaction



Antibody design and catalysis



Small-molecule catalyst



The Catalytic Asymmetric Aldol Reaction

Timothy D. Machajewski and Chi-Huey Wong*

Dedicated to Professor Richard A. Lerner

The construction of C–C bonds with complete control of the stereochemical course of a reaction is of utmost importance for organic synthesis. The aldol reaction—the simple addition of an enolate donor to a carbonyl acceptor—is one of the most powerful reactions available to the synthetic chemist. In general, control of the relative and absolute configuration of the newly formed stereogenic centers has been

achieved through the use of chiral starting materials or chiral auxiliaries. In recent years the search for catalytic methods that efficiently and effectively transfer chirality information has become a major effort in synthetic organic chemistry. Two different approaches have been taken toward the catalytic asymmetric aldol reaction: biocatalysis and catalysis with small molecules. Both approaches have spe-

cific advantages and limitations, and as a result are complementary to each other. The important efforts toward both approaches are reviewed in this article.

Keywords: aldol reactions • asymmetric catalysis • catalytic antibodies • enzyme catalysis • organometallic catalysis

1. Introduction

The aldol reaction is one of the most powerful methods of forming carbon–carbon bonds. The ability to control the absolute configurations of the newly formed stereogenic centers is of paramount importance for the synthesis of natural products. In general, control of stereochemistry has been accomplished diastereomerically through either the use of chiral aldehyde starting materials or stoichiometric chiral auxiliaries attached to the donor enolate.^[1] The control of stereochemistry using chiral aldehydes as substrates has some limitations. While chiral aldehydes undergo stereospecific addition in a very predictable fashion,^[2] the formation of all possible stereoisomers from a single chiral aldehyde is not possible. Chiral auxiliaries have solved this problem and depending on the choice of auxiliary, all possible stereoisomers can be realized;^[3] however, while this approach has been quite successful, it requires additional steps to introduce and remove the chiral auxiliary.

The search for methods that predictably transfer chirality efficiently and catalytically by reagent control has been a

challenging goal in organic synthesis. A number of methods have been developed in recent years for the catalytic asymmetric aldol addition with both high efficiency and selectivity. This review will focus on those efforts in two areas: 1) the exploitation of biochemical catalysts such as aldolases and catalytic antibodies, and 2) the design of chiral chemical catalysts such as chiral Lewis acids and bases.

2. Biochemical Catalysts

Enzymes are increasingly recognized as useful catalysts for organic synthesis.^[4] Their attractiveness arises from a number of important advantages over traditional chemical methods. Enzymes are generally highly chemo-, regio-, diastereo-, and enantioselective. As a result of this high selectivity and the mild conditions employed, protecting group chemistry can be kept to a minimum. Since most enzymes operate at room temperature in aqueous solutions at or near neutral pH values, their reactions are often compatible with one another, making it possible to combine several enzymes in a one-pot, multistep operation. Their use in aqueous solution free of heavy metals and with biodegradability make enzymes an environmentally advantageous option, though in certain cases the reaction is limited to a narrow range of substrates and the isolation of the products from water could be a problem.

There are two types of enzymatic catalysts that effect the aldol addition: the aldolases, a group of naturally occurring enzymes that catalyze *in vivo* aldol condensations; and

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catalytic antibodies that have been developed in recent years to mimic the aldolases but with improved substrate specificity.

2.1. Aldolases

The aldolases are a specific group of lyases that typically catalyze the stereoselective addition of a ketone donor to an aldehyde acceptor. Over 30 aldolases have been identified to date. Two distinct types of aldolases have been identified and classified according to their mechanism (Scheme 1).^[5] As a general rule type I aldolases are primarily found in animals and higher plants, while type II aldolases are found in bacteria and fungi.

Type I aldolases activate the donor by forming a Schiff base as an intermediate in the active site. This activated donor then adds stereoselectively to the acceptor aldehyde. In several cases the Schiff base has been isolated by reduction with borohydride,^[6] but no three dimensional structure of the complex exists. Recently, however, a three-dimensional structure of the reduced Schiff base intermediate of transaldolase B from *Escherichia coli* was determined (Figure 1).^[7] Crystallographic studies of free transaldolase reveal a similar three-dimensional structure and active site to other type I aldolases.^[8–10]

Type II aldolases, on the other hand, contain a Zn^{2+} cofactor in the active site. There have been several mechanistic hypotheses for the mechanism of this class of aldolase. According to NMR and ESR studies on the relaxation rate of a Mn^{2+} -substituted holoenzyme, the Zn^{2+} ion polarizes the carbonyl donor through an intervening imidazole group of an amino acid side chain.^[11] FT-IR spectroscopic and deuterium exchange studies led to the conclusion that activation occurs

by an additional direct coordination of Zn^{2+} to the carbonyl donor.^[12] A crystal structure of fuculose-1-phosphate aldolase containing an inhibitor that mimics the enediolate transition state of dihydroxyacetone phosphate (DHAP) was recently solved (Figure 2).^[13]

A clearer picture of the mechanism of type II aldolases arises from this three-dimensional information. The active site is located at the interface of two subunits of a homotetramer, and contains the Zn^{2+} cofactor coordinated to three histidine residues (His-92, His-94, His-155). In the absence of DHAP a glutamate residue (Glu-73) further stabilizes the Zn^{2+} ion. The phosphate group is bound in a pocket containing several hydrogen-bond donors (Ser-72, Ser-71, Thr-43, Gly-44, Asn-29). The glutamate residue also functions as a base to remove the proton from the donor. A tyrosine residue (Tyr-113') from the adjoining subunit assists in the activation of the incoming aldehyde by donating a proton to stabilize the developing charge. In both types of aldolases the formation of the enolate (that is, the deprotonation step) is rate determining. Armed with this structural and mechanistic information, site-directed mutagenesis and directed evolution may find use in developing new aldolases with improved substrate specificities and properties.

With only a few exceptions, the stereoselectivity in both types of aldolases is controlled by the enzyme and does not depend on the structure or stereochemistry of the substrate, which allows for highly predictable products. These enzymes generally tolerate a broad range of acceptor substrates but have stringent requirements for donor substrates.

The aldolases that have been investigated for their synthetic utility can be divided into four main groups on the basis of the donor substrate accepted by the enzyme. The first group uses dihydroxyacetone phosphate (DHAP) as the donor to

Chi-Huey Wong, born in 1948, received his BS and MS degrees from the National Taiwan University and his PhD in chemistry with George M. Whitesides from the Massachusetts Institute of Technology in 1982. He then moved with Professor Whitesides to Harvard University as a postdoctoral fellow for another year. He was appointed to the faculty of chemistry at Texas A&M University in 1983 and rose through the ranks in four years. Since 1989 he has been a Professor and Ernest W. Hahn Chair in Chemistry at The Scripps Research Institute. He has also been associated with the Skaggs Institute for Chemical Biology at Scripps since 1996 and was Head of the Frontier Research Program on Glycotechnology at RIKEN (Institute of Physical and Chemical Research) in Japan from 1991 to 1999. He has received numerous awards and is a member of the American Academy of Sciences. His current interests are in the areas of bioorganic and synthetic chemistry, especially in the development of new synthetic chemistry based on combined enzymatic and chemical reactions, the study of molecular glycobiology, and the rational development of mechanism-based inhibitors of enzymes and carbohydrate receptors.

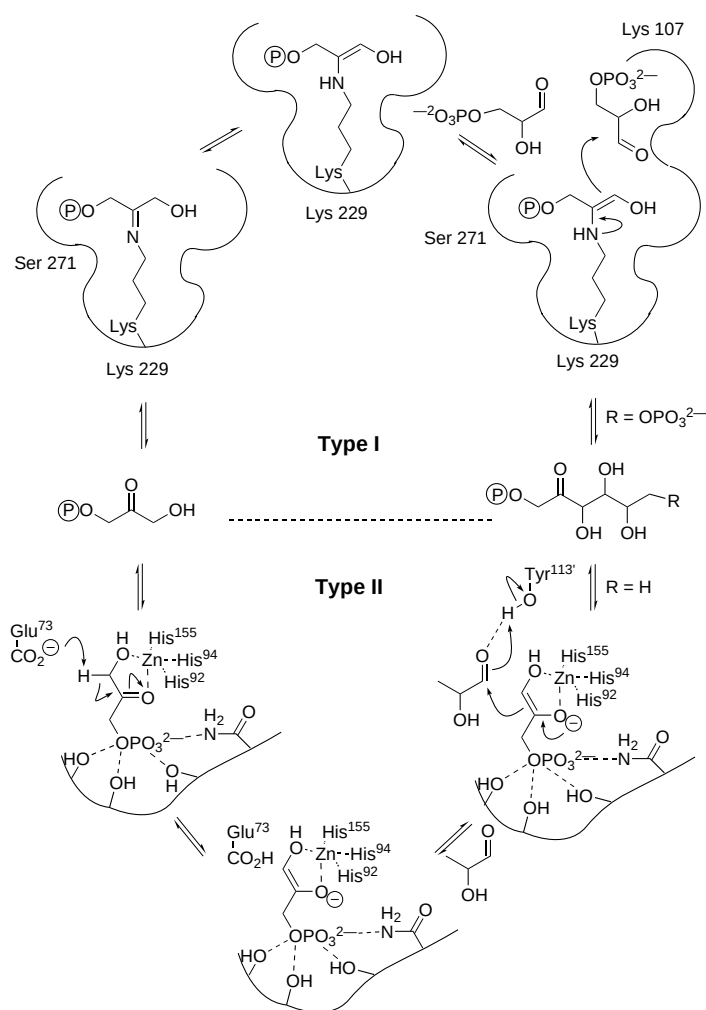
Timothy D. Machajewski, born in 1966, received a BS degree from the University of Texas at Austin, and a PhD in chemistry from Stanford University under Barry M. Trost in 1997. He spent two years as a postdoctoral research associate at The Scripps Research Institute with C.-H. Wong. His research interests include the study of catalytic methods for asymmetric synthesis and the synthesis of bioactive natural products.



C.-H. Wong



T. D. Machajewski



Scheme 1. The two types of aldolase mechanisms: The type I Schiff base forming aldolase is represented by rabbit muscle FDP aldolase (RAMA, top), and the type II zinc enolate aldolase is represented by fuculose-1-phosphate aldolase (bottom). $\text{P} = \text{PO}_3^{2-}$.

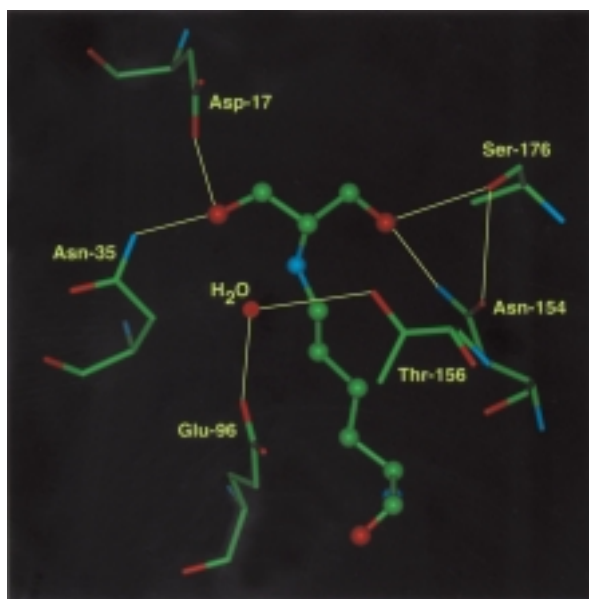


Figure 1. Structure of the active site of the reduced substrate-enzyme complex of transaldolase B (type I aldolase) as determined by X-ray crystallography.

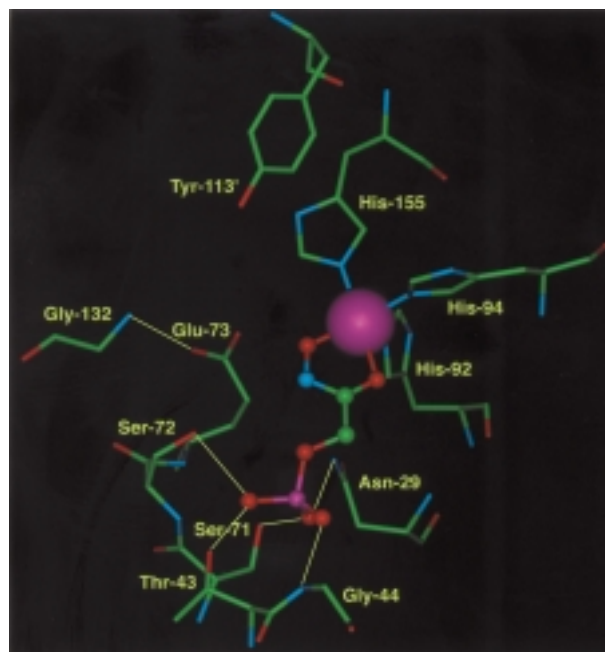


Figure 2. Structure of the active site of fuculose-1-phosphate aldolase (type II aldolase) as determined by X-ray crystallography.

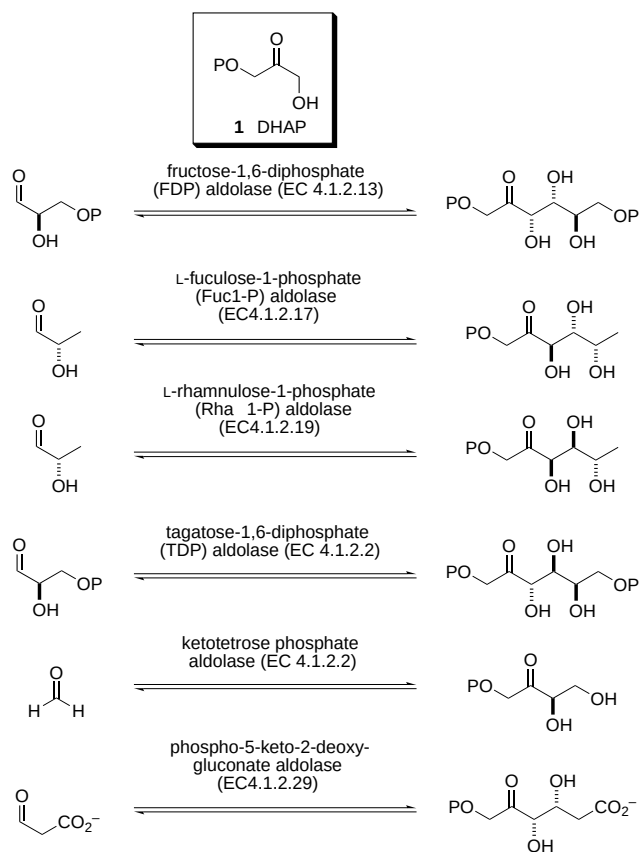
produce 2-keto-3,4-dihydroxy adducts. The second group uses pyruvate or phosphoenol pyruvate to form 3-deoxy-2-keto acids. The third group uses acetaldehyde as the donor, which results in the formation of 3-hydroxyaldehydes. The fourth group utilizes glycine as the donor to produce β -hydroxy- α -amino acids. As a consequence of the limited space available here, the other types of aldolases [4, 14] and transaldolases are not covered.

2.1.1. DHAP-Dependent Aldolases

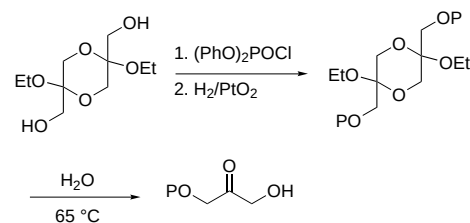
The known DHAP-dependent aldolases and their in vivo catalyzed reactions are shown in Scheme 2. These enzymes accept a broad range of acceptor substrates,[4] including unhindered aliphatic aldehydes, α -heteroatom substituted aldehydes,[15a] and monosaccharides and their derivatives.[15b] Aromatic aldehydes, sterically hindered aldehydes, and α,β -unsaturated aldehydes are generally not substrates,[15a] however, aromatic aldehydes and α -branched aldehydes have been reported to be substrates for cross-linked enzyme crystals.[16]

Since these aldolases show a very strict requirement for the donor substrate, an efficient method of DHAP preparation is essential. Several chemical and enzymatic methods for generating DHAP have been developed.[17–26] The use of relatively pure DHAP favors the formation of the aldol products and simplifies the purification process.

Phosphorylation of the dihydroxyacetone dimer with $(\text{PhO})_2\text{POCl}$ [25] followed by reductive cleavage of the phenyl esters gives the DHAP dimer, which can be easily hydrolyzed to provide clean DHAP in 61 % overall yield (Scheme 3). The phosphate group can be easily removed from the aldol product by enzymatic hydrolysis with acid phosphatase (EC 3.1.3.2).



Scheme 2. Dihydroxyacetone phosphate (DHAP) dependent aldolases. P = PO_3^{2-} .

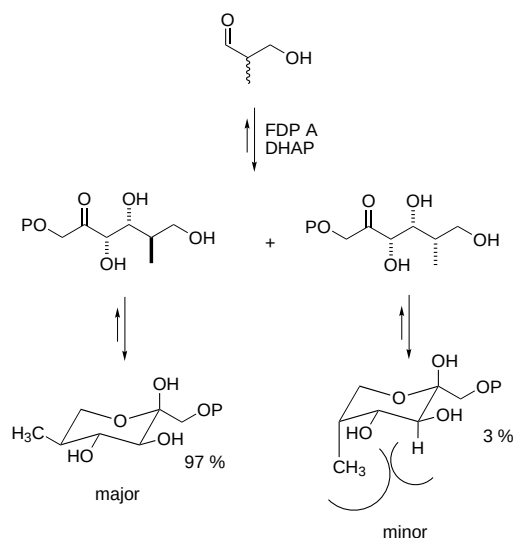


Scheme 3. Chemical synthesis of DHAP.

The configuration of the vicinal diols produced from the aldolase-catalyzed condensation of DHAP with unnatural acceptor aldehydes usually follows that of the natural substrates. Almost without exception, fructose-1,6-diphosphate (FDP) aldolase produces products with the *D-threo* configuration of FDP. L-Fucose-1-phosphate (Fuc1-P) aldolase and L-rhamnose-1-phosphate (Rha 1-P) aldolase generate diols with the *D-erythro* and *L-threo* configurations, respectively. For a few substrates, however, the stereoselectivity at C4 is diminished.^[27] In almost every case investigated, TDP aldolase yielded diastereomeric mixtures,^[28–30] and for this reason it is not yet synthetically useful.

In many cases the aldehyde substrates may be used as racemic mixtures. For example, *D*-glyceraldehyde-3-phosphate (G3P) reacts with DHAP in the presence of FDP aldolase 20 times faster than *L*-G3P. Fuc1-P aldolase and Rha 1-P aldolase show an even higher kinetic preference for

the *L*-enantiomer of 2-hydroxyaldehydes (>95:5).^[31] Therefore, as long as the reaction is stopped before reaching equilibrium, a kinetic resolution of the aldehyde substrate can be effected and a single diastereomeric and enantiomeric adduct can be obtained. In some cases, differentiation of racemic aldehydes can be accomplished under thermodynamic control. In cases where the aldol product can cyclize to form pyranoses, the product with an equatorial bulky substituent and the fewest 1,3-diaxial interactions will predominate at equilibrium, as illustrated in Scheme 4 for the reaction of 2-methyl-3-hydroxypropanol (**14**).



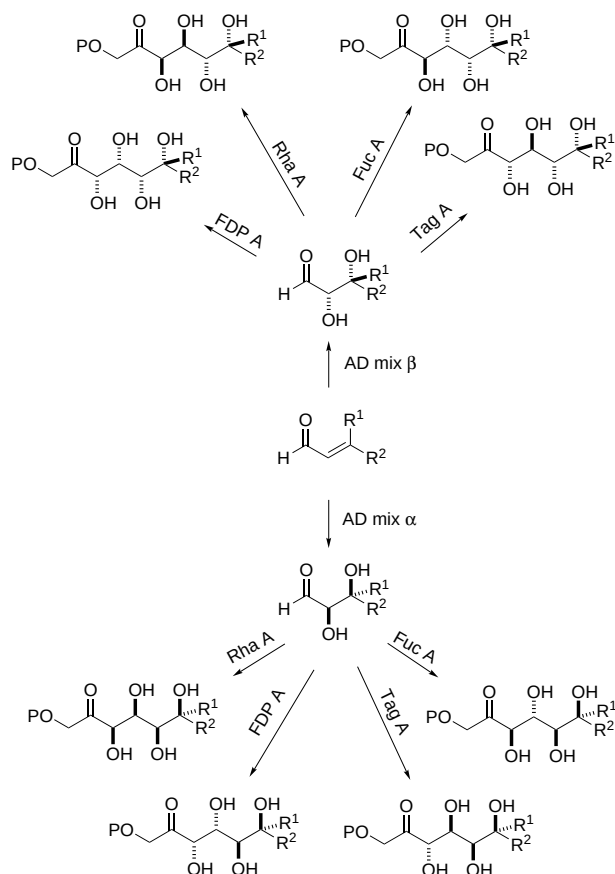
Scheme 4. Thermodynamic control of the product stereochemistry. A = aldolase.

The utility of the DHAP-dependent aldolases has been demonstrated in the synthesis of ^{13}C -labeled sugars, heteroatom-substituted sugars, deoxy sugars, fluoro sugars, long-chain sugars, and cyclitols. Well over 100 aldehydes have been used as acceptor substrates.^[4, 32]

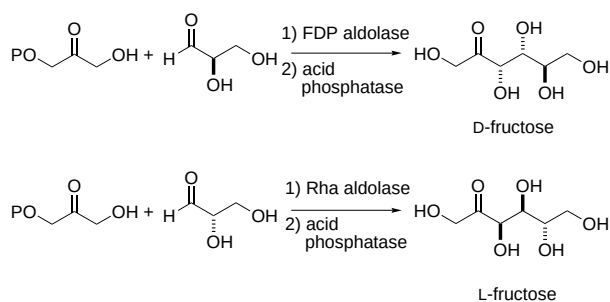
Tandem use of the Sharpless asymmetric dihydroxylation (AD) and aldolase-catalyzed addition provides a rapid method for the synthesis of both enantiomers with complete stereocontrol (Scheme 5).^[33] A multitude of carbohydrates and derivatives are potentially accessible by the appropriate choice of alkenal, AD-mix, and aldolase. In addition to the natural *D*-sugars, *L*-sugars are easily prepared by the appropriate choice of aldolase. For example, while *D*-fructose is formed from the FDP-catalyzed reaction of *D*-glyceraldehyde and DHAP, *L*-fructose is prepared from the Rha 1-P-catalyzed reaction of DHAP with *L*-glyceraldehyde (Scheme 6).^[34]

The aldolase-catalyzed reaction of DHAP and pentoses or hexoses provides access to novel long-chain sugars that are difficult to obtain from chemical synthesis or natural sources. Derivatives of sialic acid and 2-keto-3-deoxyoctanoate (KDO) have been prepared in this manner (Scheme 7).^[15]

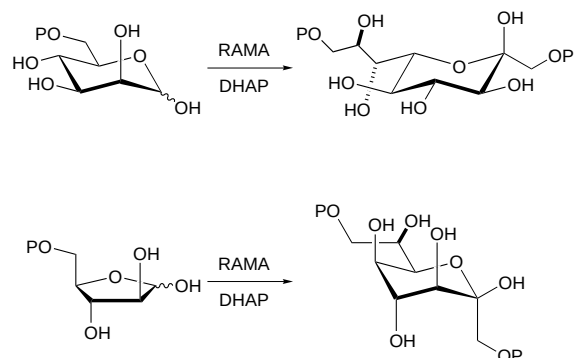
Heteroatom-substituted carbohydrates are readily assembled through the aldolase-catalyzed condensation of an appropriately substituted aldehyde with DHAP. Azides are well tolerated in the reaction and provide an efficient means



Scheme 5. Tandem asymmetric dihydroxylation (AD) and aldolase reaction.

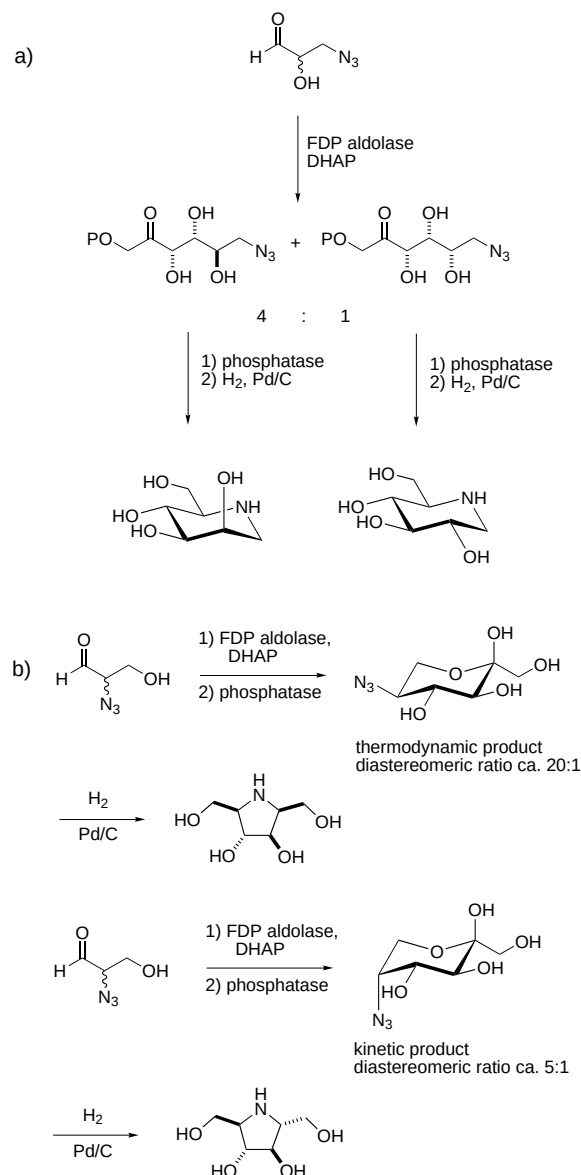


Scheme 6. Synthesis of D- and L-fructose by a reaction catalyzed by rhamnulose-1-phosphate aldolase and fructose-1-6-diphosphate aldolase, respectively.



Scheme 7. Synthesis of novel long-chain sugars.

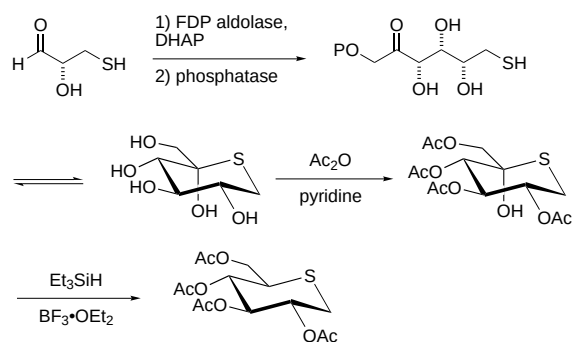
of preparing iminocyclitols, such as deoxynojirimycin and deoxymannojirimycin (Scheme 8a).^[35, 36] Polyhydroxylated pyrrolidines can be synthesized with 2-azido aldehydes (Scheme 8b). The FDP aldolase catalyzed condensation of



Scheme 8. a) Synthesis of iminocyclitols from azidoaldehydes and DHAP. b) Synthesis of substituted pyrrolidines from azidoaldehydes and DHAP.

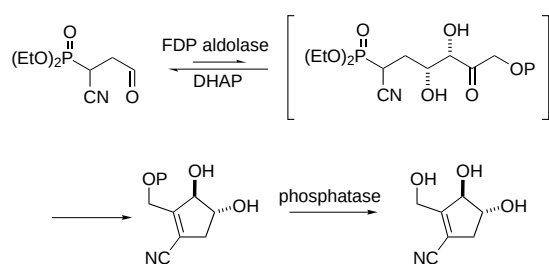
racemic 2-azido-3-hydroxypropanal with DHAP under thermodynamic control and subsequent removal of phosphate with acid phosphatase afforded the azido sugar. Reduction of the azide group with hydrogen and palladium on carbon afforded the substituted pyrrolidine.^[37] The subsequent reaction under kinetic control afforded the diastereomeric azido sugar, which was converted into a substituted pyrrolidine.^[38] The aldolase-catalyzed condensation of sulfur-substituted aldehydes with DHAP followed by reduction of the resulting thioketoses provides a rapid synthesis of thio sugars (Scheme 9).

Cyclitols, an interesting class of biologically active compounds, have been prepared chemoenzymatically from the



Scheme 9. Synthesis of thio sugars from thioaldehydes and DHAP.

reaction of nitroaldehydes^[39a] and phosphonate-substituted aldehydes (Scheme 10).^[39b] Other novel polyhydroxy structures prepared by aldolases are illustrated in Scheme 11.^[4, 32, 40]



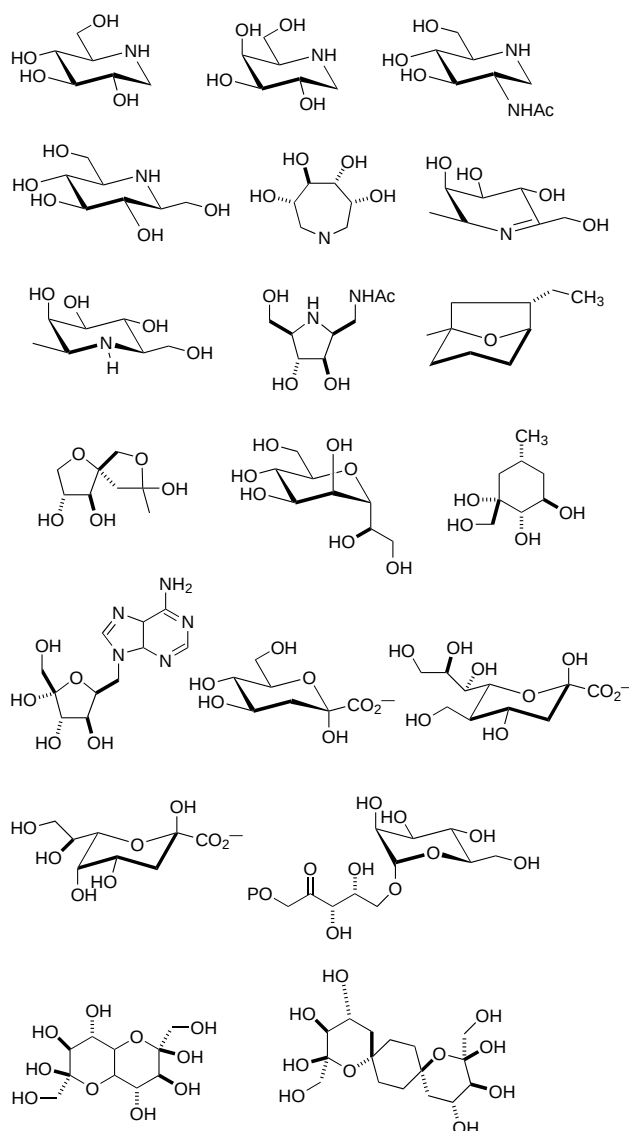
Scheme 10. Chemoenzymatic synthesis of cyclitols.

2.1.2. Pyruvate- and Phosphoenolpyruvate-Dependent Aldolases

The pyruvate-dependent aldolases (Scheme 12) and the phosphoenolpyruvate-dependent aldolases (Scheme 13) can be used to prepare similar α -keto acid products. The pyruvate-dependent aldolases have a catabolic function in vivo, whereas the phosphoenolpyruvate-dependent aldolases are involved in the biosynthesis of keto acids. For synthetic purposes the equilibrium of the pyruvate-dependent aldolases is shifted toward the condensation product through the use of excess pyruvate.^[41] Purification of the products can be most easily achieved by decomposing the excess pyruvate with pyruvate decarboxylase.^[42]

The commercial availability of *N*-acetylneuraminic acid (NeuAc) aldolase (also known as sialic acid aldolase) has led to extensive studies on this enzyme. It is highly specific for pyruvate as the donor substrate, but tolerates a variety of acceptor substrates, including hexoses, pentoses, and tetroses in both enantiomeric forms.^[32] Substitutions at C4, C5, and C6 are allowed with slight preferences for the same absolute stereochemistry as the natural substrate, *N*-acetyl-D-mannosamine. The substitutions at C2 and C3 are more restrictive; the C2 position favors relatively small substituents with the natural stereochemistry and the C3 position requires a free hydroxyl group.^[43]

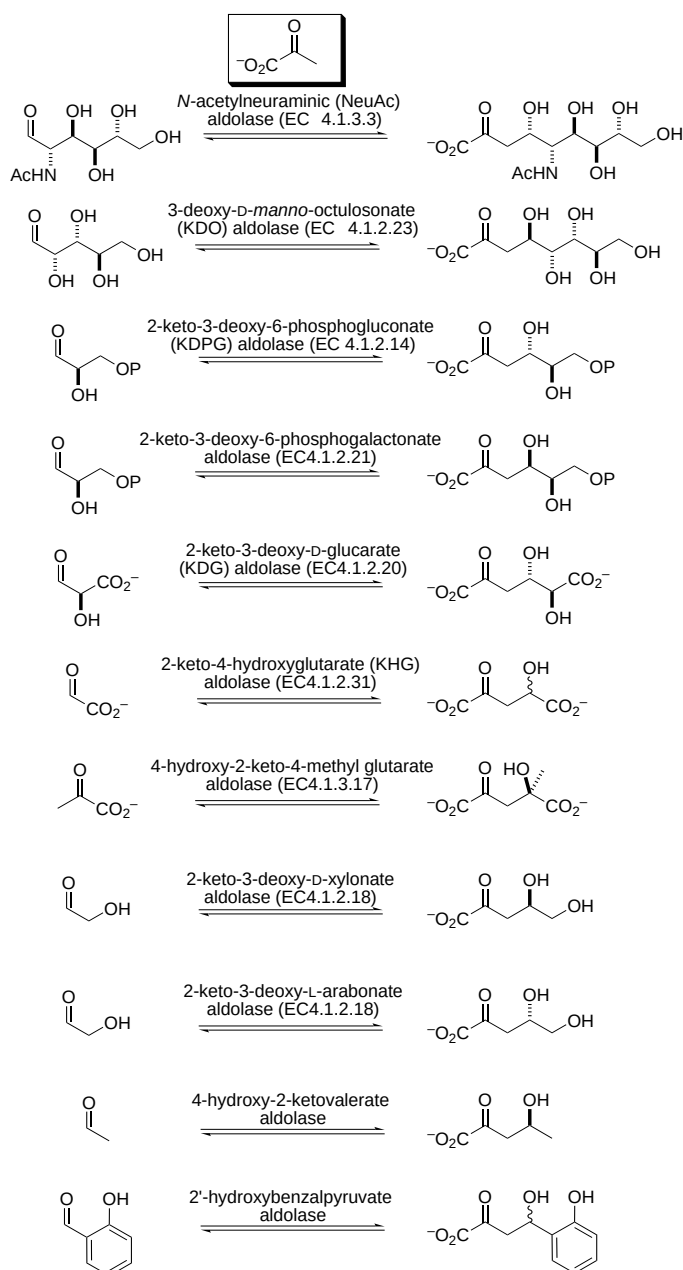
Unlike most aldolases the stereochemical outcome of reactions catalyzed by NeuAc aldolase depends on the structure of the substrate. In acceptor substrates with the



Scheme 11. Novel polyhydroxy structures prepared by aldolase-catalyzed reactions.

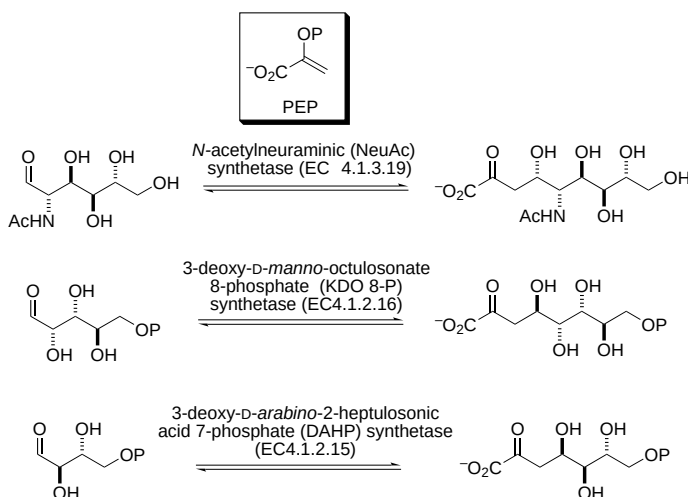
natural *S* configuration at C3, the carbonyl group is attacked from the *si*-face to form a new stereogenic center with *S* configuration. Substrates with the opposite configuration at C3, however, lead to attack of the carbonyl group from the *re* face, which gives rise to the *R* configuration (Scheme 14). In general, attack at the *si* face is kinetically favored over attack at the *re* face.^[43] The stereochemical outcome seems to be under thermodynamic control. In all cases where *re*-face attack predominates, the resulting *R*-configured product is thermodynamically more favored with the newly formed stereocenter in the equatorial configuration. This substrate-controlled stereoselectivity has been used in the synthesis of D- and L-sialic acid analogues and several other novel sugars and their enantiomers.^[42]

Aza sugars have been prepared with NeuAc aldolase.^[44] The enzyme-catalyzed addition of pyruvate to *N*-Cbz-D-mannosamine followed by reductive amination gave the pyrrolidine, which was further converted into 3-(hydroxymethyl)-6-epicastanospermine (Scheme 15).

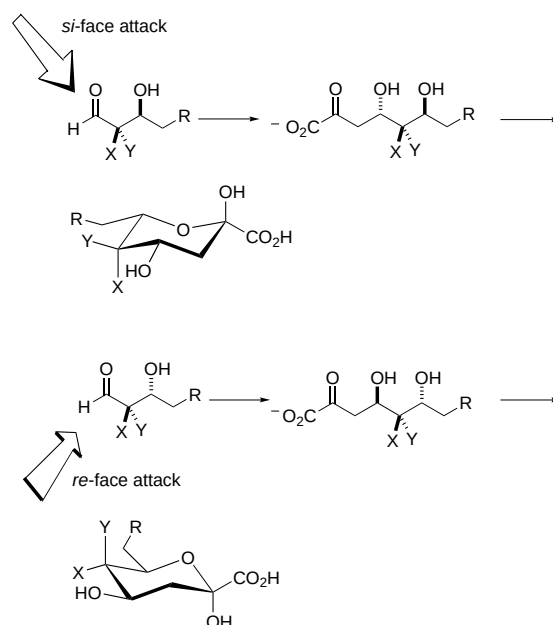
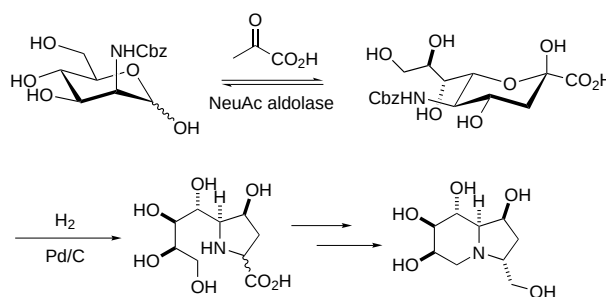


Scheme 12. Pyruvate-dependent aldolases and the reactions they catalyze.

Other pyruvate- and phosphoenolpyruvate-dependent aldolases have been isolated and purified, but have not been extensively investigated for their use in synthesis. KDO aldolase accepts D-ribose, D-xylose, D-lyxose, L-arabinose, D-arabinose-5-phosphate, and N-acetylmannosamine at less than 5% of the natural substrate, D-arabinose.^[45] The enzyme is specific for substrates with the *R* configuration at C3. In all cases observed to date, the carbonyl group is attacked from the *re* face. 2-Keto-3-deoxy-6-phosphogluconate (KDPG) aldolase was shown to accept various unnatural substrates at very low rates (<1%) relative to the natural substrate.^[46a] The stereochemistry of the newly formed stereocenter invariably has the *S* configuration. By using the technique of directed evolution by DNA shuffling and error-prone polymerase chain reaction (PCR), KDPG has been altered with regard to

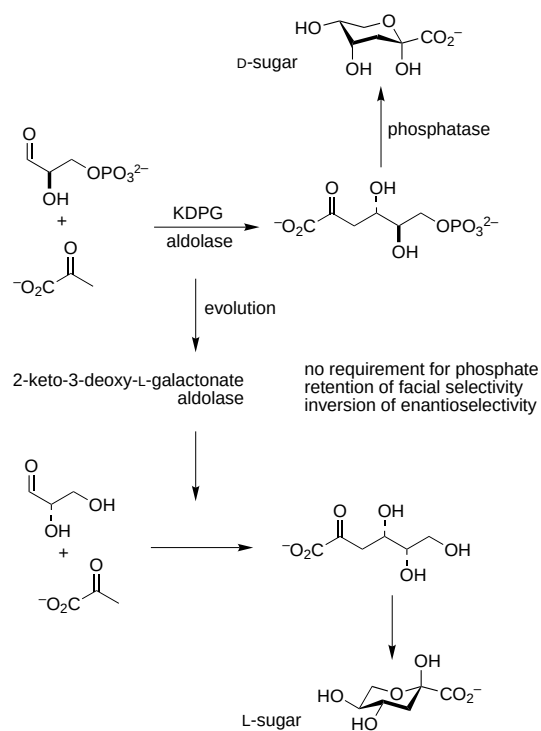


Scheme 13. Phosphoenolpyruvate-dependent aldolases and the reactions they catalyze.

Scheme 14. Stereochemical outcome of the reaction catalyzed by sialic acid (NeuAc) aldolase: comparison of *re* (top) with *si* addition to the carbonyl group (bottom).

Scheme 15. NeuAc aldolase catalyzed preparation of aza sugars. Cbz = benzyloxycarbonyl.

its acceptor enantioselectivity and phosphate requirement to accept the non-phosphorylated enantiomeric aldehydes to form interesting L-sugars (Scheme 16).^[46b]



Scheme 16. Directed evolution of KDPG aldolase to alter the acceptor enantioselectivity and to eliminate the requirement of a phosphate group in the substrate.

2.1.3. Acetaldehyde-Dependent Aldolases

Currently, there is only one known member of this class of aldolase: 2-deoxyribose-5-phosphate aldolase (DERA), which catalyzes the synthesis of 2-deoxyribose-5-phosphate from acetaldehyde and D-glyceraldehyde-3-phosphate. While not yet commercially available, it has been overexpressed in *E. coli* and large quantities of the enzyme can be simply and readily obtained.^[47–49] DERA, a type I aldolase, is the only known aldolase that performs a cross-aldol reaction of two aldehydes.

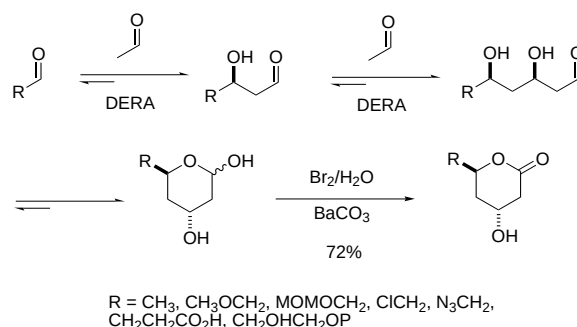
The enzyme shows a broad range of tolerance towards the acceptor substrate and a relatively large donor tolerance. In addition to acetaldehyde, the enzyme tolerates propanal, acetone, and fluoroacetone as donor substrates.^[48] The acceptor substrates have very few structural requirements: 2-hydroxyaldehydes react fastest, with D-isomers preferred over L-isomers. Azidoaldehydes, thio-substituted aldehydes, and α -methylaldehydes are all accepted as substrates.^[48] The configuration of the newly formed center is invariably determined by the enzyme and gives products that generally have the *S* configuration. Several iminocyclitols have been prepared from the DERA-catalyzed aldol condensation of various donors with 3-azido-2-hydroxypropanal (Table 1).

The products from the DERA-catalyzed reaction with acetaldehyde as the donor are themselves aldehydes, which can participate as an acceptor substrate for a second aldol condensation.^[50] For aldehyde substrates that are substituted in the α -position and cannot cyclize to form a hemiacetal, a second reaction with acetaldehyde takes place. The products of the second addition cyclize to a stable hemiacetal, which

Table 1. DERA-catalyzed synthesis of iminocyclitols.

donor	product	iminocyclitol

prevents further addition (Scheme 17). These products can be oxidized to provide the lactone moiety of the compactins in a remarkably short route starting from inexpensive, achiral starting materials.

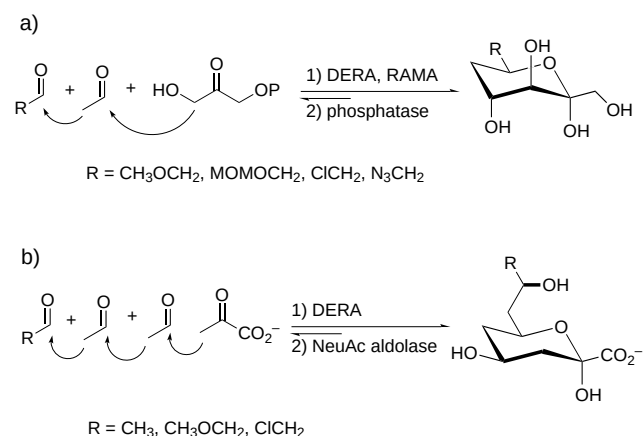


Scheme 17. Deoxyribose-5-phosphate aldolase (DERA) catalyzed, three component, double aldol condensation. MOM = methoxymethyl.

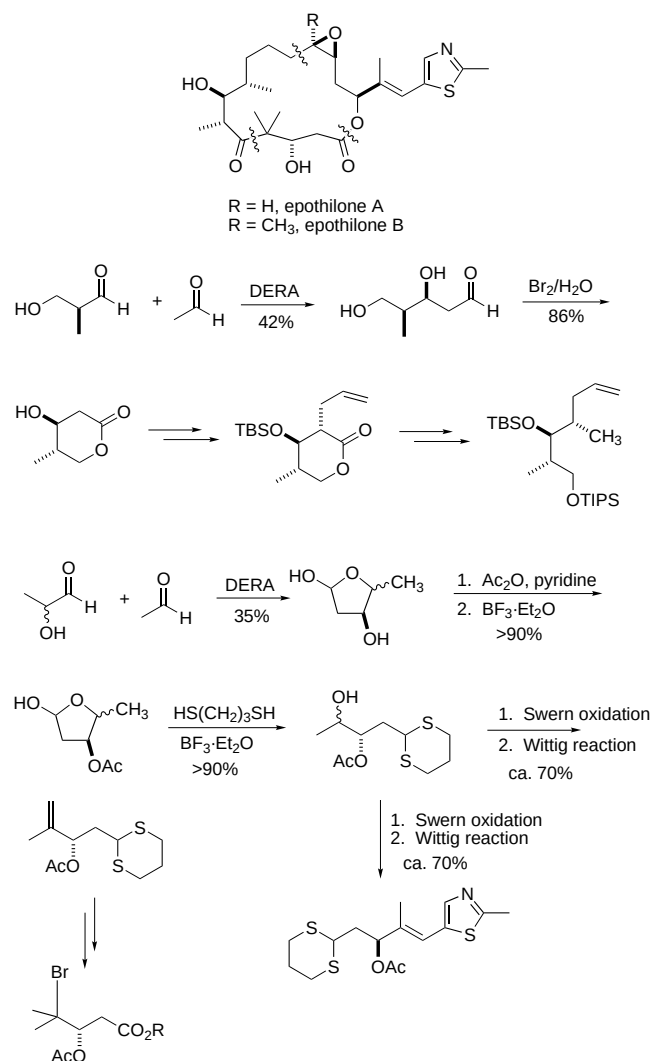
DERA can be combined with DHAP-dependent aldolases in a one-pot sequential reaction to produce 5-deoxy ketoses with three substituents in the axial position (Scheme 18a).^[51a] The combination of DERA and NeuAc aldolase in a sequential manner gives deoxy sialic acid derivatives^[51b] (Scheme 18b). This conversion was not possible in a one-pot system owing to the different reaction conditions needed for the two enzymes. The enzyme has also been used in the synthesis of key epothilone fragments (Scheme 19).^[52]

2.1.4. Glycine-Dependent Aldolases

The glycine-dependent aldolases (Scheme 20) catalyze the reversible condensation of glycine with an aldehyde acceptor to form a β -hydroxy- α -amino acid. These enzymes have been used extensively for the resolution of racemic β -hydroxy- α -amino acids; however, only a few examples of their use in bond-forming reactions is known. L-Threonine aldolase was found to accept a broad range of substrates,^[53] but often



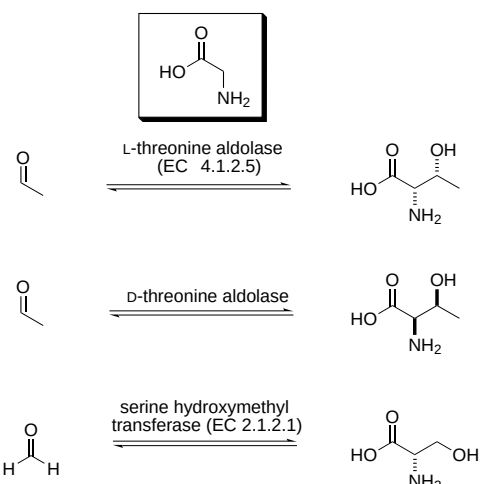
Scheme 18. a) DERA/RAMA-catalyzed tandem reaction. b) DERA/NeuAc aldolase catalyzed tandem reaction.



Scheme 19. DERA-catalyzed synthesis of key epothilone fragments. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

mixtures of *erythro* and *threo* products were formed, with the *erythro* product preferred (Table 2).

The use of hydroxyaldehydes gave complex mixtures of products as a result of interactions with free amino groups.



Scheme 20. Glycine-dependent aldolases and the reactions they catalyze.

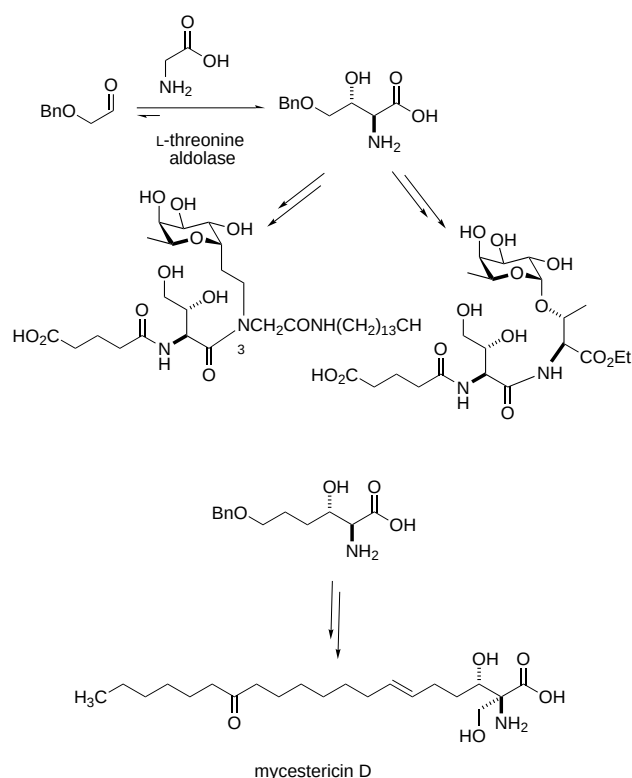
Table 2. L-Threonine aldolase catalyzed synthesis of L-β-hydroxy α-amino acids.

R	Yield [%]	<i>Erythro:threo</i>
CH ₃	38	93:7
Ph	87	60:40
N ₃ CH ₂	45–75	70:30 to 100:0
BnOCH ₂	78	92:8
BnOCH ₂ CH ₂	53	53:47
BnOCH ₂ CH ₂ CH ₂ OCH ₂	45	92:8
PhSCH ₂ CH ₂	80	50:50
	10	86:14

Protecting the hydroxyl group circumvented this problem. In general, heteroatom substitution in the α-position led to high *erythro:threo* ratios. As with the other types of aldolases, α,β-unsaturated aldehydes were not acceptor substrates; however, thiophenol-substituted aldehydes were accepted, which provided a potential route to unsaturated amino acids. The products resulting from the L-threonine aldolase catalyzed condensation of (benzyloxy)acetaldehyde and (benzyloxy)-butanal with glycine have been used in the synthesis of potent sialyl Le^x mimetics^[54a,b] and the immunosuppressant mycetericin D (Scheme 21).^[54c]

2.2. Catalytic Antibodies

In recent years catalytic-antibody technology has provided a method of developing new protein catalysts that catalyze a variety of reactions.^[55] In the past several years monoclonal antibodies elicited against a number of haptens designed to

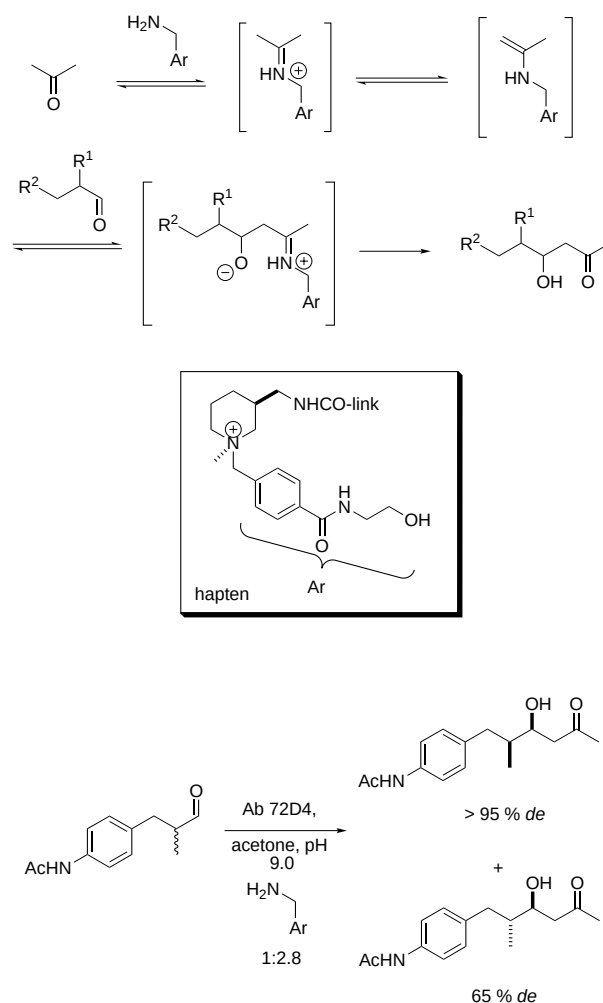


Scheme 21. L-Threonine aldolase route to sialyl Lewis^x mimetics. Bn = benzyl.

resemble the transition states of specific reactions have been shown to be capable of catalyzing those reactions with remarkable rate accelerations. By the appropriate design of the antigens, specific functional groups can be induced into the binding site of an antibody to perform general acid/base catalysis, nucleophilic/electrophilic catalysis, and catalysis by strain or proximity effects. To date, many new catalytic reactions, including those that are disfavorable or not attainable otherwise, or which have different reaction mechanisms or specificities compared to the corresponding enzymatic reactions, have been developed using the catalytic antibody approach. The antibodies are readily generated and prepared in large amounts. Aldolase catalytic antibodies developed recently have the ability to match the efficiency of the natural aldolases while accepting a more diverse range of substrates.

Initial progress in this area was made by developing antibodies that bind a primary amine cofactor as a mimic of the type I aldolases. The use of a designed hapten as a mimic of the transition state of the high-energy iminium ion resulted in the production of an antibody that catalyzed the aldol condensation of acetone and aldehyde acceptors (Scheme 22).^[56] Even though no stereochemical information was built into the transition-state mimic, the antibody catalyzed the stereoselective addition to the *si* face of the aldehyde.

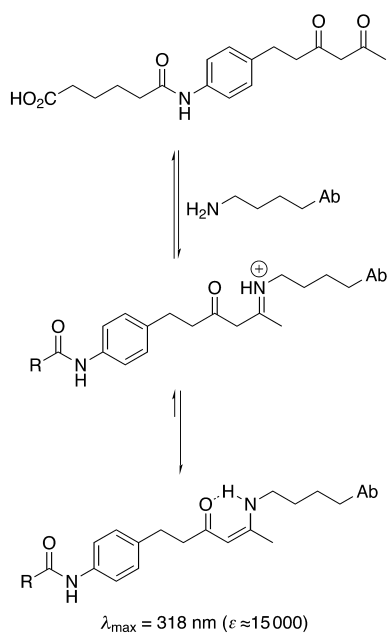
Further progress was made in this field with the development of the concept of reactive immunization.^[57, 58] Rather than raise antibodies against a hapten that mimics the transition state, the antibodies were raised against a β -diketone that serves as a chemical trap to imprint the lysine-



Scheme 22. Preparation of the first generation of catalytic antibodies with aldolase activity. Ab = antibody.

dependent type I aldolase mechanism in the active site (Scheme 23).^[59] The ϵ -amino group of a lysine side chain in the active site reacts with the β -diketone to give a β -ketoimine, which tautomerizes to the stable vinylogous amide. The formation of the vinylogous amide can be monitored by UV spectroscopy. By using this method two catalytic antibodies with aldolase selectivity, 38C2 and 33F12, were found and subsequently shown to have remarkable scope.^[60] The structure of 33F12 has been determined and shown to have the Schiff base forming Lys residue buried in a hydrophobic pocket at the base of the binding site, which accounts for its lower pK_a value of 5.5 (Figure 3).^[59]

Unlike natural aldolases, the catalytic antibodies were found to accept a wide range of ketone donor substrates (Figure 4a). Small aliphatic ketones were well tolerated; however, mixtures of products resulted with unsymmetrical ketones from the reaction at both α -positions. α -Heteroatom-substituted ketones showed much higher levels of regioselectivity, with reaction occurring almost exclusively at the carbon atom bearing the heteroatom. Interestingly, the regiochemistry of the reaction of fluoroacetone is opposite to that observed with the natural aldolase DERA, thus providing a complementary approach.



Scheme 23. Preparation of catalytic antibodies with aldolase activity by the reactive immunization approach.

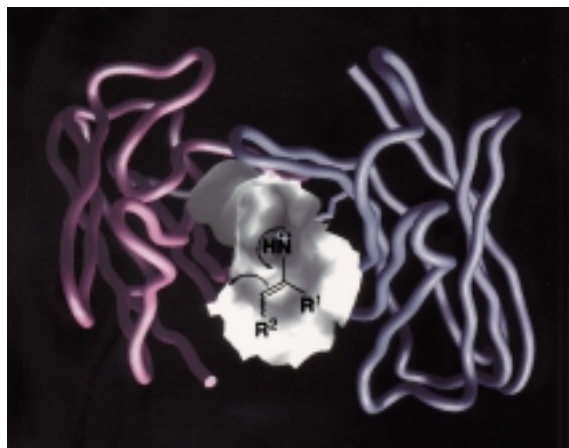


Figure 3. Spatial representation of the binding pocket of the Fab fragment of the catalytic antibody 33F12. The nucleophilic Lys¹⁹³ residue is found at the bottom of the hydrophobic environment.

A wide variety of aldehydes serve as acceptors (Figure 4b). In addition to aldehyde acceptors that resemble the hapten used to generate the antibody, simple aliphatic aldehydes are well tolerated. Polyhydroxylated aldehydes, such as glycer-aldehyde, glucose, and ribose, were not substrates, most likely because of the hydrophobic nature of the active site. In contrast to the natural aldolases, aromatic and α,β -unsaturated aldehydes are excellent substrates.

The stereochemistry of the addition is donor dependent. When acetone is used as the donor substrate, addition occurs from the *si* face of the carbonyl group; with hydroxyacetone, addition occurs from the *re* face. The stereoselectivity is generally quite high, with *ee* values greater than 99% commonly observed. As a general rule, high enantioselectivity is observed with acceptors having an sp^2 center in the α -position. Somewhat lower enantioselectivities result from acceptors with an sp^3 center in the α -position.

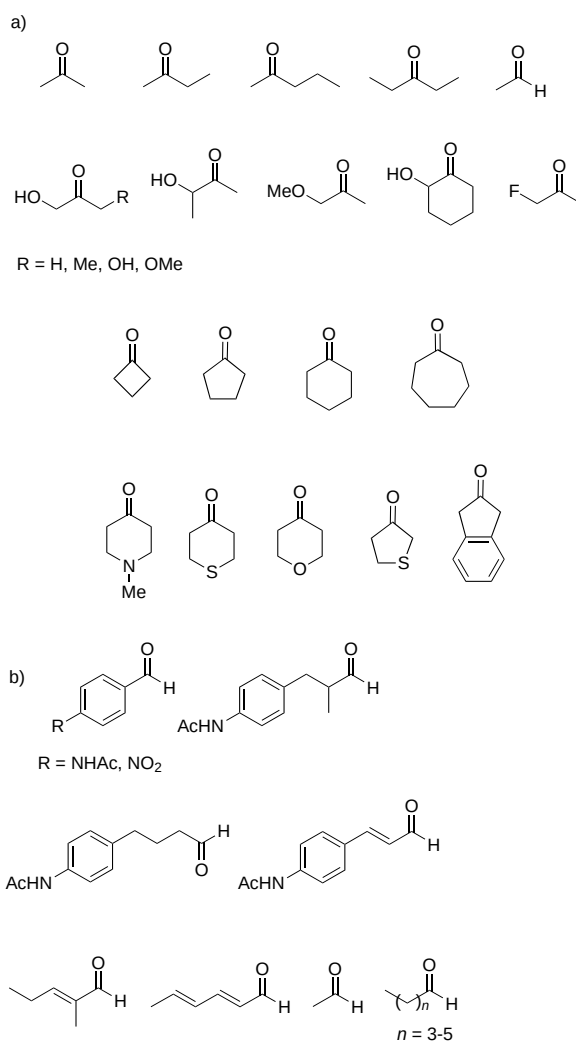
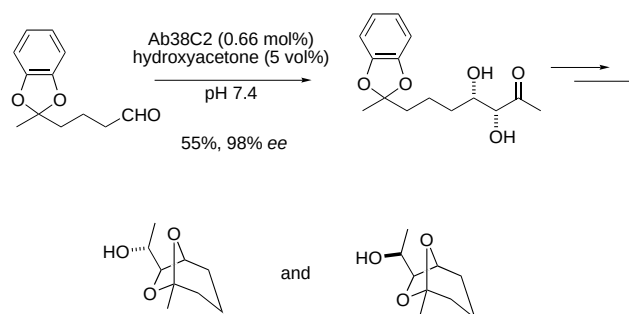
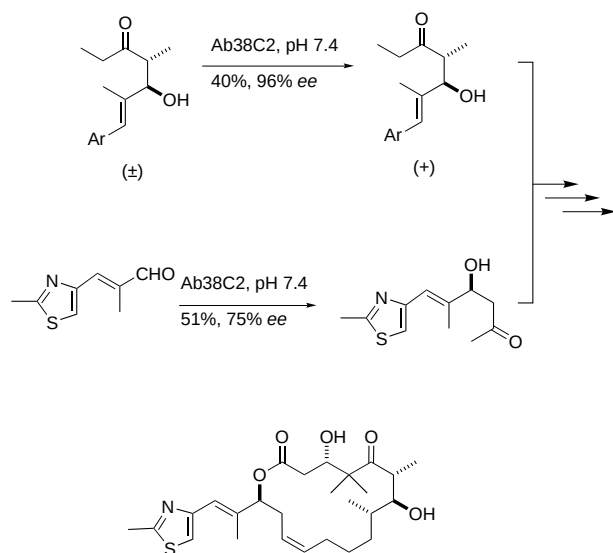


Figure 4. a) Donors and b) acceptors suitable as substrates for the catalytic antibodies with aldolase activity.

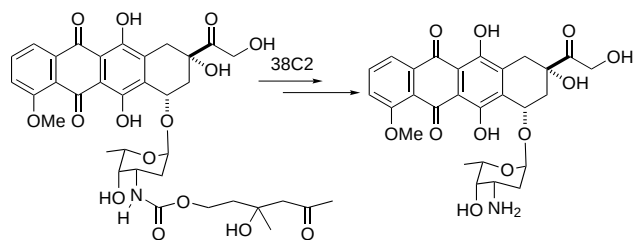
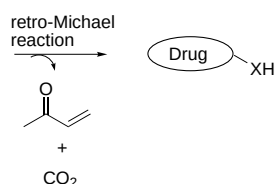
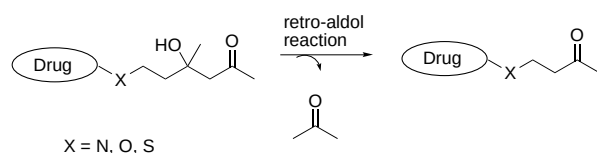
The utility of this method was demonstrated with the antibody-catalyzed aldolase approach to the brevicomins^[61] (Scheme 24) and the epothilones^[62] (Scheme 25). Antibody Ab38C2 is commercially available and has recently been used as a catalyst to activate prodrugs.^[63] Generic, drug-masking groups can be selectively removed by sequential retro-aldol and retro-Michael reactions catalyzed by 38C2 (Scheme 26). The antibody was also used in the enantioselective retro-aldol reaction of tertiary aldols containing structurally varied



Scheme 24. Antibody-catalyzed approach to the brevicomins.

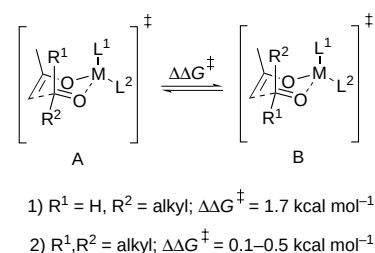


Scheme 25. Antibody-catalyzed approach to the epothilones.

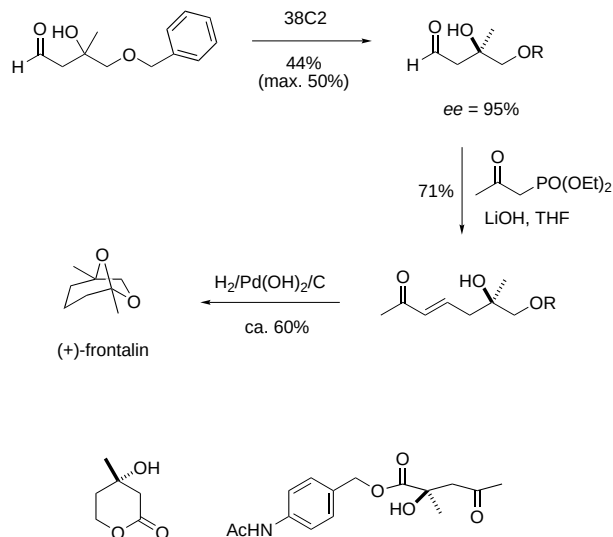


Scheme 26. Top: prodrug activation by a sequential retro-aldol and retro-Michael reaction. Bottom: doxorubicin prodrug activation by antibody 38C2.

heteroatom-substituted quaternary carbon centers^[64] to give enantiomerically enriched tertiary aldols, most with *ee* values greater than 95%. Synthesis of enantiomerically pure tertiary aldols using the catalytic asymmetric aldol reaction with ketone acceptors represents a significant challenge as the energy difference between the diastereomeric transition states complexed with a small ligand is relatively low (<0.5 kcal mol⁻¹) compared to the aldehyde acceptor case ($\Delta\Delta G^\ddagger \approx 1.7$ kcal mol⁻¹; Scheme 27). Several tertiary aldols prepared in this study have been used in the synthesis of (+)-frontalin, the side chain of saframycin H, and mevalonolactone (Scheme 28).



Scheme 27. Proposed diastereomeric transition states in the synthesis of a tertiary aldol.



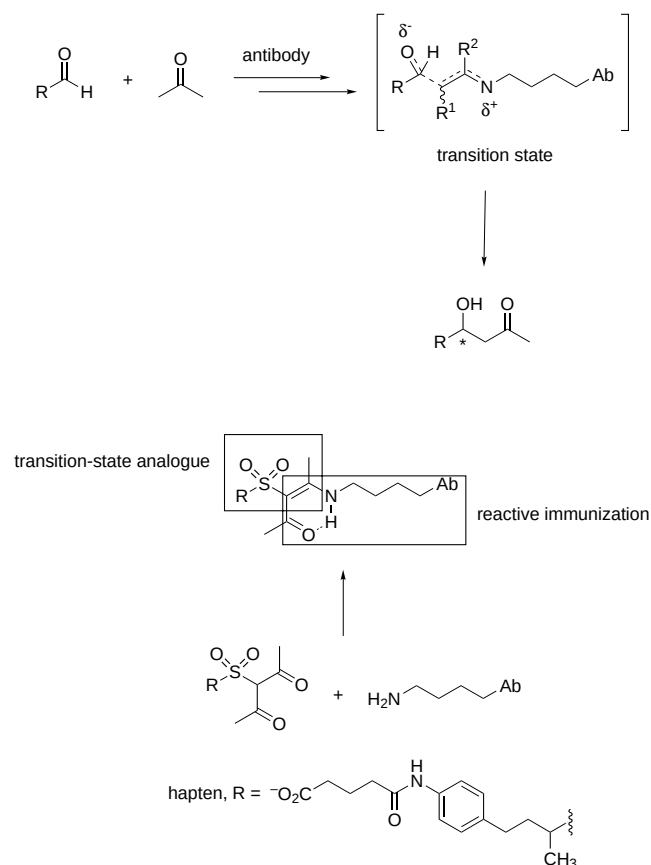
Scheme 28. Representative example of the synthesis of tertiary aldols using the catalytic antibody 38C2.

In order to further increase the repertoire and efficiency of the aldol reaction and to develop antibodies with complementary enantioselectivity, a β -diketone sulfone was used as the hapten^[65] (Scheme 29). The tetrahedral geometry of the sulfone moiety in this hapten mimics the rate-determining, tetrahedral transition state of the C–C bond forming reaction and is thus expected to facilitate nucleophilic attack of the enaminone intermediate on the acceptor aldehyde. It was indeed demonstrated that more catalytic antibodies with a broad scope of reactions can be generated by using this approach. In addition, antibody 93F3 generated in this study was more efficient ($k_{\text{cat}} \approx 3$ min⁻¹) than and enantioselective to 38C2, providing the unreacted (*S*)-aldol with $>96\%$ *ee*.

The mechanism-based approach to eliciting catalytic antibodies combined with the rapid, immune-selection process as illustrated in these studies provides a new exciting direction for catalyst design and development.

3. Chemical Methods

The search for simple catalysts that mimic the selectivity of biochemical methods yet offer more general substrate acceptance has been the subject of intense research in recent years.^[66] Several excellent methods have been developed and



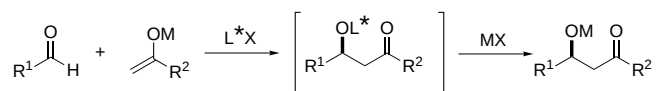
Scheme 29. Use of a β -diketone sulfone as a hapten to elicit catalytic antibodies.

for the purposes of this review, they will be grouped into the following categories: 1) activation of the acceptor; 2) activation of the donor; 3) simultaneous activation of the donor and acceptor.

3.1. Acceptor Activation

The catalytic activation of the acceptor aldehyde toward the addition of a silyl enol ether, commonly referred to as the Mukaiyama reaction,^[67] has been a particularly successful means of performing aldol reactions. Since the initial discovery^[68] that chiral Lewis acids promote enantioselective addition to the activated aldehyde partner, steady improvements have been realized.

Mechanistically, the catalyst coordinates to the aldehyde creating an asymmetric environment, which is then attacked by an enolate species from the less-hindered face to produce the aldol adduct. As shown in Scheme 30, an important exchange reaction between L^* and M must then occur to



L^* = chiral Lewis acid, M = metal

Scheme 30. The Mukaiyama reaction.

regenerate the catalyst and for this reason the proper choice of L^* is very important. A successful catalyst must coordinate strongly enough with the oxygen atom of the acceptor aldehyde to form a tight transition state for effective transfer of chirality and at the same time not form such a strong bond with the resulting alkoxide that turnover does not occur. A second common problem that must be overcome is the generation of M^+ ,^[69] which may also catalyze the reaction through an achiral pathway and lead to decreased enantioselectivities. A number of systems have been developed using both metallic and nonmetallic Lewis acids to address these issues.

3.1.1. Tin Complexes

The first successful catalytic asymmetric Mukaiyama reactions were achieved with tin(II) complexes.^[70] The catalysts are prepared in situ from the addition of tin(II) triflate (triflate = Tf = trifluoromethanesulfonate) to a chiral diamine derived from L-proline. Figure 5 shows the more successful diamines.

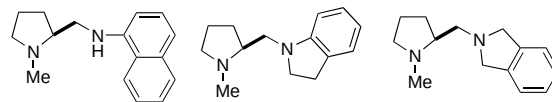
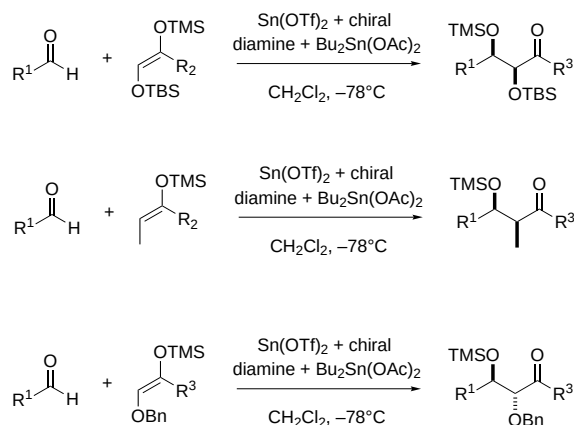


Figure 5. Chiral diamines used in the preparation of Sn(II) complexes that act as catalysts in the asymmetric Mukaiyama-aldol reaction.

The reaction between aldehydes and ketene silyl acetals prepared from either esters or thioesters is highly enantioselective with *ee* values usually greater than 98%. A cofactor, such as dibutyltin diacetate,^[71] is required for high levels of enantioselectivity. The cofactor has an affinity for silicon and presumably serves to connect the silyl enolate with the promoter,^[72] which leads to a tighter transition state and more effective transfer of chirality. NMR studies have shown that there is no metal exchange from silicon to tin in the silyl enol ether, which implies that the reaction does not proceed through a tin enolate.^[73]

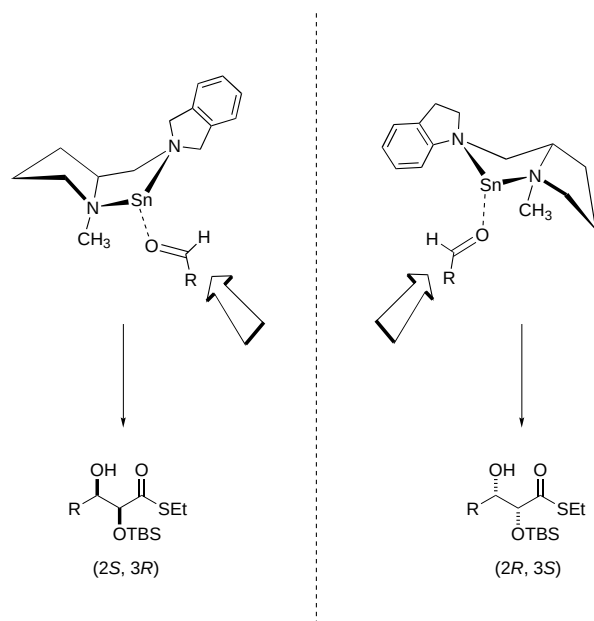
Both *syn* and *anti* diol products are possible with the proper choice of ketene silyl acetal (Scheme 31). Noncoordinating α -



Scheme 31. Tin(II)-catalyzed asymmetric Mukaiyama-aldol reaction. TMS = trimethylsilyl.

substituents, such as alkyl and *tert*-butyldimethylsiloxy, are stereoselectively converted into the *syn* products. Coordinating substituents, for example an α -benzyloxy group, coordinate to the tin and lead to the formation of *anti* products.^[74] A wide range of aldehydes can be used: aliphatic, aromatic, and α,β -unsaturated aldehydes all afford products in high yield and with high levels of enantioselectivity.

The origin of the selectivity arises from the conformation of the tin(II)-diamine complex, which adopts a bicyclo[3.3.0]octane-like structure (Scheme 32).^[75] The absolute configuration of the reaction can be controlled by the appropriate



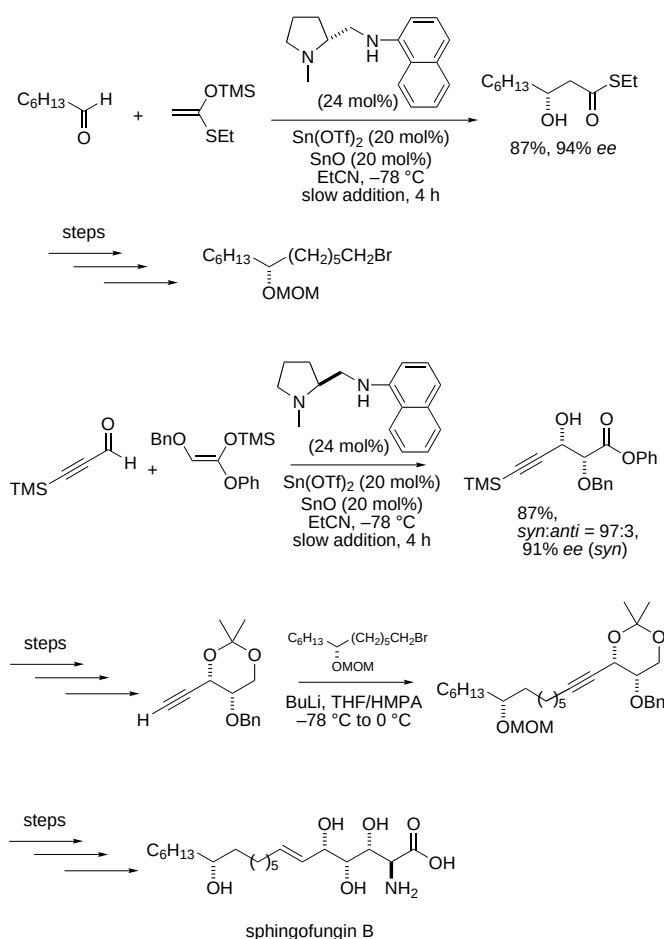
Scheme 32. Both enantiomers formed from catalysts derived from L-proline.

choice of chiral diamine. Remarkably, simply changing the point of attachment of a benzene ring leads to a complete reversal of configuration.^[73] By changing the conformation of the catalyst the indoline and isoindoline groups provide pseudo-enantiotopic transition states (Scheme 32) and thus opposite stereoisomers. This catalyst system was successfully employed as a key step in the total synthesis of the antifungal sphingofungin natural products (Scheme 33)^[76a] and febrifugine/isofebrifugine with antimalarial activity.^[76b]

3.1.2. Titanium Complexes

Considerable attention has been paid to titanium(IV) catalysts for the asymmetric Mukaiyama aldol reaction.^[69, 77–81] The most successful catalysts are derived from a titanium(IV) source and an (*R*)- or (*S*)-BINOL-type ligand (Figure 6), although some effort has been devoted to examining the effects of other ligands.^[69, 74]

The simple BINOL catalysts are effective catalysts for the aldol reaction of aldehydes and ketene silyl acetals of thioesters (Scheme 34).^[78, 81] Aromatic, aliphatic, α,β -unsaturated, α -heteroatom substituted, and α -branched aldehydes are all well tolerated, and afford the corresponding aldol



Scheme 33. Chiral tin(II)-diamine-catalyzed aldol addition approach to the sphingofungins. HMPA = hexamethyl phosphoramide.

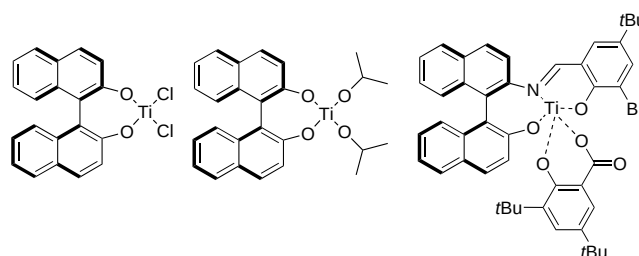
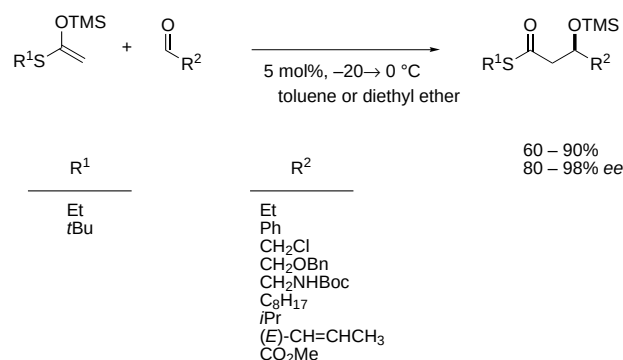
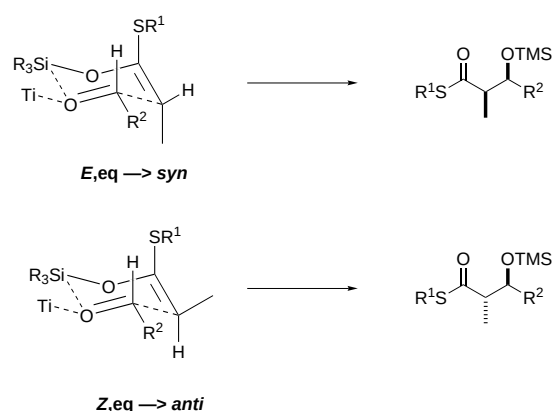


Figure 6. Titanium catalysts used successfully in the asymmetric Mukaiyama-aldol reaction.



Scheme 34. BINOL-titanium(IV)-catalyzed aldol reaction. Boc = *tert*-butoxycarbonyl.

adducts in good to excellent yields. Several factors contribute to the generally excellent enantioselectivity (up to 98% *ee*). The size of the group on the sulfur atom of the thioester-derived ketene silyl acetal is important: the larger *tert*-butyl group results in higher *ee* values than the smaller ethyl group.^[81] Enantiofacial selectivity is influenced by the polarity of the solvent: the selectivity being enhanced in the toluene than the more polar solvents dichloromethane, propionitrile, and nitroethane.^[81] However, diethyl ether also appears to be a good solvent in some cases.^[78] Enantiofacial selectivity is quite predictable, with the (*R*)-BINOL catalyst generally affording the *R*-configured product and the (*S*)-BINOL catalyst the *S*-configured product. With α -substituted ketene silyl acetals the relative configuration of the product is influenced by the olefin geometry: *E* isomers lead to *syn* products and *Z* isomers to *anti* products. A cyclic transition state model can be used to explain the stereospecificity (Scheme 35).^[81]

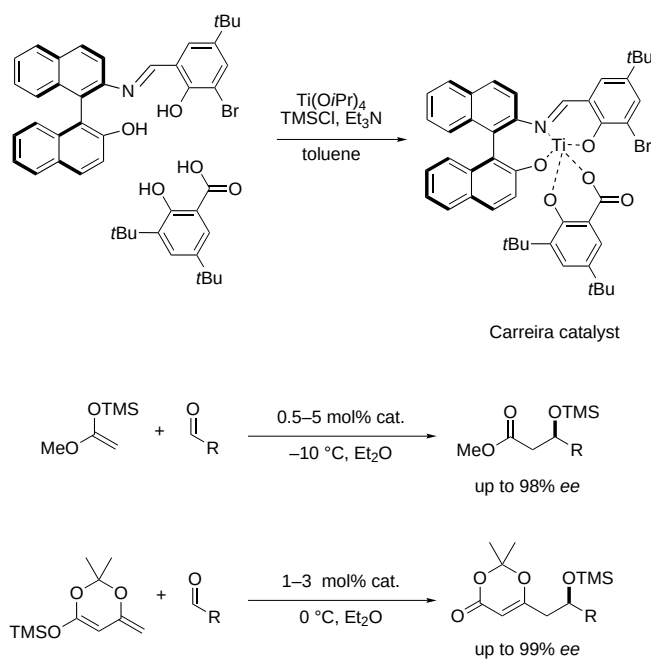


Scheme 35. Model of the silatropic ene transition state.

Further improvement was made with the Carreira catalyst,^[80] which is prepared in situ by combining the tridentate ligand derived from BINOL, $\text{Ti}(\text{O}i\text{Pr})_4$, and salicylic acid in the presence of trimethylsilyl chloride and triethyl amine (Scheme 36). This titanium species catalyzes the aldol reaction of a wide variety of aldehydes with ketene silyl acetals derived from esters and silyl dienolates.^[82a] The reactions can be performed with as little as 0.5 mol % of catalyst at -20°C . The salicylic acid probably serves to trap and transfer “ Me_3Si^+ ”, which is known to catalyze the reaction through an achiral pathway,^[69] and thereby improves the enantioselectivity of the reaction.

The reaction of ketene silyl acetals derived from esters affords β -hydroxy ester products in high yields and up to 98% *ee* (Scheme 36). Aliphatic, aromatic, and unsaturated aldehydes are excellent substrates, with alkenyl and alkynal aldehydes being particularly good substrates. The silyl dienolate is an excellent donor substrate and results in the formation of acetoacetate adducts, also in high yield and enantioselectivity.^[82a] This catalyst has been used in the synthesis of antibiotics such as macrolactin A^[82b] and roflamycin.^[82c]

Solvent choice is an important consideration. The reaction is generally conducted in a nonpolar solvent such as toluene or

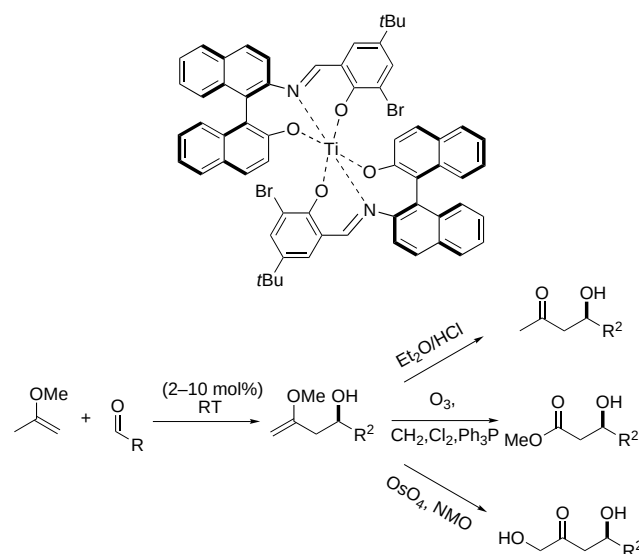


R = alkyl, alkenyl, alkynyl, phenyl

Scheme 36. Top: Preparation of the Carreira catalyst. Bottom: Reactions performed with the Carreira catalyst.

benzene to reduce the possibility of producing “ Me_3Si^+ ”, although high enantioselectivity is also observed in diethyl ether. Polar aprotic solvents such as dichloromethane and tetrahydrofuran, which favor the formation of “ Me_3Si^+ ”, result in a significant loss of enantioselectivity.

A similar catalyst derived from two equivalents of tridentate ligand in the presence of a hindered amine base catalyzes the aldol reaction of the commercially available 2-methoxypropene with a wide variety of aldehydes in 79–99% yields and up to 99% *ee* (Scheme 37).^[83] Upon acid workup, β -hydroxyketone adducts are isolated. In the absence of an acid

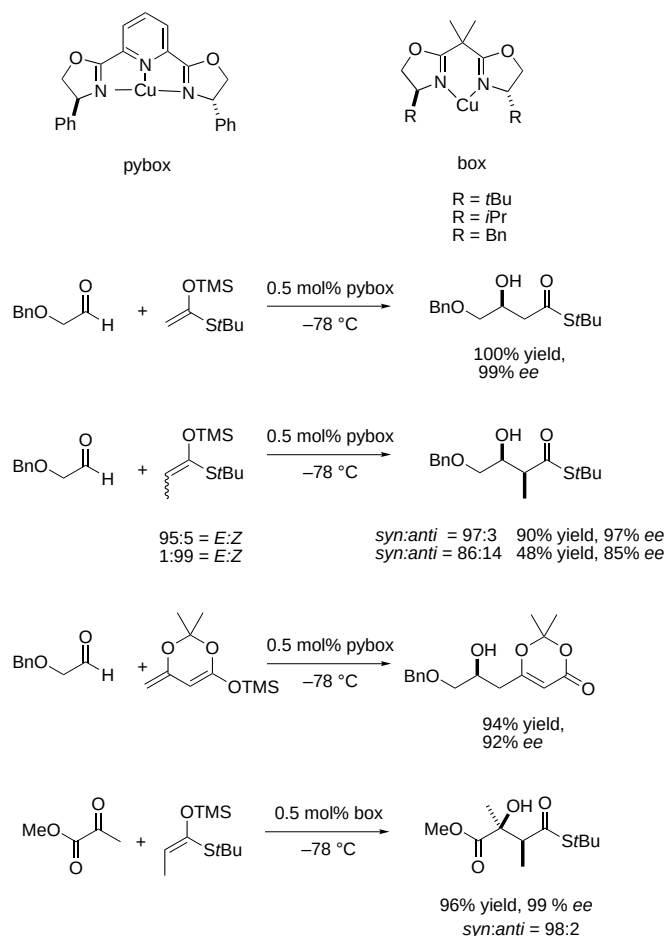


Scheme 37. Titanium-catalyzed asymmetric aldol reaction with 2-methoxypropene. The titanium catalyst is shown at the top. NMO = 4-methylmorpholine *N*-oxide.

workup, the vinyl ether intermediate can be isolated and further converted into a number of useful products.

3.1.3. Copper Complexes

Bis(oxazolinyl)copper(II) complexes have been shown to be effective chiral Lewis acid catalysts for the Mukaiyama aldol reaction of ketene silyl acetals (Scheme 38).^[84, 85] Acceptor aldehydes with α -substitution capable of chelation are required; α -benzyloxyaldehydes and pyruvate esters are very good substrates and afford the corresponding aldol adducts in very high yield (85–100%) with excellent enantiofacial selectivity (92–99% *ee*). The reaction with pyruvate esters provides an important method for the preparation of a tertiary alcohol.



Scheme 38. Copper-catalyzed asymmetric aldol reaction.

A five-membered chelate is essential; the reaction with β -(benzyloxy)propionaldehyde gives a racemic product. ESR studies reveal a square pyramidal catalyst–aldehyde complex.^[84a] Two modes of binding are possible for the aldehyde: the stronger binding position lies in the plane of the ligands, and the weaker binding site in the axial configuration, which leads to a single mode of coordination of the substrate (Figure 7). Attack of the donor enolate occurs from the less sterically hindered *si* face.

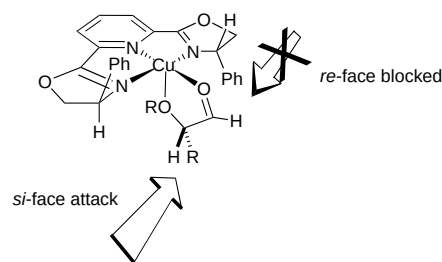


Figure 7. Complex formed between the copper catalyst and the aldehyde.

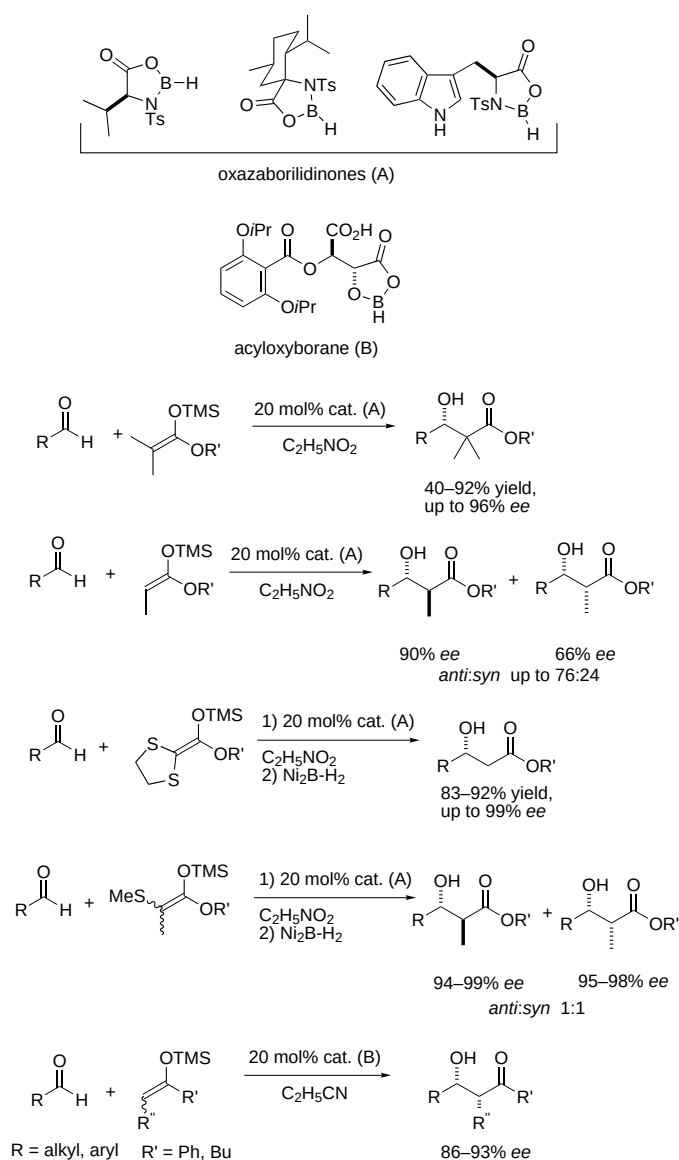
Both (*E*)- and (*Z*)- α -substituted ketene silyl acetals afford predominantly the *syn* adducts, but a significant reduction in both yield and facial selectivity is observed with the *E* isomer.^[84a, 85] The BINAP–copper(II) complex developed by Carreira has been investigated mechanistically^[86a] and applied to the synthesis of the polyol fragment of amphotericin.^[86b] Remarkably, replacing Cu^{II} with Sn^{II} in the complex resulted in the highly selective formation of the *anti* adducts in the reaction with methyl pyruvate (*anti*:*syn* up to 99:1; up to 99% *ee*).^[87] Recently, the copper(II) system complexed with bis(oxazoline) was shown to function in aqueous systems such as water and water/alcohol, although the enantiofacial selectivity and efficiency are lower than that in aprotic solvents.^[85]

3.1.4. Boron Complexes

Achiral boron catalysts such as dibutylboron triflate (Bu₂BOTf)^[88] were used in the synthesis of the anticancer agent althohyrtin C. Chiral boron catalysts, such as chiral oxazaborolidinones^[89–91] and chiral (acyloxy)boranes,^[92] have been used to catalyze the asymmetric aldol condensation of aldehydes with ketene silyl acetals and silyl enol ethers (Scheme 39). Both catalysts are prepared by simple addition of borane to either α -amino acids or tartaric acid derivatives. The reaction catalyzed by boranes derived from (*S*)-amino acids and natural tartrate lead to (*R*)-aldol adducts. Recently, a polymer-supported chiral oxazaborolidinone was described that demonstrated lower levels of enantioselectivity.^[93]

In the reaction with ketene silyl acetals, α -substitution is important for high levels of enantioselectivity. The dimethyl- and monomethyl-substituted ketene silyl acetals are highly effective donors. With oxazaborolidinone catalysts, monosubstituted ketene silyl acetals give predominantly the *anti* products, but the enantioselectivity is somewhat lower. In contrast, the (acyloxy)boranes are highly *re*-face-selective on the aldehyde and *syn*-selective on the product in the reaction of silyl enol ethers, regardless of the starting enol geometry.

The parent unsubstituted ketene silyl acetal leads to products with greatly decreased enantioselectivity. To circumvent this problem, sulfur substituents can be introduced to provide the steric bulk required for high levels of enantioselectivity, then removed with a nickel borohydride reagent to provide the corresponding products in high yield and enantioselectivity. This approach has been used quite successfully in a short asymmetric synthesis of a portion of bryostatin.^[94] A similar reaction can be accomplished with sulfur-substituted

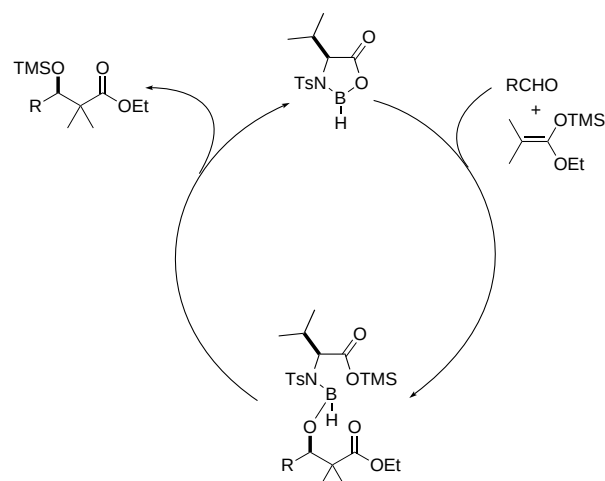


Scheme 39. Oxazaborolidinone-catalyzed asymmetric aldol reaction. $\text{Ni}_2\text{B-H}_2$ = nickel borahydride, Ts = toluene-4-sulfonyl.

propionate ketene silyl acetal. Both *syn*- and *anti*-aldol adducts are obtained with excellent enantioselectivity. However, a 1:1 *syn:anti* ratio results from a scrambling of the C2 stereochemistry during the radical desulfurization.

The tryptophan-derived oxazaborolidinone^[90] performs best with terminal trimethylsilyl enol ethers derived from methyl ketones and a range of aldehydes to afford β -hydroxyketone products with high enantiomeric excess. Ketene silyl acetals react with poor enantioselectivities using this catalyst.

Mechanistically, an intramolecular B–Si exchange transfer involving the ligand may facilitate the important silicon transfer (Scheme 40). The metal affinity between aldehyde, enolate, and chiral ligand will thus affect catalyst turnover. The enantioselectivity can be explained by invoking a conformation of the aldehyde bound to the oxazaborolidinone that is fixed by a hydrogen-bonding interaction between the Lewis acid and the aldehyde (Figure 8).^[95]



Scheme 40. Proposed mechanism for the oxazaborolidinone-catalyzed aldol reaction.

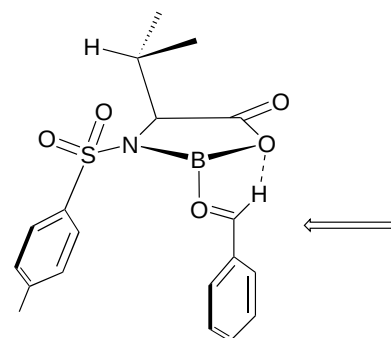
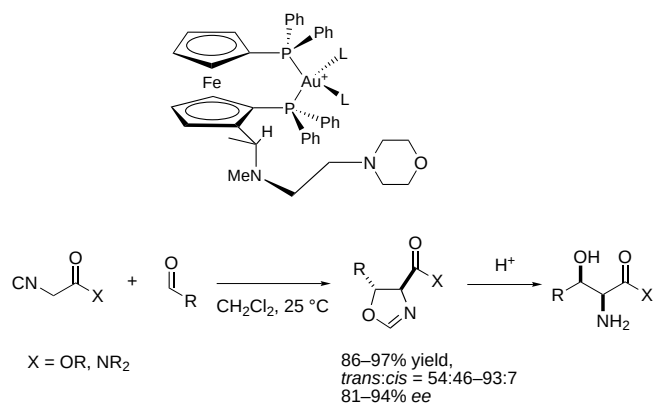


Figure 8. Three-dimensional structure of the aldehyde–oxazaborolidinone complex.

3.1.5. Gold and Silver Complexes

The first example of a catalytic asymmetric aldol reaction was the gold(i)-catalyzed reaction of an α -isocyanoacetate and an aldehyde reported in 1986.^[96] The reaction is both diastereo- and enantioselective and gives *trans*-oxazolines with excellent enantioselectivities. These oxazolines can be converted into the corresponding *syn*- β -hydroxy- α -amino acids^[97a] by hydrolysis (Scheme 41).



Scheme 41. Gold(i)-catalyzed reaction of α -isocyanoacetates or -amides with aldehydes.

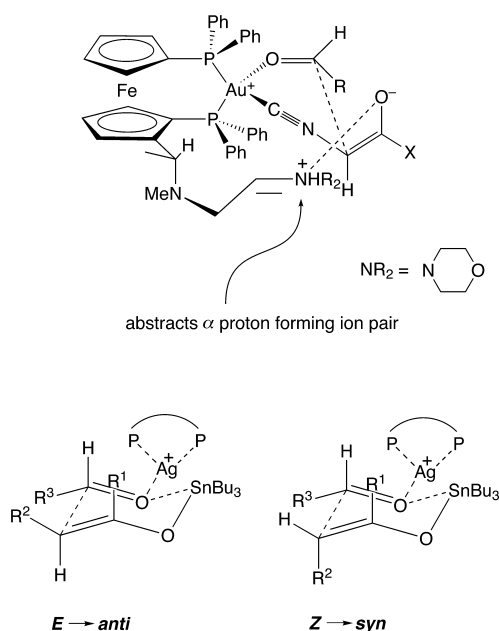


Figure 9. Proposed structure of the transition state of gold- and silver-catalyzed aldol reactions.

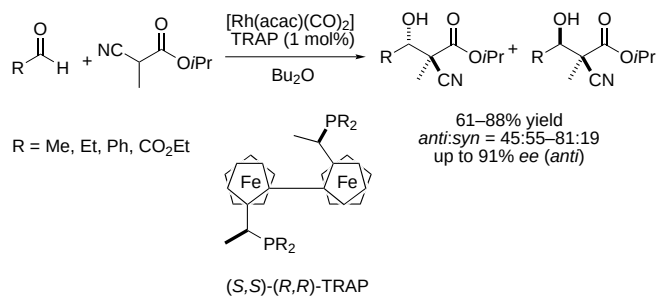
The high selectivity has been explained by a proposed transition state structure,^[97b] where the terminal amino group abstracts one of the active methylene hydrogen atoms of the gold-coordinated isocyanoacetate derivative to form an ion pair between the enolate anion and the ammonium cation. The amine sidearm is important for high levels of enantioselectivity. The aldehyde binds to the gold center away from the sidearm (Figure 9). The aldol adduct immediately cyclizes to the oxazoline, which no longer coordinates to the gold center, thereby regenerating the catalyst. This catalytic system can also be considered as one in which both donors and acceptors are activated. A representative BINAP/AgOTf catalyst system reported by Yamamoto^[98] for the reaction of tin enolates with aldehydes suggests that Ag is another effective metal Lewis acid catalyst. Transition-state models have been used to explain the *anti* selectivity from the (*E*)-enolate and the *syn* selectivity from the (*Z*)-enolate (Figure 9).

3.2. Donor Activation

Catalytic activation of the donor rather than the acceptor provides an alternative to the asymmetric Mukaiyama aldol reaction. Numerous approaches have been developed that incorporate a variety of catalysts from organometallic reagents to phosphoramidate Lewis bases.

3.2.1. Rhodium Complexes

A rhodium-catalyzed asymmetric aldol reaction was described recently.^[99] A rhodium(I) complex coordinated with the *trans*-chelating chiral diphosphane TRAP promotes the enantioselective condensation of α -cyanopropionates with aldehydes (Scheme 42). Bulky esters are required for high levels of enantioselectivity. The enantioselectivity is also



Scheme 42. Rhodium(I)-TRAP-catalyzed reaction of α -cyanocarboxylates or -amides with aldehydes.

dependent upon the choice of acceptor aldehyde. Simple aliphatic aldehydes afford products with modest to good enantioselectivities (up to 86% *ee*), while glyoxaldehyde results in the highest level of selectivity (91% *ee*). The *anti* isomers are generally formed preferentially, suggesting an open, anti-periplanar transition state (Figure 10).

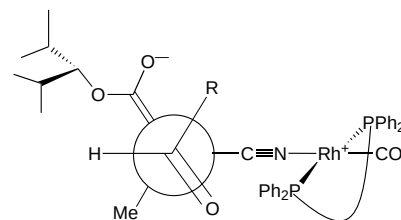
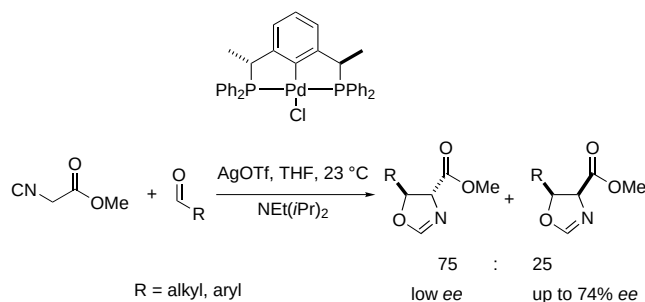


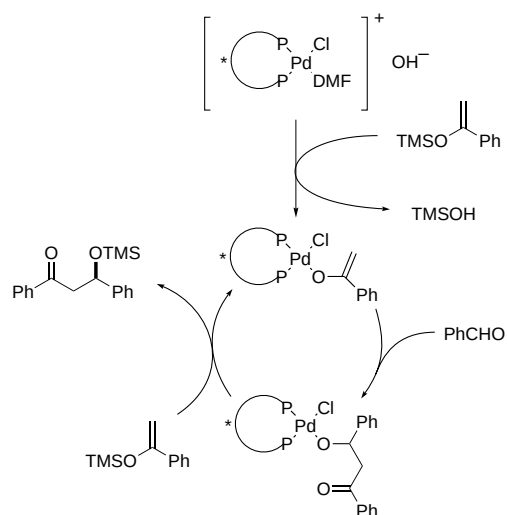
Figure 10. Proposed transition state of rhodium-TRAP-catalyzed aldol condensation of α -cyanoaldehydes.

3.2.2. Palladium Complexes

Palladium catalysts have shown an unsurpassed degree of flexibility in the reactions they catalyze. Two catalyst systems have been recently developed which catalyze the asymmetric aldol condensation. A palladium(II) complex with chiral PCP-type tridentate ligands has been shown to catalyze the asymmetric aldol condensation between methyl isocyanoacetate and aldehydes^[100] (Scheme 43). Similar to the gold(I) catalyst, the reaction produces predominantly the *trans*-oxazoline; however, in contrast to the gold catalyst the *cis* isomer is formed in higher *ee* values (up to 74%). The deeper chiral pocket of the chiral PCP-type ligands effects the enantioselective bond formation without the need for the pendent amine that is required for the gold catalyst. Both aromatic and alkyl aldehydes were examined, with higher enantioselectivities observed with aliphatic aldehydes.

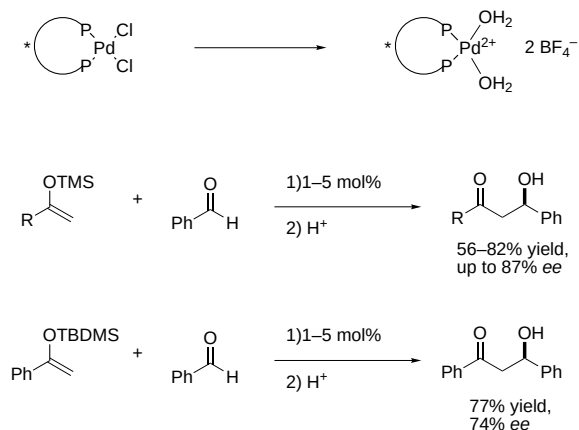


Scheme 43. PCP-Pd^{II}-catalyzed asymmetric aldol reaction.



Scheme 44. Pd^{II}-catalyzed asymmetric aldol reaction by formation of a Pd^{II}-enolate.

A second catalyst system based on palladium was described which proceeds through formation of a transition metal enolate (Scheme 44).^[101a] The mechanism is similar to that of the achiral rhodium(i) complex studied extensively by Bergman, Heathcock, and Slough.^[102] A dichloropalladium(II) complex with BINAP catalyzed the aldol condensation of silyl enol ethers derived from ketones with aldehydes. The reaction produces, after hydrolysis of the intermediate silyl ether, β -hydroxyketones in excellent yields and up to 78% *ee*. The air- and moisture-stable diaquapalladium(II)–BINAP complex, prepared from the dichloro complex, was shown to effect the same transformation with *ee* values up to 87% (Scheme 45). Of particular importance is the ability of this catalyst to activate *tert*-butyldimethylsilyl enol ethers, which are less susceptible to hydrolysis and therefore easier to purify and isolate. The X-ray crystal structure of the catalyst has been determined.^[101b]



Scheme 45. Pd^{II}-catalyzed asymmetric aldol reaction.

3.2.3. Phosphoramides

In contrast to the organometallic reagents described above, phosphoramides act as Lewis bases to catalyze the aldol reaction by coordinating temporarily to the electrophilic

silicon atom of trichlorosilyl enolates, thus generating a strongly activated donor which reacts with a variety of aldehydes (Figure 11). In this process, the silicon center is able to expand its valence by two to coordinate both the aldehyde and the chiral ligand. In addition to silicon, tin, titanium, zirconium, and aluminum also possess such valence expansion properties. The ligand used in such a process should not be too nucleophilic to affect cleavage of the O–Si bond.^[103] This effect was first noticed with hexamethyl phosphoramide (HMPA), which was found to catalytically accelerate the aldol reaction.^[103] Chiral phosphoramides have been used successfully to afford aldol adducts in excellent yields with a high degree of enantioselectivity (up to 97% *ee*) (Scheme 46).^[103, 104] The diphenyl-substituted catalyst was found to give the optimal results.

The phosphoramidate-catalyzed reaction of (*E*)-enolates affords mostly *anti*-aldol adducts (*anti:syn* ratio up to >99:1), which is in sharp contrast to the uncatalyzed reaction, where

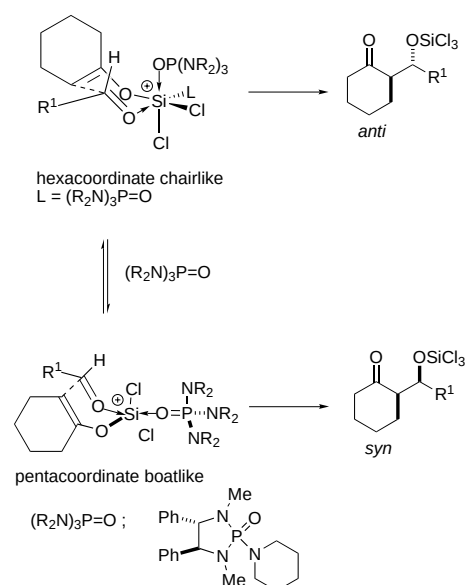
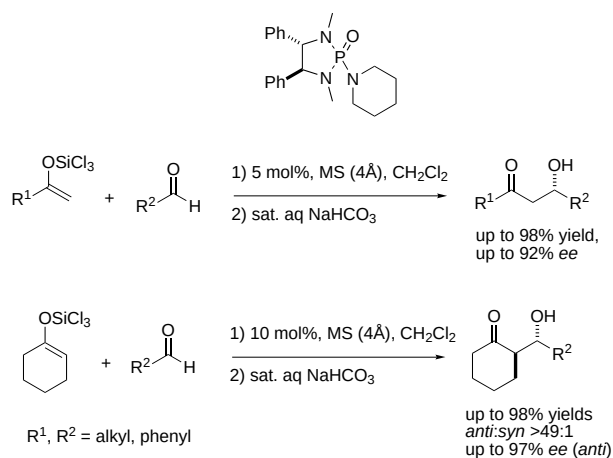


Figure 11. Proposed phosphoramidate-mediated activation of trichlorosilylenolates. The chairlike hexacoordinate transition state gave the *anti* product, while the boatlike pentacoordinate transition state gave the *syn* product.



Scheme 46. Phosphoramidate-catalyzed asymmetric aldol reaction. MS = molecular sieves.

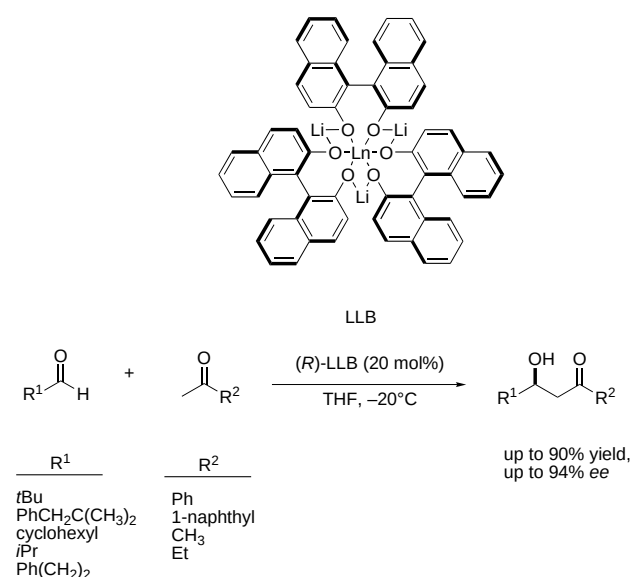
the *syn* isomer is the major product. It has been proposed that only the *anti* diastereomer proceeds through the hexacoordinate chairlike siliconate species coordinated to two chiral ligands.^[105] The *syn* product arises from the pentacoordinate boat transition state with one chiral ligand (Figure 11).^[105b] Further structural studies on the chiral ligand complexed with tin and benzaldehyde reveal a torsion around the P–N(piperidinyl) bond, which provides some insights into the origin of selectivity.^[105c]

Simple alkyl- and aryl-substituted donor trichlorosilyl enol ethers and acceptor aldehydes function well in the reaction. More electron-rich aldehyde acceptors form a tighter transition structure, which leads to higher enantio- and diastereoselectivities.^[105] The slow addition of aldehyde is crucial for high levels of diastereoselectivity.

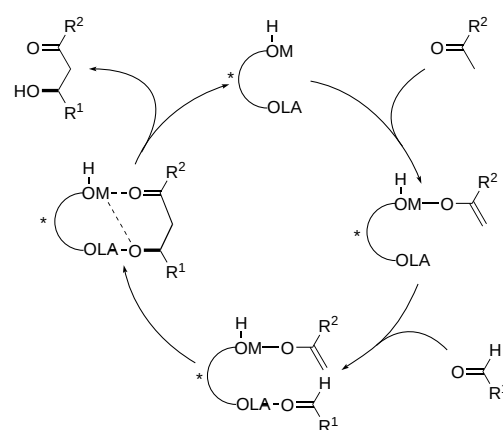
3.3. Activation of Both Donor and Acceptor (Bifunctional Catalysts)

While catalytic activation of aldehyde acceptors by chiral Lewis acids has achieved great success in the asymmetric aldol condensation, pre-conversion of the donor to a more reactive species such as enol silyl ether, enol methyl ether, or ketene silyl acetal is a necessity. Two catalysts have been developed that mimic the mechanism of the type II aldolases, where both Lewis acidic and Brønsted basic sites participate in the reaction, which catalyze the reaction of unmodified ketones with aldehydes.

The multifunctional catalyst LLB catalyzes the direct transformation of aldehydes and ketones to aldol adducts (Scheme 47).^[106] The catalyst incorporates a central lanthanum atom, which serves as a Lewis acid, and a lithium binaphthoxide moiety, which serves as a Brønsted base. The reaction is speculated to proceed through the mechanism shown in Scheme 48. The synergistic effect of both functionalities allows the reaction to proceed without the need for any other activation of the starting materials. The reaction affords aldol adducts in good to excellent yields (45–90%) with



Scheme 47. LLB-catalyzed aldol condensation of ketones with aldehydes.

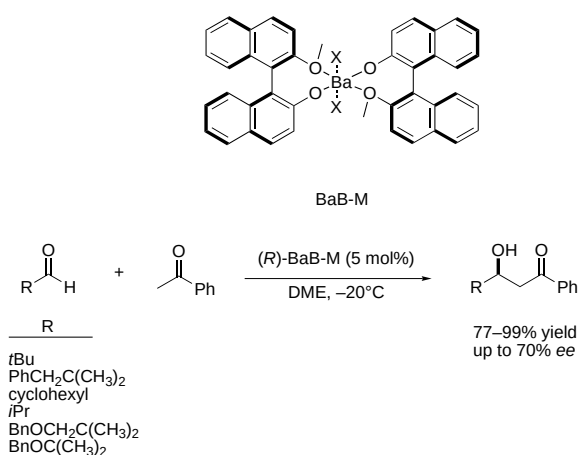


Scheme 48. Proposed mechanism of bifunctional catalysts. LA = Lewis acid, M = metal of the Brønsted base.

moderate to high levels of enantiomeric excess (up to 94% *ee*). Higher yields and *ee* values are observed when excess ketone is used.

A major shortcoming of this catalyst is the need for excess ketone and long reaction times. The catalytic activity of LLB can be enhanced by the addition of lithium hydroxide, which forms an LLB·LiOH heteropolymetallic complex.^[107] Recently, it was found that the addition of KOH (generated in situ from the reaction of potassium hexamethyldisilazane with water) results in a heteropolymetallic complex that rapidly promotes the aldol reaction when used in small amounts (3 mol %).^[108] Cyclopentanone can be used directly for a diastereoselective aldol reaction without modification. This catalyst has been used in the synthesis of key fragments for the synthesis of epothilone A and bryostatins.^[108] Mechanistic studies of the reaction suggest that deprotonation of the ketone is rate-determining and the water molecule may coordinate to La and K during the catalytic process.^[108]

A similar catalyst derived from barium phenoxide was developed to eliminate the shortcomings of the LLB catalyst (long reaction times, excess ketone).^[109] The catalyst, BaB-M, prepared from Ba(OiPr)₂ and BINOL-Me, effects the enantioselective aldol condensation of acetophenone and various aldehyde acceptors (Scheme 49). Reaction times are greatly



Scheme 49. BaB-M-catalyzed aldol condensation of ketones with aldehydes. DME = 1,2-dimethoxyethane.

reduced compared to those with the LLB catalyst. In addition to tertiary aldehydes, secondary aldehydes with acidic α -hydrogen atoms are suitable substrates and result in the cross-aldol condensation without the formation of self-aldol adducts. The enantioselectivities are currently modest (up to 70%), but there is great possibility for further improvement of this catalyst. Platinum–acyl complexes coordinated with BINAP or other phosphane ligands have been developed for the enantioselective aldol addition of ketene silyl acetals to aldehydes.^[110] The presence of oxygen and water during activation of the catalyst is required to achieve enantioselectivity.

4. Summary and Outlook

The progress toward efficient, selective, and predictable catalysts in the asymmetric aldol reaction has been astounding. While aldolases and catalytic antibodies can tolerate substrates with unprotected functional groups and perform the reaction in aqueous solution, the chemical aldol reactions work well in various organic solvents with a wide range of less polar substrates. A high degree of complementarity thus exists between biochemical catalysts and chemical catalysts. It is now possible to control the stereochemical outcome to produce any relative and absolute configuration desired. There is, however, room for improvement. There are still limitations with regard to the scope and catalyst preparation, which may present additional difficulties, especially on large scales.

The catalytic-antibody approach based on “reactive immunization” has been revolutionary, providing a new direction to the development of biochemical catalysts with a broader scope in substrate specificity and stereospecificity. In addition, recent structural studies of the aldolases and catalytic antibodies combined with techniques in molecular biology provide means to improve the preparation of catalysts and change the scope of the catalytic reactions, especially with regard to substrate acceptability, which renders them generally more useful. The future design of chemical catalysts that mimic the action of the aldolases offers great opportunity for the development of simple systems with high efficiency and selectivity and broad specificity. It is hoped that these two fields, namely the chemical and biological approaches to the development of the aldol reaction, will converge and a truly general solution to the catalytic asymmetric aldol reaction will emerge.

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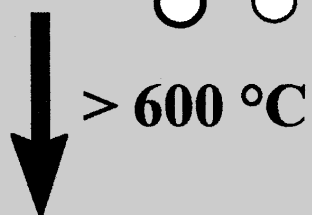
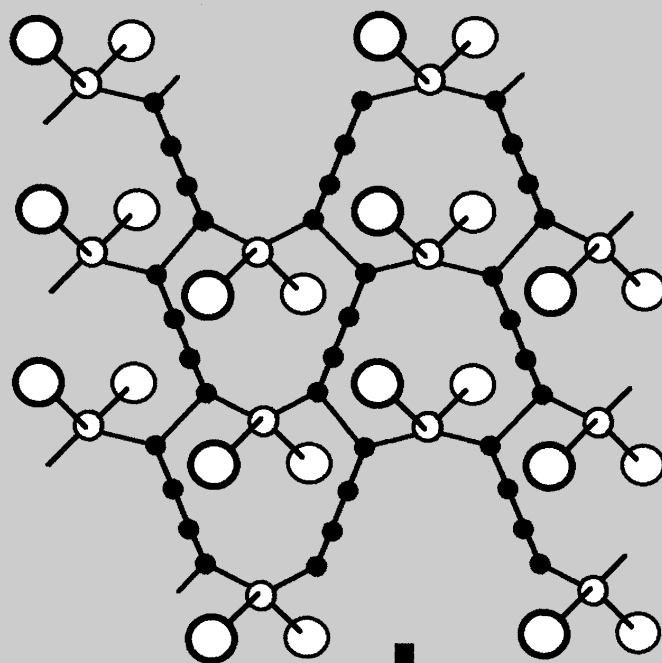
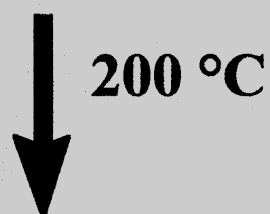
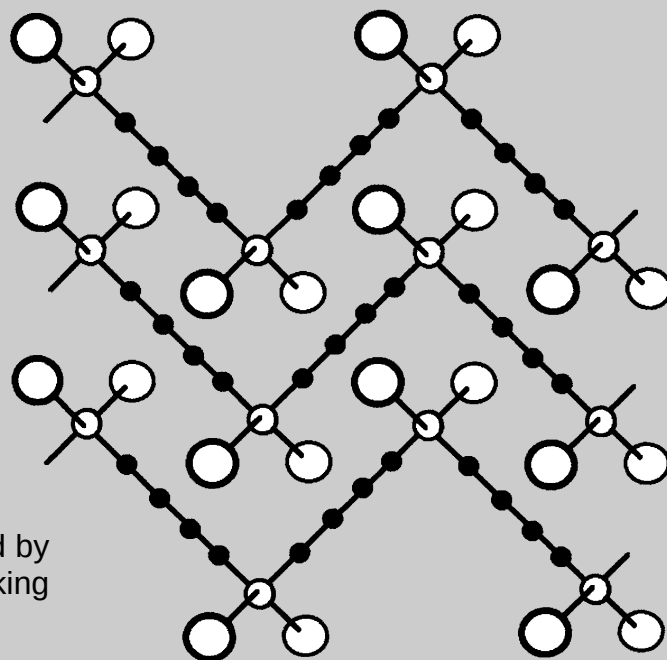
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SiC formation in a
carbon matrix obtained by
bisacetylenic cross-linking



Ceramics and Nanostructures from Molecular Precursors

Robert J. P. Corriu*

The elaboration of solids from the molecular scale by a kinetically controlled methodology is one of the main challenges of molecular chemistry. In the long term, this should permit the design of solids with desired properties. Here, some examples are given which show a few methods that have been used for the preparation of solids from molecular precursors. The one-pot synthesis of rheologically controlled SiC is

described. Access to a new kind of ceramic is obtained by the same methodology using molecular precursors. Mixed ceramics with interpenetrating networks are not accessible by the chemical thermodynamic route. The chemistry of hybrid materials obtained from molecular precursors through inorganic polymerization is presented. This class of materials offers wide perspectives because of 1) the large

possibilities opened by the organic unit, 2) the kinetic control, which permits any kind of texture for the solid, and 3) the aptitude of these solids to become nanostructured.

Keywords: ceramics • materials science • nanostructures • polymers • silicon

1. Introduction

The evolution of chemistry is now more and more controlled by developments in life sciences and in material sciences. All the classical divisions of chemistry are concerned with these two highly demanding trends, and little by little a change can be observed corresponding to an ever closer interaction between the different subdisciplines of chemistry, a change necessitated by a variety of new research objectives. For example, both solid-state chemistry and polymer chemistry have borrowed from, and even created, methods belonging to the realm of physical chemistry. The development of modern catalysis involves the chemistry and physical chemistry of surfaces, as well as organometallic coordination chemistry and the design of solid catalyst supports. Molecular chemistry, which is the fruit of cross-fertilization between organic and main group element chemistry, will grow over the next few years to become the chemistry of the elaboration of solids.

The use of molecular chemistry was very successful in opening new routes for chemical synthesis and in explaining the microscopic approach to chemical reactivity. Many synthetic tools were developed with some great successes, including the step-by-step construction of very complicated

natural architectures (e.g. vitamine B₁₂^[1] and palytoxine^[2]). Molecular chemistry was also successfully applied for elaborating sophisticated, purely inorganic molecules (i.e., ladder polymers,^[3] polysilahedranes,^[4] and complicated phosphorus rings^[5]) and for controlling the elaboration of clusters,^[6] polyoxometallic anions,^[7] and dendrimers.^[8]

In material science and solid-state chemistry, solids are classically prepared by thermodynamic routes. In contrast, both organic and inorganic molecular synthetic chemistry are based on the kinetic control of reactions. This molecular approach to synthesis is a multistep approach that implies a good knowledge of reaction mechanisms and product distribution. Until now, this method was not used extensively in materials synthesis. However, polymer elaboration, which is strongly connected to the molecular approach in that it requires a very precise knowledge of reactions mechanism, must be pointed out as the exception.

The elaboration of ceramic fibers and chemical vapor deposition from organometallic compounds (OMCVD) are the first approaches to preparing materials from molecular precursors. The pioneering work of Verbeeck and Winter^[9] and Yajima et al.^[10] were certainly the first attempts for building up a material starting from a single molecule or compound. They succeeded in preparing films and fibers of highly thermomechanically resistant materials (silicon carbides and oxycarbides as well as silicon nitrides and oxynitrides).

Many interesting possibilities were created by the development of “chimie douce” processes^[11, 12] and sol–gel polymerization, which is particularly well adapted for bridging solid-

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state and molecular chemistry.^[13] Thus, nowadays one of the main challenges for molecular chemistry is the control of properties by elaboration of solid materials beginning at the molecular scale. The most ambitious aim is to create chemistry that permits control of the organization of properties in the material using a step-by-step synthesis.

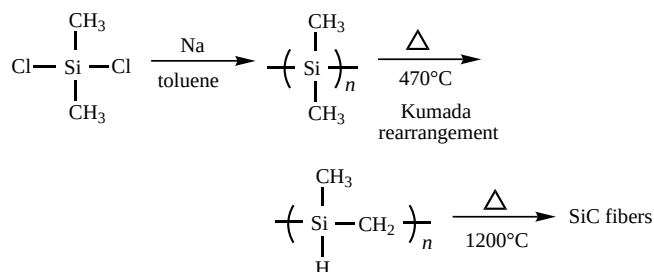
This review describes the main results obtained during the last decade in our attempts to elaborate materials and nanostructures using molecular precursors. These results are given as an example, as other results have been published.^[22]

2. SiC Films and Matrixes via a Rheologically Controlled Preceramic Polymer

2.1. SiC Fibers obtained by the Yajima Process

SiC fibers have been obtained by the discovery of a step-by-step process beginning with $(\text{CH}_3)_2\text{SiCl}_2$ ^[9, 10] (Scheme 1).

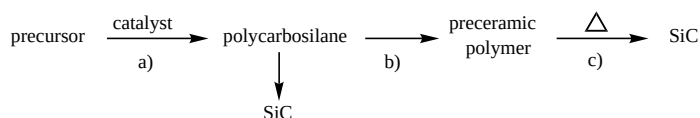
The polydimethylsilane is rearranged into a polycarbosilane by thermal treatment. This preceramic polymer is exposed to high temperature, leading to a polymer whose rheology permits processing (after heating) of silicon oxy-carbide fibers. This process is a great chemical success since it is the only way to obtain, as a fiber, a material that offers high thermomechanical properties (Nicalon fibers are highly resistant until 1200 °C). However, if we consider this process from the chemical point of view, it is a stoichiometric process involving the use of sodium or potassium. It is also possible to consider another route that permits one to synthesize the polycarbosilane by a catalytic reaction.



Scheme 1. The Yajima process for obtaining SiC fibers.

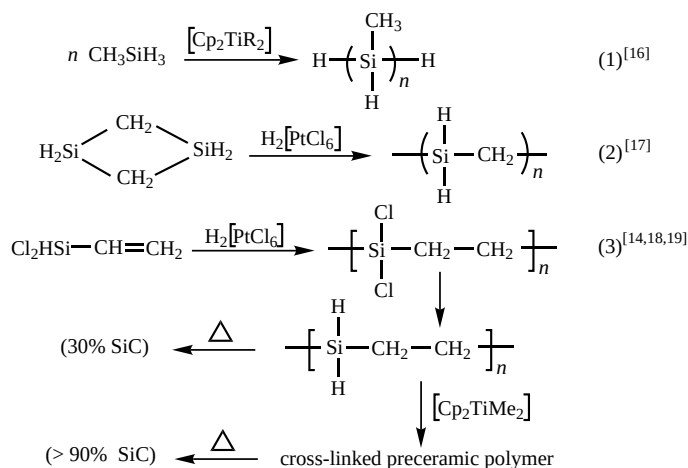
2.2. Catalytic Access to Polycarbosilanes

A general access to SiC using a catalytic procedure has been described (Scheme 2). The polycarbosilane is elaborated by a catalytic reaction in the first step (a). However, the direct pyrolysis of this polymer can lead to a low yield of SiC.^[14] Cross-linking (step b) is necessary for preparing a preceramic polymer that can be transformed into SiC in good yield and with a controlled morphology, which then allows the formation of films or fibers (step c).^[15]



Scheme 2. The principle for catalytic access to SiC.

Three ways have been developed based on hydrosilanes (Scheme 3). For systems represented by reactions (1) and (2), the cross-linking step is not separated from the pyrolysis. In the case of reaction (1) the polymerization leads to a partially cross-linked polymer which can be transformed into SiC with



Scheme 3. Catalytic routes to SiC.

Robert Corriu, born in 1934 in Port-Vendres, France, obtained his Docteur es Sciences Physiques in 1961 from the Université de Montpellier. He became Assistant Professor at the Université de Perpignan in 1963, Associate Professor at the Université de Poitiers in 1964, and Professor at the Université de Montpellier in 1969. His research interests in organometallic chemistry have been focused on organosilicon, organogermanium, and organophosphorus compounds, transition metal complexes, and hypercoordinated silicon and phosphorus compounds. More recently, he has concentrated his research efforts on the elaboration of solids from molecular precursors. His main interest is now connected with hybrid organic-inorganic materials and molecular chemistry permitting organization of solids. He has obtained awards from the French Chemical Society (Prix Sue in 1969 and Prix Lebel in 1985), the CNRS (silver medal in 1982), and the American Chemical Society (Kipping Award in 1984). He was elected to the French Academy of Sciences in 1991 and the Polish Academy in 1997. He obtained the Alexander von Humboldt Research Award in 1992, the Max Planck Research Award in 1993, and the Wacker Silicon Award in 1998.



77% conversion. The results reported in reaction (2) correspond to the formation of SiC in 96% yield. Cross-linking occurs during the mineralization step.

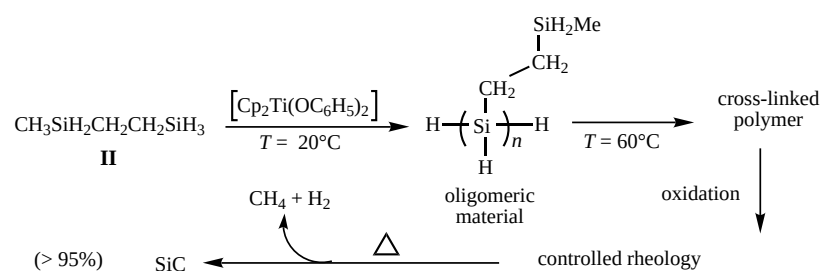
In contrast, in reaction (3), we observed a very great difference in the yield of SiC when the pyrolysis is performed with or without the cross-linking step.^[20] The polymer (SiH₂–CH₂CH₂)_n has been characterized as a soluble linear polymer corresponding to a degree of polymerization ranging from 20 to 95, depending on the experimental conditions, and containing SiH₃ and SiH₂CH=CH₂ chain ends. After pyrolysis, the ceramic yield is low (about 30%), and it is still lower when the vinylic end groups are not present.^[20] As expected the linear polymers which do not cross-link^[18–20] decompose on pyrolysis without giving ceramic residue in acceptable yields. However, after cross-linking with Harrod's catalyst,^[16] it is possible to obtain pure SiC in good yields.^[19]

2.3. Preceramic Polymers with Controlled Rheology

We have succeeded in obtaining a preceramic polymer with a controlled rheology by a one-pot procedure. This process makes use of very simple silaalkanes: 1,4-disilabutane (**I**), 1,4-disilapentane (**II**), and 2,5-disilahexane (**III**).^[19–21]

These precursors were cross-linked separately using Harrod-type catalysts [Cp₂TiR₂] (R = Me, OC₆H₅, etc.). The first step, performed at low temperatures, leads to an oligomeric material. Increasing the temperature from room temperature to 60 °C induces an increase in molecular weight and some cross-linking. To control the rheology of the preceramic polymer, it is possible to poison the catalyst by very brief contact with air. This oxidation is reversible since the medium is highly reductive owing to the great number of Si–H bonds. This method permits control of the cross-linking, making it possible to obtain rheologically controllable material (films or matrixes) before pyrolytic conversion into ceramics. Interestingly, all the precursors provide pure SiC in good yields without excess of C nor Si.^[21] Scheme 4 shows results obtained for 1,4-disilapentane.

This summary of the preparation of ceramics having high thermomechanical performance, such as SiC, illustrates the potential of molecular chemistry. This step-by-step approach is the only method that provides access to ceramic films or fibers with exceptional thermomechanical properties such as SiC or Si₃N₄ and the corresponding silicon oxycarbides and silicon oxycarbonitrides. Since this work was completed, new precursors have been obtained, and new kind of ceramics have been reported.^[22]



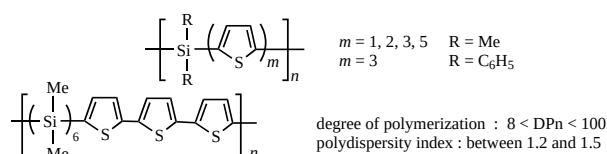
Scheme 4. The one-pot, rheologically controlled pathway to SiC, shown with the example of 1,4-disilapentane (**II**).

3. Elaboration of Ceramics in a Carbon Matrix: Access to Nano-Composite Mixed Ceramics

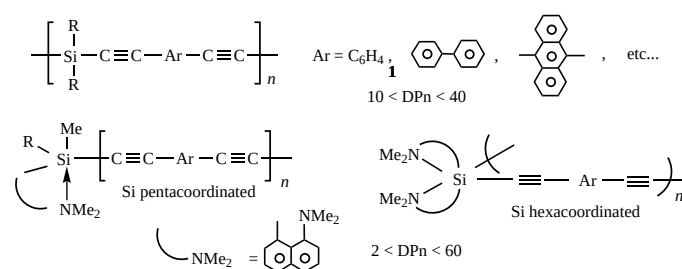
3.1. Silicon-Containing Polymers: Synthesis and Conductivity

In the course of our work concerning the synthesis of silicon-containing polymers, we have prepared three sets of polymers in which –(SiR₂)– units bridge unsaturated organic units (Scheme 5). After doping, all these polymers exhibit conductivity in the range of 10^{–3} to 10^{–6} S cm^{–1}.^[23–28] The materials in Scheme 5B offer second (χ₂)^[24c] and third harmonic (χ₃) nonlinear optic properties.^[24c, d]

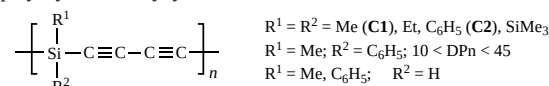
A) polysilylene thiophenylene^[22]



B) polysilylene alkynylene phenylene^[23]



C) polysilylene bisalkynylene^[24, 25]



Scheme 5. Silicon-containing polymers obtained in the author's laboratory.

The case of polysilylene bisalkylene (Scheme 5C) is interesting since, although the acetylenic units are not favorable to conduction,^[25] these polymers exhibit conductivities between 10^{–5} and 10^{–3} S cm^{–1}. Furthermore, the values are dependent on the groups attached to silicon. The highest values (3 × 10^{–3} S cm^{–1}) are obtained with Ph₂Si, the lowest with Me₂Si (8 × 10^{–5} S cm^{–1}). This observation is in agreement with an electronic interaction induced by silicon atoms which favors charge delocalization. A possible explanation corresponding to a chain-to-chain conduction mechanism can be eliminated since, in this hypothesis, the highest values should be obtained with the dimethyl polymer **C1**, which exhibits the best crystallinity^[29] and the shortest distance between the acetylenic chains (4.6 Å). In contrast, the phenylated polymer **C2** should

exhibit a lower conductivity since the steric hindrance, which increases the repulsion between the polymeric chains, should prevent the chain-to-chain conduction mechanism. The experimental results clearly show that aromatic substituents at silicon are the best for increasing the conductivity.

3.2. Ceramization of Polydimethylsilylene Bisalkylene

The bismethylated polymer **C1** (see Scheme 5) was pyrolyzed under argon.^[30] Surprisingly, a residue was obtained that was analyzed as having a composition ratio of Si/5C. On heating to 1400 °C, β -SiC crystallizes, and the analysis corresponds to SiC/4C. During pyrolysis no gaseous products containing silicon were eliminated: Only CH₄ and H₂ were formed (Figure 1).

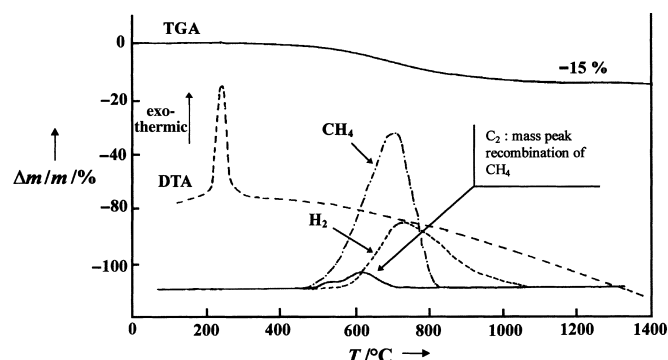
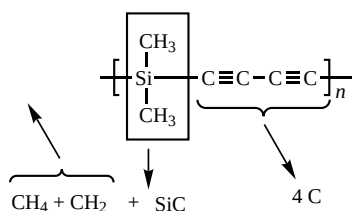


Figure 1. Thermal and gas analyses in the pyrolysis of polymer **C1**. m = mass, DTA = differential thermal analysis, TGA = thermogravimetric analysis.

Differential thermal analysis (DTA) exhibits a sharp exotherm at 200 °C (Figure 1). This exotherm takes place before the evolution of CH₄ (450 °C) and H₂ (550–600 °C). Given that linear precursor polymers depolymerize into short volatile units during pyrolysis, a cross-linking process is always necessary to obtain ceramics in good yields.^[14, 31, 36] Taking this fact into account and considering the results obtained by elemental analysis, thermogravimetric analysis (TGA), and DTA, the best working hypothesis is that presented in Scheme 6: The 4C residue should originate from the bisacetylenic units, and the SiC should form from SiMe₂ groups with concomitant elimination of CH₄ and H₂. In other words the exothermic transformation observed at 200 °C should correspond to the formation of a carbon matrix by 1,4-addition of bisacetylenic units, as already observed in related systems.^[32] This transformation is likely the key step leading to a cross-linked material which aids the formation of SiC.



Scheme 6. Mechanistic hypothesis for formation of SiC from **C1**.

As a chemical proof, we checked that the formation of SiC correlates with the presence of bisacetylenic units in the molecule: The saturated polymer [Me₂Si(CH₂)₄]_n does not form SiC, and the semisaturated polymer [Me₂Si(CH₂)₄SiMe₂C≡C-C≡C]_n provides less than 40 % of the theoretical amount of SiC.^[29] In the case of polymer **C1**, the formation of the carbon matrix was detected by both IR and ¹³C CP-MAS NMR spectroscopy (CP-MAS = Cross-polarization magic angle spinning), which shows the transformation of sp into sp² carbon atoms, corresponding to the transformation of C≡C-C≡C units into enynes and butatrienes at 200 °C and then final formation of the sp²-carbon matrix above 400 °C.^[30]

In agreement with this explanation, we observed that the exothermic transformation is highly dependent on the steric hindrance of the groups attached to silicon. In the case of **C1**, the X-ray diffraction (XRD) pattern reveals the presence of a lattice in which the repeat distance of the diacetylene backbone is 4.6 Å.^[29, 30] The crystallinity decreases in the order Me > Ph > SiMe₃, as observed by XRD, and the temperature of cross-linking follows the same order (Me: 200 °C, Ph: 225–315 °C, SiMe₃: 350 °C; Figure 2).

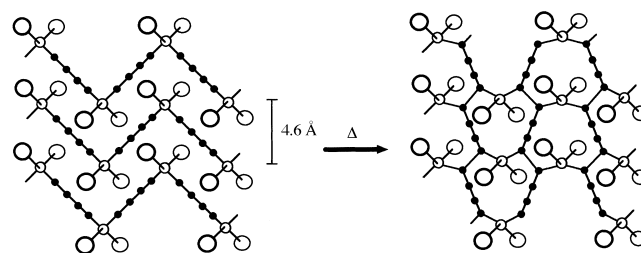


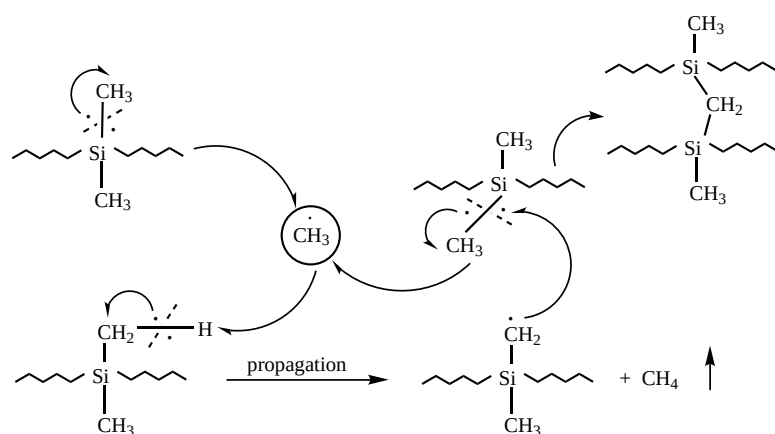
Figure 2. Representation of the cross-linking process.

This cross-linking reaction between the C≡C-C≡C chains explains why the isolated dimethylsilyl units react with each other to form a SiC network. Although the SiMe₂ groups are chemically isolated, they are in a fixed geometric position inside of the carbon matrix—this permits their reaction with elimination of H₂ and CH₄. In this case, the cross-linking reaction does not occur between functionalities at SiC. A mechanism that can be proposed for the ceramization is presented in Scheme 7.^[30]

The initiation step is the formation of a CH₃· radical by cleavage of a Si-CH₃ bond. The abstraction of H· leads to evolution of CH₄ and formation of a SiCH₂· radical, which permits the formation of SiCH₂Si units and regeneration of CH₃· (propagation step).

The evolution of H₂ takes place at higher temperature (>500 °C). It can be explained by cleavage of C-H bonds followed by reaction of the SiCH₂Si radical on a Si atom located in the vicinity. This reaction occurs with cleavage of the bond linking this Si atom to the unsaturated cross-linked carbon matrix. In this way, the SiC network is formed from the (SiCH₂Si) units.

Whatever the substituents are at silicon (SiMe₂, SiEt₂, Si(C₆H₅)Me, Si(C₆H₅)₂), the conservation of Si and its transformation into SiC is high (95–99 %). Furthermore, when the

Scheme 7. Mechanism of the formation of $-\text{Si}-\text{CH}_2-\text{Si}-$ chains.

ceramization is performed under NH_3 , amorphous Si_3N_4 is formed at 600°C as the only residue since the carbon matrix is eliminated as HCN above 800°C .^[30, 33]

3.3. Elaboration of Mixed-Metal Carbide Ceramics

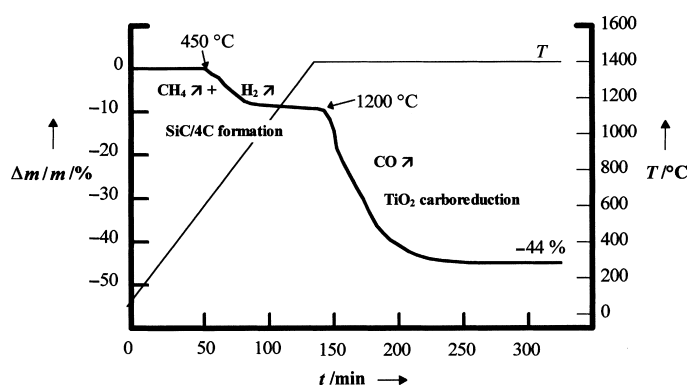
The basic idea was to use the excess of carbon present in the residue to perform carbothermal reduction of oxides and obtain mixed-metal carbides as a ceramic residue.^[34] This is a possible target since the formation of SiC and the carbothermal reduction occur at very different temperatures (450 – 750 and above 1200°C , respectively;^[35] the temperature of the reduction is highly dependent on the experimental conditions^[36]).

Our aim was to explore the possibility of preparing mixed ceramics by making use of the difference in temperature between SiC formation and carbothermal reduction. Moreover, the formation of the sp^2 -carbon matrix clearly opened some interesting possibilities, since the SiC is embedded in a sp^2 -carbon matrix and since a sp^2 -carbon matrix is potentially very efficient for carbothermal reduction. This route was particularly attractive since it is a kinetic way for preparing two ceramics successively in the same process. This method is completely different from the classic route using powders and working under thermodynamic control.

The case of TiO_2 is described as an example: Particles of TiO_2 (1 – $5\ \mu\text{m}$) are mixed with a solution of the polymer **C1** in THF through the use of ultrasonication ($0.5\ \text{h}$). After elimination of the solvent, the residue is pyrolyzed under argon. The exothermic transformation occurs at 210°C with formation of the carbon matrix. After pyrolysis, a residue is obtained that corresponds to a mixed carbide SiC/TiC in which all particles exhibit the same $\text{Si}:\text{Ti}$ ratio of $3:4$ (as determined by energy-dispersive X-ray spectroscopy (EDAX)). Figure 3 shows the TGA and the gas analysis observed during this experiment. Evolution of CH_4 and H_2 occurs between 450 and 800°C . This evolution corresponds to the formation of SiC from the SiMe_2 groups covalently bound to the carbon matrix. Above 800°C , SiC forms and the XRD shows the presence of TiO_2 . Elimination of CO corresponding to carbothermal reduction is observed between 1200 and

1400°C , a temperature much lower than that reported for the carbothermal reduction of TiO_2 with other reducing systems (1700 – 1900°C).^[34]

With the use of XRD, it is possible to follow the carbothermal reduction of TiO_2 between 1000 and 1400°C . At 1000°C only a diffraction pattern for TiO_2 is observed. At 1200°C TiO_2 , Ti_3O_5 , and Ti_2O_3 as well as some titanium oxycarbide ($\text{Ti}_x\text{O}_y\text{C}_z$) appear.^[37] The complete elimination of TiO_2 occurs at 1300°C : Only Ti_3O_5 , Ti_2O_3 , and (Ti_xO_y) remain. The increase in temperature is accompanied by a decrease in oxide peaks and an increase in peaks associated with oxycarbides. After two hours only TiC is observed by XRD along with weaker signals corresponding to SiC .

Figure 3. TGA analysis of **C1**/ TiO_2 dispersion under argon.

Carbothermal reduction is a general process that occurs between 1200 and 1400°C no matter which oxide is used. Refractory materials like ZrO_2 and HfO_2 normally undergo carbothermal reduction between 2000 and 2500°C ^[36] (Table 1).

Table 1. Synthesis of SiC –metal carbide ceramics by pyrolysis of **C1** and metal oxide dispersions under an argon flow.

Equiv of polymer [SiMe_2C_4]	Metal oxide (equiv)	Ceramic yield [%] ^[a]	Stoichiometry of the ceramic ^[b] (MC [%])
3	TiO_2 (4)	56 (56.5)	$3\text{SiC}/4\text{TiC}$ (66.7)
3	ZrO_2 (4)	62 (65.5)	$3\text{SiC}/4\text{ZrC}^{[c]}$ (77.4)
3	HfO_2 (4)	71 (76.0)	$3\text{SiC}/4\text{HfC}^{[d]}$ (86.4)
13	V_2O_5 (8)	52 (52.2)	$13\text{SiC}/4\text{V}_4\text{C}_3$ (64.8)
7	Nb_2O_5 (4)	62 (62.1)	$7\text{SiC}/8\text{NbC}$ (74.9)
7	Ta_2O_5 (4)	72 (72.6)	$7\text{SiC}/8\text{TaC}$ (84.6)
7	MoO_3 (8)	59 (58.7)	$7\text{SiC}/4\text{Mo}_2\text{C}$ (74.4)
1	WO_3 (1)	69 (69.8)	SiC/WC (85.0)
7	B_2O_3 (8)	35 (38.6)	$7\text{SiC}/4\text{B}_4\text{C}$ (44.1)
3	SiO_2 (4)	49 (50.0)	SiC (–)

[a] Theoretical values. [b] Determined by IR spectroscopy and XRD. MC = analytical results of the metal carbide. [c] For total conversion of ZrO_2 into ZrC , the pyrolysis time was increased to $5\ \text{h}$. [d] For total conversion of HfO_2 into HfC , the pyrolysis time was increased to $7\ \text{h}$.

3.4. Mechanism of Formation of Mixed Carbides

The effect due to the carbon matrix and its formation around the oxide particles is the driving force of these processes. A chemical proof can be afforded by comparing the results of ceramization by mixing the oxide before or after formation of the carbon matrix. In the case of TiO_2 and ZrO_2 complete carbothermal reduction is observed when the carbon matrix is formed in the presence of the oxide particles. However, in the second procedure (mixing the oxide with the cross-linked polymer) 30 % of TiO_2 and 70 % of ZrO_2 are not transformed into TiC or ZrC .

Transmission electron microscopy performed after the cross-linking step shows the TiO_2 grains embedded inside the carbon matrix (Figure 4). Moreover, after treatment at 800°C the TiO_2 is not modified and nanoparticles corresponding to SiC are visible. The fact that the oxide particles are closely embedded by the carbon matrix explains the lower temperature observed for the carboreduction with respect to the values reported in the literature.

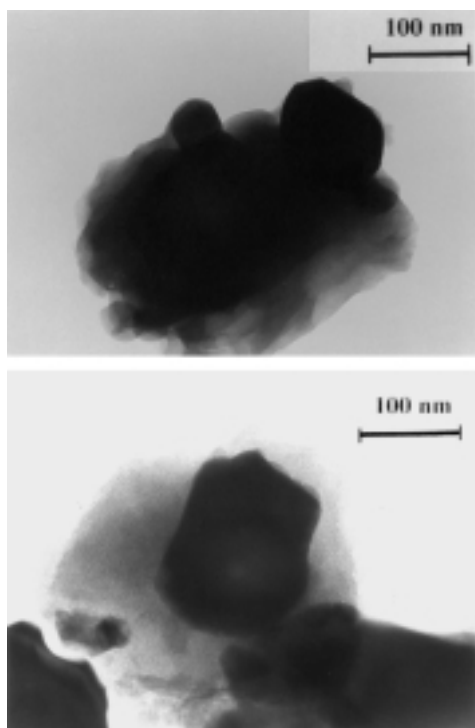
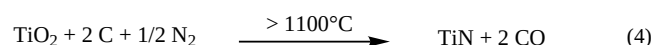


Figure 4. Transmission microscopy for a) $\text{TiO}_2/\text{C1}$ at 300°C and b) $\text{TiO}_2/\text{SiC}/4\text{C}$ at 800°C .

3.5. Preparation of Mixed SiC–Metal Nitrides

It is well known that the carbothermal reduction of some metal oxides under N_2 gives nitrides.^[36] This reaction occurs at temperatures above 1100°C , as illustrated for TiO_2 [Eq. (4)].^[38]



We performed the ceramization under a flow of nitrogen and observed the formation of residues corresponding to mixed ceramics of SiC and metal nitrides^[34–39] (Table 2). Interestingly, materials are obtained with ceramic yields quite close to the expected values. In every case, reactions occur at lower temperatures and with a higher rate than reported in the literature.^[36]

Table 2. Synthesis of SiC –metal nitride ceramics by pyrolysis of **C1** and metal oxide dispersions under a nitrogen flow.

Equiv of polymer	Metal oxide (equiv.)	Ceramic yield [%] ^[a]	Stoichiometry of the ceramic ^[b] (MN [%])
1	TiO_2 (2)	64 (62)	$\text{SiC}/2\text{TiN}$ (75.6)
1	ZrO_2 (2)	66 (71)	$\text{SiC}/2\text{ZrN}$ (84.0)
1	HfO_2 (2)	84 (81)	$\text{SiC}/2\text{HfN}$ (90.6)
5	V_2O_5 (4)	58 (57)	5 $\text{SiC}/8\text{VN}$ (72.2)
5	Nb_2O_5 (4)	71 (66)	5 $\text{SiC}/2\text{Nb}_4\text{N}_{3.92}$ (81.0)
3	B_2O_3 (4)	49 (53)	3 $\text{SiC}/8\text{BN}$ (62.3)
3	Al_2O_3 (4)	62 (62)	3 $\text{SiC}/8\text{AlN}$ (73.2)
1	SiO_2 (2)	62 (59)	$\text{SiC}/\frac{2}{3}\text{Si}_3\text{N}_4$ (70.0)

[a] Theoretical values are given in parentheses. [b] Determined by IR spectroscopy and XRD. MN = analytical results of the metal nitride.

The mixture of a carbide and a nitride is also possible since these two kinds of ceramics can be obtained by different chemical routes. Degradation under nitrogen of the polymer **C1** leads only to SiC , and the formation of metal nitrides takes place at a higher temperature. In the case of metals like Ti and Zr , the most reasonable explanation is the direct reaction of nitrogen with the metal.^[34b], 36, 38, 39] However, in the case of silicon, Si_3N_4 formation can result from the reaction of N_2 with low oxides (compounds with low oxide content) formed as intermediates during the carbothermal reduction, since it is well established that Si_3N_4 cannot be obtained by reaction of nitrogen with the polymer or with SiC in this temperature domain. The identification was carried out by XRD; Figure 5 shows an example for the β - SiC and hexagonal HfN ceramic.

Thus, as shown in Scheme 8, the mechanism of carbothermal reduction takes place with initial formation of metal oxides and/or low oxides as intermediates.^[36, 38] When the transformation is performed under argon, the excess of carbon reacts with these intermediates, leading to metal

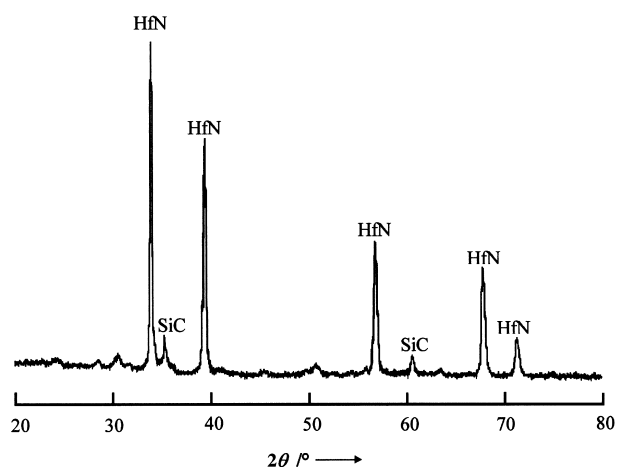
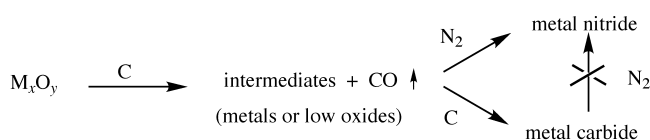


Figure 5. X-ray diffraction pattern of a SiC – HfN ceramic.



Scheme 8. Proposed mechanism for metal nitridation.

carbide. In contrast, under a nitrogen atmosphere the reaction with the metal (or in some cases with low oxides) is faster since 1) the gas/solid contact is more efficient than the solid/solid contact and 2) the products are thermodynamically more stable.^[36] Only metal nitrides are obtained under these conditions; no nitrides are assumed to be formed by the reaction of nitrogen with carbides.

3.6. The Nature of the Mixed Ceramics Obtained

The oxide powders used for the ceramization studies were submicron powders. The analyses show that the distribution of particle sizes is wider in the final material than in the starting material. The IR spectra demonstrate clearly that the silicon is present only as SiC (830 cm⁻¹)—neither SiO₂ (1000–1200 cm⁻¹)^[40] nor any other oxide (TiO₂, ZrO₂, etc...) is observed.

As an example, the XRD pattern of the ceramic resulting from pyrolysis of polymer **C1** and Nb₂O₅ under argon shows only carbides (β -SiC and NbC), corresponding to complete carbothermal reduction of the oxides (no oxide is detected by FT-IR spectroscopy and XRD at the end of the process; Figure 6). The XRD pattern shows that SiC is formed in

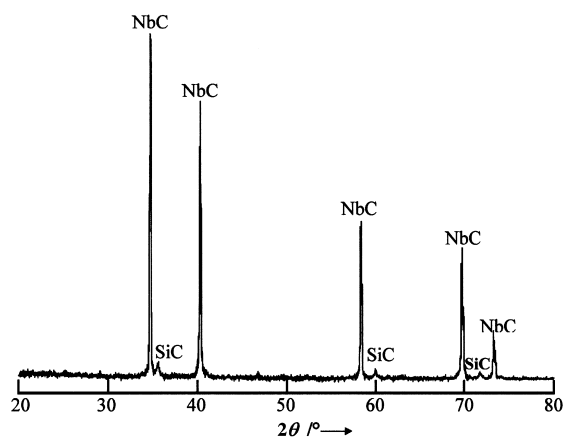


Figure 6. X-ray diffraction pattern of a SiC-NbC ceramic.

addition to the carbides (or the nitrides). However, its signals are broader and weaker than those of the carbides (or the nitrides) resulting from the carbothermal reduction. We can conclude that both ceramics are present as separated phases. However, the crystalline domains resulting from carbothermal reduction are larger than the β -SiC crystals, as easily observed in transmission electron microscopy.

A solid solution or an alloy can be excluded as a possible structure since the XRD diagrams of both the components are observed. The two possibilities are now either a mixture

consisting of particles of SiC beside particles of other carbides (or nitrides), or particles containing the two kinds of ceramics. In order to discriminate between the two, we considered the EDAX diagram of the particles (Figure 7). This diagram shows that the ratio of Si to metal is identical to the ratio introduced in the starting material. Furthermore, this ratio is quite constant at each point of one particle and for all the particles considered.

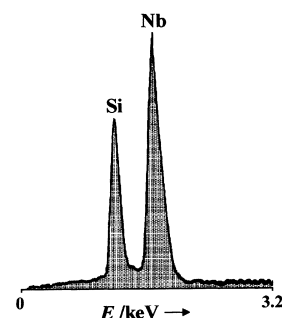


Figure 7. EDAX spectrum of a SiC-NbC ceramic showing retention of the initial Si:Nb ratio (7:8) in the final material.

All these results show that we are faced with a ceramic structure which cannot be described as an alloy since we could not observe the XRD patterns for both components. However, the ceramics obtained are not a mixture of particles of β -SiC and particles of the other metal carbide (or nitride). We observe an intermediate situation in which the powder is chemically homogeneous, all particles exhibiting the same chemical composition. However, it is possible to detect crystalline components, showing that each particle is an agglomerate of crystals of both β -SiC and the carbide (or nitride) resulting from carbothermal reduction. The alloy is not formed since the crystals do not have the same crystalline variety and since the rather low temperature does not permit alloy formation or phase separation.

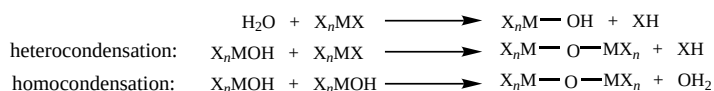
By comparison with the case of mixing polymers,^[41] the ceramic obtained could be described as a mixed ceramic with interpenetrating networks. However, following the terminology proposed in ceramic science, the term nanocomposite ceramic^[42] seems more appropriate.

In conclusion, the results described in Section 3 show that the molecular approach to materials permits one to obtain solid materials that have not been reported previously. These nanocomposite ceramics or interpenetrating networks^[42] are accessible only by a step-by-step kinetic preparation and by controlling the chemistry throughout the process. Thus β -SiC (cubic diamond) is formed at a rather low temperature (below 800 °C). The carbothermal reduction gives the second ceramic at a temperature which does not permit the transformation of β -SiC into α -SiC (hexagonal). Moreover, since these transformations are performed in the carbon matrix obtained by the cross-linking of C₄ units, the two ceramics are maintained in the same particle without any thermodynamic transformation. This situation was never described before and it can be obtained only by a kinetic route.

4. Sol–Gel Chemistry

The “chimie douce”^[11, 12] methods include the sol–gel processes,^[13] which correspond to hydrolytic polycondensations in which the leaving groups at the metal are substituted by nucleophilic attack of H₂O, followed by elimination of the leaving group and formation of a metal hydroxyde. This in

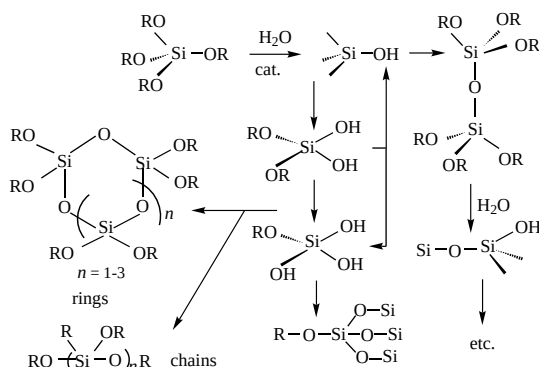
turn leads to metal oxide bonds either by homo- or heterocondensation^[43] (Scheme 9).



Scheme 9. Hydrolytic condensation of metal alkoxides.

Hydrolytic polymerization is a general process that occurs at many metal centers and makes use of many different leaving groups: X can be, among others, halide, sulfide, alkoxide, or nitride. However, the most widely used are the alkoxides and the most intensively studied element is silicon, which leads to silica.^[44, 45]

It is important to point out that polycondensation is always a very complex mechanism, even for SiO₂ formation, which is considered the most simple process.^[46] Scheme 10 illustrates this complexity, at least in the first steps. When polycondensation goes further, the situation becomes even more complex since many reactions occur in competition: redistribution, ring closure, and ring opening. Finally, colloids form, leading to sol production. The coalescence of these colloids at the gel time leads to formation of xerogels.



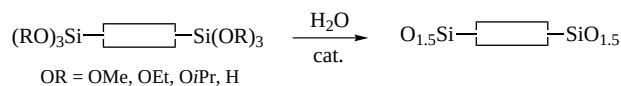
Scheme 10. Illustration of the chemical complexity of sol-gel hydrolytic polycondensations.

Importantly, the details of the polymerization mechanism are not well known, and only few reliable kinetic data have been reported concerning the first steps.^[47] Moreover, it is difficult to compare the sets of experiments reported in the literature since most authors use pH as a measure of medium acidity or basicity although it is well known since the work of Hammet and Deyrup that only the H_0 functions are valid when the experiments are carried out in aqueous-organic media.^[48] Moreover it was established that the solid is formed after a set of very complexed steps:^[13b] precursor $\rightarrow$ oligomers $\rightarrow$ polymers $\rightarrow$ colloids $\rightarrow$ sol $\rightarrow$ gel. Thus it is impossible to predict the properties of the final solid, since the nature and the degree of influence of the parameters controlling each step are not known.

However, despite the lack of precise knowledge concerning the details of the mechanisms of gel formation, this field of research is very attractive because it opens wide possibilities for the preparation of materials. Scheme 11 illustrates the

high efficiency of sol-gel processes for the elaboration of solids. This method is particularly attractive for molecular chemists since elaboration can be performed at room temperature under the same experimental conditions used in organic or inorganic chemistry. There is why these processes have been named “chimie douce”.^[11, 12]

In previous reviews, we have described the sol-gel chemistry of new kinds of precursors and nonhydrolytic gelation methods.^[13g, 49] The present article focuses on organic-inorganic hybrid materials.^[49-55] The number of investigations performed on this topic is growing very quickly and the possibilities are wide open. More precisely, Section 5 will be devoted to the elaboration of nanostructural materials (nanostructures) by building up an inorganic matrix around an organic unit starting from a molecular precursor used as a building block (Scheme 12).

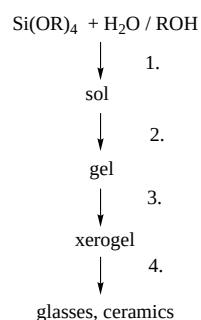


Scheme 12. A method for elaboration of nanostructural materials from molecular precursors.

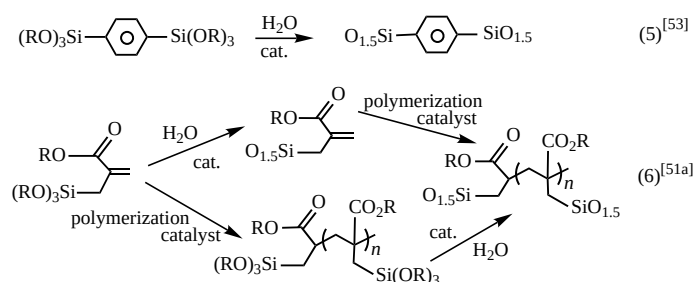
5. Organic-Inorganic Hybrid Materials: Scope and Limitations

5.1. Nanostructural (Monocomponent) and Nanocomposite (Polycomponent) Hybrid Materials

The phrase “organic-inorganic material” is used widely and covers many kinds of solids. The greatest possibilities are available to polycomponent materials that are generally obtained by mixing organic molecules or polymers with metal alkoxides. The materials are obtained by polycondensation of the alkoxides into oxides using sol-gel methods. Although most of these systems appear homogeneous (single phase), they correspond to a polycomponent system since they can be separated into two phases by classical separation techniques (washing with an organic solvent, for instance). In contrast, all systems in which the components are bound by covalent bonds exhibit different behavior. Whatever separation methods are used, they always appear as a homogeneous single phase: They cannot be separated by analytical techniques since all atoms are covalently bound. For instance, one hybrid prepared by polycondensation with a molecular precursor as a building block^[53] (Scheme 13, reaction (5)) and another obtained by polymerization of organic units inside an oxide matrix^[51a] (reaction (6)) are both monocomponent systems, and can be considered as nanostructured materials. However, it is obvious that the two materials are very different with respect to homogeneity and short- to medium-range organ-



Scheme 11. General scheme of the sol-gel process: 1. hydrolysis/condensation; 2. sol-gel transition; 3. drying; 4. densification.



Scheme 13. Two possible pathways to monocomponent solids. cat. = H^+ , OH^- , F^- .

ization in the solid. Furthermore, in the case of reaction (6), the two possible routes provide very different solids. When the polymerization is the first step, the material contains polymeric chains cross-linked by hydrolytic polycondensation of $\text{Si}(\text{OR})_3$ groups. When polycondensation is the first step, polymerization leads to the linkage of $\text{R}-\text{SiO}_{1.5}$ clusters.

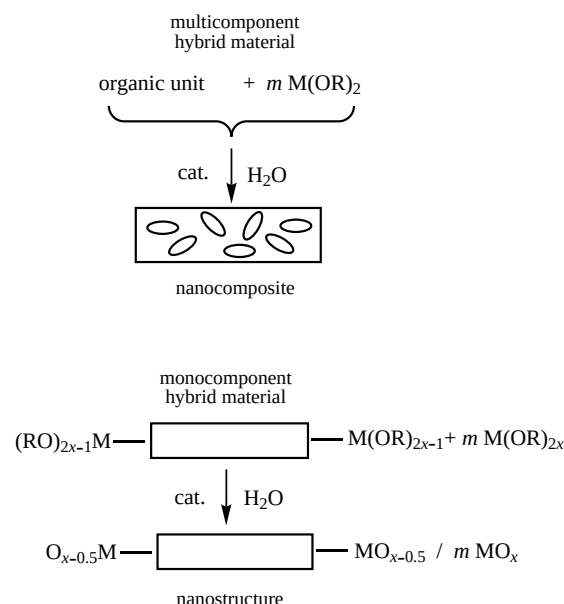
In contrast, hybrid materials obtained by mixing organic moieties with one (or more) alkoxide precursors correspond to nanocomposites after formation of oxides by precursor polycondensation.^[50, 51] These solids can be separated into different components by classical separation techniques, for instance, washing of the solid. The term nanocomposite seems the most appropriate for them.

It is important to point out that Gibb's rule is difficult to apply here since all these solids form under kinetically controlled conditions (see Section 6). They are far away from equilibrium and cannot be described as stable phases. Most of these solids are not crystalline and behave as amorphous materials with a morphology whose evolution depends on the experimental conditions.

This review is devoted to those nanostructural materials (or nanostructures) that correspond to monocomponent hybrid organic–inorganic solids elaborated from a molecular precursor used as a building block, and are designed to permit hydrolytic polycondensation around the organic unit (Scheme 14). More precisely, the preparation of monocomponent hybrid materials following Scheme 14 is determined by the chemistry of the building block. The first condition is the existence of nonhydrolyzable and nonoxidizable covalent bonds between the organic unit and the oxide matrix. The second condition is the presence in the building block of $\text{M}(\text{OR})_{2x-1}$ groups that allow formation of the oxide matrix by hydrolytic polycondensation.

Silicon chemistry provides one of the best solutions to this problem. The use of a $\text{Si}-\text{C}$ bond brings a stable link between the organic unit and the oxide matrix. The presence of a trifunctional silicon atom (SiX_3) provides access to the SiO_2 matrix by hydrolytic polycondensation. Trialkoxysilyl groups $\text{Si}(\text{OR})_3$ ($\text{R} = \text{Et}$, Me , $i\text{Pr}$) are used most commonly.^[53–55] However, SiCl_3 ^[56] and SiH_3 groups^[57] can also lead to silica matrices.

Interest in silicon is also based on the very facile formation of silicates and polysiloxanes by hydrolysis of functional groups at silicon. Moreover the $\text{Si}-\text{C}$ bond is highly resistant to hydrolysis and oxidation. Finally, the organic chemistry of silicon has been widely developed, and provides many chemical ways to introduce silicon-containing groups in an



Scheme 14. Schematic illustration of the difference between nanostructures and nanocomposites. In the case of nanocomposites (top) the organic units are embedded in the oxide matrix and can be separated from the matrix. For nanostructures (bottom; the rectangle represents a building block) a homogeneous system is formed in which the organic units are bound to the matrix and therefore nonseparable.

organic molecule^[58] for the synthesis of molecular building blocks.

This section focused on nanostructural materials obtained from precursors containing at least two $\text{Si}-\text{C}$ bonds. The case of monocomponent hybrids with only one $\text{Si}-\text{C}$ bond will be discussed separately (Section 5.2).

5.2. Monocomponent Hybrids with Only One $\text{Si}-\text{C}$ Bond

This case is the most commonly studied since monocomponent systems provide functionalized surfaces that are very useful for catalysis or separation technologies.^[59] This field was reviewed recently.^[52]

It is interesting that here the organic part of the precursor is located mainly at the surface after the solid forms. This fact can be demonstrated by time-of-flight secondary ion mass spectroscopy (TOF-SIMS). In all cases studied, TOF-SIMS permits detection of specific organic fragments.^[60] Some examples are given in Table 3.

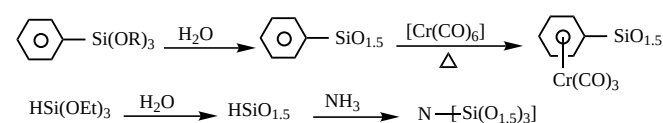
The TOF-SIMS data can be corroborated by other experimental data, such as the hydrophilicity and/or chemical reactivity. The fact that the hydrophilicity of silsesquioxanes ($\text{R}-\text{SiO}_{1.5}$) is poor is easily explained by the presence of hydrophobic organic groups at the surface of the solid, instead of hydrophilic OH groups expected for SiO_2 .^[60, 61, 63]

The chemical reactivity corroborates these facts: R groups located at the surface are chemically accessible and highly reactive. Two examples are the facile complexation of phenyl groups by $\text{Cr}(\text{CO})_3$ in phenyl silsesquioxanes,^[62] and the transformation of $\text{HSiO}_{1.5}$ into oxynitride by reaction in a simple flow of NH_3 ^[63] (Scheme 15).

Table 3. Main ions observed in the time-of-flight secondary ion mass spectra (TOF-SIMS) of various gels.^[a]

Hybrid gel	Ions
CH ₃ SiO _{1.5}	15 (CH ₃) ⁺ , 43 (SiCH ₃) ⁺
ICH ₂ CH ₂ CH ₂ SiO _{1.5}	127 I ⁺ , 141 (ICH ₂) ⁺ , 155 (ICH ₂ CH ₂) ⁺ (negative ions: 127 I ⁻ , 254 I ²⁻)
H ₂ NCH ₂ CH ₂ CH ₂ SiO _{1.5}	30 (CH ₂ =NH ₂) ⁺ , 44 (H ₂ NCH ₂ CH ₂) ⁺
[1-(NMe ₂ CH ₂)-2-(SiO _{1.5})]C ₆ H ₄	58 (CH ₂ =NMe ₂) ⁺ , 134 (C ₆ H ₅ CH ₂ NMe ₂) ⁺
C ₆ H ₅ NHCH ₂ CH ₂ CH ₂ SiO _{1.5}	106 (CH ₂ =NHC ₆ H ₅) ⁺
(C ₆ H ₅) ₂ PCH ₂ CH ₂ SiO _{1.5}	109 (C ₆ H ₅ PH) ⁺ , 123 (C ₆ H ₅ PCH ₃) ⁺
Fe[(η ⁵ -(C ₅ H ₄)(SiO _{1.5}))[η ⁵ -C ₅ H ₅]	183 (C ₁₂ H ₈ P) ⁺ , 185 [(C ₆ H ₅) ₂ P] ⁺
Fe[(η ⁵ -(C ₅ H ₃)(SiO _{1.5})(CH ₂ NMe ₂))[η ⁵ -C ₅ H ₃]	56 Fe ⁺ , 121 (C ₅ H ₃ Fe) ⁺ (negative ions: 65 (C ₅ H ₃) ⁻)
Fe[(η ⁵ -(C ₅ H ₃)(SiO _{1.5})(CH ₂ NMe ₂))[η ⁵ -C ₅ H ₃]	56 Fe ⁺ ; 58 (CH ₂ =NMe ₂) ⁺ ; 121 (C ₅ H ₃ Fe) ⁺

[a] The major fragments are shown in bold characters.



Scheme 15. Chemical evidence for the surface location of organic groups.

5.3. Identification of Nanostructural Materials

The identification of the hybrid materials must be considered at three levels: The first level is the classical identification of the solid in terms of macroscopic data (granulometry, specific surface area, porosity, density, hydrophilicity, etc.). This set of experimental data permits one to characterize the *texture* of the material, which corresponds to a macroscopic description of the amorphous solid.

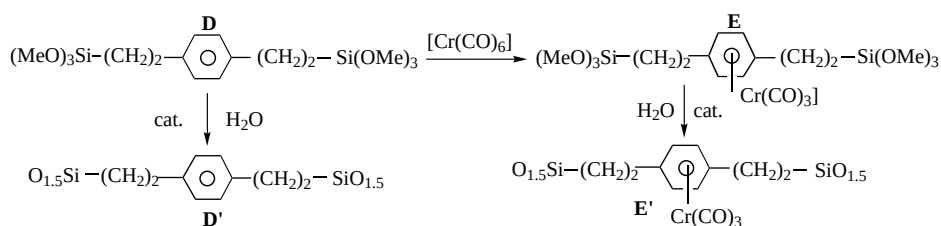
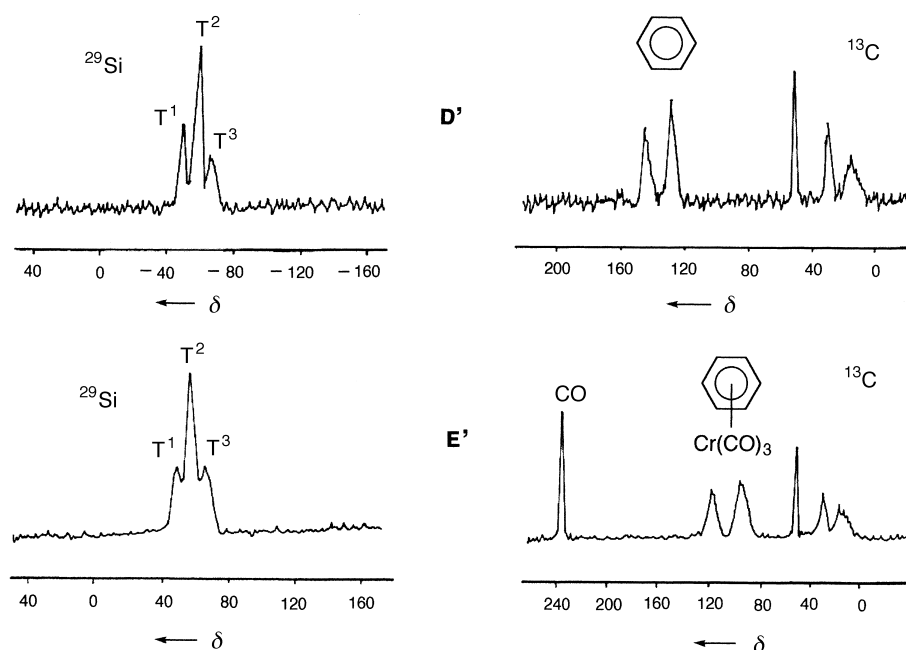
However, in the case of nanostructured hybrid materials, a microscopic aspect of characterization must be taken into account. There is the *molecular* level, which corresponds to the presence of the organic part in the solid and to the degree of polycondensation around the silicon atom. Moreover, organic moieties can exhibit a short- to medium-range order in the solid. There is the *structural* level, reflecting the possible relative arrangement of the organic units within the solid.

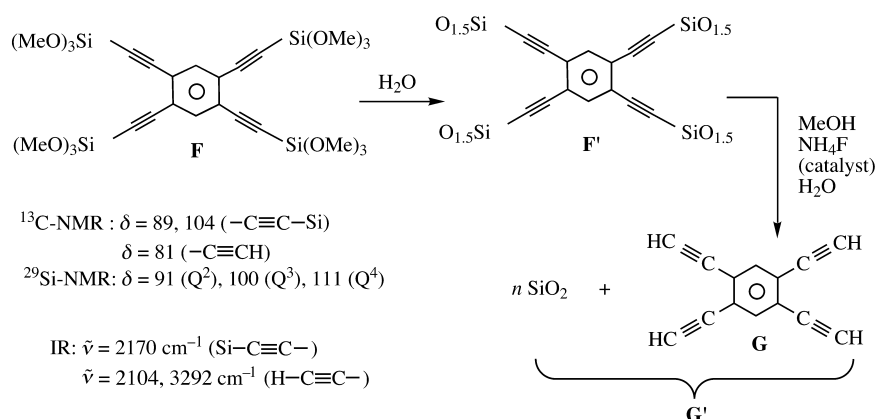
These three levels will be discussed successively. Sections 6 and 7 will deal with the identification of the texture of the material as well as the

evidence connected to possible structural organization within the solid.

Let us consider identification at the molecular level: Solid-state ¹³C NMR spectroscopy is a means of identifying the molecular units present in the solid, while ²⁹Si NMR spectroscopy provides information about the degree of polycondensation of the silica network. For example, two different precursors **D** and **E** can be used for the elaboration of two nanostructural materials; **E** is obtained by treatment of **D** with [Cr(CO)₆] (Scheme 16). After polycondensation the nanostructures **D'** and **E'** are formed from **D** and **E**.^[57b, 64] ²⁹Si CP-MAS NMR spectroscopy permits one to determine the degree of polycondensation (T^y) at silicon (Figure 8) and to show that this degree is highly dependent on experimental conditions (see Section 6). It is interesting that this method may allow quantitative evaluation when cross-polarization is not used.^[65] ¹³C CP-MAS NMR spectroscopy permits assignment of all the carbon atoms of the organic moiety.

A second example for the use of solid-state ¹³C and ²⁹Si NMR spectroscopy is as follows: In the course of our studies concerning the controlled elimination of organic units from


 Scheme 16. Preparation of the nanostructured materials **D'** and **E'**.

 Figure 8. The ²⁹Si and ¹³C CP-MAS NMR spectra of **D'** and **E'**. The T^y value (degree of polycondensation) of a carbon-bound Si center describes the number of tetrahedra: C-Si(OSi)_y(OR)_{3-y} with SiOSi bonds.

Scheme 17. Identification of molecule **G** encapsulated in silica.

hybrid materials, we used polyethynylated aromatic systems, which permit chemically induced selective elimination of the organic unit when NH_4F is used as catalyst^[57] (see Section 8). Scheme 17 shows the case of a tetraethynylbenzene. From precursor **F** the nanostructural material **F'** is obtained by hydrolytic polycondensation. After treatment with NH_4F as catalyst (2%) in the presence of MeOH and H_2O , the molecule **G** is formed.^[66]

Surprisingly, **G** could not be separated from SiO₂ regardless of the separation technique used. However, the IR and NMR features of solid **F'** and solid **G'** (silica-containing **G**) permit unambiguous identification of cleavage of the Si-CC bond and the presence of **G** inside the silica matrix. The complete transformation of T units into Q units is particularly illustrative and obvious in the ²⁹Si NMR spectrum.^[65] (The Q^x value of a Si center describes the number of directly bound SiO₄ tetrahedra: Si(OSi)_x(OR)_{4-x}, *x* = 0–4; the T^y value is analogous for carbon-bound Si centers: C–Si(OSi)_y(OR)_{3-y}, *y* = 0–3.) The disappearance of signals for SiC≡C and the presence of HC≡C characteristics are also evidenced by IR and ¹³C NMR spectroscopy (Scheme 17).

In conclusion, in all cases studied until now, the organic unit is always attached to the silica network without any transformation.^[53–55] The Si–C bond is stable enough to provide a homogeneous nanostructural material in which the organic moieties bound to two SiO_{1.5} units are distributed as elementary building blocks. Solid-state NMR spectroscopy permits one to verify that the building blocks are not chemically modified during elaboration of the solid.

The only case where Si–C bond cleavage is observed is when Si–C≡C single bonds are cleaved by nucleophilic attack of H₂O promoted by nucleophilic activation by F[–].^[57] This will be discussed in Section 8.

²⁹Si NMR spectroscopy, which reflects the degree of polycondensation, exhibits very great differences between the solids, depend-

ing to a large part on the nature of the organic unit. This point will be discussed in more detail in Section 6.

Most of the nanostructural materials that have been obtained and identified to date are presented in Scheme 18. The bisacetylenic structures will be described in Section 8.

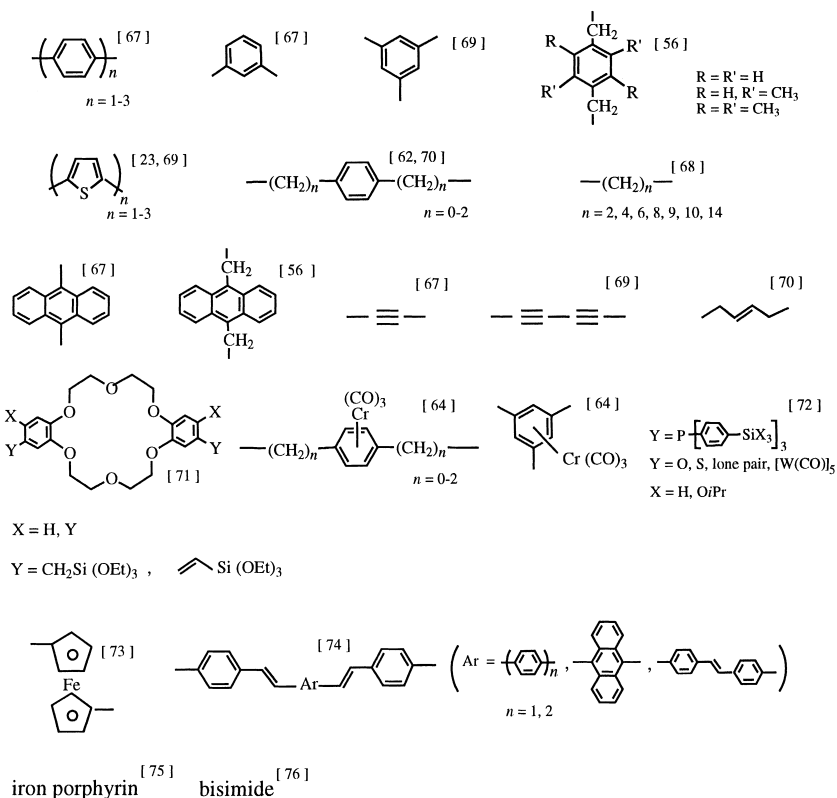
5.4. Identification of the Solid

The identification of solids is divided into two parts: The first corresponds to the macroscopic data that permit a description of the texture of the solid, for example specific surface area, granulometry, porosity, hydrophilicity. This aspect will be discussed in regard to kinetic control of the solids. The description of the solid corresponding to the between the organic units and the possible in the solid will be discussed in more detail in

6. Nanostructural Materials: Kinetic Control of the Formation of the Solid

6.1. Control of the Texture by Kinetics

It is well known that the texture of oxide materials obtained by sol – gel methods is highly dependent on the experimental



Scheme 18. Examples of organic units included in nanostructured materials.

conditions.^[43–47] Among others, the gelation time, specific surface area, porosity, and granulometry change with all the parameters used for hydrolytic polymerization (e.g. concentration of reagents and catalyst, solvent). The solids obtained are described as thermodynamically unstable materials.^[43]

In the case of nanostructures obtained from building blocks, the effect is more drastic since the nature of the organic moiety plays an important role in the polycondensation reaction and since polymerization occurs on six SiX groups in the case of bisilylated precursors (or more when tri- or polysilylated precursors are used). The texture of the solid is controlled by all the parameters able to modify the kinetics of polycondensation. This is illustrated by several examples in Table 4, in which the texture is shown to be a function of catalyst,^[77a,b] concentration of the reagents,^[77a,b] leaving groups,^[56, 57] organic spacer,^[77a,b] solvent,^[77a,b] and temperature.^[77a]

These results illustrate very well the very narrow connection between the macroscopic data that describe the texture of the solid and the microscopic parameters controlling the kinetics of all the chemical reactions involved in the elaboration of the solid: hydrolytic polycondensation leading to the colloids (sol formation) and cross-linking reactions transforming the sol into a gel.^[77]

Kinetic control is also illustrated by the effect of catalyst type on the degree of polycondensation, as measured by ²⁹Si

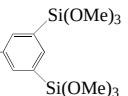
NMR spectroscopy. Figure 9 shows, for instance, the great difference in the solid obtained simply by changing the counterion used in nucleophilic catalysis; all other parameters were identical.^[64, 77]

All these experiments are reproducible. However, the reproducibility in texture and polycondensation is obtained only when the experimental conditions (including the purity of chemicals) are carefully controlled.

6.2. Effect of Weak Interactions on the Organization of the Solid

Another interesting example of the close relationship between the texture of the material and the kinetic parameters is the effect due to weak interactions. In the case of SiO₂, the effect of weak interactions is best illustrated by the preparation of silicas with a controlled pore size and shape through the use of surfactants and micellar media. In the case of hybrid systems, this effect can be best understood by studying solid formation using charge transfer complexes. It is known that terthiophene and 7,7,8,8-tetracyano-*p*-quinodimethane (TCNQ) form such complexes.^[78] As illustrated in Scheme 19, bis(trimethoxysilyl)terthiophene (**H**) gives charge complex (**I**) upon reaction with TCNQ.^[23c] By cohydrolysis with Si(OMe)₄, a solid (**J**) is obtained, which exhibits a poor

Table 4. Relationship between kinetic parameters and the texture of the hybrid materials.

Precursor	<i>c</i> [mol L ⁻¹]	Solvent	Catalyst ^[a]	<i>t</i> ^[b] [min]	<i>S</i> ^[c] [m ² g ⁻¹]
(MeO) ₃ Si—  —Si(OMe) ₃	0.5	MeOH	NH ₄ F (10 ⁻²)	60	558
	1	MeOH	Bu ₄ NF (10 ⁻²)	4	1050
	0.5	MeOH	Bu ₄ NF (10 ⁻²)	160	550
	1	THF	Bu ₄ NF (10 ⁻²)	4	1240
	0.5	THF	Bu ₄ NF (10 ⁻²)	135	370
	0.5	THF	NH ₄ F (10 ⁻²)	10	388
	0.5	THF	NH ₄ OH (10 ⁻²)	95	380
(MeO) ₃ Si(CH ₂) ₂ —  —(CH ₂) ₂ Si(OMe) ₃	0.5	MeOH	Bu ₄ NF (10 ⁻²)	720 ^[d]	< 10
	0.5	MeOH	Bu ₄ NF (10 ⁻²)	45	< 10
	1	MeOH	Bu ₄ NF (10 ⁻²)	10 ^[d]	< 10
	0.5	THF	Bu ₄ NF (10 ⁻²)	< 5	565
	1	THF	Bu ₄ NF (10 ⁻²)	2	531
	0.5	THF	NH ₄ F (10 ⁻²)	3900	< 10
H ₃ Si—  —SiH ₃	0.5	THF	Bu ₄ NF (10 ⁻³)	300	931
	1	THF	Bu ₄ NF (10 ⁻³)	0.2 ^[e]	1200
	0.5	THF	[(Ph ₃ P) ₃ RhCl] (10 ⁻³)	5160	54
	1	THF	[(Ph ₃ P) ₃ RhCl] (10 ⁻³)	1380	360
H ₃ Si(CH ₂) ₂ —  —(CH ₂) ₂ SiH ₃	0.5	THF	Bu ₄ NF (10 ⁻³)	35	362
	1	THF	Bu ₄ NF (10 ⁻³)	25	494
	0.5	THF	[(Ph ₃ P) ₃ RhCl] (10 ⁻³)	30	100
	1	THF	[(Ph ₃ P) ₃ RhCl] (10 ⁻³)	20	518
(MeO) ₃ SiCH ₂ —  —CH ₂ Si(OMe) ₃	0.5	MeOH	Bu ₄ NF (10 ⁻²)	45 ^[d]	< 10
	1	MeOH	Bu ₄ NF (10 ⁻²)	20 ^[d]	< 10
	0.5	THF	Bu ₄ NF (10 ⁻²)	< 1	277
	1	THF	Bu ₄ NF (10 ⁻²)	< 1	12
(MeO) ₃ Si—  —Si(OMe) ₃	0.5	MeOH	Bu ₄ NF (10 ⁻²)	7	1018
	1	MeOH	Bu ₄ NF (10 ⁻²)	1	1152 ^[f]
	0.5	THF	Bu ₄ NF (10 ⁻²)	4	766
	1	THF	Bu ₄ NF (10 ⁻²)	1	882

[a] The value in parentheses is the concentration of the catalyst [mol L⁻¹]. [b] Gel time. [c] Specific surface area. When the solid exhibits a specific surface area higher than 10 m² g⁻¹ the porosity is dispersed from micro- (< 20 Å) to mesoporosity (200 Å). [d] Precipitate. [e] At – 15 °C. [f] The pore size is between 40 and 80 Å.

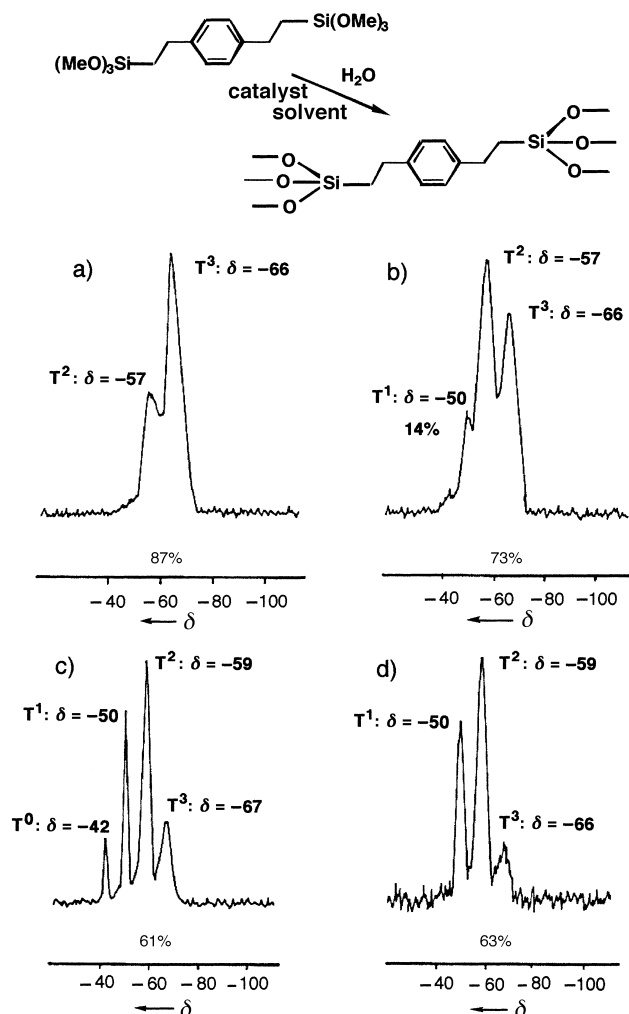
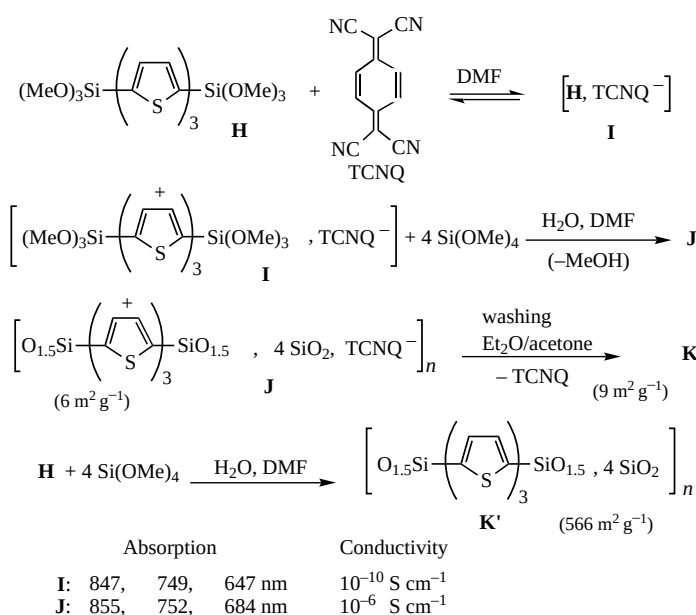


Figure 9. ^{29}Si NMR spectra showing the effect of kinetic parameters on the ratio of polycondensation at silicon: a) THF/ $n\text{Bu}_4\text{F}$; b) THF/ NH_4F ; c) MeOH/ $n\text{Bu}_4\text{F}$; d) MeOH/ NH_4F .



Scheme 19. Effect of the charge-transfer complex [terthiophene · TCNQ] on the formation of the solid.

specific surface ($6 \text{ m}^2 \text{ g}^{-1}$), a visible absorption similar to that of **I**, and a higher conductivity than **I** (10^{-6} instead of 10^{-10} cm^{-1}). The absorption spectrum provides evidence that the charge transfer complex is maintained in the solid. Upon washing with diethyl ether/acetone, a solid (**K**) is obtained and there is a disappearance of both the conductivity and the visible spectrum. This corresponds to destruction of the charge transfer complex.^[23c] This experiment illustrates how weak this interaction is since a simple washing permits its elimination. However, the key point is the comparison of the Brunauer–Emmett–Teller (BET) surface area measured for **J** and **K** (6 and $9 \text{ m}^2 \text{ g}^{-1}$, respectively). A value of $566 \text{ m}^2 \text{ g}^{-1}$ is observed for the solid **K'**, which results from hydrolytic polycondensation performed without TCNQ and under the experimental conditions used for **J**. The two solids **K** and **K'** have the same IR and NMR features, but are very different materials from the point of view of texture.

In conclusion, all these experiments suggest that the formation of the solid is controlled by the kinetics of different chemical steps leading to the solid: polymerization, polycondensation, formation and collapse of colloids. Thus, the texture of the solid might be considered as the result of a very complex kinetic process in which all the experimental parameters play a role. We have checked that the texture can be reproduced by controlling the reaction parameters very carefully. We have observed that it is possible to obtain the same specific surface area and porosity when the experiments are strictly repeated under the same conditions. The preparation must be carried out with the same precision as for physico-chemical experiments. The purity of the solvent (water is a reagent), the purity and concentration of the catalyst and reagents (including water), the temperature, the method of mixing, and the mode of stirring (ultrasonic stirring leads to different textures) are among the factors that could potentially modify the texture. In other words, reproducibility is always possible, but predictability is not. To date, very little is known about the precise mechanisms of polycondensation (initial steps) and aggregation of colloids (gelation). Oxide synthesis by sol–gel processes is considered to lead to unstable solids.^[43] The concept of kinetically controlled solids is more useful since it introduces the possibility of controlling the texture of the solid experimentally by a large number of methods: All the parameters influencing the kinetics of formation listed can be adjusted to control the texture.

7. Short-Range Organization in the Solid

7.1. Generalities

All the nanostructural materials described until now appear as totally amorphous solids since their XRD patterns exhibit signals corresponding to those for amorphous silica. However, XRD patterns are only observed in the case of a solid that exhibits long-range organization. In other words, classical XRD only permits the study of a long-distance organization. Nowadays several methods can be used to probe the “molecular” level (solid-state NMR, X-ray absorption, spectroscopies like XANES and EXAFS). There is no general

physical method that permits study of a short-range organization in solids. Only small-angle X-ray scattering (SAXS) is available for such a purpose; however, until now this technique was used mainly for the macroscopic description of materials.

7.2. Influence of the Molecular Structure on the Solid Organization

In the case of bis-trialkoxysilylated building blocks used for elaboration of nanostructural materials, some preliminary observations have shown that the molecular geometry is a very important parameter in controlling solid organization. Two examples can be given: The first example concerns the results obtained by TOF-SIMS analysis of precursors containing two $\text{Si}(\text{OR})_3$ groups. As reported in Section 5.2 the monosilylated precursors $\text{R}-\text{Si}(\text{OR})_3$ form solids in which the R groups are mainly located at the surface. This was evidenced by TOF-SIMS, which permits detection of mass fragments formed from R.^[60a] With bisilylated systems, the mass fragments corresponding to the organic unit can be detected in only a few cases. Table 5 shows results obtained with three different solids **L'**, **D'**, and **M'**.^[60b]

Table 5. Fragments observed for **L'**, **D'**, and **M'** by TOF-SIMS.

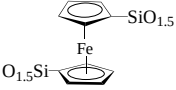
	Xerogel	Ions
L'	$\text{O}_{1.5}\text{Si}-\text{C}_6\text{H}_4-\text{SiO}_{1.5}$	45 (SiOH^+), 59 (SiOCH_3^+)
D'	$\text{O}_{1.5}\text{Si}(\text{CH}_2)_2-\text{C}_6\text{H}_4-(\text{CH}_2)_2\text{SiO}_{1.5}$	77 (C_6H_5^+), 91 (C_7H_7^+)
M'		45 (SiOH^+)

Table 5 illustrates clearly that each case presented here corresponds to a different arrangement of the organic unit in the solid. The TOF-SIMS of **L'** and **M'** do not exhibit any fragment corresponding to the molecular units attached to silica, suggesting a solid arrangement in which these moieties are located in the core of the solid. This location can be observed in the case of **M'** by electrochemistry.^[73] The cyclic voltammogram of **M'** is characteristic of diffusion-controlled charge transfer: The anodic peak current is linearly proportional to the square root of the scan rate (Figure 10).

The second example is the comparison between **L'** and **D'**: Although the two precursors **L** and **D** are very similar, the solids **L'** and **D'** obtained under the same experimental conditions are completely different. As illustrated in Scheme 20 they behave quite differently.^[64]

Solid **L'** is hydrophilic and has a high specific surface area ($550 \text{ m}^2 \text{ g}^{-1}$). The SIMS does not exhibit any fragments that derive from C_6H_4 ; only SiOH fragments can be detected. Interestingly, **L'** does not react with $[\text{Cr}(\text{CO})_6]$, in agreement

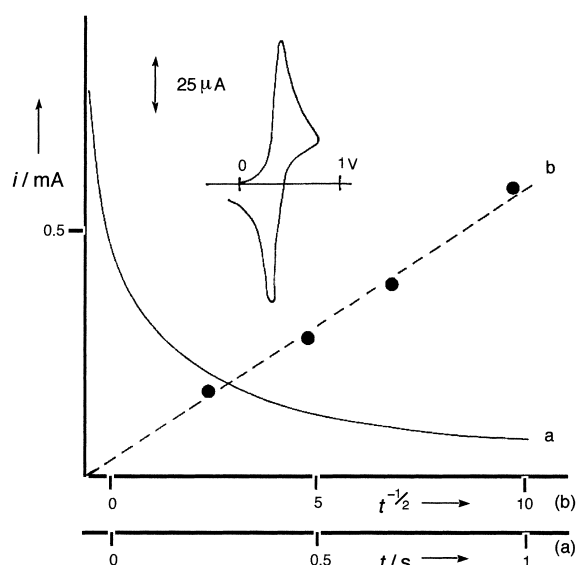
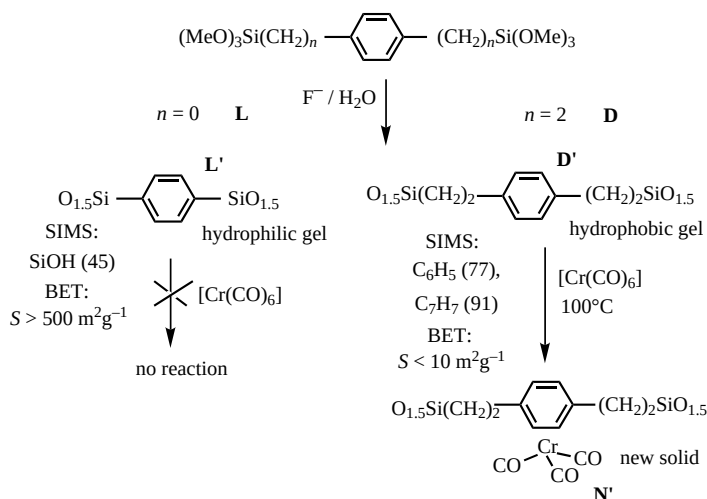


Figure 10. Typical chronoamperometric and linear Cottrell curves of a gel prepared from a bisilylated ferrocene precursor: a) plot of current i versus time t ; b) plot of current i versus $t^{-1/2}$.



Scheme 20. Reactions of gels containing bisilylated phenylene groups.

with the fact that the organic groups are embedded in the core of the solid.

In contrast, **D'** is a hydrophobic resin with a very poor specific surface area. The TOF-SIMS mass fragments corresponding to the phenyl and benzyl units can be detected; moreover the peak for $\text{Si}-\text{OH}$ peak is not detected.^[60b] These results suggest strongly that the organic groups are located at the surface of the solid. The reactivity of **D'** is in good agreement with this assumption, since the reaction with $[\text{Cr}(\text{CO})_6]$ takes place with good yield to provide the solid **N'** (Scheme 20), in which most of the aromatic groups are complexed with $\text{Cr}(\text{CO})_3$ units. This facile complexation is only possible when the aromatic units are accessible.

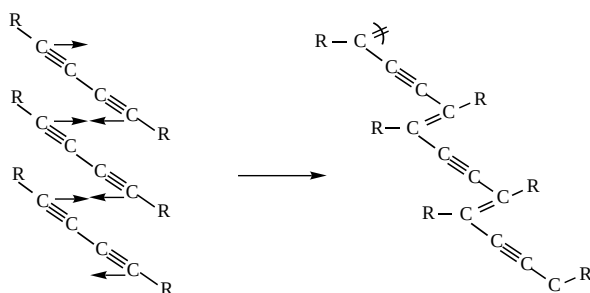
These two examples illustrate very well the importance of the organic unit in controlling the solid arrangement under identical processing conditions. The rigid precursor **L** leads to a solid **L'** that is completely different from the solid **D'** obtained by polycondensation of the more flexible **D**.

7.3. Chemical Evidence for Short-Range Organization in the Nanostructure

To circumvent the lack of physical methods, the chemical reactivity of the organic component of hybrid solids can provide evidence of short-range organization in amorphous nanostructural materials. The organic moieties can be chosen for selective/specific interactions easily detected spectroscopically and induced by well-defined conditions.

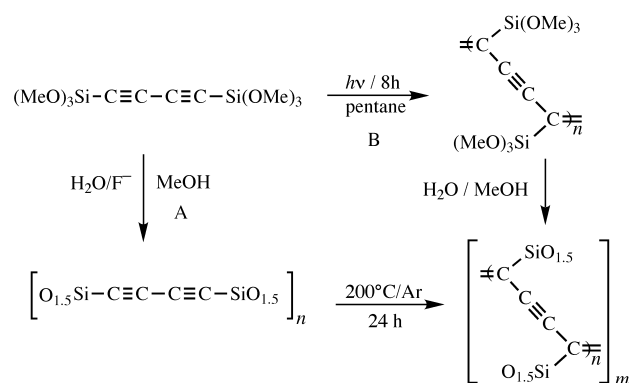
7.3.1. Evidence for Cross-Linking between Diynes Units

As illustrated in Section 3.2, diynes polymerize topochemically by 1,4-addition to form enynes.^[29, 30, 69b] This reaction requires that the $C\equiv C-C\equiv C$ units be parallel^[32] (Scheme 21).



Scheme 21. Topochemical polymerization of diacetylene units.

A gel containing diacetylene units was prepared from 1,4-bis(trimethoxysilyl)buta-1,3-diyne (^{13}C NMR: $\delta = 79.4, 87.8$ ($C\equiv C-C\equiv C$); IR: $\tilde{\nu} = 2202, 2091\text{ cm}^{-1}$; Scheme 22). Upon heating at 200°C under argon, enynes form and the associated



Scheme 22. Synthesis of gels containing bisacetylene units.

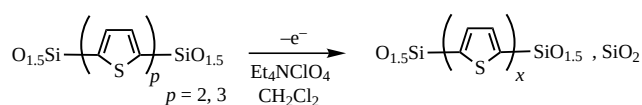
cross-linking is detected by spectroscopy (^{13}C NMR: $\delta = 133$; ^{29}Si NMR: $\delta = -74$; IR: $\tilde{\nu} = 2169\text{ cm}^{-1}$).^[69b] Moreover, the same spectroscopic features result regardless of whether gelation occurs before cross-linking (route A) or whether cross-linking is induced by irradiation before gelation (route B).

One can compare this polymerization with the cross-linking observed for the polymers $[-SiR_2-C\equiv C-C\equiv C-]_n$ discussed in Section 3.2. Here, the DTA curve is highly dependent on the organization in the solid.^[29, 30] A sharp peak at 200°C is observed for the semicrystalline $SiMe_2$ -containing polymer

C1, and a broad peak appears at 350°C for the amorphous $Si(SiMe_3)_2$ -containing polymer (see Scheme 5). In the case of gels the cross-linking reaction starts at lower temperatures, the DTA exotherm occurs between 100 and 450°C with a maximum at about 250°C . The facile reactions between the diyne fragments at relatively low temperatures within the amorphous gel are indicative of a favorable arrangement of the diyne moieties. Enyne formation involves alignment of several diacetylene units within the solid. Since the polycondensation at silicon is mainly T^2 ($C-Si(OSi)_2OR$) without any T^0 ($C-Si(OR)_3$) observed in the solid, the organic units cannot move in the solid. Thus, these results suggest the presence of short-range order in the nanostructural material, which permits the addition between the organic units.

7.3.2. Polymerization of Thiophene Units in the Solid

Polythiophenes are obtained by electropolymerization,^[79] and silylated thiophenes have been shown to be very efficient precursors, leading to polymers in which the thiophene units are bonded to each other mainly at the α position.^[28a, 80–83] Gels containing bissilylated mono-, bis-, and terthiophene have been prepared. The ^{13}C and ^{29}Si CP-MAS NMR spectra show that the structure of the precursor remains intact in the solid without cleavage of the Si–thiophene bond. The electrochemical oxidation of gels deposited as films on electrodes leads to rapid polymerization of the thiophene units in the hybrid matrix^[23c] (Scheme 23).



Scheme 23. Electropolymerization of gels containing silylated thiophenes.

The same reaction is also possible by chemical oxidation using $FeCl_3$ as the oxidizing agent. The polythiophenes formed in situ by the two methods cannot be separated from the solid; they were identified by Raman resonance spectroscopy ($\tilde{\nu} = 1458, 1220, 1171, 1047, 700, 682, \text{ and } 652\text{ cm}^{-1}$) and visible absorption.^[23c]

Since polymerization occurs on bissilylated units the polythiophene obtained is terminated by a $SiO_{1.5}$ moiety at each end. This is why it is impossible to separate it from silica, and why it is not possible to characterize the degree of polymerization.

Thus, the fast polymerization occurring in the gel, where the mobility of thiophene units is highly restricted, suggests strongly the presence of short- to medium-range organization within the solid. This conclusion is reinforced when the mechanism of polymerization is taken into account. It is known that oxidative electropolymerization occurs by coupling of two radicals cations,^[23c, 82, 83] which has severe stereoelectronic requirements (Figure 11). This coupling involves

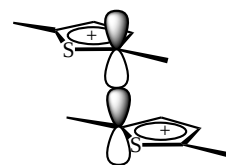


Figure 11. Stereoelectronic requirements for polymerization.

both the close proximity and a parallel arrangement of the two thiophene units.

Thus, the polymerization observed in the cross-linked nanostructural solid suggests strongly the existence of a medium-range organization of thiophene units inside the solid.

8. Control of the Porosity in Silica by Organic Templates

8.1. Generalities

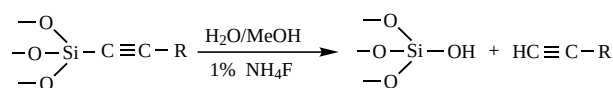
Molecular imprinting is an attractive topic for organic chemistry^[66, 84, 85] since the imprinting of a molecule in a solid can open up interesting possibilities for catalysis and highly selective separations. However, the main difficulties are in finding reliable methods for building up a solid around the molecule (or the group of molecules) without transformation of the geometry and highly selective methods that permit elimination of the molecular unit without any reorganization of the solid network.

Controlling porosity in silica by organic molecular templating is a topic connected to this problem. Many attempts have been made to control the pore size distribution in silica derived by sol–gel techniques.^[86] The general method is to form a hybrid solid by introducing organic templates including micelles, followed by oxidative elimination of the organic component (sacrificial route).^[86–88] The solids used are mostly nanocomposites. However, some nanostructured solids have also been studied, and several narrow pore size distributions have been obtained by these methods.^[84, 85]

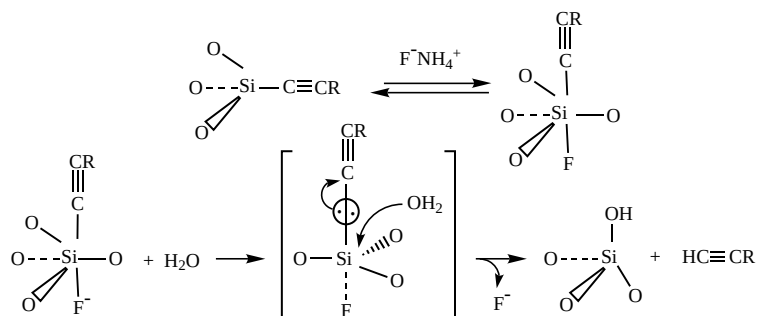
In the course of studies concerning hybrid materials, we sought to develop smooth chemical methods that permitted elimination of the organic unit from a nanostructured material.^[69] The aims of the project were: 1) to find an alternative to the sacrificial route that allows recovery of the organic component under mild conditions; 2) to compare the porosities obtained by oxidation with those obtained by chemical elimination; 3) to consider as building blocks molecular precursors with a rigid and well-defined geometry (linear, planar, or spherical) as well as a very precise size in order to make a more direct comparison between pore size and molecule size; and 4) to compare the porosities obtained from thermal and chemical elimination methods with those occurring from molecular precursors with more flexible organic units.

8.2. Selective Chemical Cleavage

In previous work^[69a] we described methods of cleaving Si–C≡C single bonds under mild conditions using NH₄F as catalyst and H₂O as a reactant (Scheme 24). These catalytic conditions correspond to nucleophilic activation by F[−] for nucleophilic substitution at silicon. This well-documented process^[91] (Scheme 25) corresponds to reversible coordina-



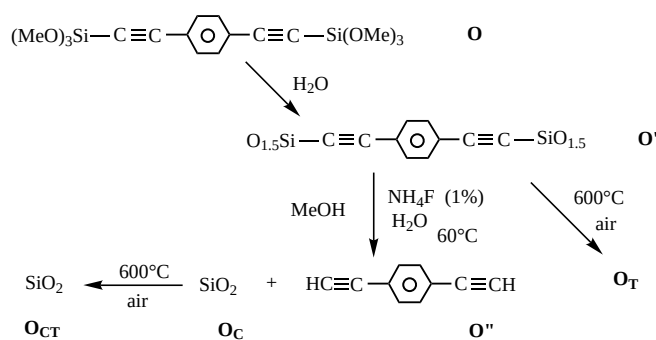
Scheme 24. Catalytic and mild cleavage of Si–C≡C single bonds



Scheme 25. Mechanism of nucleophilic catalysis by F[−] for cleavage of Si–C≡C single bonds.

tion of F[−] at silicon, leading to a pentacoordinated center in which the negative charge is delocalized on the substituents bound to silicon. In the second step, nucleophilic attack of H₂O at Si cleaves the Si–C bond with formation of Si–OH and HC≡C–R via a hexacoordinated intermediate.

This selective cleavage was tested with the most simple rigid hybrid (Scheme 26). The precursor **O**, containing two ethynyl groups, generates solid **O'** upon hydrolysis performed without any catalyst. The treatment of **O'** with NH₄F in the presence of H₂O/MeOH at 60 °C results in cleavage of the Si–C bonds and allows almost quantitative recovery of **O''** from **O'** with formation of a templated SiO₂ residue **O_C**.^[84]



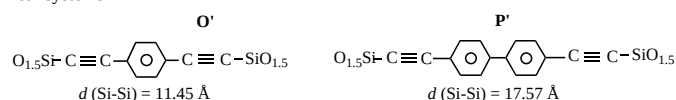
Scheme 26. Selective and quantitative cleavage of the Si–C≡C single bond. **O_T** = SiO₂ solid obtained from precursor **O** after thermal treatment; **O_C** = SiO₂ solid obtained from precursor **O** after chemical treatment; **O_{CT}** = SiO₂ solid obtained from precursor **O** after chemical treatment followed by thermal treatment.

The ¹³C CP-MAS NMR spectrum of **O_C** does not exhibit any signals attributable to **O**. Only signals for the unhydrolyzed OCH₃ groups are observed. After treatment of **O_C** at 600 °C in air, **O_{CT}** is obtained. This silica is carbon-free (less than 0.2 %). Another carbon-free silica, **O_T**, can be obtained by thermal treatment (600 °C in air) of the hybrid material **O'**.

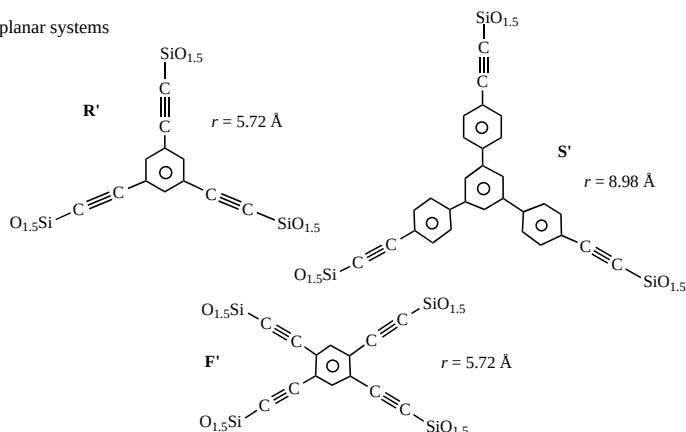
8.3. Studies of Nanostructural Materials

Nanostructural materials obtained using molecular building blocks that have a well-defined size and geometry have been studied and compared to more flexible systems. All the solids were obtained from molecular precursors by hydrolysis without catalysts. They are listed in Scheme 27.^[66]

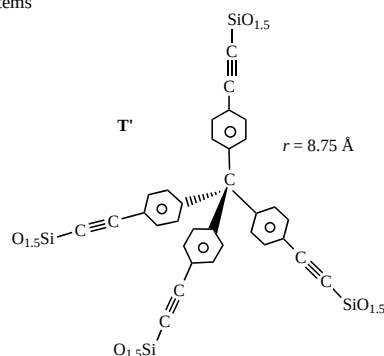
linear systems



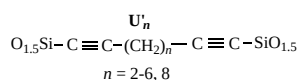
planar systems



globular systems



flexible systems



Scheme 27. Bisacetylenic hybrid materials prepared and treated for elimination of the organic component.

8.4. Results

Scheme 26 shows that depending on the treatment used, **O** provides three kinds of silica: **O_T** (thermal treatment), **O_C** (chemical treatment), and **O_{CT}** (chemical followed by thermal treatment). The same treatment has been carried out on most of the solids listed on Scheme 27.

The first experiments performed were measurements of specific surface areas of the silicas obtained after chemical

treatment. In all cases studied, the elimination of the organic component corresponds to a drastic increase in porosity (Table 6).

Table 6. Specific surface areas *S* of the hybrid materials before treatment and after chemical and thermal treatment.

	<i>S</i> ^[a]	After chemical treatment ^[b]	After thermal treatment ^[c]
O'	19	656	480
R'	45	617	440
S'	25	736	–
T'	717	1090	–
U'₃	< 10	685	–
U'₄	< 10	440	345

[a] Specific surface area (BET) [m² g^{−1}]. [b] NH₄F, H₂O/MeOH, 60 °C. [c] 600 °C in air.

Let us consider now, as an example, the results obtained in the case shown in Scheme 26.^[84] Figure 12 shows the pore size distribution of these materials. Clearly there is a great difference between **O_T** on one hand and **O_C** and **O_{CT}** on the

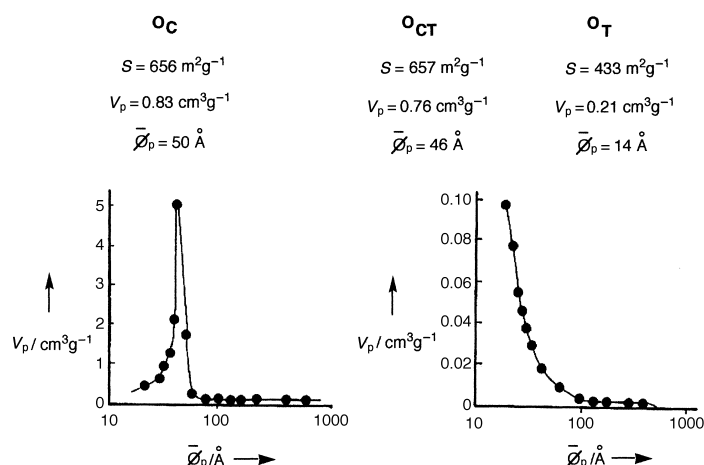


Figure 12. Studies on the textures of silicas obtained from nanostructured hybrid **L**. Comparison of thermal and chemical treatment. *S* = surface area, *V_p* = pore volume, $\bar{\varnothing}_p$ = mean pore diameter.

other. The silica **O_T** exhibits a pore size distribution in the range from about 90 Å to the level of microporosity (< 20 Å). In contrast, **O_C** exhibits a narrow porosity where the maximum is 50 Å. Interestingly both **O_C** and **O_{CT}** (following thermal treatment of **O_C** at 600 °C in air) exhibit almost similar textures (BET, porous volume). The porosity of **O_{CT}** is also narrow (46 Å).

The similarity between **O_C** and **O_{CT}** is supported by SAXS data. This technique permits a direct comparison between the two solids, which exhibit the same diffraction diagram. These data are completely different from that observed for silica obtained by the pyrolytic route (**O_T**; Figure 13), and they are in agreement with the BET results.^[84]

The treatment of the SAXS data^[89] obtained for **O_C** and **O_{CT}** suggests that both silicas follow Porod's law (a slope of *q*^{−4} for the linear correlation between ln(*qi*) versus *q*^{2[90]}), corresponding to a clear-cut electronic density between the solid

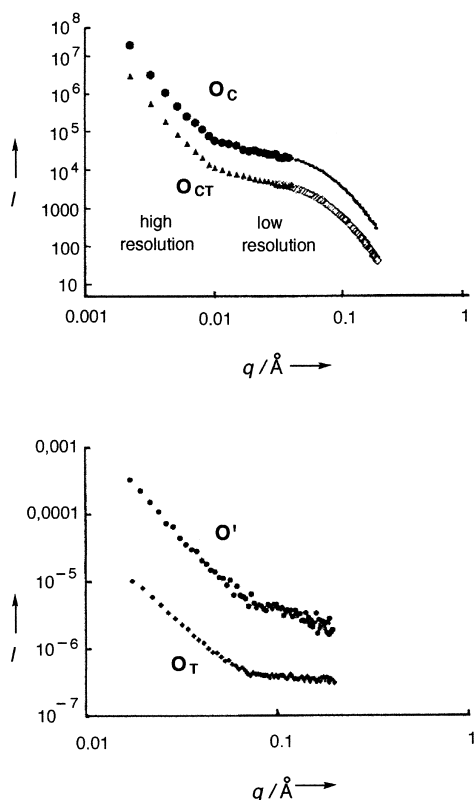


Figure 13. Small-angle X-ray scattering obtained with the solids $\mathbf{O}_C$, $\mathbf{O}_{CT}$ and $\mathbf{O}_T$; plots of intensity I versus the scattering vector q , log scale. a.u. = arbitrary units.

silica and the void. This observation is evidence of a smooth surface without roughness and a homogeneous geometry of the pores. Thus the texture of these two silicas may be described as elongated cylinders. A bimodal distribution of pore sizes ((42 ± 2) and (32 ± 2) Å) can be calculated for $\mathbf{O}_C$ and $\mathbf{O}_{CT}$, respectively. The value of 42 Å can be attributed to porosity by comparison with the BET values (50 Å for $\mathbf{O}_C$ and 46 Å for $\mathbf{O}_{CT}$). It is not surprising to obtain a different value by SAXS and BET; SAXS focuses on the dominant porosity and the BET provides a measure of the accessible porous volume and is not a direct measure of the pore size. The total value of 32 Å might be assigned to the solid phase surrounded by pores.^[84] The results of transmission microscopy support these conclusions (Figure 14).

As expected, the SAXS data for $\mathbf{O}_T$ exhibits completely different features: A power law of $q^{-3.2}$ is observed, suggesting the possibility of a fractal surface or bushy behavior; that is a surface without regularity and defined geometry.^[84]

The same experiments were performed with the other hybrid solids listed in Scheme 27. Two examples are considered here: In the first instance, the solids are obtained from rigid building blocks having a precise size and geometry ($\mathbf{O}$ to $\mathbf{T}$). In all cases the results obtained are similar to those described for $\mathbf{O}$: the BET measurements show that solids obtained after chemical treatment ($\mathbf{R}_C$) and solids resulting from postthermal treatment ($\mathbf{R}_{CT}$) exhibit narrow and similar pore size distribution. In contrast, the solids resulting from direct pyrolysis at 600 °C in air ($\mathbf{R}_T$) show a broad pore size distribution with curves similar to those observed for $\mathbf{O}$ (Table 7).

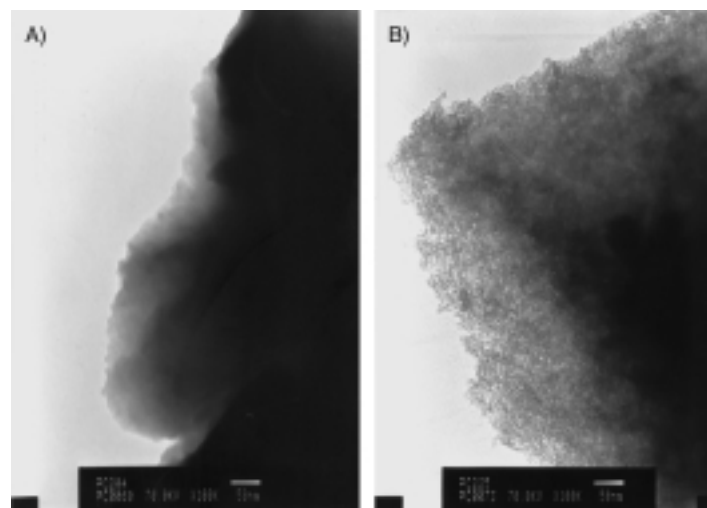


Figure 14. Micrograph of the hybrid material (A) compared to the micrograph of the silica $\mathbf{O}_{CT}$ (B).

Table 7. Specific surface area S and pore volumes V_p of the silicas obtained after chemical and thermal treatment.

Starting material	Silica	S [m ² g ⁻¹]	V_p [cm ³ g ⁻¹]
$\mathbf{O}'(19)$	$\mathbf{O}_C^{[a]}$	656	0.83
	$\mathbf{O}_{CT}^{[b]}$	657	0.76
	$\mathbf{O}_T^{[c]}$	483	0.24
$\mathbf{R}'(45)$	$\mathbf{R}_C^{[a]}$	617	0.68
	$\mathbf{R}_{CT}^{[b]}$	610	0.66
	$\mathbf{R}_T^{[c]}$	440	0.20
$\mathbf{S}'(25)$	$\mathbf{O}_C^{[a]}$	736	1.1
	$\mathbf{S}_{CT}^{[b]}$	706	1.15
	$\mathbf{S}_T^{[c]}$	—	—
$\mathbf{T}'(717)$	$\mathbf{P}_C^{[a]}$	1090	1.05
	$\mathbf{T}_{CT}^{[b]}$	1070	0.9
	$\mathbf{T}_T^{[c]}$	—	—

[a] Chemical treatment. [b] Chemical treatment followed by thermal treatment at 600 °C in air. [c] Direct thermal treatment at 600 °C in air.

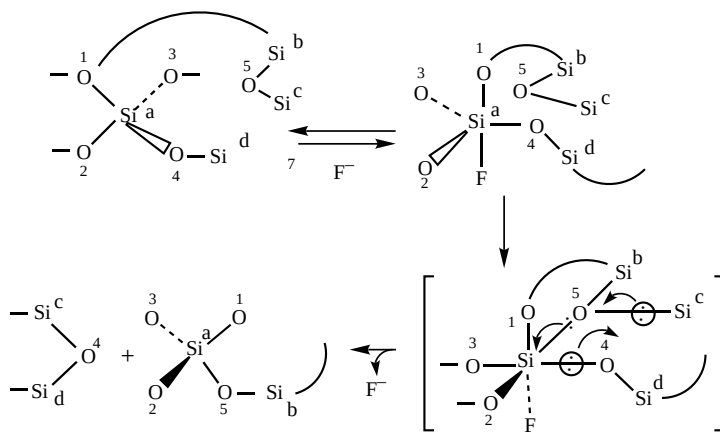
The case of the solid $\mathbf{F}'$ is an exception. As presented in the Section 5.3 cleavage occurs, but the organic molecule cannot be separated from silica.

The silicas obtained from the hybrid solids corresponding to the flexible building blocks $(\text{MeO})_3\text{SiC}\equiv\text{C}(\text{CH}_2)_n\text{C}\equiv\text{C}-\text{Si}(\text{OMe})_3$, $\mathbf{U}_n$ ($n = 2-6, 8$) exhibit completely different behaviors.^[84b, 85] Thermal treatment leads in all cases to the same kind of BET, showing a wide pore size distribution in the range of microporosity (<15 to 80 Å). These curves are similar to those obtained with silicas $\mathbf{O}'_T$ to $\mathbf{T}'_T$ resulting from the thermal treatment of hybrid solids $\mathbf{O}'$ to $\mathbf{T}'$. However, the silicas resulting from chemical treatment, $\mathbf{U}_{nC}$ or $\mathbf{U}_{nCT}$, do not exhibit a pore size distribution as narrow as those observed for the solids obtained from rigid building blocks. This distribution lies from 27 Å ($n = 2$) to 70 Å ($n = 4$). The SAXS data for $\mathbf{U}'_6$ after chemical treatment^[85] follow Porod's law with a clear-cut density between the solid silica and the void. Moreover, they show that the geometry of the pores can be described as consisting of elongated cylinders with a diameter of (64 ± 2) Å. This value is in the range of the maximum value measurable by BET (70 Å).

In all cases, the good agreement between BET and SAXS ensures that there are no artifacts in the porosity results. The main observations are as follows:

- 1) In the case of precursors having a well-defined size and rigid geometry, there is a great difference between the narrow porosities observed with chemical elimination versus the wider distribution observed after the sacrificial elimination by oxidation in air.
- 2) It is also interesting to point out the great similarity in the porosity dispersion curves observed after thermal treatment in all cases. All these curves are more or less identical, regardless of the nature of the molecular precursor (rigid or flexible) and its size and geometry. These results and the wider distribution of the pores suggest that thermal treatment cannot be used for molecular imprinting. The silica network does not correlate with the molecular geometry, but is certainly controlled by the thermal rearrangement of SiO_2 .
- 3) The geometry of the precursor is also of importance since only rigid organic components give narrow pore size distributions, regardless of their geometry (linear, planar, or spherical). Flexible structures lead to a wider pore size distribution which exhibits a maximum.
- 4) Although rigid precursors lead to a narrow pore size distribution, there is a large discrepancy between the size of the pores and the size of the organic moiety. The pores obtained are in all cases larger than the molecules used to elaborate the building block.

One possible explanation may be the crossover of two features. The first is the possible short-range organization in the solid occurring during hydrolytic polycondensation of the precursor, which might imply the elimination of more than one organic unit (see Section 7). The second is connected to the reorganization of the solid network during the chemical cleavage of $\text{Si}-\text{C}$ bonds. This chemical reaction catalyzed by NH_4F transforms $\text{R}-\text{SiO}_{1.5}$ into SiO_2 with formation of $\text{Si}-\text{OH}$ bonds (Schemes 24 and 25). This reaction corresponds to an increase in polycondensation at silicon as observed by ^{29}Si NMR spectroscopy.^[66–84a] In competition, the coordination of F^- at silicon can induce a catalytic redistribution of the oxygen atoms around silicon (Scheme 28).



Scheme 28. Reorganization of the silica network catalyzed by F^- .

This redistribution permits complete reorganization of the remaining SiO_2 through formation of new $\text{Si}-\text{O}$ bonds and cleavage of others. As shown in Scheme 28, this process may result in cleavage of chains with formation of rings (or vice versa), inducing the evolution of the solid. Under these circumstances it is not surprising to find pores larger than the size of the molecule.

All these experiments show that the silica is certainly not the best material for molecular imprinting because of its great aptitude to reorganization. However, these results open up interesting perspectives for the rearrangement of silica networks catalyzed by F^- . This rearrangement corresponds to a chemically induced transformation in the texture of a xerogel, occurring by a mechanism which has been established in silicon chemistry. The redistribution induced at silicon by nucleophilic activation is a well-documented process.^[91]

9. Summary and Outlook

This review presents some perspectives on molecular chemistry in the field of material science. The access to SiC is a good illustration of the high flexibility of molecular chemistry. The Yajima process was the first to provide a ceramic with high thermomechanical properties in a rheologically controlled way, leading to films, fibers, or matrices. The adaptability of molecular chemistry has opened further routes to new catalytic processes, new precursors, and even a one-pot procedure.

The combination of molecular chemistry with the wide possibilities opened by the “chimie douce” processes permits access to completely new fields of research in the elaboration of materials. This is based on the very high flexibility of the inorganic polymerization process, which can be easily adapted and combined with organic chemistry. This methodology of materials synthesis is the natural bridge between molecular and solid-state chemistry. The number of possibilities is very large and the field of organic–inorganic materials appears to be a very promising one. It is possible to induce physical and chemical properties with the organic component. Molecular imprinting and chirality in solids are also very exciting open fields. It will be possible to work with matrices other than silica to couple the physical and chemical properties of the organic unit with those of the oxide matrix. In the future, the possibility of working with solids other than oxides will be available by developing polycondensation reactions that permit elaboration of new solid matrices. This chemistry has been already described in the case of nitrides and diimides.^[92]

It is important to point out that kinetic control permits one to play with all the processing parameters and adjust the microstructure of the solid. Moreover, all these hybrid monocomponent materials consist of a homogeneous network. Interestingly, short- to medium-range organization can be observed and presents a challenge to molecular chemists to control the organization of the organic units inside the inorganic network. This control will be the first step in the organization of the physical properties in materials. Owing to the possibility of coupling the chemical and/or physical properties of the organic part and the matrix, it will be

possible to obtain very sophisticated materials. These assertions are not a dream since the chemistry that will permit us to reach these targets exists at the present time.

Finally, this field of research is a great challenge for molecular chemistry because of the very wide possibilities of creating new forms of the matter with expected and unexpected properties. It will be possible to induce the development of a new solid-state chemistry based on kinetic concepts instead of relying on the usual thermodynamic approach. As already pointed out, molecular chemistry, which permits one to investigate these perspectives, is basically known. It simply has to be adapted to the elaboration of mixed solids obtained by polycondensation routes. One of the most illustrative examples given in this review is the access to nanocomposite ceramics, which are accessible only because of the very specific formation of a carbon matrix around the mineral precursor.

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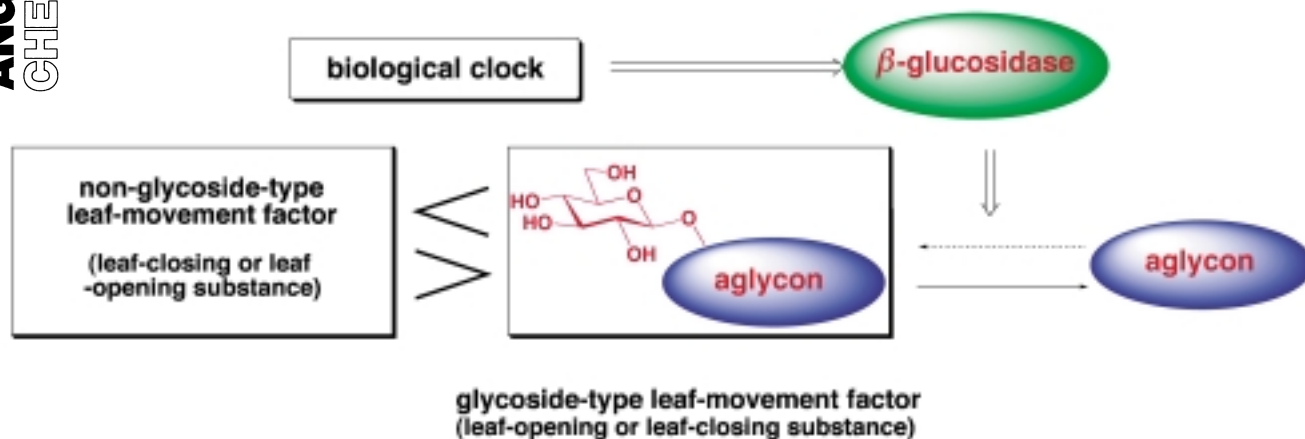
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The opening and closing of the leaves of plants such as *Mimosa pudica* are controlled by a biological clock.

β -Glucosidase plays a decisive roll in this mechanism; activation of the enzyme initiates the circadian rhythm which the leaf movement follows.



Chemistry and Biology of Plant Leaf Movements

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The leaves of *Mimosa pudica* L. are well known for their rapid movement when touched. Recently, we were able to isolate an excitatory substance in small quantities from this plant, which consists of three different components (potassium L-malate, magnesium *trans*-aconitate, and dimethylammonium salt). Many plants close their leaves in the evening, as if to sleep, and open them early in the morning (nyctinastic leaf movement). This circadian rhythm is known to be controlled by the bio-

logical clock of such plants. Extensive studies on other nyctinastic plants led to the isolation of a variety of leaf-opening substances (LOSs) and leaf-closing substances (LCSs). Based on our experiments on these bioactive substances, we found that the circadian rhythmic leaf movement of these plants is initiated by the regulated balance of LOSs and LCSs. The balance of concentration between the two leaf-movement factors (LMFs) is inverted during the day. The glycoside-

type LMF is hydrolyzed with β -glucosidase, the activity of which is regulated by the biological clock. The circadian rhythm observed in the leaf movement is introduced by activation of β -glucosidase regulated by the biological clock.

Keywords: bioorganic chemistry • glycosidases • glycosides • phytochemistry • plant physiology

1. Introduction

Plants are rooted and unable to move from one place to another by themselves. However, they are not static; they sensitively respond to a variety of factors such as light, darkness, temperature, and humidity, and also to chemical substances represented by allelopathic compounds. The result is a visual movement with or without cell elongation. Plant movement is mainly classified into three kinds: 1. tropism (movement in a particular direction due to a stimulus), 2. nasty (movement triggered by a stimulus but with no relation to the direction of the stimulus), and 3. taxis (stimulus-triggered movement directed either towards the stimulus or away from it). The movements of *Mimosa pudica* L. (Figure 1) and *Dionaea muscipula* (Venus flytrap), which belong to type 2, are especially famous.

In 1880, Charles Darwin, well known for his biologically important book entitled “On the Origin of Species” also published an invaluable and voluminous book entitled “The Power of Movement in Plants” based on his own experiments, assisted by his son Francis, with more than three hundred different kinds of plants including nyctinastic ones represent-

ed by *Mimosa pudica*.^[1] From the viewpoints of plant physiology and phytochemistry in particular, their ingenious experiments on phototropism led to the discovery of auxin, the first plant hormone of the six known classes in higher plants: auxins, ethylenes, gibberellins, cytokinins, abscisic acids, and brassinolides. Similar results have also been obtained in the leaf movement of nyctinastic plants including *Mimosa pudica*, *Albizia julibrissin* and *Cassia mimosoides*.

The present review is focused on a variety of bioactive compounds related to the leaf movement of plants. The plant leaf movement can be divided into two categories; one is the seismonastic rapid movement observed in only a few plants, and the other is the nyctinastic slow movement observed in nyctinastic plants; their leaves fold up at night and unfold by day according to a circadian rhythm with a period of about 24 hours (Figure 2).

Nyctinastic leaf movement is observed in almost all leguminous plants. This periodic leaf movement controlled by an internal biological clock can take place in continuous daylight or continuous darkness.^[2] The origin of the biological clock can be traced to careful observation of the nyctinastic leaf movement of *M. pudica* in the 18th century.^[26] A French scientist found that *M. pudica* extended its leaves in the daytime (“awake”) and folded them at night (“sleep”) even if the plant was kept in continuous darkness in a cave. After that, Bünning in Germany developed and expanded the science of biological clocks, and now a biological clock, which

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Figure 1. The rapid leaf movement of *Mimosa pudica* L.

is considered to be one of the main themes of science in the 21st century, has been proved to exist in all living organisms from prokaryote to human beings. Both the rhythmic bioluminescence of dinoflagellate *Gonyaulax polyedra* emitted at night and the jet lag we experience are attributed to an internal clock.

In addition to nyctinastic movement, the plant *Mimosa pudica* shows seismonastic movement. Such an exciting biological phenomenon has been attracting much attention since the fourth century BC. The 2000 year history of research on the movement of *M. pudica* was cited in part of the excellent review by Schildknecht.^[3]

2. Excitatory Substances in *Mimosa pudica*

When touched, the plant *Mimosa pudica* L. closes its leaves very rapidly one by one, in a movement like that of animals. When etherized, it did not show any response to stimulation. This rapid movement of the leaf is observed only in the *Mimosa* family, *Biophyllum*, and *Dionaea muscipula*. This surprising phenomenon has prompted both biologists and chemists to make great efforts to understand the mechanism of the leaf movement of the Mimosaceae. One of the most interesting problems is how the stimulant is transported from the stimulated point to other areas.

From the viewpoint of electrophysiology, different rates of stimulus conduction were observed by Houwink^[4] and Shibaoka.^[5] The stimulant, which is transported in the xylem sap stream, elicits a response in the neighboring tissue in the form of a variation potential (slow-wave or s-wave). Either the signal substance itself or the variation potential which is generated by it triggers a rapid action potential (medium or

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Figure 2. *Albizzia julibrissin* DURAZZ. during the day (left) and at night (right).

rapid wave; m- or r-wave, respectively), which can travel ahead of the slower variation potential, as summarized by Schildknecht.^[3] Regardless of the mode of action, some stimulants may interact directly or indirectly with a motor cell.

The actual leaf movement is explained by movement of water into or out of cells which is driven by fluxes of ions, especially K^+ ions.^[6] The leaf-movement organ of the plant leaf is the pulvinus. Two groups of the cells in the pulvinus, the flexor and extensor cells, are arranged above and below the central vascular tissue, respectively. The flexor cells swell and the extensor cells shrink to bend the pulvinus and flex or fold the leaf or leaflet, whereas the flexor cells shrink and the extensor cells swell to straighten the pulvinus. Biologists have revealed that the pulvinar cells lose K^+ ions when shrinking and actively take up the K^+ ions when swelling; as many as 60% of the total K^+ ions within the pulvinus move from the flexor side to the extensor side and back again during a complete cycle of leaf movement.^[7] K^+ ions can enter and leave plant cells by other channels which are differently regulated.^[8] However, the signals by which a biological clock might control the nyctinastically regulated leaf movement, through the change of the K^+ channel state, have long remained unknown.

Recently, the water distribution in the pulvinus of *M. pudica* was visualized by an NMR imaging technique, which indicated that water in the lower half of the main pulvinus disappeared after stimulation of a *Mimosa* plant. The water previously contained in this area is apparently transferred to the upper half of the main pulvinus. Movement of the water in conjugation with *Mimosa* movement was also visualized by a noninvasive NMR imaging technique.^[9]

In 1916, Ricca strongly suggested that some stimulants related to leaf movement are included in the *Mimosa* plant.^[10] This theory was based on his ingenious experiments using two parts of a cut shoot of the *Mimosa* plant, which were connected to each other through a glass tube filled with salt water or water. Since then, many scientists have been attempting to locate the true stimulants of *M. pudica*, and a wide variety of bioactive compounds have been isolated from the *Mimosa* plant, some of which are shown in Figure 3.^[3, 11–14]

Many common amino acids were also detected. Of these, interestingly, L-glutamic acid (**1**) caused periodical closure and opening movements at intervals of 5 to 10 min; however, it was proved not to be a true excitatory substance of the *Mimosa* plant.^[12] In connection with this phenomenon, it is quite interesting that Nakajima et al. carried out electrophysiological approaches using the stem surface of *M. pudica* and obtained results which indicated that sodium L-glutamate was the active compound responsible for the strong pulse, while D-glutamate was not active.^[15] The nitrogen-containing heterocyclic compounds **2–4** shown in Figure 3 were not related to the leaf movement.^[11, 12]

In 1983, after their extensive efforts in searching for the true leaf-movement factors (LMFs) of *M. pudica*, Schildknecht and Bender finally succeeded in the isolation and structure elucidation of four compounds (K-PLMF 1 (**5**), K-PLMF 2 (**6**), S-PLMF (**7**), and M-LMF (**8**)) from *M. pudica*, *Acacia karroo*, *Oxalis stricta*, and others,^[16] as shown in Figure 3. K-PLMF 1 (**5**), one of the representative compounds, was also synthesized by Schildknecht et al.^[17] Both natural and synthetic samples showed leaf-closing activity at concentrations of 10^{-4} g L⁻¹. In addition, they also obtained some cyclic nucleotides as leaf-movement cofactors (**10** and **11**).^[3]

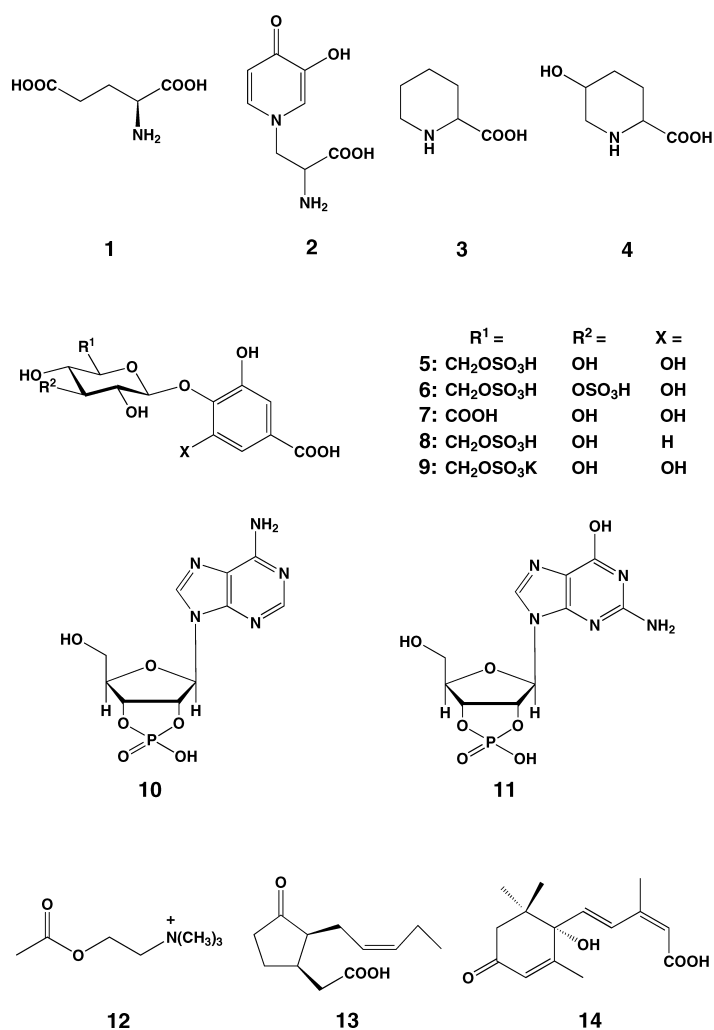


Figure 3. Chemical substances isolated as leaf-movement factors of *M. pudica*.

Through these experiments, they proposed that the leaf-movement factors (**5**–**8**), named turgolins, are a new class of phytohormones which control the nyctinastic and seismonastic movements. However, **5** with a free sulfate function seems to be questionable because **5** has been isolated not as a free acid, but as a potassium salt **9** from *M. pudica*, *Cassia mimosoides*, and others in our careful experiments.^[18] This potassium salt was also effective for leaf closing of *M. pudica*. However, its activity (about 10^{-1} g L^{-1}) was very weak in both natural and synthetic samples,^[19] and its leaf-closing activity was not observed for the leaf of other nyctinastic plants. Furthermore, in 1984, **5** was proved by Umrath et al. not to be the genuine excitatory substance of *M. pudica*.^[20]

Umrath et al. extracted the pinnae of *M. pudica* with boiling water in a short-step process and chromatographed the aqueous extracts on a Sephadex LH 20 column with methanol/water (92/8) as the mobile phase to afford two bioactive fractions (substances E and G).^[20] The proportional activities were 80% for E and 20% for G; β -glucosidase was not effective on the former, while the G substance lost its activity when treated with β -glucosidase. This result indicated that the main leaf-closing substance (LCS) E, assigned to be

the excitatory substance of *M. pudica*, is not **5**, as the structure of this consists of gallic acid and a D-glucose derivative linked by a β -glycosidic bond. In addition, they reported that the substance E is an unstable oxyacid which completely lost its leaf-closing activity through further purification.^[20] Therefore, it was apparently almost impossible to obtain such an unstable substance from *M. pudica*. However, quite recently, we were able to find a solution to this seemingly insurmountable problem, a solution which has been sought since the last century.^[21]

The methanol extract of *M. pudica* was carefully separated based on our own bioassay (Figure 4), similar to the Fitting-Hess–Schildknecht test. The test must be carefully carried

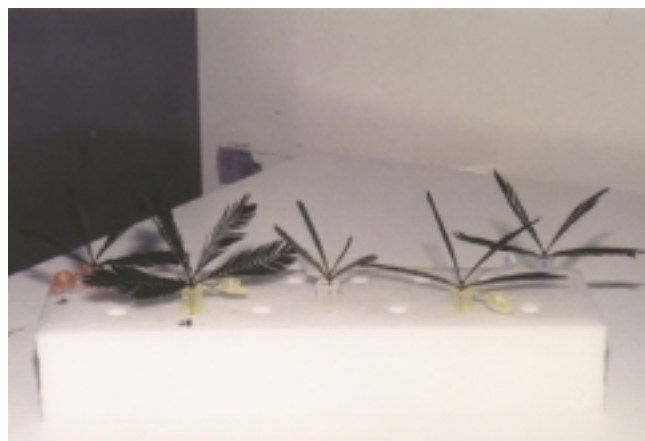
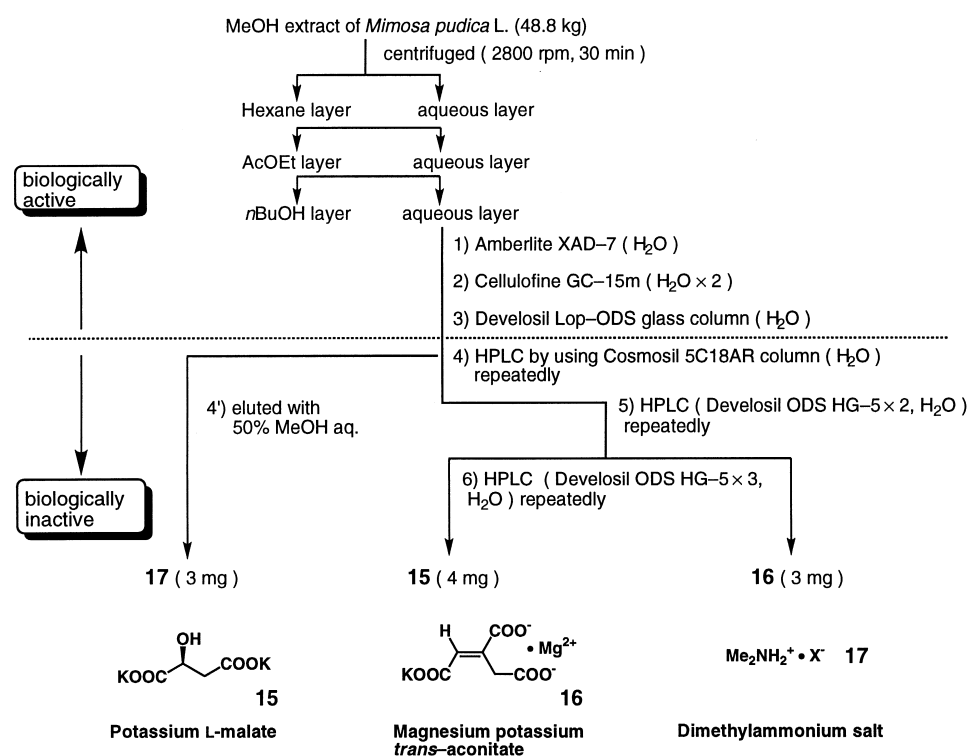


Figure 4. Bioassay for the detection of the chemical substances which induce rapid leaf movement in *M. pudica*.

out, because the leaves are very sensitive to H^+ ions (the leaves fold on addition of dilute sulfuric acid (10^{-2} g L^{-1})), temperature, humidity, and so on. We carried out the bioassay in midsummer because of the good reproducibility. The isolation procedure is shown in Scheme 1, where each separated fraction completely lost its activity during the 4th step (HPLC purification),^[21] as previously reported by Umrath et al. The disappearance of the bioactivity in the 4th step was highly reproducible; thus, we assumed that plural components are necessary for the leaf-closing activity. Therefore, each fraction was carefully combined, one by one, and monitored by a combination of the *Mimosa* test and ^1H NMR spectroscopy, leading to the finding of three fractions related to the rapid movement of *M. pudica*. Thus, the genuine excitatory substance consists of three different components: 1) potassium L-malate (**15**), 2) magnesium *trans*-aconitate (**16**), and 3) the dimethylammonium salt **17**.

Mimosa leaves folded very rapidly on addition of this mixture in a concentration of 10^{-8} – 10^{-9} M .^[21] In addition, metal ions are also important for the activity. When calcium was used instead of magnesium as the counter ion of **16**, the resulting mixture did not show any leaf-closing activity. In conclusion, the mixture of **15**, **16**, and **17** is the genuine excitatory substance related to the rapid movement of *M. pudica*, the activity of which disappears on further purification in accordance with the result obtained by Umrath et al.^[20] We assume that **15** corresponds to the “unstable

Scheme 1. Isolation of the stimulatory substances from *M. pudica*.

oxyacid” of Umrath and co-workers. It is important that our three-component excitatory substance induces only the rapid movement of *Mimosa*, and no slow leaf movement was observed with it.

Parallel to the leaf-closing substances, the leaf-opening substances (LOSs) for the nyctinastic leaf movement of *Mimosa* have also been studied by many groups. In particular, indole-3-acetic acid (IAA) caused the leaf opening of *M. pudica* at night. In the experiments with cut pinnae in the dark, IAA induced optimal opening of the leaflets at concentrations from 3×10^{-3} to 5×10^{-4} M; lower concentrations were ineffective.^[22] On the other hand, Tsurumi et al. indicated that the excised pulvinus opened with IAA at concentrations from 10^{-7} to 10^{-4} M.^[23] This difference has not been clarified, but the high sensitivity of the excised pulvinus to IAA may be due to direct treatment with the IAA solution. Regarding the circadian rhythm of *M. pudica*, it is suggested that IAA may be necessary for the pulvinus to manifest the effect of day–night cycles or the action of the biological clock through control of osmotic pressure, as well as for maintenance of the permeability of motor cell membranes in *Mimosa* pulvini.^[24] In addition, Suda indicated that acetylcholine (ACh, **12**) was able to induce opening of *Mimosa* leaflets at night, but only in high concentrations (5×10^{-3} M).^[25]

In connection with IAA-induced leaf opening of *Mimosa* pulvinus, jasmonic acid (**13**) was isolated from the *Mimosa* plant.^[13] Jasmonic acid (**13**) and abscisic acid (**14**) each inhibited both IAA- and light-induced opening of the pulvinus at concentrations of 10^{-5} M. Both of them are proposed to be the regulators of *Mimosa* pulvinus movement. However, as previously pointed out by Umrath et al. and

Schildknecht, chemical substances which induce the slow leaf-closing and leaf-opening movements and differ from the plant hormones must be included in the *Mimosa* plant.^[21] We will describe these bioactive substances of *Mimosa* in Section 3.2. When compared with *M. pudica*, other nyctinastic plants, which open their leaves early in the morning and close them at night according to the circadian rhythm, seem to be much simpler in their leaf movement.

3. Leaf-Movement Factors in Nyctinastic Plants

Nyctinastic movement was believed to be controlled by Schildknecht’s turgorins which induce leaf-closing movement of the plants.^[3] However, we revealed that turgorin is not a

genuine leaf-movement factor, and nyctinastic movement is regulated by a chemical substance that differs depending on the plant species. Our present results are in accordance with the physiologically significant opinion of Umrath et al. that every family or subfamily of plants has its own leaf-movement factor that is effective only for plants belonging to that family, although they have not identified any leaf-movement factors.^[20]

We tried to isolate genuine leaf-movement factors of nyctinastic plants. An important problem in the chemical studies of nyctinasty by Schildknecht is the difference between the plants used in the bioassay and for extraction. They used *Mimosa* leaves for the detection of the leaf-closing activity from all nyctinastic plants. If the hypothesis of Umrath et al. is true, the plant used in the bioassay must be the same as the one extracted. In order to detect the leaf-movement factors of nyctinastic plants, we developed a bioassay using the original leaves. The movement of the leaves, which were detached from each stem and immersed in water, was also found to follow the circadian rhythm. The young leaves of the nyctinastic plant to be tested were immersed in distilled water and allowed to stand at room temperature overnight. The leaves that opened again the next morning were used for the bioassay. The bioactivity was judged by the closure of the leaves in the daytime (Figure 5).

The bioactive substance closes the leaves a few hours after the addition. In the course of the isolation, we noted that a leaf-opening substance was contained together with the leaf-closing one in a nyctinastic plant (Figure 5). Thus, we have to divide the leaf-movement factor into two categories, one is leaf-closing substances, which close the plant leaf even in the



Figure 5. Bioassay for the detection of chemical substances responsible for nyctinasty; leaf-closing (above), and leaf-opening (below) substances.

daytime, and the other is leaf-opening substances, which keep the plant leaf open even at night.

The presence of leaf-opening substances indicates that nyctinastic movement is controlled not only by the change in the concentration of the leaf-closing factor, but also by the competitive interaction between leaf-closing and leaf-opening substances. The idea of the coexistence of a leaf-opening substance with a leaf-closing one is very reasonable in terms of the previously mentioned result that K^+ ions enter and leave plant cells through ion channels which are regulated differently.^[8]

3.1. The Isolation of Leaf-Movement Factors

The most difficult problem encountered in the chemical studies of nyctinastic movement lies in the isolation of leaf-closing and leaf-opening substances. The difficulty in the isolation comes from the weak biological activity of the plant extract observed by bioassay. We decided that this weak bioactivity is due to the coexistence of the leaf-opening substance with the leaf-closing one in the same fraction. When both of them coexist in the same fraction, the respective bioactivities should cancel each other out, and, as a result, no

bioactivity can be monitored by bioassay. All of the previous attempts for the purification of the leaf-closing substance were carried out with a combination of gel filtration chromatography and HPLC. It is supposed that all such studies of the isolation failed because no attempt was made to separate the leaf-closing substance from the leaf-opening one. Thus, it is crucial to separate these inversely bioactive substances from each other in the first step of the isolation procedure.

We attempted to apply polymer gel chromatography to the separation of leaf-opening and leaf-closing substances. After many separation conditions were examined, we found that an Amberlite XAD-7 chromatography column could separate the compounds completely, based on the difference in polarity. The highly polar leaf-closing substance was eluted with 100% H_2O ; on the other hand, the comparatively less polar leaf-opening substance was eluted with MeOH-containing eluent. The bioassay gave completely distinct results in the full course of the isolation.

After the separation of the two bioactive fractions with leaf-closing and leaf-opening activities, each fraction was separated with gel filtration chromatography, MPLC (Medium Pressure Liquid Chromatography) using an ODS (octadecyl silyl) glass column, and preparative HPLC using an ODS column. HPLC using a combination of three columns showed a particularly good separation which enabled us to isolate the leaf-closing substance. Thus, we have succeeded in the isolation of several bioactive substances controlling the leaf movement of nyctinastic plants (Figure 6).

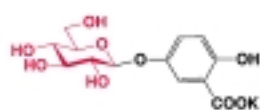
3.2. Leaf-Movement Factors of *Mimosa pudica* L.

The nyctinastic movement of *Mimosa*, which is another leaf-movement of this plant, was neglected for a long time, because the slow movement was thought to be caused by the same chemical substance as that in the rapid movement.^[3] For this reason, the two leaf-movements of *Mimosa* have often been confused. We have disclosed the true character of the leaf-movement factors of *Mimosa* and demonstrated that the rapid and slow leaf movements are caused by different chemical substances.

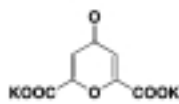
Our three-component stimulant, described in Section 2, induced only the rapid movement of the *Mimosa* leaf, and no slow leaf closure was observed even at the threshold-level concentration. Therefore, we assumed that the bioactive substance regulating the nyctinastic leaf movement should also be contained in *Mimosa*. As already mentioned, Umrath et al. obtained weak leaf-closing substance G from *M. pudica*.^[20] We assumed that substance G is assigned to be the leaf-closing substance of *M. pudica* which induces a nyctinasty.

A modified bioassay was used for the separation of leaf-movement factors. We used a *Mimosa* leaf, cut at the lamina, instead of a four-pinnae leaf and carried out the bioassay in a glass tube, because the *Mimosa* leaf folded easily in gentle wind through the long period needed for bioassay. This method was inferior in sensitivity to the previous method using the four-pinnae leaf; however, its reproducibility was satisfactory.

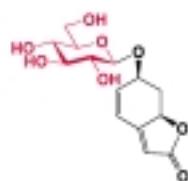
Leaf-Closing Substances



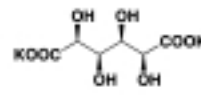
Potassium 5-*O*- β -D-glucopyranosylgentisate (**18**)
(*Mimosa pudica* L.)



Potassium chelidonate (**20**)
(*Cassia mimosoides* L.,
Cassia occidentalis L.)

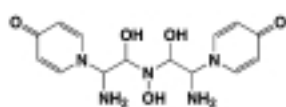


Phyllanthurinolactone (**22**)
(*Phyllanthus urinaria* L.)

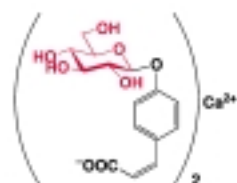


Potassium D-idarate (**24**)
(*Lepedeza cuneata* G. Don)

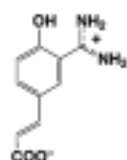
Leaf-Opening Substances



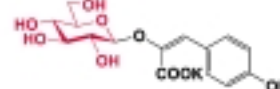
Mimopudine (**19**)
(*Mimosa pudica* L.)



Calcium 4-*O*- β -D-glucopyranosyl *cis*-*p*-coumarate (**21**)
(*Cassia mimosoides* L.)



Phyllurine (**23**)
(*Phyllanthus urinaria* L.)



Potassium lespedezate (**25**)
(*Lepedeza cuneata* G. Don)

Figure 6. Four pairs of leaf-movement factors. Each pair was isolated from the same nyctinastic plant.

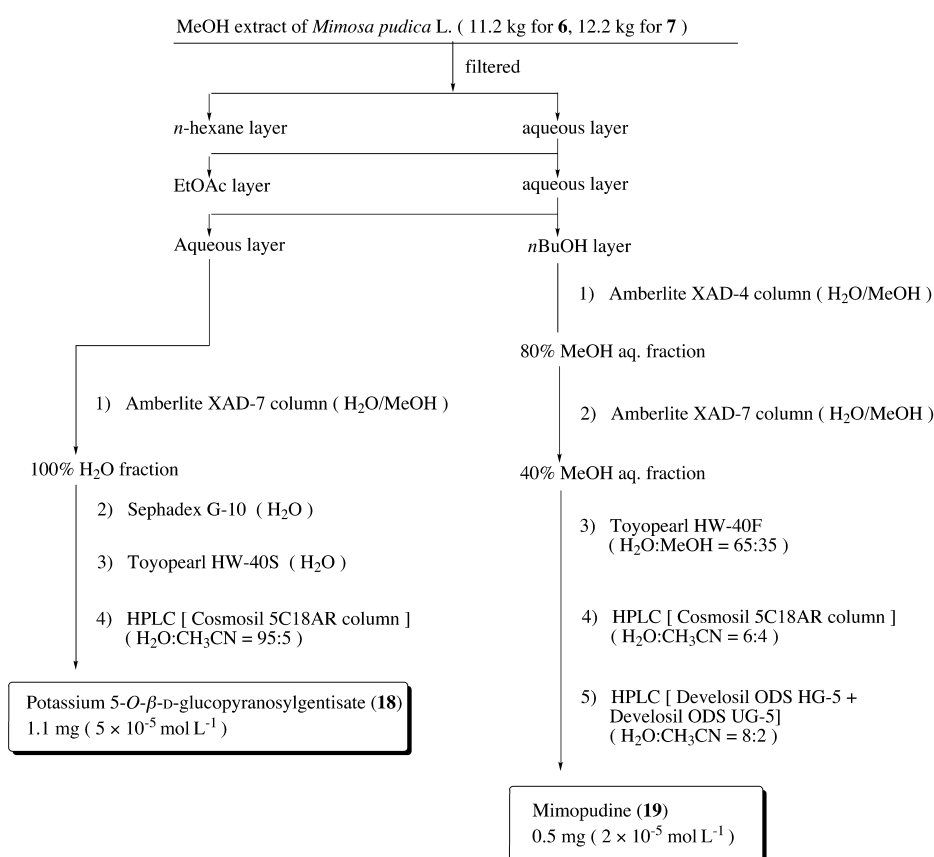
After the separation with XAD-7, fractions with strong leaf-closing activity were obtained. However, only the seismonastic activity that induces the rapid leaf closure was observed. We assumed that the nyctinastic activity which induces the slow leaf closure could be masked by the strong activity attributed to the excitatory substances. It was crucial to separate these two bioactivities for the detection of nyctinastic leaf-closing activity (Scheme 2).

Based on the report by Umrath et al.,^[20] we examined the application of the gel filtration chromatography using Toyopearl HW-40S columns for the separation of the excitatory and leaf-closing substances.^[27] We thought that the excitatory substance corresponded to substance E and the leaf-closing substance **18** was substance G, as described by Umrath et al. On the other hand, the leaf-opening substance was also isolated from *M. pudica*.^[28] It was supposed that strong leaf-closing activity masked the bioactivity of the leaf-opening substance. Thus, the *n*-butanol layer, which contains almost no excitatory substances, was separated with HPLC to give mimopudine (**19**).

Structure determinations of **18** and **19** were carried out by means of NMR spectroscopy and ESI mass spectrometry experiments. Compound **19** was unstable in aqueous solution, and decomposed

easily to give pyridone. An ESI-linked scan experiment was useful in the structure determination of **19** (Figure 7).^[28]

Compound **18** was quite effective for leaf closing of *M. pudica* at night at concentrations of 5×10^{-5} M and **19** was effective for the leaf opening of the same plant in the daytime at concentrations of 2×10^{-5} M, but neither was



Scheme 2. Procedures for the isolation of the leaf-closing and leaf-opening substances of *M. pudica*.

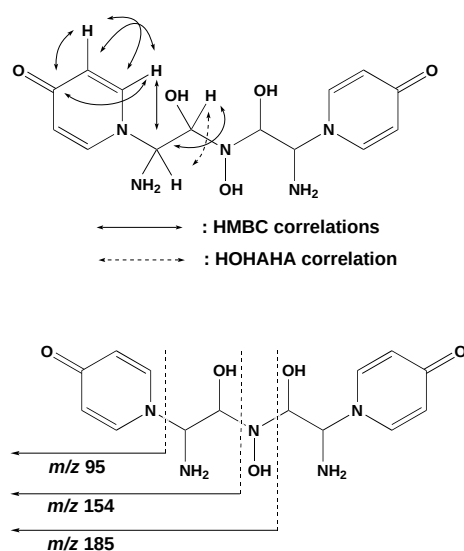


Figure 7. HMBC and HOHAHA correlations (above) and linked-scan ESI MS (below) for the structure determination of mimopudine (**19**).

effective for other nyctinastic plants. Compound **18** induced only the slow leaf closure of the *Mimosa* leaf.^[27]

Interestingly, the leaves of *M. pudica* kept open with **19** at night were sensitive to physical stimulus by touch, as observed in the daytime. This result suggests that **19** is effective only for the obstruction of the slow nyctinastic leaf closing movement, but not effective against the rapid seismonastic movement. We have now been able to separate these two leaf movements at the molecular level, and to demonstrate that the slow nyctinastic movement of *Mimosa* is initiated by a different mechanism from that of the rapid seismonastic movement.^[28]

We have succeeded in the identification of the chemical substances concerning rapid and slow leaf movements of *Mimosa*, which have been discussed for more than 80 years.

3.3. Leaf-Movement Factors of *Cassia mimosoides* L.

As shown by its name, *C. mimosoides* resembles *Mimosa*. However, its leaves do not respond to physical stimulus. Only the nyctinastic movement is observed in this plant. Potassium chelidonate (**20**) was isolated as a leaf-closing substance from *C. mimosoides*.^[18] Compound **20** was also found in *Cassia occidentalis* L., which belongs to the same genus as *C. mimosoides*.^[8] This result suggests the universality of the leaf-movement factor among a plant genus.

The natural and synthetic **20** induced the closure of *Cassia* leaves in the daytime at concentrations of 10^{-6} – 10^{-7} M. Interestingly, the corresponding sodium salt, as well as the free acid, showed no bioactivity. Also, the potassium acetate, potassium oxalate, and potassium salt of phloroglucinol did not show any leaf-closing activity in the plant. Thus, both the potassium ion and chelidonate anion are necessary for bioactivity. Potassium chelidonate (**20**) as a “turgorin” plays an important role in the leaf movement of nyctinastic plants *C. mimosoides* and *C. occidentalis*.

On the other hand, calcium 4-*O*- β -D-glucopyranosyl-*cis-p*-coumarate (**21**) was isolated as the leaf-opening substance of *C. mimosoides*.^[29] Compound **21** lost its bioactivity under strongly polar isolation conditions. This is because the counter cations that dissociated from the carboxylate of **21** were exchanged with other cations during the separation using polar solvents. We depressed the dissociation of the carboxylate group by using apolar solvents in the isolation of **21**. Compound **21** effectively opened the leaves of *C. mimosoides* at night at concentrations of 4×10^{-6} M. The potassium salt of **21**, which was isolated together with **21**, exhibited no biological activity, and calcium acetate was effective only at a concentration of 1×10^{-2} M. Thus, both the calcium ion and its counter ion were essential for the bioactivity of **21**.

3.4. Leaf-Movement Factors of *Phyllanthus urinaria* L.

Phyllanthurinolactone (**22**)^[30] and phyllurine (**23**)^[31] were isolated as the leaf-closing and leaf-opening substances, respectively, from the nyctinastic plant *Phyllanthus urinaria* L., which belongs to the *Euphorbiaceae* family. Since other leaf-closing substances have been isolated from the *Fabaceae* family, it would be interesting to study the difference in the chemical structure of the leaf-movement factors between these two plant families. Due to this difference in the plant family, the structure of bioactive substances greatly differs from those of other nyctinastic plants belonging to the *Leguminosae* plants.

The structure determinations of **22** and **23** were carried out by means of 2D NMR experiments. The absolute configuration of **22** was determined from the total synthesis by Mori et al.^[32, 33] They also synthesized all the possible stereoisomers relative to the diol moiety of the aglycon. Bioactivity was observed only in the natural *syn*-6*S*,7*aR* form. Phyllanthurinolactone (**22**) was effective for the leaf closure of *P. urinaria* in the daytime at a concentration of 1×10^{-7} M, and phyllurine (**23**) was effective for leaf opening at a concentration of 5×10^{-5} M.

3.5. Leaf-Movement Factors of *Lespedeza cuneata* G. DON.

Potassium D-idarate (**24**) as a leaf-closing factor,^[34] and both potassium lespedezate (**25**) and potassium isolespedezate (**28**, geometrical isomer of **25**) as leaf-opening substances^[35] were isolated from *L. cuneata*, according to the bioassay using the leaves of *C. mimosoides*.

Due to the stiffness of the stem, the leaves of *L. cuneata* transported the sample solution poorly, and were insufficient for use in the bioassay. We used the leaves of *C. mimosoides* for the bioassay instead of the leaves of *L. cuneata* to overcome this experimental difficulty. The bioactivities of **24**, **25**, and **28** were quite specific for the leaves of *C. mimosoides* in the daytime at a concentration of 5×10^{-7} M.

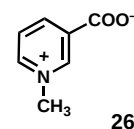
The stereochemistry of **24** was determined by comparing its spectroscopic data and bioactivity with those of various potassium tetrahydroxydicarboxylates prepared from D-hexo-

ses. All other diastereomers are biologically inactive or only very weakly active;^[34] thus, the bioactivity of **24** was specific with respect to its stereochemistry.

Compounds **25** and **28** were the first leaf-opening substances which were isolated from nyctinastic plants. To investigate structure–activity relationships, various analogues of **25** were synthesized and subjected to bioassay (Figure 8).^[36] The bioactivities of sodium salts and free acids

was effective for the leaf closure of *A. indica* at a concentration of 1×10^{-7} M.

Trigonelline (**26**) was also reported to be a G2 factor, present in the cotyledons of garden peas, that promotes cell arrest in the G2 stage (DNA postsynthetic stage) of both roots and shoots.^[39] Compound **26** promotes cell arrest in the G2 stage in 40 % of all root cells. In the absence of **26**, this cell population is arrested in the G1 stage. Tramontano et al. reported that **26** is the first chemically identified “hormone” that controls the cell cycle in plants or animals.^[39c] These results are very interesting in terms of the relationship between the cell cycle and the biological clock.



3.7. *cis-p*-Coumaroylagmatine, the Leaf-Opening Substance in *Albizzia julibrissin* DURAZZ

The nyctinastic movement of the leaves of the silk tree, *Albizzia julibrissin* DURAZZ, is as well known as the rapid movement of *Mimosa* leaves. We isolated *cis-p*-coumaroylagmatine (**27**) from *A. julibrissin* as the leaf-opening substance.^[40] Compound **27** kept the leaves open at a concentration of 5×10^{-6} M. We also revealed that an unknown leaf-closing substance is also contained in the extract of this plant.

It is interesting that *A. julibrissin* contains only the thermodynamically unstable *Z* isomer, and no *E* isomer. *cis-p*-Coumaroylagmatine (**27**) and its *trans* isomer were synthesized from agmatine and *cis-p*-coumaric acid.^[41] Synthetic **27** shows the same level of activity as the authentic sample of natural *cis-p*-coumaroylagmatine, and the synthetic *trans* isomer of **27** opened the leaves of *A. julibrissin* at concentrations as high as 1×10^{-3} M.

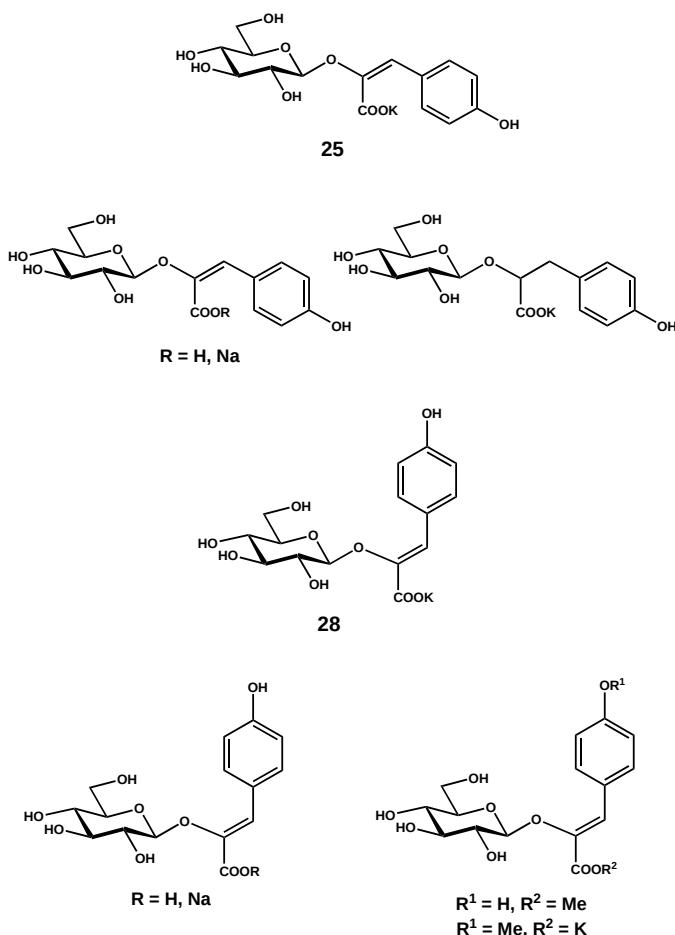
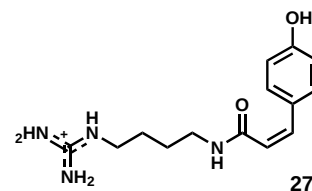


Figure 8. Potassium lespedezate (**25**), potassium isolespedezate (**28**), and their analogues.

were as strong as those of the natural products. Interestingly, *p*-hydroxyphenylpyruvic acid (**29**) and its potassium salt (**30**) opened the leaves at concentrations of 10^{-4} M even at night. Moreover, variation of the sugar moiety in **25** gave compounds which exhibited almost the same bioactivity as **25**.^[37] From these results, it is obvious that one of the most important structures for leaf-opening activity is a *p*-hydroxyphenylpyruvate unit in the enol form.^[36, 37] The sugar moiety would serve only to improve the solubility and stabilize the enol double bond.

3.6. Trigonelline from *Aeschynomene indica*

We isolated trigonelline (**26**) as a leaf-closing factor of the nyctinastic plant *Aeschynomene indica*.^[38] Trigonelline (**26**)

4. Common Properties of Leaf-Movement Factors

It has been believed that nyctinastic movement is controlled by turgorin, a leaf-closing plant hormone common to all nyctinastic plants. However, the leaf-closing substances of nyctinastic plants were proved to be different from each other. There also exist leaf-opening substances that compete with leaf-closing ones in controlling the leaf movement of nyctinastic plants.

It is most important that the bioactivity of all leaf-movement factors is specific to the original plant; these substances were not effective for other nyctinastic plants. Therefore, contradictory to Schildknecht's theory, each nyctinastic plant has its own leaf-opening and leaf-closing substances, and nyctinasty is controlled not by a plant hormone, but by these specific compounds.

It is also important that both leaf-closing and leaf-opening substances have been isolated from some nyctinastic plants, as shown in the cases of *Mimosa pudica*,^[27, 28] *Cassia mimo-*

soides,^[18, 29] *Lespedeza cuneata*,^[34, 35] and *Phyllanthus urinaria*.^[30, 31] One of the leaf-movement factors is always a glycoside (Figure 6). There are two types of nyctinastic plants: one has a glycoside-type leaf-closing substance, examples are *M. pudica* and *P. urinaria*; the other has a glycoside-type leaf-opening substance, as in *C. mimosoides* and *L. cuneata*. Leaf-opening substances differ in certain aspects from indole-3-acetic acid (IAA) which is believed to induce the leaf opening of nyctinastic plants:^[22] 1. the bioactivities of the leaf-opening substances (active at concentrations of approximately 1×10^{-6} M) were much stronger than that of IAA ($> 1 \times 10^{-4}$ M), and 2. the bioactivities of the leaf-opening substances were specific to the genus of the plant while that of IAA was nonspecific.

L-Trp, which was also isolated as a weak leaf-opening substance from some nyctinastic plants,^[28, 31] was effective on the leaves of all nyctinastic plants at concentrations as low as 1×10^{-4} M in a similar manner to IAA. It is proposed that the bioactivity of L-Trp is attributed to IAA, which is known as an important metabolite of L-Trp. The bioassay was carried out by the addition of the sample solution at 11.00 a.m., and the bioactivity was checked by study of the leaf opening at 9:00 p.m.; the long period necessary for the bioassay to detect the leaf-opening activity is sufficient for the metabolism of L-Trp into IAA. Thus, L-Trp is not a genuine leaf-opening substance. Moreover, these leaf-movement factors have six properties in common:

- 1) The amount is always very low; a few milligrams of the leaf-movement factor were isolated from approximately ten kilograms of plant material.
- 2) At a concentration of approximately 10^{-6} – 10^{-7} M, all bioactive substances exert their effect, but only on the plants where they originate. This concentration is almost the same as that of known phytohormones, such as IAA and gibberellin.
- 3) The bioactivity of all leaf-movement factors is specific to the original plant from which they were isolated.
- 4) All leaf-closing substances have a common physiological property, in that they compete with IAA at 10^{-6} M. However, much more IAA (approximate concentration of 10^{-4} M) is required to achieve a competitive state than occurs in natural abundance in a plant body.
- 5) The bioactivity of these compounds is dependent on their stereochemistry. Optically active **22** and **24** were the only bioactive compounds among their stereoisomers. This suggests that a specific receptor participates in the process of signal transduction by these substances.
- 6) The leaf-opening substance competes with the leaf-closing substance (Tables 1 and 2). When the concentration of the

Table 1. Competitive interaction between **20** and **21**.^[a]

	Concentration of 20 [mol L ⁻¹]	ratio of 20 to 21					control sample
		1:0	1:0.2	1:1	1:5	0:1	
daytime	1×10^{-3}	--	--	++	++	++	++
	1×10^{-6}	--	--	++	++	++	++
night	1×10^{-3}	--	--	++	++	++	--
	1×10^{-6}	--	--	--	++	++	--

[a] The scale reaches from “completely open” (++) to “completely closed” (– –).

Table 2. Competitive interaction between **24** and **25**.^[a]

	Concentration of 24 [mol L ⁻¹]	ratio of 24 to 25					control sample
		1:0	1:0.5	1:1	0.5:1	0:1	
daytime	1×10^{-4}	--	--	--	++	++	++
	1×10^{-5}	--	--	++	++	++	++
	1×10^{-6}	--	--	++	++	++	++
night	1×10^{-4}	--	--	++	++	++	++
	1×10^{-5}	--	--	++	+	++	--
	1×10^{-6}	--	--	++	++	++	--

[a] The scale reaches from “completely open” (++) to “completely closed” (– –).

leaf-closing substance was higher than that of the leaf-opening substance, the leaves were closed during the day and vice versa.

5. Chemical Control of Leaf Movement in Nyctinastic Plants

From the viewpoint of chemical studies, the most important problem to be solved is how a biological clock controls the nyctinastic leaf movement with these compounds. We have isolated two leaf-movement factors of contrasting bioactivities from the same nyctinastic plant. This was unexpected, and is not compatible with the theory proposed by Schildknecht.^[3] The discovery of leaf-opening substances from nyctinastic plants prompted us to assume that nyctinastic leaf movement is controlled by a competitive interaction between leaf-closing and leaf-opening substances. It was confirmed that leaf-opening and leaf-closing substances actually compete with each other. As described above, four sets of leaf-movement factors were isolated from four plants, *Mimosa pudica* L., *Lespedeza cuneata* G. Don, *Cassia mimosoides* L., and *Phyllanthus urinaria* L. We assumed that the concentrations of the two substances change through a day.

Moreover, we have made an important discovery that plant extracts of all the nyctinastic plants collected in the daytime and at night exhibited opposite bioactivity to each other; the former exhibited leaf-opening activity, while the latter exhibited leaf-closing activity.^[41–44] It is important that the bioactivity of the plant extract completely reflects the status of the collected leaves; the extract collected when the leaves were closed showed leaf-closing activity and vice versa.

Presumably, these bioactive substances are not stored, but are metabolized in the course of time. The enzymatic transformation during metabolism should be controlled by a biological clock. Thus, chemical studies on this transformation should give us an important clue to understanding the chemical control of leaf movement by a biological clock.

As examples, we will discuss the chemical mechanisms for the control of nyctinasty of *Lespedeza cuneata* G. Don^[42] and *Phyllanthus urinaria* L.^[44] in the next two sections.

5.1. Chemical Control of the Nyctinasty in *Lespedeza cuneata* G. Don

The extracts of *L. cuneata* collected in the daytime (around 10.00 a.m.) and at night (around 7.00 p.m.) showed inverse

Table 3. Quantitative HPLC analysis of the concentration of **25**, **28**, and **29** collected in the daytime and at night from *Lespedeza cuneata* G. Don.

Time of collection	concentration [mol L ⁻¹]		
	25	28	29
daytime	2.7×10^{-5}	4.1×10^{-5}	2.5×10^{-5}
night	2.7×10^{-5}	1.8×10^{-5}	1.2×10^{-4}

bioactivity; in other words, the former showed leaf-opening activity but the latter showed leaf-closing activity. This result suggests that the balance of concentration between **24** and **25** (or **28**, *cis* isomer of **25**) is reversed in these two extracts.^[41, 42] HPLC analysis revealed that the extract collected in the daytime contained twice as much **25** and **28** as the extract collected at night (Table 3). This twofold increase in the concentrations of **25** and **28** is sufficient to inverse the bioactivity of the extract from the competition experiment between **24** and **25** (or **28**). As shown in Table 2, potassium D-iodate (**24**), a leaf-closing substance of *L. cuneata*, interacts competitively with potassium lespedezate (**25**), a leaf-opening substance of the same plant. When the concentration of **24** was higher than that of **25**, the leaves were closed during the day, and vice versa. Thus, both **25** and **28** are metabolized in the evening, and biosynthesized in the morning.

Moreover, we discovered that the concentrations of **25** and **28** in the plant are inversely proportional to that of 4-hydroxyphenylpyruvic acid (**29**) (Table 3). The effectiveness of **29** was one-hundredth that of **25** and **28** (effective concentrations of **29** and **25**, **28** were 5×10^{-5} and 8×10^{-7} M, respectively) for inducing leaf-opening movement. The extract collected at night contained fivefold as much **29** as the extract collected in the daytime. This result strongly suggests that **25** is biosynthesized from **29** in the morning, and is metabolized (and deactivated) to **29** by enzymatic hydrolysis in the evening, as shown in Figure 9. The mechanism of cell contraction in the nyctinastic leaf movement is not clear, but we assume that it is similar to that of seismonstic movement of *Mimosa*.^[45]

This new model for the regulation of leaf movement was strongly supported by the measurement of β -glucosidase activities of the crude plant preparations collected in the daytime and evening.^[42, 43] We collected the leaves of *L. cuneata* and prepared acetone extracts.^[46] We used **25** and **28** as

substrates of the enzyme and quantitatively analyzed **29**, produced from the acetone extracts, by HPLC. β -Glucosidase activity was observed only in the acetone extract prepared from the plant collected in the evening (Table 4). The balance

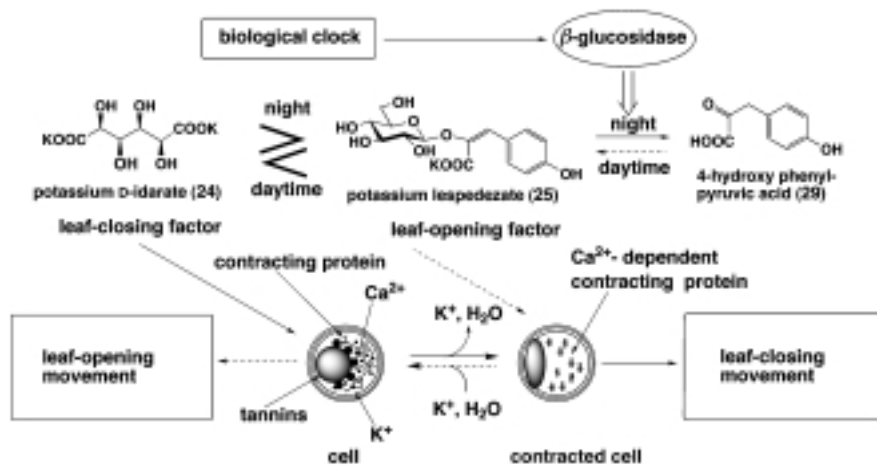
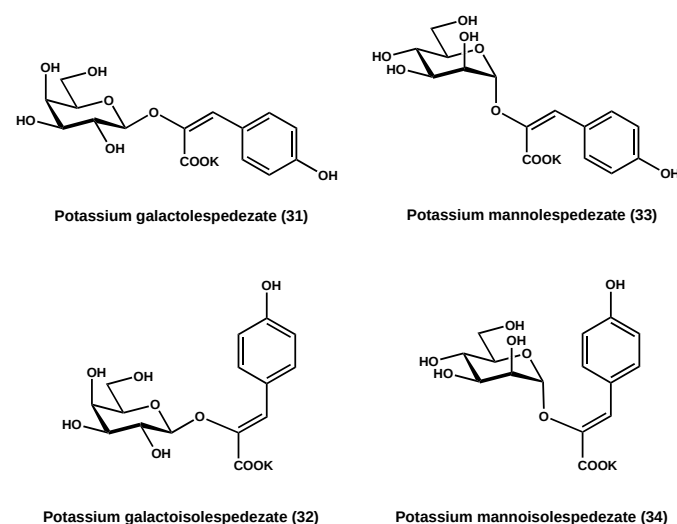
Table 4. Transformation from **25** into **29** by the action of crude enzyme.

Conditions	concentration [mol L ⁻¹]	
	25	29
a) crude enzyme (from leaves collected in the daytime) + 25	1.0×10^{-3}	ND ^[a]
b) crude enzyme (from stems collected in the daytime) + 25	1.0×10^{-3}	ND
c) crude enzyme (from leaves collected at night) + 25	1.0×10^{-3}	2.2×10^{-3}
d) crude enzyme (from stems collected in the daytime) + 25	1.0×10^{-3}	ND
e) crude enzyme (from leaves collected in the daytime) + buffer	1.0×10^{-3}	ND
f) buffer + 25	1.0×10^{-3}	ND

[a] ND = not determined.

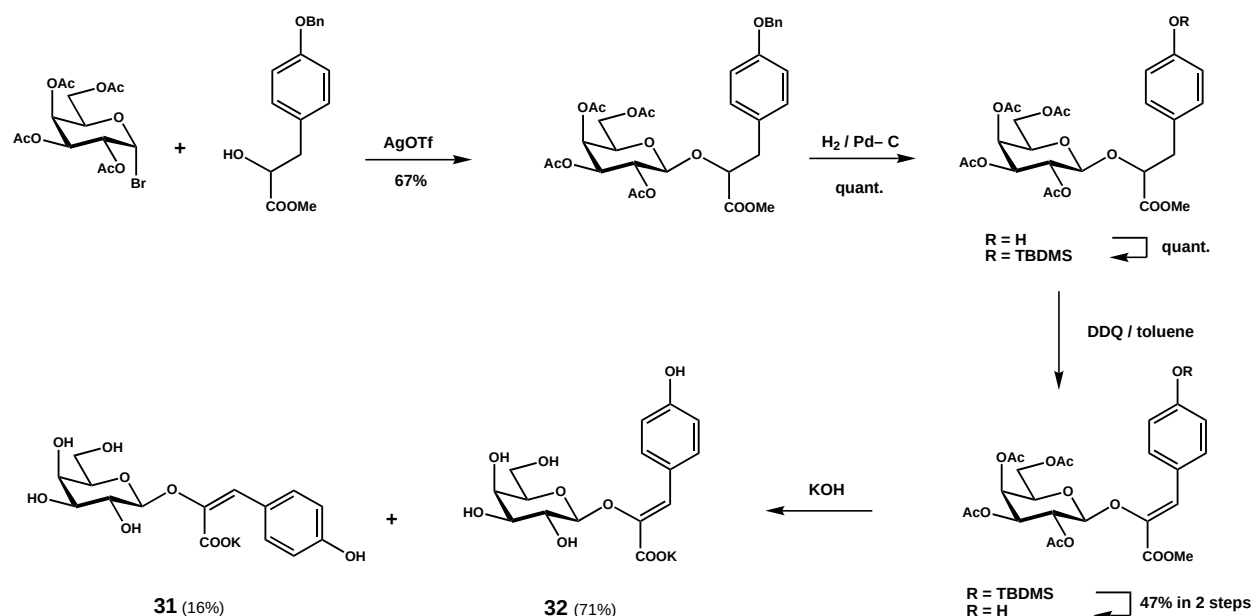
of concentration between **24** and **25** (or **28**) was inverted by the hydrolysis of **25** (and **28**) into **29** (Figure 9).

Interestingly, the artificial leaf-opening substances **31–34**, sugar derivatives of **25** which were synthesized by us

Figure 9. The chemical control of nyctinasty in *Lespedeza cuneata* G. Don.

(Scheme 3), were effective at a concentration of 8×10^{-7} M in the bioassay, making them as strong as **25**.^[37, 47] The leaf-opening activity of **25** lasted for only two days; after that, the leaf closed at night again. On the other hand, that of **31–34** lasted even after a week. This result suggested that **25** would be completely hydrolyzed into **29** by β -glucosidase; however, the enzyme could not hydrolyze **31–34**. The importance of β -glucosidase in the regulation of nyctinasty is also verified by these results.^[37, 47]

We propose a new model for the regulation of nyctinastic movement in *L. cuneata*; enzymatic transformation of leaf-movement factors **25** and **28** to **29** inverted



Scheme 3. Chemical synthesis of potassium galactosylpedezate (**31**) and potassium galactoisolespedezate (**32**). Ac = acetyl, AgOTf = silver trifluoromethanesulfonate, Bn = benzyl, TBDMS = *tert*-butyldimethylsilyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

the balance of concentration between **24** and **25** and **28**, wherein a biological clock should control leaf-movement by activation or expression of the enzyme concerned in this step.

5.2. Chemical Control of the Nyctinasty in *Phyllanthus urinaria* L.

Our study^[44, 48] on the nyctinastic movement of *L. cuneata* revealed that nyctinastic leaf movement is controlled by a biological clock through regulation of the activity of β -glucosidase which hydrolyzes the leaf-opening substance of this plant. On the other hand, *P. urinaria* has a glycoside-type leaf-closing substance, and another type mechanism should operate in this plant.

We prepared six extracts collected from the plant *P. urinaria* every four hours through a day, and discovered that the extracts collected in the daytime and at night exhibited opposite bioactivity; the ones collected in the daytime exhibited leaf-opening activities and kept the leaves open even at night, while the ones collected at night exhibited weak leaf-closing activities and kept the leaves closed even during the daytime (Table 5). It is important that the bioactivity of the plant extract completely reflected the status of the collected leaves through a day; the extract collected when

the leaves were closed showed leaf-closing activity and vice versa. This result suggested that the balance of concentration between **22** and **23** inverted through a day in the plant body.

We have carried out a quantitative HPLC analysis of both **22** and **23** to measure the internal change in their concentration through a daily cycle, using the plant extracts prepared every four hours during a day. The moderately low polarities of **22** and **23** were suitable for the quantitative analysis. The result showed that the content of **23** was almost constant throughout a day; on the other hand, the content of **22** changed remarkably during a day (Table 6). The extract collected at 8.00 p.m. contained about tenfold as much **22** as

Table 6. Quantitative HPLC analysis of the concentration of **22**, **23**, and **35** in the leaf extracts from *P. urinaria*.

Time of collection	concentration [mol L ⁻¹]			
	22	23	35	23:22
midnight	3.1×10^{-4}	7.8×10^{-4}	1.4×10^{-3}	2.5
4.00 a.m.	1.1×10^{-4}	9.1×10^{-4}	1.4×10^{-3}	8.3
8.00 a.m.	0.6×10^{-4}	8.3×10^{-4}	1.5×10^{-3}	13.8
noon	0.5×10^{-4}	9.7×10^{-4}	1.5×10^{-3}	19.4
4.00 p.m.	0.9×10^{-4}	8.2×10^{-4}	1.4×10^{-3}	9.1
8.00 p.m.	5.0×10^{-4}	7.6×10^{-4}	1.4×10^{-3}	1.5

the one collected at midnight. As the leaves stayed open from 4.30 a.m. until 4.30 p.m. and closed during the rest of the day, the concentration of the leaf-closing substance increases before the closure of the leaves, and decreases before the opening of them.

There are two plausible mechanisms to deactivate **22**: by hydrolysis of the ester or the glycoside linkage. The content of phyllanthuric acid (**35**) proved to be constant through a day (Table 2); thus, it is revealed that **22** was not decomposed by the hydrolysis of the ester linkage in the plant body. This result suggests that **22** would be hydrolyzed to its aglycon similar to the case of *L. cuneata* (Figure 10).

Table 5. Bioactivity of the leaf extracts from *P. urinaria*.^[a]

Time of collection (status of leaves)	daytime	night
midnight (– –)	–	– –
4.00 a.m. (– –)	–	– –
8.00 a.m. (+ +)	++	+
noon (+ +)	++	+
4.00 p.m. (–)	–	– –
8.00 p.m. (– –)	–	– –

[a] Concentration of leaf extracts = 0.1 g L⁻¹. The scale reaches from “completely open” (+ +) to “completely closed” (– –).

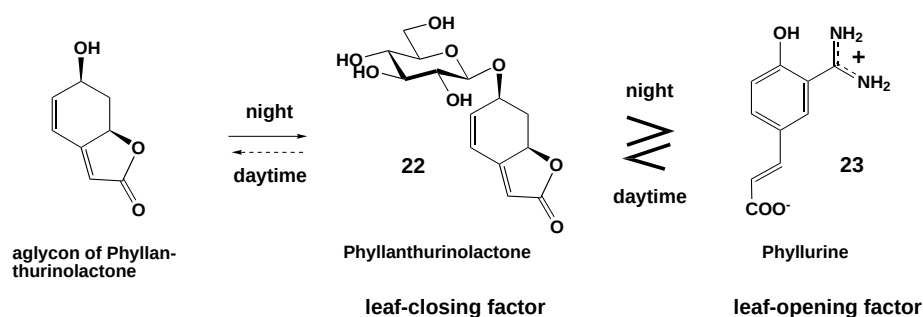


Figure 10. A model for the chemical control of nyctinasty in *Phyllanthus urinaria* L.

The HPLC analysis shows that the content of **22** was one-twentieth that of **23** in the daytime and increased to a half at night. The competition experiment between **22** and **23** was compatible with this result. When the existence of **24** was half that of **23**, the leaf was closed; on the other hand, when it was one-twentieth that of **23**, the leaf opened (Table 7). Thus, the difference in bioactivity between the plant extracts has been attributable to the difference in the content of the leaf-closing substance **22**.

Table 7. Competitive interaction between **22** and **23**.^[a]

	<i>c</i> (22) [mol L ⁻¹]	ratio 22 : 23						control sample
		1:0.5	1:1	0.5:1	1:5	1:10	1:20	
daytime	1 × 10 ⁻⁴	--	--	--	--	++	++	++
night	1 × 10 ⁻⁴	--	--	--	--	--	++	--

The scale reaches from "completely open" (++) to completely closed (--).

The above results show the complete mechanism for the chemical control of nyctinasty. The transformation of **22** into its aglycon by the activation of β -glucosidase should be controlled by a biological clock. It is noteworthy that the concentration of glycoside-type bioactive substances changed through a day in both the cases of *L. cuneata* and *P. urinaria*. A common mechanism would operate in both plants. An important difference between them lies in the fact that the leaf-closing substance, which is a glucoside, would be hydrolyzed by the β -glucosidase in the case of *P. urinaria*.

5.3. The Universal Mechanism for the Regulation of Nyctinasty by a Biological Clock

We have demonstrated that the regulation of all nyctinastic leaf movements can be explained by one mechanism, namely, that either the leaf-closing or leaf-opening substance is a glycoside, and the glycoside is deactivated by a β -glucosidase, the

activity of which is controlled by a biological clock.^[21, 44] Our universal model for the regulation of leaf movement is shown in Figure 11. According to this model, there exist two types of plants; one has a glycoside-type leaf-opening substance which is deactivated by the activation of a β -glucosidase in the evening, the other has a glycoside-type leaf-closing substance which is deactivated by β -glucosidase in the morning.

6. Summary and Outlook

Leaf movement in nyctinastic plants has long been believed to be controlled by a common plant hormone. However, our results contradict this theory. Indeed, we advance a new theory of the chemical control of nyctinastic leaf movement; nyctinastic leaf-movement is controlled by the balance of concentration between two bioactive substances, leaf-opening and leaf-closing substances. This balance is inverted through the day according to the rhythm of the biological clock. The biological clock regulates this balance through the control of the β -glucosidase activity.

Our leaf-movement factors, whose concentrations have been proved to change according to a circadian rhythm, are thought to be genuine chemical signals that control leaf

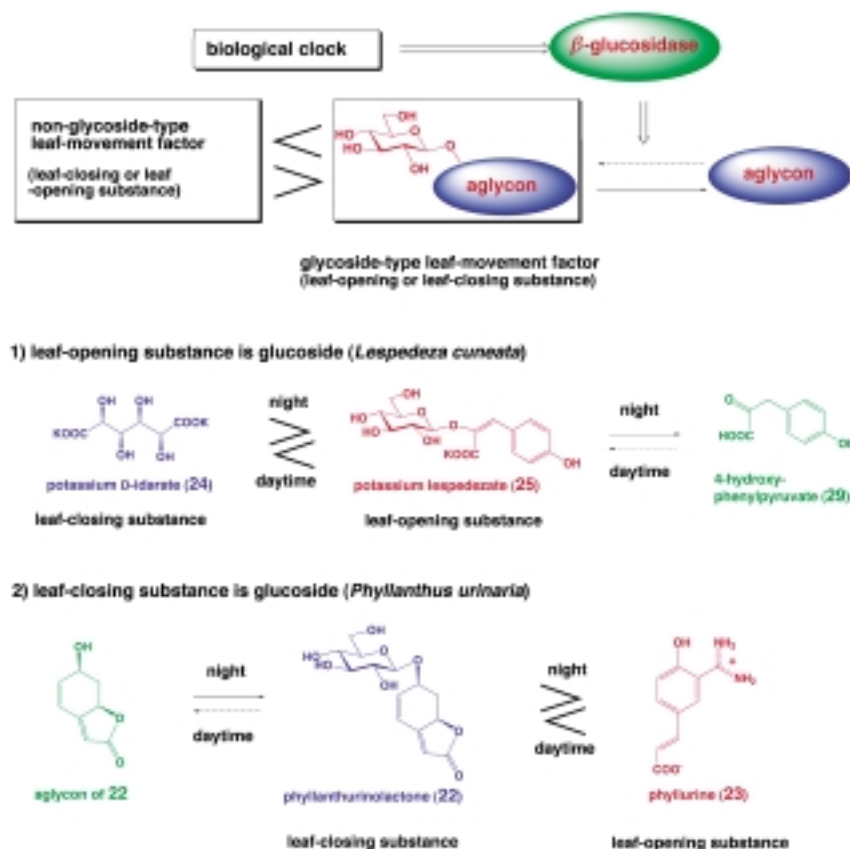


Figure 11. Model for a universal mechanism of chemical control of nyctinasty.

movement in nyctinastic plants under physiological conditions. They can be used as a tool for understanding the mechanism of leaf movement. Our present result will develop the science of this field from plant physiology into bioorganic chemistry.

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Syntheses of CP-225,917 and CP-263,114

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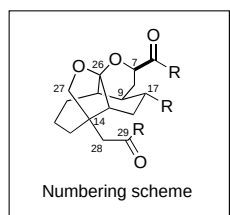
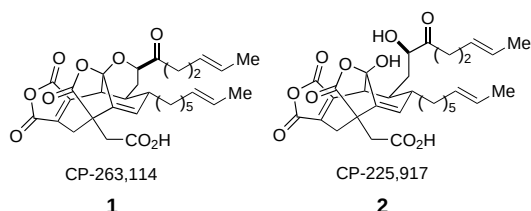
The synthesis of complex structures provides a stringent test of known methods, and when these fail, the endeavor challenges the modern synthetic chemist to innovate. The isolation and structure elucidation of novel natural products provides an important well-spring of challenges that can drive the development and study of reaction chemistry. Research programs aimed at the synthesis of structurally complex natural products thus can lead to the discovery of novel reaction methods, as well as the development of innovative strategies for molecular synthesis. Historically there have been natural products that have especially piqued the imagination of chemists. The study of the syntheses of these important natural products provides in-depth chronological evaluation of the field of organic synthesis, highlighting the important advances in the science, as well as the remaining gaps that require additional work.^[1]

The recent isolation of CP-263,114 (**1**) and CP-225,917 (**2**) adds to the lineage of natural products that pose daunting synthetic problems, leading to opportunities for much discov-

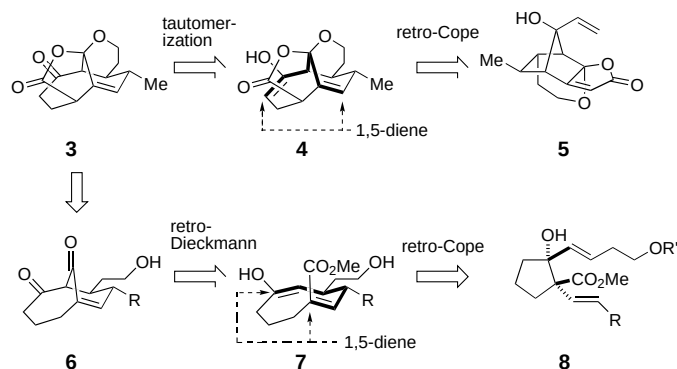
ery and innovation. These fungal metabolites were documented by Pfizer as part of a program aimed at identifying novel, powerful inhibitors of squalene synthetase, as well as

farnesyl transferase.^[2] Inhibitors of these enzymes have proven useful in the development of potential cholesterol-lowering agents and anticancer chemotherapeutics.^[3] These intriguing metabolites made their appearance in the wake of another class of novel, structurally unusual squalene synthetase inhibitors, namely, the zaragozic acids, which have been of broad interest in the pharmaceutical industry.^[4] The polycyclic array found in CP-263,114 (**1**) and CP-225,917 (**2**) possesses daunting stereochemical and structural complexity that provides challenging problems in molecular synthesis, including an anti-Bredt bridgehead olefin along with a collection of unusual, densely packed, labile functional groups. It is not surprising that these structures have piqued the imagination of many research groups worldwide producing a number of elegant, creative approaches. The most prominent contributions include those by the groups of Armstrong,^[5] Clive,^[6] Danishefsky,^[7] Fukuyama,^[8] Leighton,^[9] Nicolaou,^[10] and Shair.^[11] Recently, the efforts of two of these groups, those of Nicolaou and Danishefsky, have culminated in successful total syntheses. The diverse strategies that have been reported by these groups attest to the power and vitality of organic synthesis and validate the fact that natural products synthesis programs offer a unique way to discover and invent novel, interesting reactions that directly address specific problems in synthesis (see also Lit. [1]).

Shair et al. and Leighton et al. have independently reported two innovative strategies en route to this class of natural products. These approaches are based on retrosynthetic analyses consisting of two different oxy-Cope rearrangements (Scheme 1). In the Leighton analysis, enone **3** is accessed from



ery and innovation. These fungal metabolites were documented by Pfizer as part of a program aimed at identifying novel, powerful inhibitors of squalene synthetase, as well as

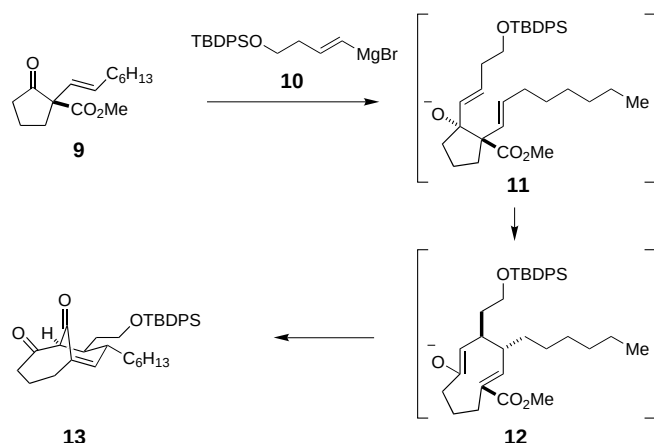


Scheme 1. Leighton's and Shair's (top and bottom, respectively) retrosynthetic strategies for the CP molecule core bicyclic.

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a suitable 1,5-diene **4** by an oxy-Cope rearrangement (**5** to **4**). In the Shair route, the bridgehead ketal is retrosynthetically converted into the corresponding ketone, wherein the resulting 1,3-dicarbonyl relationship serves as the keying element for a retro-Dieckmann disconnection (**6** to **7**). The resulting enone (shown as its enol tautomer **7** in Scheme 1) immediately suggests assembly by oxy-Cope rearrangement (**8** to **7**). The successful implementation of these oxy-Cope rearrangements in both strategies allows considerable efficiency in the assembly of the CP core. In addition, the application of these molecular rearrangements within a sequence of tandem reactions lends further efficiency to each of the strategies.

The Shair approach commences with the nucleophilic addition of **10** to cyclopentenone **9**, leading to the formation of **11** (Scheme 2). This 1,5-diene is ideally functionalized as a

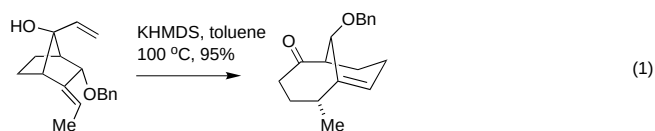


Scheme 2. The one-pot oxy-Cope rearrangement and Dieckmann reaction reported by Shair et al. for the synthesis of the model bicycle **13**. TBDPS = *tert*-butyldiphenylsilyl.

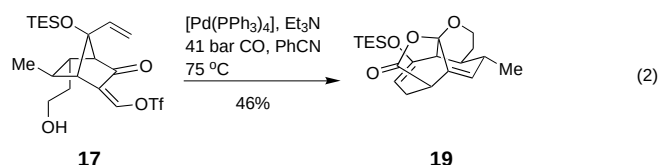
substrate for an anion-accelerated oxy-Cope rearrangement to afford enolate **12**. The enolate intermediate undergoes Dieckmann cyclization affording the desired functionalized CP bicyclic core **13**. In the experiment, when **9** was treated with **10**, diketone **13** was isolated directly from the reaction mixture in an impressive 64% yield.

The Leighton synthesis commences with keto ester **15** which is readily prepared following a previously reported route from diene **14** (Scheme 3).^[12] In eight steps, **15** is converted into ketone **16** which functions as a critical precursor to the substrate for the oxy-Cope rearrangement. Treatment of **16** with KHMDS and methyl formate provided a vinyl alcohol that was subsequently transformed into the corresponding vinyl triflate, which was then desilylated to give **17**. A Pd-catalyzed carbonylation reaction then furnished lactone **18**. When **18** was heated in toluene at reflux for one hour, the expected Cope rearrangement occurred and **19** was isolated in excellent yield. Leighton speculates that the inherent strain of lactone **18** resulted in a significant rate acceleration

over a similar rearrangement that had been reported by Clive in an independent approach to a model of the CP core [Eq. (1)].

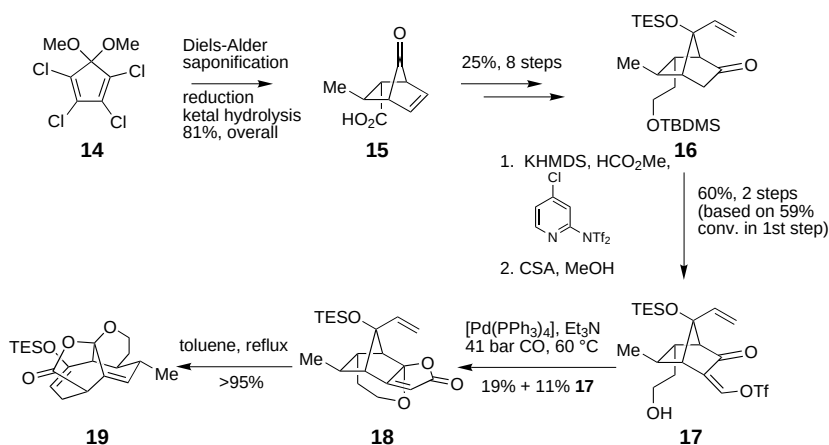


Having established the viability of their bold strategy, Leighton and co-workers examined the possibility of effecting the conversion of vinyl triflate **17** to the rearranged structure **19** by conducting the Pd-catalyzed carbonylation reaction and subsequent Cope rearrangement sequentially in a single pot [Eq. (2)]. Indeed, this strategy was successfully implemented;

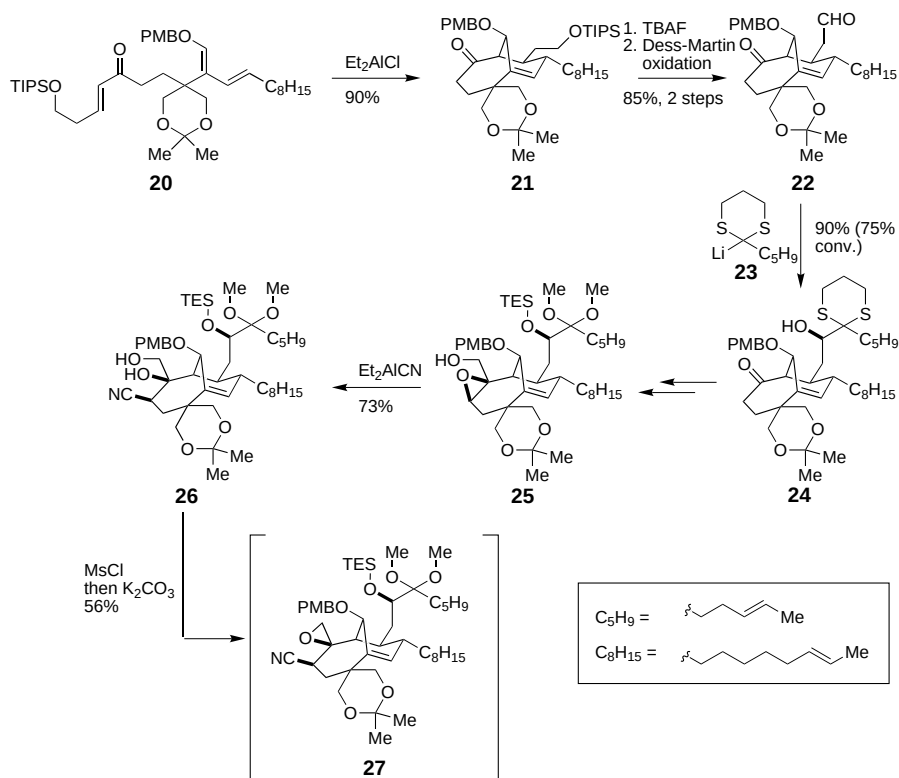


thus, treatment of **17** with CO (41 bar) in the presence of [Pd(PPh₃)₄] in benzonitrile (75–110 °C) furnished **19** directly in a remarkable 46% yield (compared to 19% yield in the stepwise version).

The focal point of the Nicolaou strategy that lead to the successful total synthesis of CP-225,917 (**2**) and CP-263,114 (**1**) is the assembly of the requisite [4.3.1] core through an unusual Diels–Alder reaction, wherein **20** undergoes intramolecular cycloaddition to afford **21** in the presence of Me₂AlCl catalyst (15 mol%) in an impressive 90% yield (Scheme 4). In a related study, Fukuyama has independently reported a similar cycloaddition reaction, albeit on a model system [Eq. (3)].^[8] The fact that **20** is prepared in only 13 steps and that the cycloaddition reaction proceeds in high yield, allowed Nicolaou and co-workers to readily prepare multi-gram quantities of this key, advanced intermediate. This point is not to be underestimated, as the unusual juxtaposition of



Scheme 3. Synthesis of tetracyclic model compound **19** by Leighton et al. TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, KHMDS = potassium bis(trimethylsilyl)amide, CSA = camphorsulfonic acid, Tf = trifluoromethanesulfonyl.

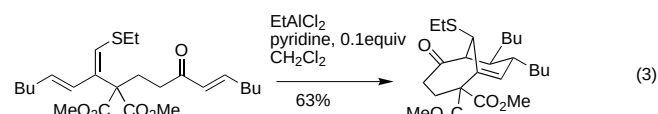


Scheme 4. Early steps of the total synthesis by Nicolaou et al. including intramolecular Diels–Alder construction of the core bicycle and subsequent side-chain elaborations. TIPS = triisopropylsilyl, PMB = *para*-methoxybenzyl, Ms = methanesulfonyl, TBAF = tetrabutylammonium fluoride.

furnish cyano-epoxide **27**. Epoxide **27** underwent a remarkable series of cascade reactions to directly provide anhydride **30**. Thus, following treatment with base and then acid under an oxidizing atmosphere (air) anhydride **30** was isolated in 56% yield (Scheme 5).

Despite the fact that a sizeable portion of the structure had been masterfully assembled at this point in the route, the synthetic obstacles remaining were significant. These included the necessary homologation at C28, oxidation at C27, and the installation of the bridgehead ketal.

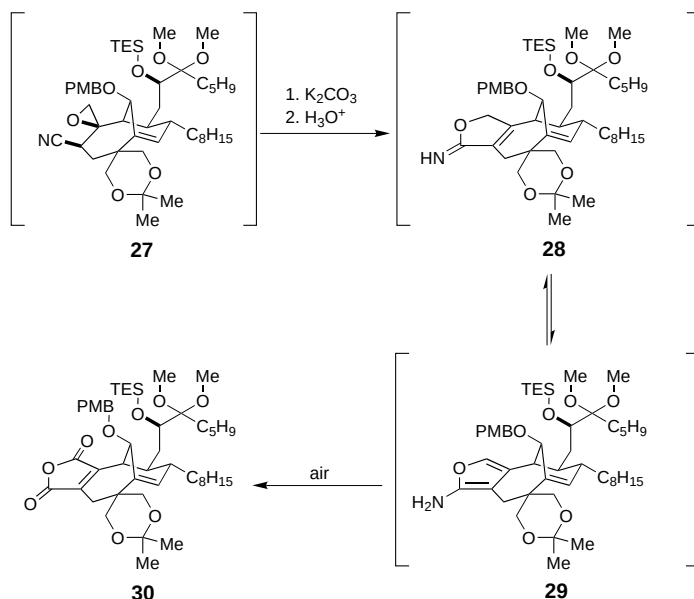
The completion of the synthesis was possible as a consequence of the development of new reaction methodology and careful strategic planning. The requisite oxidations required clever timing of the oxidation and ring-closing sequences as a series of investigations had revealed a number of troublesome side reactions of this densely functionalized bicyclic ring system. Straightforward protecting group manipulation provided **31**



functionality in C-263,114 (**1**) and CP-225,917 (**2**) assured challenging steps further along the route which would necessitate an efficient route that would provide large quantities of advanced densely functionalized intermediates for study.

One of the first remarkable discoveries after the preparation of the bicyclic system following oxidation of **21** to afford **22** was that the addition of lithium dithiane **23** to aldehyde **22** proceeds in 11:1 diastereoselectivity to give the desired adduct **24**. This impressive level of diastereoselectivity may be related to similar results that have been independently documented by Danishefsky and co-workers in their elegant study of the epimerization chemistry of CP-225,917 and CP-263,114 (*vide infra*). In that study Danishefsky et al. observed a similarly strong and unexpected stereochemical bias imparted by the surrounding ring system in the context of an epimerization study of this stereocenter. These unanticipated results attest to the curios to be discovered in a complex molecule synthesis.

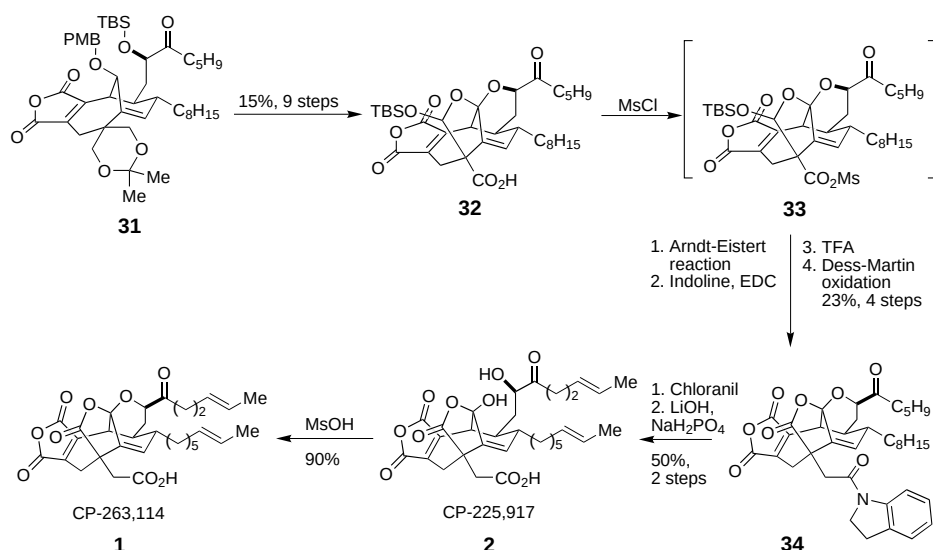
In the synthesis of Nicolaou et al., the subsequent installation of the anhydride of the CP core provided additional surprises. Treatment of **25** with Nagata's reagent (Et_2AlCN) lead to product **26** which is formally derived from an unexpected *syn* epoxide-ring-opening reaction. Diol **26** was subsequently subjected to cyclodehydration conditions to



Scheme 5. One-pot conversion of cyanoepoxide **27** to the requisite anhydride **30** in 56% overall yield by Nicolaou et al.

which, through a carefully orchestrated series of reactions was transformed into **32** (Scheme 6). This intermediate appropriately masks the C27 alcohol and allows selective oxidative manipulation as the corresponding lactol.

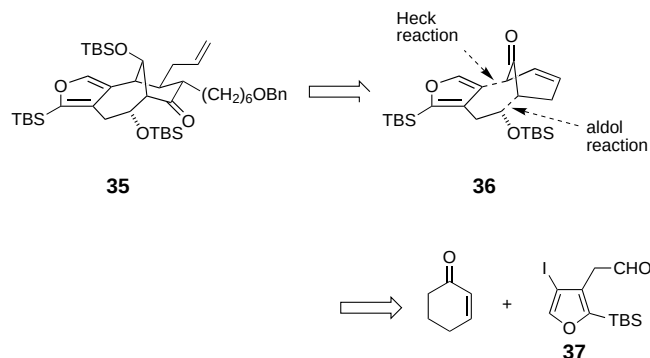
Homologation at C28 proved to be a challenge as a consequence of the highly hindered nature of this carboxyl group. In this regard, standard methods for carboxyl activa-



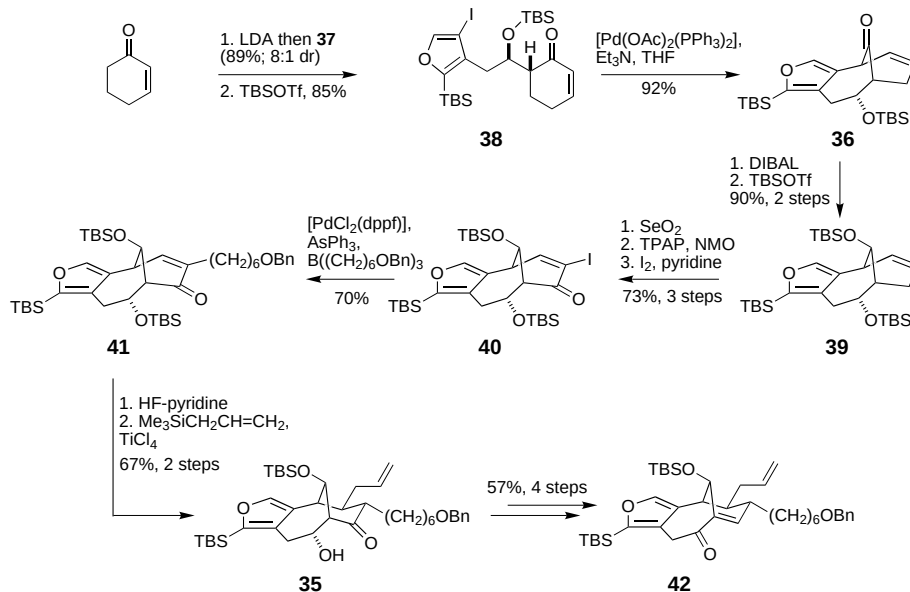
Scheme 6. Final steps of the total syntheses by Nicolaou et al. EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride.

tion that have been employed for the Arndt–Eistert homologation reaction proved unsuccessful. Nicolaou and co-workers subsequently devised a novel strategy for the activation of such hindered carboxylic acids. It was established that the hindered carboxylic acid in **32** could be converted into the corresponding acyl mesylate **33** which in turn would react with diazomethane. The intermediate diazoketone undergoes a Wolff rearrangement to give the desired acetic acid side-chain which is subsequently condensed with indoline to afford amide **34**. A methodological study of carboxyl activation by preparation of the corresponding mixed anhydride has revealed the unique aspects of this strategy and its general application to the preparation of hindered acyl mesylates.^[10d]

It was necessary to protect the C29 carboxyl group as an amide in the final stages of the approach in order to close the final ring through the formation of the ketal at C26. The decision to employ an indoline amide as a protecting group for the C29 carboxylic acid was based on unsuccessful use of an aniline amide. In this regard, the acyl anilide was found to undergo oxidation and then participate in an intramolecular cycloaddition reaction with the bridgehead olefin. By contrast the indoline amide did not undergo deleterious oxidation and yet was amenable to subsequent removal under remarkably mild conditions. Thus, in the final steps of the synthesis, chloranil oxidation of the indoline followed by LiOH hydrolysis gave CP-225,917 (**2**). Following treatment with methanesulfonic acid, CP-225,917 (**2**) was converted into CP-263,114 (**1**).



Scheme 7. Danishefsky's retrosynthetic analysis. An aldol reaction and a Heck reaction are key bond-forming steps in the synthesis of the bicyclic core.

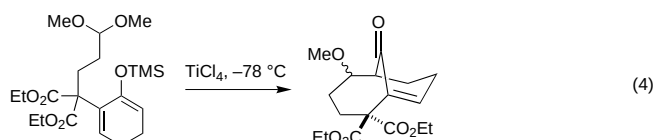


Scheme 8. Early steps in the synthesis by Danishefsky et al. including the key aldol and Heck reactions and incorporation of side-chain precursors. TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide, LDA = lithium diisopropylamide, DIBAL = diisobutylaluminumhydride, dppf = 1,1'-bis(diphenylphosphanyl)ferrocene.

The strategy pursued by Danishefsky and co-workers is based on a retrosynthetic analysis which efficiently dissects the bicyclic core into two simple fragments, furan **37** and 2-cyclohexenone (Scheme 7). This plan was elegantly and efficiently realized in an approach that provides ready access to a variety of compounds incorporating the critical bicyclic core with varied side-chains.

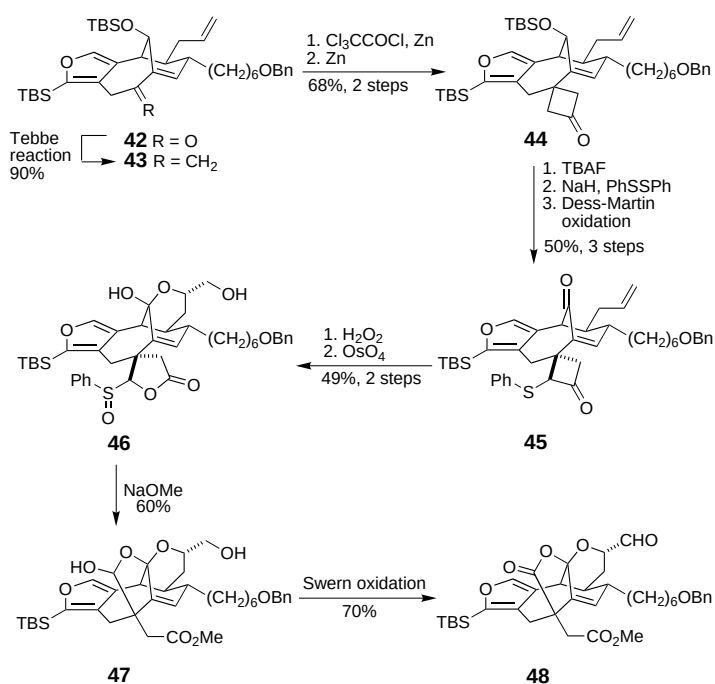
The Danishefsky synthesis commenced with the aldol addition between 2-cyclohexenone and **37** to afford adduct **38** in high yield and good diastereoselectivity (8:1) (Scheme 8). The stage was set for subsequent ring closure to afford the desired bicyclic ring

system. When **38** was subjected to Heck conditions the product **36** of an intramolecular vinylation reaction was isolated in 92 % yield. The combination of these two steps assembled the bicyclic system in an efficient and convergent manner allowing a straightforward synthesis of the natural product. The fused furan ring serves as a mask for the anhydride that will be revealed late in the synthesis, and the olefin in **36** is ideally positioned for subsequent elaboration of the cyclohexyl ring. In an independent study of a model system en route to the synthesis of the CP core, Armstrong has documented a related aldol cyclization reaction that gives rise to the [4.3.1] bicyclic CP core [Eq. (4)].



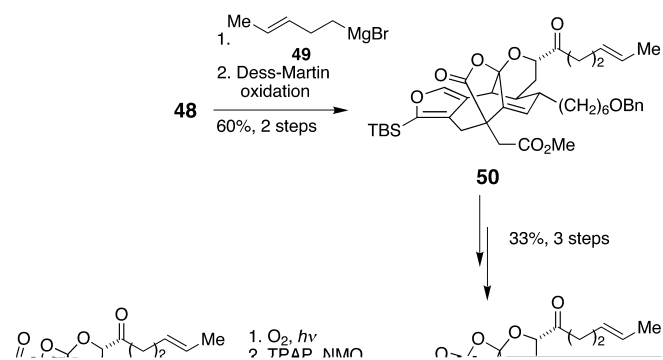
Functionalization at the endocyclic olefin by treatment of **39** with SeO_2 effected allylic oxidation and yielded an intermediate alcohol that was subsequently oxidized to the corresponding unsaturated ketone; this was iodinated to give vinyl iodide **40**. A Suzuki coupling reaction with the C17 side-chain then efficiently provided **41**. Although direct conjugate addition to enone **41** proved difficult, it was observed that the corresponding desilylated enone readily undergoes a Sakurai conjugate addition reaction in excellent yield to give adduct **35** with the desired *trans* stereochemical relationship at C17 and C9. The bridgehead alkene was then installed through selective manipulation of the hydroxyl and keto functionalities followed by a dehydration reaction.

Installation of the critical C14 carboxyl side-chains was accomplished by a cyclobutane ring fragmentation reaction (Scheme 9). When ketone **42** was subjected to the Tebbe olefination reaction conditions alkylidene **43** was formed in 90 % yield. Reaction of this olefin with dichloroketene afforded the corresponding dichlorocyclobutanone. Reductive removal of the geminal dichloro substituents gave **44** which underwent regioselective enolization and reaction with PhSSPh to give the corresponding substituted cyclobutanone. The importance of this substitution in controlling the selectivity in a subsequent Baeyer–Villiger oxidation, as well as a fragmentation reaction of the resulting lactone in this strategy, had been the subject of exploratory studies by the Danishefsky group. The overall transformation of the cyclobutanone proved to be ideally executed when the sulfoxide was employed. Thus, Baeyer–Villiger oxidation was followed by oxidation of the sulphenyl lactone to the corresponding sulfoxide. Following chemoselective dihydroxylation of the monosubstituted alkene in the C9 side-chain, the secondary alcohol is proposed to participate in a cascade of rearrangements mediated by NaOMe to give lactol **47** incorporating the remaining two rings found in the CP core. Oxidation of **47** then furnished lactone **48**, an important intermediate in the successful completion of the synthetic route and in accompanying studies.



Scheme 9. Formation of the pyran and lactone rings in the Danishefsky route.

Elaboration of aldehyde **48** allowed for installation of the C7 side-chain through a two-step sequence: aldehyde addition and Dess-Martin oxidation (Scheme 10). Finally, the anhy-

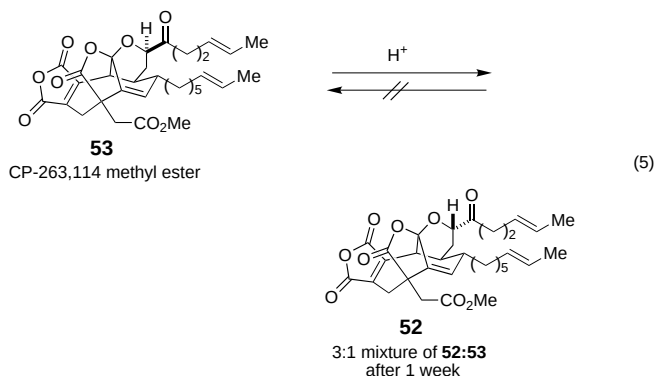


Scheme 10. Late-stage addition of the C1–C5 side chain and conversion of the furan to the maleic anhydride residue.

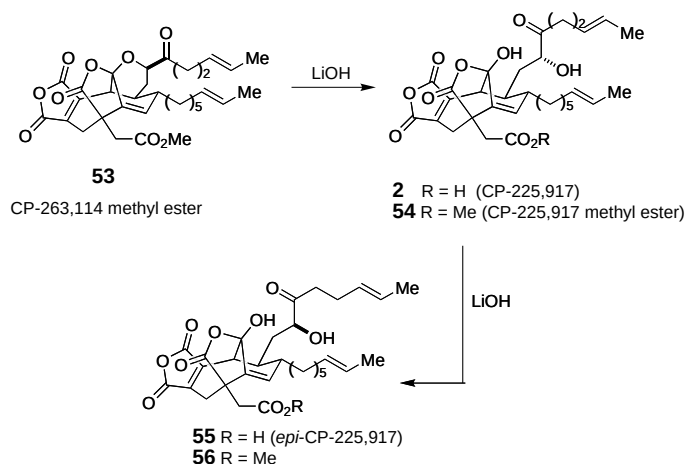
dride which had been successfully masked throughout the synthesis as a furan, could be revealed by oxidation of the heterocycle. Thus, following elaboration of the C17 side-chain, treatment of furan **51** with singlet oxygen followed by oxidation of the resulting lactol (Ley oxidation) afforded the methyl ester **52**.

At this point in the synthesis, comparison of the synthetic material **52** to the methyl ester of the authentic natural product **53** led these investigators to conclude that the compounds differed with respect to the configuration at C7. A series of elegant studies revealed intriguing issues concerning epimerization of this stereogenic center, raising the

interesting postulate that the epimeric material that had been accessed by total synthesis (**52**) may also be a natural product. In this regard, when **53**, the methyl ester of CP-263,114, was subjected to acidic conditions an approximate 3:1 mixture of **52** and **53** was obtained, indeed favoring the 7*S* epimer [Eq. 5]. However, attempted equilibration of **52** to **53** was not successful, leading to either extensive decomposition of **52** or its re-isolation.



Danishefsky and co-workers next conducted a meticulous study with CP-225,917 (**2**) and its methyl ester **54** in an effort to probe whether this ring-opened CP structure would be prone to epimerization at C7. Treatment of **2** with LiOH gave a 1:1 mixture of **2** and **55** (Scheme 11). Analogous experi-



Scheme 11. Results of the C7 epimerization studies by Danishefsky et al.

ments could be conducted with the corresponding methyl ester **53**, giving a 1.7:1 mixture of ring-opened structures epimeric at C7. These investigators subsequently demonstrated that the “closed” and “open” forms **53** and **54**, respectively, could be interconverted under alkaline conditions without attendant epimerization at C7, utilizing a procedure initially disclosed by the Pfizer workers. The methyl ester **54** of CP-225,917 could then undergo epimerization to give **56**, epimeric at C7 incorporating the 7*S* configuration. Through further studies, these workers established that the “synthetic” 7*S* configuration was considerably more stable than the “natural” 7*R* configuration of the initially reported compounds, CP-

263,114 (**1**) and CP-225,917 (**2**). When the epimeric synthetic material **52** was subjected to the epimerization regime (alkaline opening, and epimerization, followed by ring closure) and an ester hydrolysis, **1** could be detected, albeit in trace quantities. It is noteworthy that in contrast to the ready epimerization of the natural 7*R* epimers (open and closed forms) the synthetic 7*S* epimeric series does not participate in efficient isomerization reactions. In addition to revealing the remarkable natural product chemistry of these substances, the investigators noted the presence of the C7 epimers in the fermentation broths, a feature that had not been previously appreciated.

The impressive creativity, ingenuity, and tenacity exhibited in the synthetic efforts towards CP-263,114 (**1**) and CP-225,917 (**2**) underline the power of the modern synthetic chemist when faced with such daunting challenges. The work by Armstrong, Clive, Danishefsky, Fukuyama, Leighton, Nicolaou, and Shair discussed in this highlight underscores the important discoveries and innovations that target-oriented natural products synthesis projects can yield.

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 [13] Editor's note: An asymmetric total synthesis of the CP compounds has just been completed: K. C. Nicolaou, J.-K. Jung, W. H. Yoon, Y. He, Y.-L. Zhong, P. S. Baran, *Angew. Chem.*, in press.

In Spite of the Chemist's Belief: Carbonic Acid Is Surprisingly Stable

Ralf Ludwig* and Andreas Kornath*

It is conventional wisdom in any chemistry textbook that carbonic acid is kinetically unstable. Accordingly, the recently published Encyclopedia of Inorganic Chemistry^[1] still claims: "Pure carbonic acid, H₂CO₃, cannot be isolated because of its ready dehydration to carbon dioxide, CO₂." Despite belief in the nonexistence of carbonic acid, chemists succeeded in recognizing its stability in the last few years. They were able to synthesize carbonic acid at low temperatures by high-energy irradiation of cryogenic carbon dioxide/water ice mixtures^[2, 3], proton-irradiation of pure solid CO₂^[4] and by protonation of bicarbonate^[5, 6]. The resulting carbonic acid was characterised by IR spectroscopy and mass spectrometry. Recently Liedl and coworkers^[7] explained in a beautiful theoretical work why carbonic acid can exist in its free form and why chemists thought and taught for so long that this compound is unstable.

Carbonic acid is of special importance in biological and geochemical carbonate-containing systems. The equilibrium of carbonic acid with carbon dioxide and water and its significance are well recognized and carefully studied. Despite the reaction [Eq. (1)] making carbonates the most abundant minerals on earth, carbonic acid is difficult to observe spectroscopically in its free state.



Carbonic acid is known to be present to the extent of about 0.003 % in water containing dissolved CO₂. The dissociation constant of carbonic acid is large in comparison with those of other hydrates. This has been understood as a result of the

high stability of the unhydrated species, CO₂. However, an activation energy of 15.5 kcal mol⁻¹^[8] for the dissociation reaction of carbonic acid to water and carbon dioxide suggested that it should be possible to observe carbonic acid in its free state.

In fact, there had been two claims of the preparation of free carbonic acid as an etherate, but no spectral evidence was provided. Isolation of such an ether complex was achieved by the addition of an ethereal solution of anhydrous hydrogen chloride to a suspension of finely crushed sodium bicarbonate in ether at 243 K.^[9] Cooling the solution to 195 K resulted in the precipitation of a white crystalline etherate. In a similar procedure Gattow and Gerwath^[10] used dimethyl ether and sodium carbonate at 238 K to prepare the dimethyl ether complex of carbonic acid. They obtained a solid which decomposed violently above 278 K, yielding water, carbon dioxide and ether. For both studies NMR and IR spectra were not obtained.

For a long period, carbonic acid had not been detected by any spectroscopic means; its formation was only inferred from kinetic data. Schwarz et al.^[11] first demonstrated the existence of carbonic acid as a stable, discrete species. Thermal decomposition of NH₄HCO₃ gave carbonic acid in the gas phase which was detected by neutralization–reionization mass spectroscopic (NR-MS) techniques. Olah et al.^[12] found spectral evidence for carbonic acid by calculating ¹³C chemical shifts and comparing them with those obtained from NMR measurements under superacidic conditions. In this environment, the carbonic acid and its protonated species is present in an equilibrium [Eq. (2)].



Recently, the protonated carbonic acid was prepared in superacids (HF/AsF₆, HF/SbF₆) from carbonic acid bis(trimethylsilyl)ester.^[13] The salts have been characterized with vibrational spectroscopy and X-ray analysis. Obviously, the protonated carbonic acid is formed under these conditions in situ by cleavage of the silyl ester.

The analysis of the IR and mass spectral data by Moore and Khanna^[2] gave strong evidence for the formation of carbonic

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acid on irradiating a water/carbon dioxide ice mixture at 20 K. Upon warming the sample to 210 K, the residual film appeared to be principally hydrogen-bonded carbonic acid. Hage et al.^[6] synthesized carbonic acid by a different method: They obtained carbonic acid by protonating bicarbonate and characterized it in vitreous methanol films at low temperatures (150 K) by infrared spectroscopy. The authors could demonstrate that their polymorph of carbonic acid was the same than that of Moore and Khanna^[2] obtained by proton irradiation. Further, Hage et al.^[6] sublimated and recondensed solid carbonic acid without its decomposition into carbon dioxide and water. This study proved the stability of carbonic acid in the gas phase. The vapor pressure estimates were consistent with an equilibrium mixture of monomers and dimers, similar to that of formic acid (Figure 1).

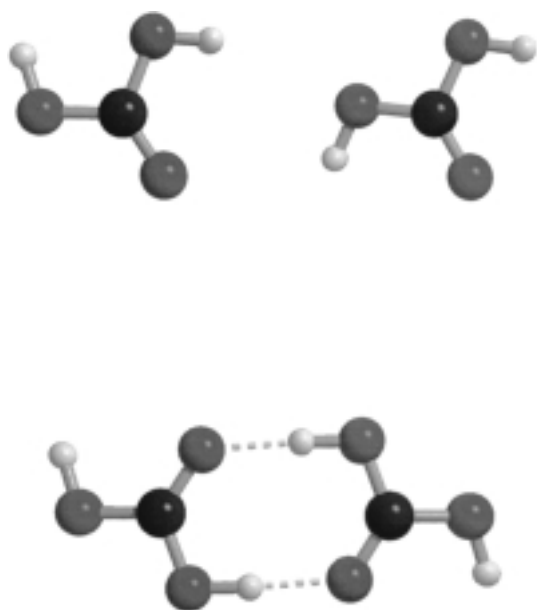


Figure 1. Representative monomers and dimer of carbonic acid proposed by quantum mechanical calculations. Experimental studies^[5] suggest a mixture of monomers and dimers in the gas phase, similar to that for formic acid.

Thus far, it has been proved that carbonic acid can be synthesized and that it is stable in the solid and the gas phase. But there still remain questions: Why is carbon acid surprisingly stable? And why does it decompose so quickly in aqueous solution?

A satisfactory answer is now given by Liedl and co-workers,^[7] who studied the influence of water on the decomposition rate of carbonic acid. Using quantum mechanical Transition State Theory (TST), they calculated accurate reaction rates. This method requires exact calculations of energy differences of reactants, transition states, and products, a multidimensional description of reaction paths, and quantum effects such as tunneling and zero-point energies. That this method generates chemically meaningful results has been proved by benchmark studies of the double proton transfer reaction in carboxylic acid dimers. The calculated reaction barriers for the decomposition of isolated carbonic acid referred to its stability. Successive addition of two water

molecules decreased the reaction barrier of about 44 kcal mol⁻¹ for pure carbonic acid to 27 kcal mol⁻¹ then 24 kcal mol⁻¹, respectively

The calculated half-lives were even more convincing. A half-life of 65.7 million days indicated that carbonic acid is still stable at room temperature (300 K). Even at 400 K, carbonic acid has a half-life of about eight days. This behavior changed drastically in aqueous solution. Adding water decomposed the carbonic acid quickly. At 300 K, the half-life of about 65.7 million days for pure carbonic acid decreased to ten hours and two minutes when catalyzed by one and two water molecules, respectively (Figure 2). Two water molecules shorten the half-life of carbonic acid by a factor of about 50 billion.

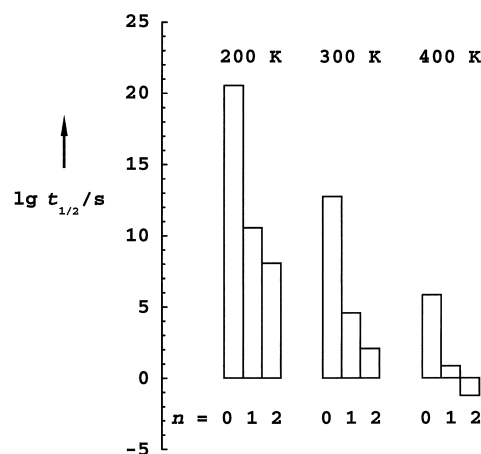


Figure 2. Half-lives of carbonic acid in the framework of Transition State Theory in the absence ($n=0$) and in the presence of one ($n=1$) and two ($n=2$) water molecules at three temperatures (data taken from ref. [7]). At 300 K it can be seen that the half-life of about 65.7 million days for the pure carbonic acid decreased to ten hours and then to two minutes.

This is—according to the authors—the reason why most chemists believe carbon acid is instable. When chemists speak of carbonic acid, they have in mind carbon dioxide dissolved in water and not H₂CO₃. The latter contains, at standard state conditions, 1.6 g carbon dioxide per liter of water. Since 99.8% of the carbon dioxide molecules are weakly hydrated, only 0.2% forms carbonic acid and thus the solution shows acidic behavior because of the H₂CO₃/HCO₃⁻ equilibrium.

The calculations of Liedl and co-workers proved that pure carbonic acid shows a surprisingly kinetic stability whereas in aqueous solution it decomposes quickly. The calculated half-lives could support previous experimental results: Measuring the kinetic stability of crystalline and amorphous carbonic acid in an ice matrix, the experimental decomposition rate was about 18 ± 7 s⁻¹ which is only 3000 times faster than the calculated value.

Why is information about the stability of carbonic acid so important? Carbonic acid, the short-lived intermediate in CO₂-HCO₃⁻/CO₃²⁻ proton-transfer reactions, is a key compound in biological and geochemical carbonate-containing systems.

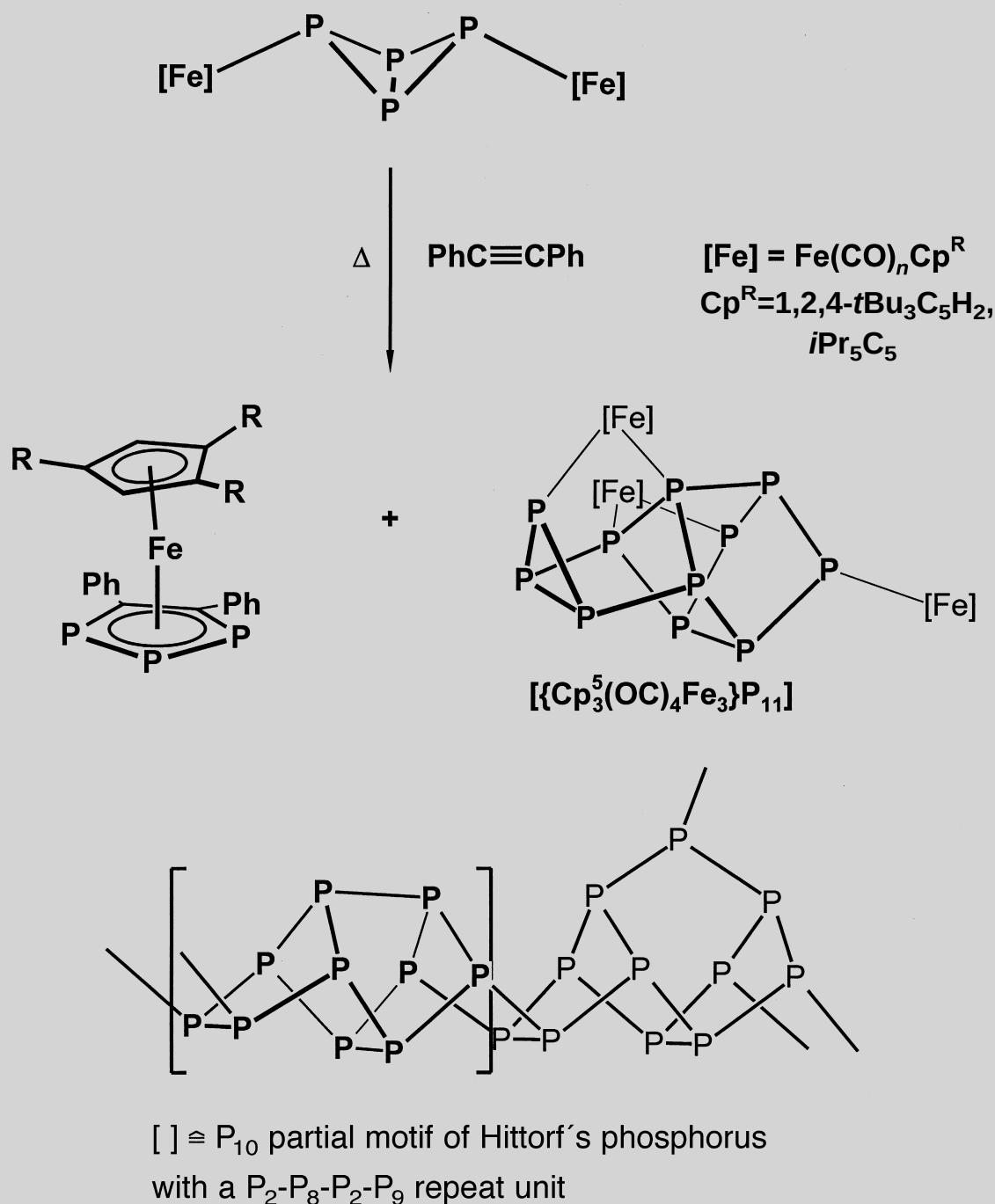
We have seen that the hydration of carbon dioxide is a slow reaction, too slow for physiological needs. In blood, the reversible combination of CO₂ and H₂O to form H₂CO₃ is

catalyzed by the enzyme carbonic anhydrase.^[14] The non-catalyzed reaction would not permit CO₂ to interchange between the blood and the tissues or between the blood and the lungs at rates sufficient for physiological requirements. The activity of carbonic anhydrase is remarkable. It has been estimated that one molecule of this enzyme can catalyze the hydration of about 36 million CO₂ molecules per minute.

The significance and implications of solid and gaseous H₂CO₃ for our upper atmosphere in polar stratospheric clouds, Mars, comets, interstellar icy grains, and outer solar bodies is clear.^[5] For example, a comparison between the IR laboratory spectrum of carbonic acid with some spectra of Mars suggests that it could be present on the surface and/or atmosphere of the red planet.^[15] It is therefore of primary relevance for understanding both the organic and inorganic chemistry taking place on Mars.

The surprising stability of H₂CO₃ should encourage experimental chemists to synthesize the compound on a preparative scale. It is also wise to look out for other candidates such as H₂SO₃ which might be more stable than we currently believe.

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Besides the desired synthesis of a sandwich complex with a 1,2,3-triphospholyl ligand, the reaction of the iron butterfly molecule with diphenylacetylene for $\text{Cp}^5(i\text{Pr}_5\text{C}_5)$ additionally affords a trinuclear iron complex, whose P_{11} framework can be derived from the P_{10} substructure of Hittorf's phosphorus by insertion of a P atom (P three-membered ring). Find out more on the following pages.

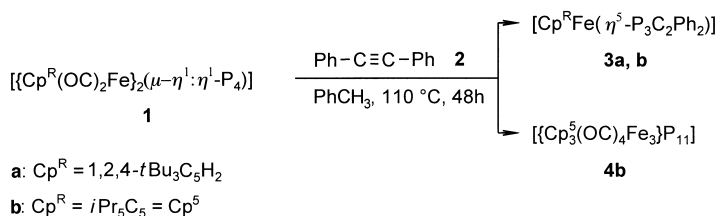
[[Cp^R(OC)₂Fe]₂(μ-η¹:η¹-P₄)]]: Starting Material for the Synthesis of Iron Sandwich Compounds with a 1,2,3-Triphospholyl Ligand and of a Trinuclear Iron Complex with a P₁₁ Ligand**

Otto J. Scherer,* Thomas Hilt and
Gotthelf Wolmershäuser

*Dedicated to Professor Gerd Becker
on the occasion of his 60th birthday*

Among phosphorus heterocycles with π bonds, polyphospholide ions [(CH)_nP_{5-n}]⁻ (*n* = 0–4) as 6π systems form an important link between inorganic and organic chemistry.^[1] In contrast to the well-studied 1,2,4-triphospholide ions,^[1] whose first representative was prepared by Becker et al. from *t*BuCP and LiP(SiMe₃)₂,^[2] both the parent compound of the 1,2,3-triphospholides, [(CH)₂P₃]⁻, as well as the tetraphospholide ion [(CH)P₄]⁻, formed, for instance, as a mixture in the thermolysis of P₄ and sodium in diglyme, were characterized by ³¹P NMR spectroscopy.^[3] A complex multistep synthesis has been described for [(CPh)₂P₃]⁻ which contains a C₂ and P₃ building block in the five-membered ring.^[4] Whereas the ligand properties of the 1,2,4-triphospholide ions have been studied in detail,^[1] to the best of our knowledge there is only one complex known with the 1,2,3-triphospholyl ligand [(CPh)₂P₃]⁻ that has been characterized by ³¹P NMR spectroscopy.^[4]

The reaction of the butterfly molecules **1a**^[5a] and **1b**^[5b] which have a P₄ bicyclobutane framework, with tolane **2** leads to the sandwich complexes **3a, b** with a 1,2,3-triphospholyl ligand in moderate yield. In the case of **1b** the trinuclear iron compound **4b** (Cp⁵ = *i*Pr₅C₅) with a P₁₁ ligand is formed in addition in approximately 10% yield.



In the sandwich complexes **3a, b** the five-membered-ring ligand [(CPh)₂P₃]⁻ can be formally built from a P₃ building block of the butterfly molecule **1** and the alkyne **2**. At the same time **1** provides the necessary Cp^RFe fragment (Cp^R = 1,2,4-*t*Bu₃C₅H₂, *i*Pr₅C₅) for the completion of the sandwich structure of **3**.

Compounds **3a, b** form an anthracite to gray-green solid, which is soluble in *n*-pentane and very soluble in toluene, and can be handled in air for short periods. The ³¹P NMR spectra^[6] of **3a, b** each display an AX₂ spin system with identical coupling constants and slightly different chemical shifts.

The crystal structure analysis^[7] of **3a** confirms its sandwich structure (Figure 1). The distances and angles of the 1,2,3-triphospholyl ligands of **3a** were compared with the calculated

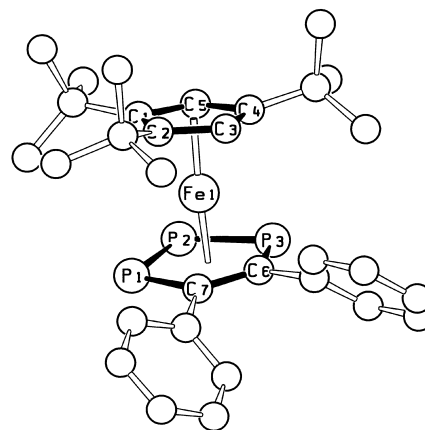


Figure 1. Structure of **3a** in the crystal. Selected bond lengths [Å] and angles [°]: P1-P2 2.1287(14), P2-P3 2.1193(15), P1-C7 1.766(4), P3-C6 1.783(3), C6-C7 1.413(5), Fe1-(P₃C₂)_{centroid} 1.655, Fe1-Cp^R_{centroid} 1.712; P1-P2-P3 99.04(5), P2-P1-C7 99.48 (12), P2-P3-C6 99.74(13), P3-C6-C7 120.1(3), P1-C7-C6 121.4(3).

value of the 1,2,3-triphospholide ion, [(CH)₂P₃]⁻ **5**,^[8] as well as those of the complex [CpFe(η⁵-P₃C₂*t*Bu₂)] **6**^[9a,b] with a 1,2,4-triphospholyl ligand. The P–P, P–C, and C–C distances and the P–P–P angles differ only slightly (P–P 2.12 (**3a**, average), 2.137 (**5**), 2.061 (**6**),^[9a] 2.144 Å (**6**);^[9b] P–C 1.77 (**3a**, average), 1.76 (**5**, average), 1.76 Å (**6**, average); C–C 1.413 (**3a**), 1.388 Å (**5**); P–P–P 99.04 (**3a**), 99.25° (**5**).^[8] In **3a** the planes of the five-membered rings deviate from a parallel orientation by 7.6° (Cp^R_{centroid}–Fe–(P₃C₂)_{centroid} = 173.5°).

For complexes with P_{*n*} ligands thus far examples have only been found with even values of *n* (8, 10, 12, and 14) for *n* ≥ 7.^[10] P₁₁ has now been coordinatively stabilized for the first time in the trinuclear iron complex **4b**. Compound **4b**^[6] forms red-brown crystals, which are poorly soluble in pentane and well soluble in toluene and dichloromethane; they can be handled for short periods in air.

The crystal structure analysis^[7] shows (Figure 2) that the P₁₁ framework of **4b** comprises a P₈P₂ substructure of Hittorf's phosphorus,^[11] in which the P9–P10 edge is bridged in addition by the P11 atom.

The structurally characterized molecules Na₃P₁₁ **7a**,^[12a] (Me₃EtN)₃P₁₁ **7b**,^[12b] (Me₃Si)₃P₁₁ **7c**,^[12c] and (*i*C₃H₇)₃P₁₁ **7d**^[12d,e] reveal exclusively a “ufosane”-type structure (polycycle consisting of six annelated P₅ rings) for the P₁₁ framework. Interestingly, in theoretical studies on P₁₁⁺^[13a,b] and P₁₁⁺^[13a,c], the P₁₁ framework, which has been confirmed for the first time by crystal structure analysis for **4b**, is discussed as a further structural alternative. The P–P bond lengths of **4b** lie in the range between 2.181(3) (P3–P8) and 2.268(3) Å (P5–P6), which is also found in **7d** (2.176 to 2.264 Å) with a

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[+] Crystal structure analyses.

[**] This work was supported by the Fonds der Chemischen Industrie and by the Graduiertenkolleg “phosphorus chemistry as a link between different chemical disciplines”. Cp^R = 1,2,4-*t*Bu₃C₅H₂, *i*Pr₅C₅.

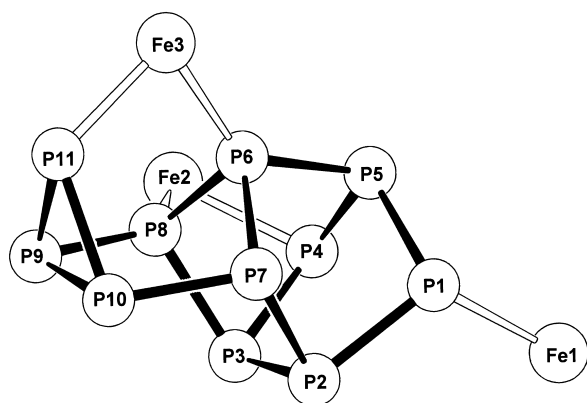


Figure 2. Structure of the framework of **4b** in the crystal (the Cp^{R} ligands are omitted for clarity). Selected bond lengths [Å] and angles [°] (Fe1 = Fe(CO) Cp^{R} (17 VE), Fe2, Fe3 = Fe(CO) Cp^{R} (15 VE)): P1–P2 2.224(3), P1–P5 2.198(3), P2–P3 2.233(3), P3–P4 2.224(3), P4–P5 2.232(3), P5–P6 2.268(3), P6–P7 2.192(3), P6–P8 2.226(3), P2–P7 2.199(3), P3–P8 2.181(3), P7–P10 2.218(3), P8–P9 2.213(3), P9–P10 2.230(3), P9–P11 2.227(3), P10–P11 2.246(3), P1–Fe1 2.322(2), P4–Fe2 2.335(2), P8–Fe2 2.247(3), P6–Fe3 2.228(2), P11–Fe3 2.290(3); P10–P9–P11 60.52(10), P9–P10–P11 59.68(10), P7–P10–P9 108.78(14), P5–P6–P8 93.03(11), P5–P6–P7 102.03(10), P7–P6–P8 96.78(11), P8–P9–P10 98.90(11), P2–P7–P6 100.21(13), P2–P7–P10 109.34(13), P6–P7–P10 96.67(10), P3–P8–P6 100.64(10), P3–P8–P9 111.76(12), P6–P8–P9 98.49(12), P8–P9–P11 101.27(11), P7–P10–P11 98.67(12).

“ufosane” framework^[12c] as well as in the P_8P_2 substructure (2.201 to 2.299 Å) of Hittorf’s phosphorus.^[11] The average values $\bar{d}(\text{P}–\text{P})$ do not differ significantly (2.22 (**4b**), 2.21 (**7b** and **7d**),^[12b,e] 2.219 Å (Hittorf’s phosphorus)^[11]). Whereas the lengths of the Fe–P σ bonds (Fe1–P1, Fe2–P4, and Fe3–P11) range from 2.290(3) to 2.335(2) Å, the two-electron bonds between the phosphorus donor center (lone pair of electrons) and the bridging 15-valence-electron (VE) iron fragments (P8–Fe2 2.247(3), P6–Fe3 2.228(2) Å) are significantly shorter (Figure 2), a trend that also occurs in $[(\eta^5\text{-C}_5\text{H}_4\text{Me})_4\text{Fe}_4(\text{CO})_6\text{P}_8]$ **8**.^[14]

The mass spectrum of **4b**^[6] displays the ions $[(\text{Cp}^{\text{R}}\text{Fe})_2\text{P}_n]^+$ ($n = 3–5$), which can be assigned to a series of cationic 30-, 29-, and 28VE-triple-decker complexes. Formally $[(\text{Cp}^{\text{R}}\text{Fe})_2\text{P}_5]^+$ can be built up from the atoms P1 to P5 and the decarbonylated fragment $\text{Cp}^{\text{R}}\text{Fe}$ of the iron atoms Fe1 and Fe2 (Figure 2). The cationic sandwich complex $[\text{Cp}^{\text{R}}\text{FeP}_5]^+$ as well as that of the molecule with two less P atoms $[\text{Cp}^{\text{R}}\text{FeP}_3]^+$ are possible fragments of an undetectable $[\text{Cp}^{\text{R}}(\text{OC})\text{FeP}_6]^+$ species ($\text{P}_6 = \text{P6 to P11}$, $\text{Fe} = \text{Fe3}$ (see Figure 2), $\text{Cp}^{\text{R}} = i\text{Pr}_5\text{C}_5$).

Experimental Section

3a [**3b**, **4b**]: Diphenylacetylene **2** (70 mg) [170 mg] was added at room temperature under stirring to a solution of **1a** (320 mg, 0.39 mmol) [860 mg]^[5a] [**1b** 0.96 mmol]^[5b] in toluene (ca. 100 mL) [250 mL], and the orange-red reaction mixture was heated to reflux at 110 °C. After 48 h the CO bands of the starting material **1a** [**1b**] were no longer visible in the IR spectra. After removal of the solvent in vacuo, the residue was dissolved in dichloromethane (ca. 10 mL), treated with silylated silica gel (ca. 2 g) and transferred to a column (20 × 1 cm) packed with Al_2O_3 and petroleum ether. With petroleum ether a gray-green fraction was eluted that contained **3a** (90 mg, 41 %) [**3b** (210 mg, 36 %)]. With petroleum ether/toluene (5/1) a pale brown fraction was isolated in each case, which according to ^{31}P NMR spectroscopy was composed of a mixture of substances, which to date has not been possible to separate. In the case of

1b, with petroleum ether/toluene (1/1) **4b** (140 mg, 10 %) was isolated in addition as a dark red fraction. Compound **4b** was recrystallized from pentane.

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- [6] Spectroscopic data of the compounds **3a**, **b** and **4b**: ^{31}P NMR (167.97 MHz, C_6D_6 , 85 % H_3PO_4 external; $T = 298$ K): **3a**: $\delta = 78.1$ (d, 2P), -18.5 (t, 1P), $^1J(\text{P,P}) = -412.0$ Hz; **3b**: $\delta = 80.3$ (d, 2P), -22.4 (t, 1P), $^1J(\text{P,P}) = -412.0$ Hz; **4b**: partially unsatisfactory resolved signal groups in the region from 200 to -100 ppm; ^1H NMR (400.14 MHz, C_6D_6 , $\text{C}_6\text{D}_5\text{H}$ internal, $T = 298$ K): **3a**: $\delta = 7.55$ (m, 5H), 7.00 (m, 5H), 4.26 (br.s, 2H), 1.36 (s, 9H), 1.28 (s, 9H), 1.18 (s, 9H); **3b**: $\delta = 7.42$ (m, 5H), 7.02 (m, 5H), 2.93 (br.s, 5H), 1.31 (br.s, 30H); IR (toluene): **4b**: $\tilde{\nu}(\text{CO})$ [cm^{-1}] = 1996 (vs), 1953 (vs), 1938 (vs), 1910 (vs); MS (EI, 70 eV): **4b**: m/z : 817 $[\text{Cp}_2^+\text{Fe}_2\text{P}_5]^+$, 100, 786 $[\text{Cp}_2^+\text{Fe}_2\text{P}_4]^+$, 19, 755 $[\text{Cp}_2^+\text{Fe}_2\text{P}_3]^+$, 24, 486 $[\text{Cp}^+\text{FeP}_5]^+$, 57, 424 $[\text{Cp}^+\text{FeP}_4]^+$, 25, 211 $[\text{FeP}_5]^+$, 11 %].
- [7] Crystal structure data of **3a** [**4b**]: $\text{C}_{31}\text{H}_{39}\text{FeP}_3$ [$\text{C}_{64}\text{H}_{105}\text{Fe}_3\text{O}_4\text{P}_{11}$ · $0.75\text{C}_3\text{H}_2$], $M_r = 560.4$ [1497.8], orthorhombic [triclinic], space group $\text{Pna}2_1$ [$\text{P}\bar{1}$], $a = 14.326(2)$ [15.1159(16)] Å, $b = 14.422(1)$ [16.7864(15)] Å, $c = 13.826(2)$ [17.9137(16)] Å, $[\alpha = 94.642(10), \beta = 105.711(11), \gamma = 106.723(12)^\circ]$, $V = 2856.6(6)$ [4127.9(7)] Å³, $Z = 4$ [2], $\rho_{\text{calc}} = 1.303$ [1.205] g cm⁻³, $T = 293(2)$ K, $\theta = 2.04–27.50$ [2.91–23.82]°, measured reflections: 4263 [41 494], independent reflections: 3685 [11 976] ($R_{\text{int}} = 0.0223$ [0.1517]); $R1 = 0.0342$ [0.0529], $wR2 = 0.0692$ [0.1089] ($I > 2\sigma(I)$); $R1 = 0.0491$ [0.1553], $wR2 = 0.0744$ [0.1293] (all data); diffractometer: Siemens P4 [Stoe IPDS]; structure solution: direct methods; programs: SHELXS-97 [SIR 92 (A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435)]; structure refinement: full-matrix least-squares methods against F^2 ; Program: SHELXL-97 (G. M. Sheldrick, Universität Göttingen, 1997); data/parameters: 3685/326 [11976/791]. 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-136248 (**3a**) and CCDC-136249 (**4b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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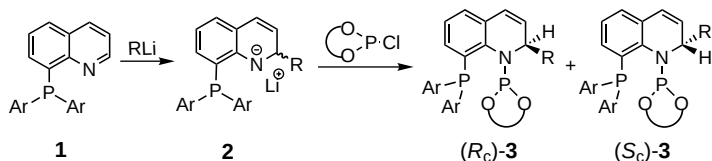
Asymmetric Catalysis with Chiral Phosphane/Phosphoramidite Ligands Derived from Quinoline (QUINAPHOS)**

Giancarlo Franciò, Felice Faraone,* and Walter Leitner*

Dedicated to Professor Dirk Walther on the occasion of his 60th birthday

The use of chiral transition metal complexes as homogeneous catalysts is a well-established and highly attractive strategy for synthesis of optically active products.^[1] Chiral bidentate phosphorus compounds are highly efficient ligands for many important reactions involving late transition metal catalysts.^[2, 3] Consequently, the quest for new efficient ligand systems is a major challenge in catalysis research. Ideally, such ligands should be accessible in both enantiomeric forms, readily available from simple starting materials, and applicable to a broad spectrum of catalytic reactions.

Here we introduce a new family of bidentate chiral ligands which contain 2-alkyl-1,2-dihydroquinoline as a simple, but highly effective chiral backbone. The ligands have two different phosphorus donor sites connected to positions 1 and 8 of the heterocycle backbone. As shown in Scheme 1, we



Scheme 1.

initially focused on phosphane/phosphoramidite ligands, but other substitution patterns can be envisaged. The first example of this series, *n*Bu-QUINAPHOS (**3a**),^[4–6] is unique in that it is among the most efficient ligands for rhodium-catalyzed hydrogenation as well as rhodium-catalyzed hydroformylation. The asymmetric induction is mainly determined by the chiral center in the 2-position of the quinoline framework, which is therefore an ideal starting point for further optimization of the ligand structure.

The new ligands **3a–d** are synthesized in a one-pot-procedure from readily available 8-bisarylphosphanylquinolines **1**^[7] by nucleophilic addition of an organometallic reagent^[8] and direct quenching of the resulting 1,2-dihydroquinoline salt **2** with phosphorochloridites^[9, 12] (Scheme 1, Table 1). A new chiral center is generated at 2-position of the quinoline skeleton during this reaction sequence.^[10] Consequently, a 1:1 mixture of diastereomers was obtained for ligands **3a, b**, and **d** containing enantiomerically pure (*R_a*)-binaphthol. The diastereomeric mixture (*R_a*,*R_C*)-**3a** was isolated in 56 % yield (based on **1**) and the two diastereomers could be separated by column chromatography.^[11] The tentative assignment of the configuration at the stereogenic carbon center is based on comparison with ¹H and ³¹P NMR spectroscopic data of related and structurally characterized monodentate 2-alkyl-1,2-dihydroquinoline phosphoramidites.^[12]

In a first set of experiments, we used the rhodium-catalyzed hydroformylation of styrene (**4**) to benchmark the potential of QUINAPHOS ligands for asymmetric catalysis (Table 2). The catalysts were prepared in situ from [(acac)Rh(CO)₂] (acac = acetylacetonate) and four equivalents of the diastereomeric mixture or the pure diastereomers of **3a**. The reactions were carried out in the neat substrate under otherwise typical hydroformylation conditions. The activities of all three catalysts were well in the range observed with the best chiral hydroformylation catalysts known to date.^[13] All catalysts lead to exclusive formation of the hydroformylation products with uniformly high regioselectivity for the desired branched aldehyde **5**.

The enantiomeric excess of **5** showed a dramatic dependence on the absolute configuration at the 2-position of the heterocycle backbone. Use of the diastereomeric mixture (*R_a*,*R_C*)-**3a** gave a moderate *ee* value of 35.6 % in favor of the *S* enantiomer, but almost racemic product was obtained with the *R_a*,*R_C* diastereomer. In contrast, the ligand (*R_a*,*S_C*)-**3a** gave 74 % *ee* for the *S* enantiomer under these nonoptimized reaction conditions. Taking into account regioselectivity and enantioselectivity, a remarkable overall selectivity of 84 % for the formation of (*S*)-**5** could be achieved with this new ligand.^[5, 13–16]

It is interesting to note that the enantiomeric excess observed with the diastereomeric mixture is almost exactly the mean value of the two *ee* values of the single diastereomers. This indicates that the two diastereomers contribute in parallel and with almost identical pathways to the overall reaction,^[17] as further supported by the observation that the separated ligands (*R_a*,*R_C*)-**3a** and (*R_a*,*S_C*)-**3a** resulted in almost identical reaction rates. The rate was significantly lower, however, when the two diastereomers were employed together in form of the mixture (*R_a*,*R_C*)-**3a**. These results are best rationalized by partial formation of a fairly stable and catalytically nonproductive complex of type [(*R_a*,*R_C*)-**3a**]Rh[(*R_a*,*S_C*)-**3a**]⁺. The possible implication of this situation for chiral amplification^[18] in asymmetric catalysis using QUINAPHOS-type ligands is currently under investigation.

The rhodium-catalyzed hydrogenation of α,β -unsaturated carboxylic acid derivatives also proceeded smoothly in CH₂Cl₂ at room temperature and elevated pressures, using

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Table 1. ^{31}P NMR spectroscopic data of QUINAPHOS-type ligands **3a–d** (C_6D_6 , room temperature).

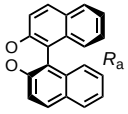
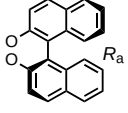
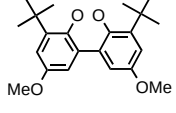
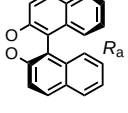
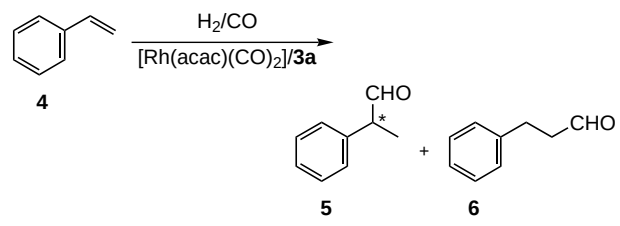
	Config. at C2	Ar	R		$\delta(\text{P}_\text{A})$	$\delta(\text{P}_\text{B})$	$J(\text{P}_\text{A}\text{P}_\text{B})$ [Hz]
3a	R_C S_C	Ph	<i>n</i> Bu		137.5 143.6	− 17.8 − 16.4	191.7 131.2
3b	R_C S_C	Ph	<i>t</i> Bu		139.0 141.6	− 19.2 − 19.1	180.2 85.2
3c	R_C/S_C	Ph	<i>n</i> Bu		144.7	− 18.6	202.7
3d	R_C S_C	 $\text{R}_\text{f} = (\text{CH}_2)_2(\text{CF}_2)_6\text{F}$	<i>n</i> Bu		136.9 143.3	− 18.3 − 16.8	194.5 130.4

Table 2. Rhodium-catalyzed hydroformylation of styrene (**4**).^[a]



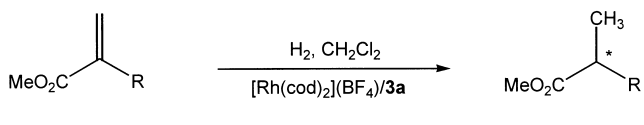
Ligand	<i>t</i> [h]	Conversion [%]	TOF ^[b] [h ^{−1}]	5/6	<i>ee</i> [%]
$(R_\text{a}, R_\text{C}^*)$ - 3a	90	54.8	13.4	96.3/3.7	35.6 (<i>S</i>)
(R_a, R_C) - 3a	74	79.3	23.6	96.0/4.0	4.8 (<i>S</i>)
(R_a, S_C) - 3a	70	75.0	23.6	96.7/3.3	74.0 (<i>S</i>)

[a] Styrene (**4**, 0.5 mL), **3a** (8×10^{-3} mmol), and $[\text{Rh}(\text{acac})(\text{CO})_2]$ (2×10^{-3} mmol) were placed in a stainless-steel high-pressure reactor ($V = 11.4$ mL) and stirred at $T = 40^\circ\text{C}$ under $p(\text{CO}/\text{H}_2, 1:1) = 100$ bar.
[b] Amount of **5** and **6** [mol] per mole of Rh per hour.

either a catalyst formed in situ from **3a** and $[\text{Rh}(\text{cod})_2](\text{BF}_4)$ (cod = cyclooctadiene) or the isolated complex $[(R_\text{a}, R_\text{C})$ -**3a**] $\text{Rh}(\text{cod})](\text{BF}_4)$ (**9**) as a catalyst precursor (Table 3). In contrast to the observations made for the hydroformylation, the opposite configuration at the chiral carbon atom was required for high *ee* values in the hydrogenation, and (R_a, R_C) -**3a** proved to be the more effective diastereomer. Increasing the amount of ligand during the in situ preparation of the catalyst leads to a marked increase in the enantioselectivity with dimethyl itaconate (**7a**), but was detrimental in the case of the dehydroamino acid ester **7b**.

The rhodium catalysts formed with the QUINAPHOS ligand show not only very high asymmetric induction, but also a significant catalytic activity and stability. Quenching the

Table 3. Enantioselective hydrogenation of dimethyl itaconate (**7a**) and methyl 2-acetamidoacrylate (**7b**).^[a]



Substrate	Ligand	3a /Rh	Conversion [%]	<i>ee</i> [%]
7a	(R_a, S_C) - 3a	1.1	> 99	64.2 (<i>R</i>)
7a	(R_a, S_C) - 3a	2.2	> 99	78.8 (<i>R</i>)
7a	(R_a, R_C) - 3a	1.1	> 99	95.6 (<i>R</i>)
7a	(R_a, R_C) - 3a	2.2	> 99	98.8 (<i>R</i>)
7b	(R_a, R_C) - 3a	2.2	8.0	12.4 (<i>S</i>)
7b	(R_a, R_C) - 3a	1.0 ^[b]	> 99	97.8 (<i>S</i>)

[a] $[\text{Rh}(\text{cod})_2](\text{BF}_4)$ (2×10^{-3} mmol), **3a**, and **7** (2 mmol) were dissolved in CH_2Cl_2 (2–6 mL) and stirred in a stainless-steel high-pressure reactor ($V = 11.4$ mL) at room temperature under $p(\text{H}_2) = 30$ bar for 24 h. [b] With $[(R_\text{a}, S_\text{C})$ -**3a**] $\text{Rh}(\text{COD})](\text{BF}_4)$ **9** as catalyst.

hydrogenation of **7a** with the preformed complex **9** (**7a**:**9** = 1000:1, $p(\text{H}_2) = 50$ bar, room temperature) by venting the reactor after five minutes revealed that product (*R*)-**8a** had already been formed quantitatively with 98.2% *ee*. The reaction mixture remaining in the reactor was charged with a second, larger batch of substrate (**7a**:**9** = 6000:1), pressurized with H_2 ($p = 70$ bar), and vented after 10 min. Hydrogenation was again quantitative and the saturated ester **8a** showed 99.4% *ee* (*R*). The total number of catalytic turnovers in these two consecutive reactions was 7000, and an average turnover frequency (TOF) of 36000 h^{-1} can be estimated as the lower limit for the catalytic activity in the second run. Taking into account the somewhat lower *ee* value obtained in

the first run, the second hydrogenation proceeded with almost perfect selectivity for the (*R*) enantiomer (99.6% *ee*).

The previously available large body of data on asymmetric catalysis suggested fairly different design principles for new ligands to be used in rhodium-catalyzed enantioselective hydrogenation and hydroformylation. The majority of highly selective chelating ligands for olefin hydrogenation has a C_2 -symmetric structure or at least two closely related binding sites,^[2] whereas ligands with highly unsymmetrical structures generally give higher *ee* values in hydroformylation.^[13a,15] The *n*Bu-QUINAPHOS phosphane/phosphoramidite ligand **3a** is the first chiral phosphorus ligand for which the formation of highly active and selective rhodium catalysts was observed for hydroformylation as well as for hydrogenation.

2-Alkyl-1,2-dihydroquinoline is a very promising backbone for chiral bidentate phosphorus ligands with two distinct binding sites. The highly flexible synthesis of QUINAPHOS-type ligands opens a broad range of possible modifications for further optimization of the individual members of this ligand family by electronic and steric variation. It is noteworthy in this context that the enantioselectivity obtained with the BINAPHOS-type ligands is largely controlled by their atropisomeric backbones,^[5] and structural modifications of this part are difficult. In contrast, the major impact on the asymmetric induction observed with the QUINAPHOS ligand **3a** comes from a "simple" and readily modified stereogenic carbon center that is embedded in a fairly rigid heterocycle skeleton.

Experimental Section

All manipulations were carried out under argon using dried and degassed solvents. The catalysis experiments were carried out in stainless-steel high-pressure reactors according to standard procedures, and the products were analyzed by ¹H NMR spectroscopy and GC.

Synthesis of (*R_a*,*R_C*)-**3a**, (*R_a*,*R_C*)-**3a**, and (*R_a*,*S_C*)-**3a**. A solution of **1a**^[7] (1.0 g, 3.2 mmol) in THF (40 mL) was treated with *n*BuLi in *n*-pentane (1.6 M, 2 mL) at –78 °C and then briefly warmed to 0 °C. The resulting dark red solution was added dropwise to a solution of (*R*)-(1,1'-binaphthalene-2,2'-dioxo)chlorophosphane in THF (20 mL) at –30 °C. After the mixture had slowly warmed to room temperature, the solvent was evaporated and the residue extracted with toluene. Removal of the solvent and crystallization from CH₂Cl₂/ethanol at –20 °C gave colorless (*R_a*,*R_C*)-**3a** (1.24 g, 1.8 mmol, 56%) as a 1:1 mixture of diastereomers.

(*R_a*,*R_C*)-**3a** (0.24 g) was subjected to column chromatography over dried and degassed silica (Merck, type 9385, 230–400 mesh). Elution with CH₂Cl₂/pentane (1/5) gave a first fraction (0.12 g, 100%) that was assigned as (*R_a*,*R_C*)-**3a** on the basis of NMR data.^[12] Subsequent elution with pure CH₂Cl₂ gave (*R_a*,*S_C*)-**3a** (0.05 g, 42%).

Selected analytical data (see also Table 1):

(*R_a*,*R_C*)-**3a**: MS (EI, 70 eV): *m/z*: 685 [*M*⁺]; ¹H NMR (C₆D₆): δ = 7.86 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.70–7.39 (m, 11H, Ar-H), 7.31 (m, 1H, Ar-H), 7.10–6.84 (m, 11H, Ar-H), 6.78 (m, 1H, Ar-H), 6.39 (d, ³*J* = 9.5 Hz, 1H, CH=CH), 5.72 (dd, ³*J* = 9.5 Hz, ³*J* = 5.6 Hz, 1H, CH=CH), 4.01 (m, 1H, CH), 1.40–0.90 (m, 6H, CH₂), 0.61 (t, ³*J* = 7.2 Hz, 3H, CH₃).

(*R_a*,*S_C*)-**3a**: MS (EI, 70 eV): *m/z*: 685 [*M*⁺]; ¹H NMR (C₆D₆): δ = 7.63–7.57 (m, 6H, Ar-H), 7.51–7.43 (m, 2H, Ar-H), 7.28–7.22 (m, 4H, Ar-H), 7.12–6.94 (m, 12H, Ar-H), 6.79 (m, 1H, Ar-H), 6.18 (d, ³*J* = 9.6 Hz, 1H, CH=CH), 5.56 (dd, ³*J* = 9.6 Hz, ³*J* = 5.7 Hz, 1H, CH=CH), 3.88 (m, 1H, CH), 1.40–0.88 (m, 6H, CH₂), 0.73 (t, ³*J* = 7.2 Hz, 3H, CH₃).

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Stereoselective Combinatorial Ugi-Multicomponent Synthesis on Solid Phase**

Kai Oertel, Gernot Zech, and Horst Kunz*

Dedicated to Professor Rudolf Mengel
on the occasion of his 60th birthday

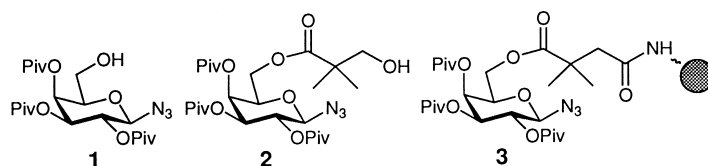
The search for new drugs has been influenced decisively by combinatorial chemistry. To prevent false results in biological evaluations of combinatorial libraries, nowadays the parallel synthesis of sets of single compounds is strongly preferred. These parallel syntheses are more readily achieved even in an automated fashion, if the reactions are carried out with substrates immobilized on a solid phase.^[1] As a consequence and according to the prototype of solid-phase peptide synthesis,^[2] numerous reactions known from solution chemistry have been transferred to the solid phase. Although it has generally long-been agreed that the preparation of enantiomerically pure compounds is indispensable for drug development, only a few asymmetric syntheses on solid phase have been reported so far.^[3]

Multicomponent reactions play an important role in combinatorial chemistry. This holds true, in particular, for the Ugi four-component condensation, because this one-pot reaction offers great potential in the generation of molecular diversity.^[4] Combinatorial Ugi reactions have successfully been carried out on solid phase, however, hitherto exclusively yielding racemic mixtures.^[5]

We here report on the first stereoselective Ugi reactions on solid phase. To accomplish the desired stereodifferentiation, the O-pivaloylated galactosylamine^[6] as an equivalent of "asymmetric ammonia" was linked to a polymeric support.

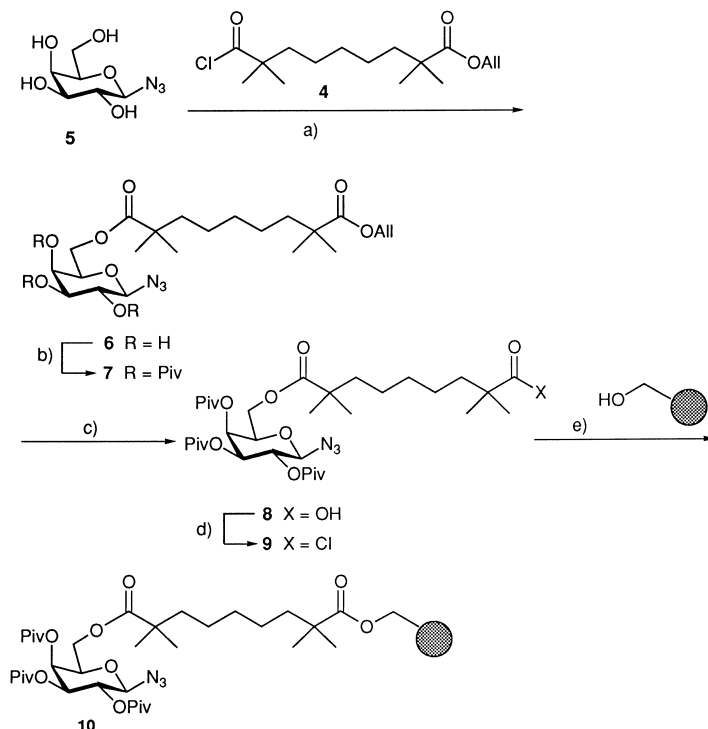
A number of problems had to be solved during this development: a) A reversible anchoring of the galactosylamine on the polymer had to be found, which would enable a direct determination of the ratios of diastereomers for the carbohydrate-linked amino acid amides. b) The galactosyl azide precursor of the galactosylamine should be immobilized first, to prevent multiple protecting group manipulations and accompanying anomerizations. The conversion of the galactosyl azide into the galactosylamine on solid phase is a prerequisite for this strategy. Heterogeneous hydrogenations^[6] are unsuitable in this context. c) The anchor as well as the structure of the spacer should not interfere with the zinc chloride catalyzed Ugi reaction to be carried out on solid phase.

The coupling of the model galactosyl azides **1** and **2** (Piv = pivaloyl, *t*BuCO) through polymer-linked silyl ethers^[7] failed because their hydroxy groups did not react with the corresponding silylation reagents. The polymer-linked galactosylamine **3**, synthesized from **1** by treatment with 4-allyl 2,2-



dimethylsuccinate and subsequent reduction of the azide, only sluggishly reacted with the other components in the Ugi reaction. The amide structure of the spacer disturbs the activation of the *N*-galactosyl imine by ZnCl₂ in the Ugi reaction.

These only partly outlined difficulties could be solved by applying $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl azelaic acid^[8] as the spacer between the galactosylamine and the polymer-linked anchor. To this end, tetramethyl azelaic acid was converted into its monoallyl ester which was then transformed to the monoacid chloride **4** by treatment with oxalic dichloride. The regioselective acylation of the galactopyranosyl azide **5** with **4** in pyridine furnished **6**, which was acylated at the secondary hydroxy groups using pivaloyl chloride in pyridine at 60 °C (Scheme 1). After palladium(0)-catalyzed removal of the allyl



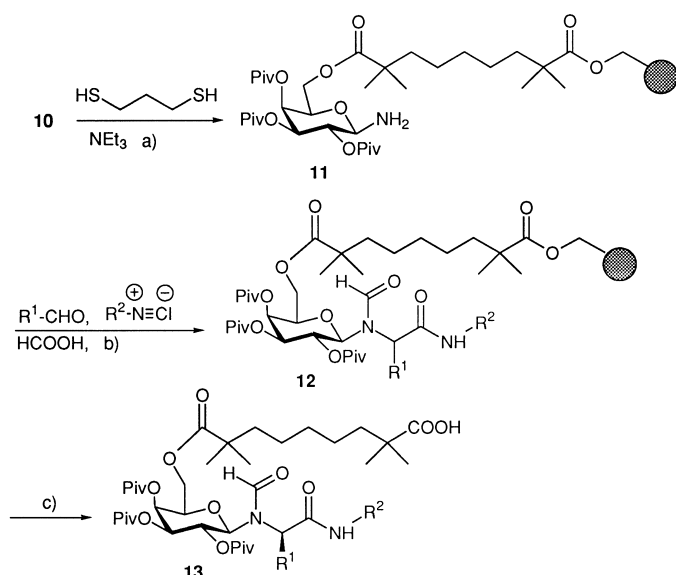
Scheme 1. a) Pyridine, 60 °C, 18 h, 61 %; b) pyridine/(CH₃)₃CCOCl, 60 °C, 6 d, 71 %; c) cat. [Ph₃P]₄Pd, THF, morpholine (10 equiv), 3 d, 68 %; d) (COCl)₂, CH₂Cl₂; e) Wang resin, DMAP, CH₂Cl₂, pyridine, loading 0.257 mmol g⁻¹.

ester **7**,^[10] the terminal carboxylic function of **8** was converted into the acid chloride **9**. For the loading, polystyrene equipped with Wang anchor^[11] was treated with **9** in dichloromethane/pyridine in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP).^[12] The loading of resin **10** was monitored by IR spectroscopy ($\tilde{\nu}$ = 2116 cm⁻¹) and quantified by elemental analysis to 0.257 mmol g⁻¹.

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The reduction of the polymer-linked galactosyl azide **10** with complex hydrides was not successful. Under the conditions of the Staudinger reaction^[13] extended anomerization occurred. However, the reaction of **10** with five equivalents each of propane-1,3-dithiol and triethylamine in dimethylformamide proved efficient for the formation of the solid-phase-linked galactosylamine **11** (Scheme 2). The reduction evidently proceeded quantitatively and without anomerization (IR spectrum, elemental analysis).



Scheme 2. a) DMF, 2 d, room temperature; b) $\text{ZnCl}_2 \cdot \text{Et}_2\text{O}$, THF, $-40^\circ\text{C} \rightarrow 0^\circ\text{C}$, 24 h; c) TFA/ CH_2Cl_2 (1:9), anisole, 12 h, Table 1.

For performing the stereoselective Ugi reactions the immobilized galactosylamine **11** was swollen in tetrahydrofuran. At room temperature the corresponding aldehyde (5 equivalents) and after 1 h at -40°C the isonitrile, formic acid (5 equivalents of each) and zinc chloride etherate (1 equivalent of a 2.2 M solution in dichloromethane) were added. After 24 h at 0°C , the polymer **12** was washed with dichloromethane, tetrahydrofuran, and diethyl ether (Scheme 2).

To detach the stereoselectively formed amino acid derivatives **13**, the Wang anchor of **12** was cleaved with trifluoroacetic acid (TFA)/dichloromethane (1:9) in the presence of anisole. After evaporation of the organic detachment and washing solutions followed by hydrolysis, the diastereomeric ratios of the crude products were determined directly (Table 1). The yields quoted in Table 1 refer to pure diaster-

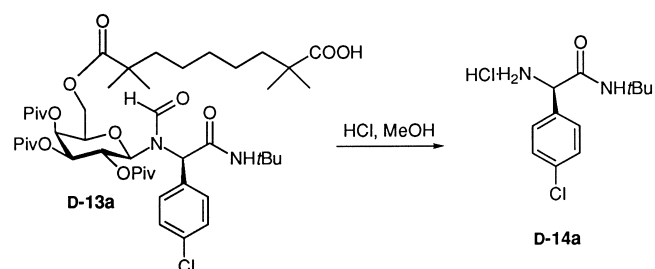
Table 1. Stereoselective solid-phase Ugi synthesis of *N*-galactosyl amino acid amides according to Scheme 2.

Compound	R ¹	R ²	d.r. (D:L)	Yield (D) [%]	Yield (L) [%] ^[a]
13a	4-Cl-Ph	<i>t</i> Bu	10:1	37	4.4
13b	4-NO ₂ -Ph	<i>t</i> Bu	15:1	38	7
13c	4-MeO-Ph	<i>t</i> Bu	6:1	35	8
13d	Ph	<i>t</i> Bu	12:1	35	8
13e	4-Cl-Ph	<i>c</i> Hex	9:1	37	5
13f	4-Cl-Ph	<i>n</i> Bu	14:1	20	3
13g	<i>i</i> Pr	<i>t</i> Bu	9:1	59	4

[a] Isolated product.

omers which have been isolated after three steps (reduction of the azide, Ugi reaction, and detachment) and after separation by preparative HPLC.

Using a set of five aldehydes, among which one was allowed to react with three different isonitriles, the corresponding *D*-amino acid amide derivatives **13** were obtained in diastereomeric ratios of 10:1–15:1. Of course, any other carboxylic acid instead of formic acid can be applied to these reactions if sets of single compounds or libraries at the stage of compounds **13** should be obtained. Formic acid was used in the synthesis described here, because the formyl group can be removed readily from **13** by treatment with HCl in methanol (Scheme 3). Only after removal of the formyl group, the

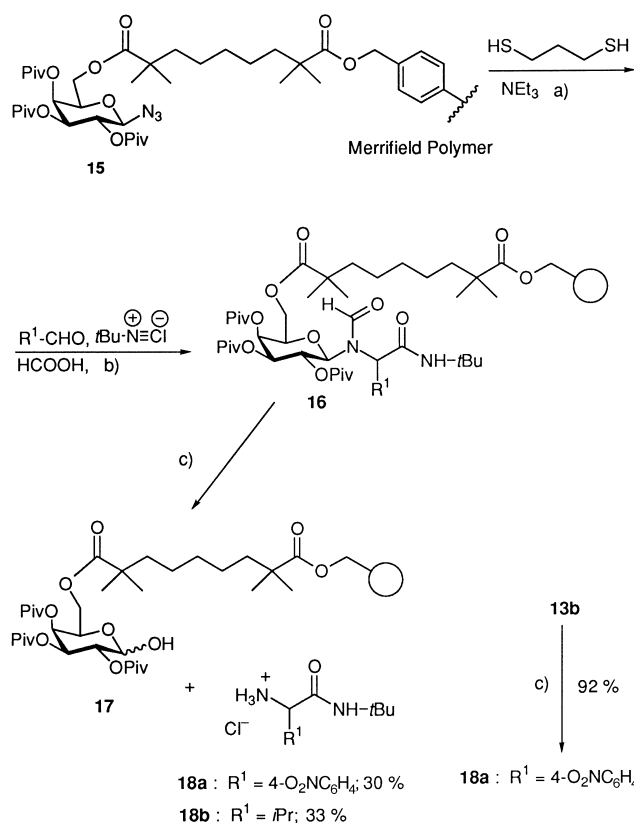


Scheme 3.

cleavage of the *N*-glycosidic bond and, thus, the liberation of the enantiopure amino acid derivatives is possible.^[6] The data of the 4-chlorophenylglycine amide **14a** obtained by this procedure from **D-13a** (Table 1) proved identical with those of the compound synthesized previously in solution.^[6] This confirms the *D* configuration of the major diastereomer **13a**.

As an alternative to the coupling through a cleavable anchor (**10**), the carbohydrate auxiliary was directly linked to a hydroxymethyl-substituted polystyrene (Merrifield resin, 0.6 mmol g^{-1}) by analogous reaction of the acid chloride **9** (see, Scheme 1). The resulting immobilized auxiliary **15** (loading 0.17 mmol g^{-1}) was subjected to reduction of the azide with propane-1,3-dithiol and subsequent Ugi reaction under identical conditions to those given for **10** (Scheme 4). Monitoring by IR spectroscopy revealed that the conversions proceeded more slowly because of the absence of the spacer effect exhibited by the anchor.

After swelling in dichloromethane, the polymer-linked Ugi products **16** were treated with HCl in methanol which resulted in successive cleavage of the *N*-formyl and the *N*-glycosidic bonds. The galactose auxiliary remained completely linked to the polymer **17**, which showed an intensive ester carbonyl ($\tilde{\nu} = 1739 \text{ cm}^{-1}$), but no amide band in the FT-IR spectrum. The detachment solutions dissolved in water were extracted with *n*-pentane. After evaporation of the aqueous solutions, the amino acid amide hydrochlorides **18** were isolated. The yields are lower than those given in Table 1 for the reactions of **10**, because of the slower conversions (three steps) on the non-modified Merrifield resin. However, the stereoselectivity of the Ugi reaction remains unchanged as was shown by comparison of the data of the *p*-nitrophenylglycine amide derivative with those of the *p*-nitrophenylglycine amide **18a** obtained from the *N*-galactosyl precursor **13b** (Scheme 4).^[14]



Scheme 4. a) DMF, 2 d, room temperature; b) $\text{ZnCl}_2 \cdot \text{Et}_2\text{O}$, THF, $-40^\circ\text{C} \rightarrow 0^\circ\text{C}$, 24 h; c) $\text{CH}_2\text{Cl}_2/\text{HCl}$ (saturated) in MeOH (3:1), 12 h, then a little H_2O .

The potential of this stereodifferentiating synthesis on solid phase becomes evident, if one keeps in mind that the corresponding L-amino acid derivatives are available by analogous use of the D-arabinopyranosylamine,^[15] that combinatorial reactions with phosphites give α -aminophosphonic acid derivatives,^[16] those with silyl ketene acetals yield β -amino acid derivatives^[17] or with silyl dienol ethers furnish mono- and bicyclic chiral nitrogen heterocycles.^[18, 19] Thus, the stereodifferentiating effect of solid-phase-linked glycosylamines of type **11** provides a versatile combinatorial access to chiral products of diverse structure.

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Ring-Opening Metathesis Polymerization: Access to a New Class of Functionalized, Monolithic Stationary Phases for Liquid Chromatography

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Monolithic separation media for liquid chromatography were described as early as the 1960s and 1970s.^[1, 2] The introduction of compressed, continuous supports by Hjertén et al. initiated an intense research activity in this field of materials science.^[3, 4] Compared to classical, packed columns, continuous stationary phases offer a series of advantages. On one hand, the time-consuming procedures of particle syn-

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thesis and column packing are no longer necessary. On the other hand, lowered back pressures (< 5 MPa), high flow rates (up to 10 mm s^{-1}), and a significantly enhanced mass transfer have to be mentioned. Finally, dead volumes are eliminated. Consequently, monolithic separation media allow fast separations with comparably high resolutions. Additionally, capillary end frits that have to be used with packed columns in capillary liquid chromatography (CLC) and capillary electrochromatography (CEC) are no longer required. So far, a variety of functionalized and nonfunctionalized monolithic columns based on either organic or inorganic polymers are available. Interestingly, almost all rods based on organic polymers have been prepared by radical polymerization.^[5, 6] Starting from polystyrene and glycidyl methacrylate, acrylate, or acrylamides, only a "simple" functionalization such as the generation of amino, alcohol, phenol, sulfonic acid, or carboxylate groups may be accomplished in a controlled way. We already combined ring-opening metathesis polymerization (ROMP)^[7] with grafting and precipitation techniques for the synthesis of functionalized separation media.^[8–11] A general advantage of ROMP is the possibility to use functional monomers. This and the controlled ("living") polymerization allow a highly reproducible functionalization.

Owing to the broad applicability of ROMP and the high definition of the resulting materials, we investigated to which extent this polymerization technique might be applied to the preparation of functionalized monolithic separation media.^[12] The following steps describe the new concept for the synthesis of functionalized monoliths (Figure 1): 1) generation of a continuous matrix by ring-opening metathesis copolymerization of suitable monomers and a cross-linker in the presence of porogenic solvents within the separation device (column); 2) consecutive in situ derivatization with a suitable ROMP-active monomer. Through the use of ROMP, this in situ derivatization is made possible for the first time. Because of the living character of this polymerization technique, the majority of the initiator remains active. The fraction of the initiator that is covalently bound to the surface of the rod is accessible and may be used for further derivatization. Thus, pumping solutions of a ROMP-active monomer over the column allows grafting of the monomer onto the surface of the monolith.

Nonfunctionalized rods were prepared, and the influence of the stoichiometry of the reactants, porogenic solvents, and the

initiator on the microstructure of the monolith was determined. Among the possible combinations of monomers and cross-linkers—for example, norbornene (NBE), norbornadiene, dicyclopentadiene, 1,4,4a,5,8,8a-hexahydro-1,4,5,8-*exo*-*endo*-dimethanonaphthalene (Q1), and 1,4a,5,8,8a,9,9a,10,10a-decahydro-1,4,5,8,9,10-trimethanoanthracene, various Grubbs catalysts of the general formula $[\text{Cl}_2(\text{PR}_3)_2\text{Ru}(\text{=CHPh})]$ ^[13] (R = cyclohexyl (Cy), phenyl) as well as different porogenic solvents—the copolymerization of NBE with Q1 in the presence of two porogenic solvents, 2-propanol and toluene, with $[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}(\text{=CHPh})]$ was found to be the best. Investigations by electron microscopy revealed that the resulting rods consist of spherical, agglomerated microglobules (Figure 2). Under adequate polymerization conditions, the diameters of the microglobules may be varied within

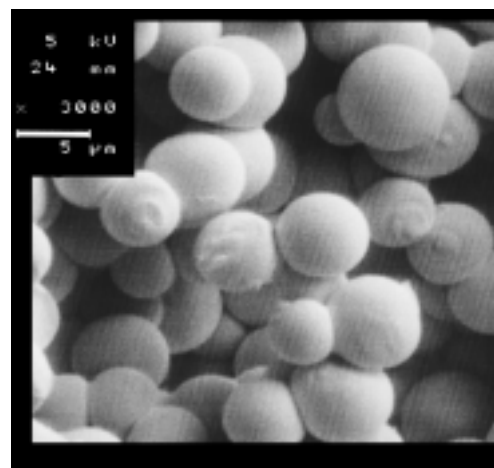


Figure 2. SEM image of the microstructure of monolith VIII.

$0.6\text{--}30 \mu\text{m}$, and comparably narrow particle size distributions ($\pm 20\%$) are achieved. As a consequence of the structural homogeneity the new materials possess excellent chromatographic properties. This was illustrated by the separation of bioactive proteins by reverse-phase chromatography (Figure 3) on a nonfunctionalized monolith.

The broad applicability of in situ functionalization was demonstrated by the derivatization of monoliths with a series of ROMP active monomers **1–7**. The extent of functionalization was checked in a qualitative way by FT-IR spectroscopy

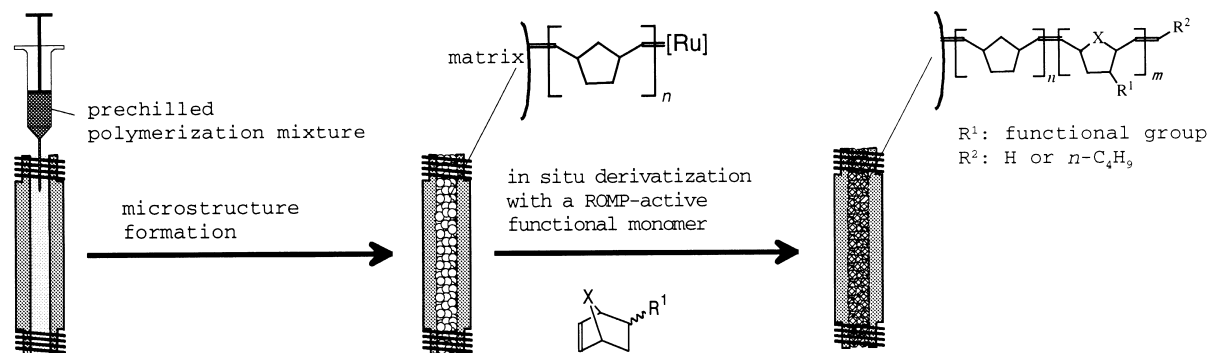


Figure 1. Preparation and in situ derivatization of continuous separation media by ring-opening metathesis polymerization. $[\text{Ru}] = [\text{RuCl}_2(\text{PCy}_3)_x]$ ($x = 1, 2$).

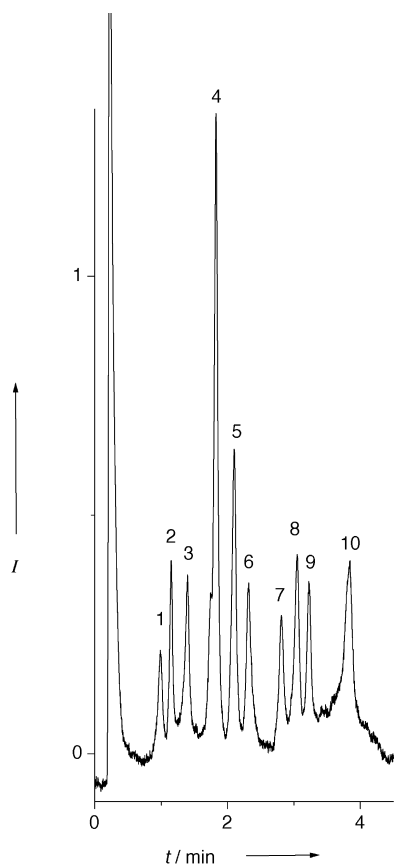


Figure 3. Protein separation by reversed-phase chromatography on monolith **VIII**. Column: 3×50 mm. Conditions: flow rate 6 mm s^{-1} ; room temperature; mobile phases: A: acetonitrile (ACN) + 0.1 % trifluoroacetic acid (TFA), B: water + 0.1 % TFA; gradient: 0–0.5 min: 21 $\rightarrow$ 36 % A, 0.5–3 min: $\rightarrow$ 40 % A, 3–6 min: $\rightarrow$ 55 % A; UV (218 nm). Analytes: 1) ribonuclease A, 2) insulin, 3) cytochrome C, 4) lysozyme, 5) β -lactoglobulin A, 6) transferrin, 7) myoglobin, 8) α -chymotrypsinogen A, 9) catalase, 10) ovalbumin. $V=1 \text{ }\mu\text{L}$; $c=50$ (1–3, 5–8), 100 (4, 9), $200 \text{ }\mu\text{g mL}^{-1}$ (10).

and in a quantitative way by acid–base titration (**I**, **II**) and elemental analysis (**III**–**VII**). The relevant IR signals of the corresponding monoliths as well as the amount of functional graft polymer are summarized in Table 1. The successful derivatization with the cyclodextrin (CD) derivative **7** was shown indirectly by a chiral separation. According to the demands on continuous supports, the enantioselective separation of proglumide was accomplished on monolith **VII** within 2.5 min (Figure 4).

In summary, the new continuous rods presented here differ from other continuous separation media as follows:^[14] 1) They possess a new poly(cyclopentadiylvinylene) backbone, 2) they offer the possibility of functionalization through use of a large variety of functional groups including chiral selectors, and 3) they possess a homogeneous microstructure that may be tailored. Despite the ease of oxidation of this backbone, these materials are completely air-stable. To the best of our knowledge, no continuous stationary phases that have a comparable homogeneous-spherical microstructure and allow an in situ derivatization have been reported so far. Thus, in addition to the applications listed here, the reported concept possesses enormous potential in the synthesis of separation media for microapplications such as CLC and CEC.

Table 1. IR signals and capacities of functionalized continuous media for monoliths **I**–**VIII**, $\sigma=90 \text{ m}^2$, $\epsilon_p=49 \%$, $\epsilon_z=8 \%$.

Mono-lith	Functional monomer	IR signals $\tilde{\nu} [\text{cm}^{-1}]$	Assignment	Capacity [mmol g ⁻¹]
I		1 1872, 1794	C=O st	0.2 ^[a]
II		2 3460 (br.) 1717	COO–H st C=O st	0.14 ^[a]
III		3 1773, 1692 1541, 1522	C=O st C–C _{arom.}	0.03 ^[b]
IV		4 1771, 1700 1570, 1510 710	C=O st C–C _{arom.} C–H _{arom.} (δ , oop)	0.22 ^[b]
V		5 3436 (br.) 1783, 1725 1560, 1501 802	O–H st C=O st C–C _{arom.} C–H _{arom.} (δ , oop)	0.06 ^[b]
VI		6 1783, 1719 1615, 1522 814	C=O st C–C _{arom.} C–H _{arom.} (δ , oop)	0.26 ^[b]
VII		7 3373 1746	O–H st C=O st	n.d. ^[c]
VIII	–	–	–	–

[a] Determined by acid–base titration. [b] Determined by elemental analysis (nitrogen analysis). [c] n.d. = not determined.

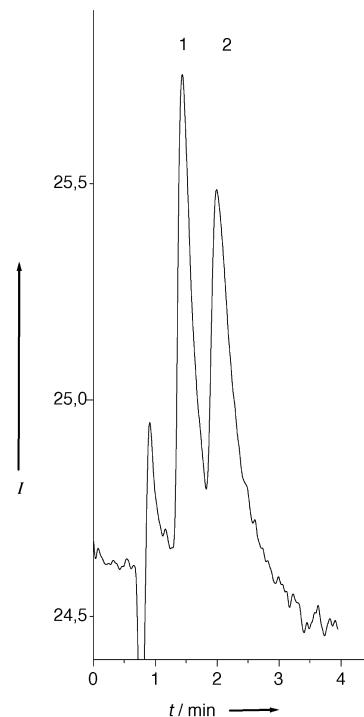


Figure 4. Enantioselective separation of proglumide on monolith **VII**. Column: 3×150 mm. Conditions: flow rate 6 mm s^{-1} ; 0°C ; $V=4 \text{ }\mu\text{L}$; $c=20 \text{ }\mu\text{g mL}^{-1}$; mobile phase: ACN/MeOH/TFA/triethylamine 99.75/0.25/0.25/0.075 (v/v/v/v); UV (254 nm).

Experimental Section

All experiments were carried out under argon using standard Schlenk techniques. Degassed and dry solvents were used throughout. Borosilicate columns (3 × 50 mm, 3 × 150 mm) silanized with bicyclo[2.2.1]hept-5-en-2-yltrichlorosilane were used. Monoliths **I–VIII** were prepared as follows: Solution A (chilled to –20 °C, NBE/Q1/2-propanol 25/25/40 (in wt %)) and solution B (toluene/[Cl₂(PCy₃)₂Ru(=CHPh)] 9.995/0.005 (in wt %))^[13] were mixed and rapidly transferred to the prechilled borosilicate column. Polymerization was allowed to proceed at 0 °C for 30 min and then at room temperature overnight. The initiator was cleaved off by passing 1-hexene/toluene (10/90) over the column. For functionalization of monoliths **I–VII**, 1 h after polymerization was started the column was purged with toluene to remove unchanged initiator. An aliquot (1 mL) of a 10 % solution of monomer **1–7** in toluene or dimethylformamide was passed over the column. The HPLC columns were sealed and kept at 60 °C overnight. The catalyst was removed as described above. The total amount of ruthenium that remained within the monolith was determined by atom absorption spectroscopy (AAS) to be less than 10 µg^{–1}. Use of the stoichiometry described here allows the preparation of monoliths whose microstructure consists of microglobules that are 4 ± 1 µm. Nevertheless, the microstructure may be varied within 0.5–30 µm by changing the stoichiometry of the reactants and the porogenic solvents. For scanning electron microscopy (SEM), samples were sputtered with Au/Pd under high vacuum. The specific surface (σ), the pore porosity (ε_p), and the interparticle porosity (ε_z) were determined by inverse gel permeation chromatography (GPC).^[15] The in situ derivatization did not cause any significant changes in these values.

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Optimized Two-Dimensional NLO Chromophores with a Threefold Symmetry Axis**

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Dedicated to Professor Dieter Hellwinkel on the occasion of his 65th birthday

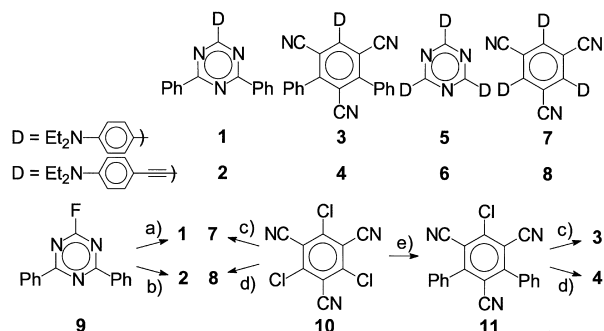
The design of nonlinear optical (NLO) chromophores without dipole moment is a current area of research in molecular nonlinear optics.^[1] Such molecules can be used for processes such as frequency doubling, frequency mixing, parametric oscillation, and electrooptical modulation. This seems to be in contradiction to the traditional opinion that efficient NLO chromophores should be designed as dipolar π systems substituted with one donor and one acceptor—like the prototype *p*-nitroaniline (*p*NA). However, in contrast to one-dimensional (1D) chromophores of the *p*NA type, non-dipolar NLO chromophores with multiple donor–acceptor substitution generally show several significant tensor elements of the second-order polarizability (β). New NLO processes where electrical fields of different polarizations can be efficiently coupled with each other only become possible through two- and three-dimensional (2D and 3D) chromophores. So far, however, effective strategies for the optimization of such nondipolar chromophores have not been found. Thus, it is still uncertain whether they are really superior to their dipolar analogues with respect to the general efficiency–transparency problem—as has been stated several times.^[2] For example, in planar, conjugated chromophores with a threefold symmetry axis, several efficient donor and acceptor groups have to be coupled to a central π system without great steric hindrance. Here we describe the most active 2D chromophores found so far and present the first systematic comparison between 2D chromophores of symmetry D_{3h} and analogous 1D chromophores of symmetry C_{2v}.

Four 1,3,5-triazine derivatives with the donor groups 4-*N,N*-diethylaminophenyl and 4-*N,N*-diethylaminophenylethynyl (**1**, **2**, **5**, **6**) were synthesized by nucleophilic aromatic substitutions of cyanuric fluoride (Scheme 1). As representatives of the second new class of compounds, 1,3,5-tricyanobenzenes **3**, **4**, **7**, and **8** with single and triple substitution were obtained starting from 1,3,5-tricyano-2,4,6-trichlorobenzene. All UV/Vis spectra are shown in Figure 1.

These two structural types were chosen after a careful analysis^[1a] of the nondipolar NLO chromophores published so

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Scheme 1. a) 4-Iodo-*N,N*-diethylaniline, *t*BuLi; b) 4-*N,N*-diethylaminophenylacetylene, *n*BuLi; c) 4-*N,N*-diethylaminophenyltributyltin, Pd⁰, CuO; d) 4-*N,N*-diethylaminophenylacetylene, Pd⁰, CuI; e) Bu₃SnPh, Pd⁰, CuO.

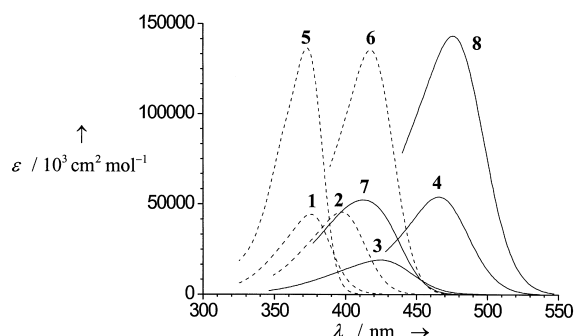


Figure 1. Optical absorption spectra of the triazine derivatives **1**, **2**, **5**, **6** (---) and the tricyanobenzene derivatives **3**, **4**, **7**, **8** (—) in dioxane.

far. Structural types that have already been investigated—such as tris-donor-substituted trinitrobenzenes,^[3] triphenyl-carbenium ions,^[4] and tris-acceptor-substituted triphenylamine derivatives^[5]—show structural deformations caused by electronic and/or steric effects, which reduce their symmetries and π conjugations, and as a consequence also their NLO efficiencies. In tetrahedral structures,^[14] like tetrasubstituted tin and phosphonium compounds, conjugation through the central element is equally insufficient. The NLO figures of merit β_0/M of the chromophores mentioned are in almost all cases^[5c] lower than that of *p*NA.^[1a] The triazines and elongated tricyanobenzenes of this work are mostly planar

(with the exception of **3** and **7**), as could be proven by X-ray determinations and semiempirical calculations. Thus, negative effects of sterically caused deformations can be avoided.

Compounds **5–8** were carefully characterized by hyper Rayleigh scattering (HRS).^[1b, 6] In contrast to the traditional method of field-induced frequency doubling (EFISH),^[7] no external electric field for poling is needed. The study of ionic and nondipolar chromophores thus becomes possible.

In addition, the dipolar 1D NLO chromophores **1–4** were characterized by electrooptical absorption measurements (EOAM).^[9] The importance of the EOAM method for the investigation of 1D NLO chromophores follows from their low-lying, intensive charge transfer (CT) bands, which mostly determine the second-order polarizability β . An analysis of the band forms yields the electrical dipole moments in the electronic ground state (μ_g), the dipole difference between ground and excited states ($\Delta\mu$), and the transition dipole moment (μ_{ag}). According to a two-level model,^[10] β is proportional to the product $(\mu_{ag})^2\Delta\mu$.^[11] The approximate validity of this model has been proven experimentally for a large number of NLO chromophores.^[11a, 10b] The second-order polarizabilities of 1D systems are associated with a main component β_{zzz} along the CT direction (z axis).

However, NLO chromophores with multiple donor–acceptor substitution often show several significant tensor elements of β , which for molecules with C_{2v} symmetry can be related to CT bands with a transition dipole moment that lies perpendicular to the electronic CT direction.^[10c, 10d] Four significant tensor elements are present in planar, π -conjugated NLO chromophores **5–8**: $\beta_{zzz} = -\beta_{zyy} = -\beta_{yzy} = -\beta_{yyz}$.

All compounds investigated show intense absorption bands in the visible range which correspond to single CT bands for the 1D structures **1–4** and to degenerate transitions for the 2D structures **5–8**. The absorptivity of the 2D structures is approximately three times that of the 1D structures. For the latter, a longer wavelength absorption is expected on the basis of solvatochromic effects associated with their dipole moments. However, Scheme 1 and Table 1 show that with the exception of **3** and **7** there is a bathochromic shift for the 2D structures. One reason for this effect is provided by the small dipole moments of **1–4**, which cause a low solvatochromism.

Table 1. Molecular properties of chromophores **1–8** and the reference *p*NA, determined by electrooptical absorption measurements and hyper Rayleigh scattering in dioxane.^[a]

	<i>p</i> NA	1	2	3	4	5	6	7	8
<i>M</i> [g mol ^{−1}]	138.1	380.5	404.5	452.6	476.6	522.7	549.8	549.8	666.9
λ_{ag} [nm]	354	375	397	425	466	373	418	413	476
ϵ_{max} [10 ³ cm ² mol ^{−1}]	15900	44200	45500	18950	53900	136500	135500	52200	143300
μ_g [10 ^{−30} Cm]	21	11	12	9	14	—	—	—	—
μ_{ag} [10 ^{−30} Cm]	16	24	26	18	28	28	31	22	34
$\Delta\mu$ [10 ^{−30} Cm]	31	36	51	47	55	—	—	—	—
$\beta_0^{(ag)}$ [10 ^{−50} Cm ³ V ^{−2}]	16	44	80	42	137	—	—	—	—
β [10 ^{−50} Cm ³ V ^{−2}]	27	96	166	—	1520	142	423	128	2680
β_0 [10 ^{−50} Cm ³ V ^{−2}]	15	42	63	—	285	63	138	43	428
$(\beta_0/M)_{rel}$	≡ 1	1.01	1.43	0.85	5.50	1.11	2.30	0.72	5.89

[a] Conversion of units: 10^{−30} Cm = 0.2998 Debye; 10^{−50} Cm³ V^{−2} = 2.694 × 10^{−30} esu. β is given according to the Taylor series convention^[12] relative to quartz $d_{11}(1064 \text{ nm}) = 0.50 \text{ pm V}^{-1}$. $\beta = \beta_{zzz}$ for chromophores **1–4** (z axis in the direction of the dipole moment); $\beta = \beta_{zzz} = -\beta_{yyz} = -\beta_{yzy} = -\beta_{zyy}$ for the D_{3h} -symmetric chromophores **5–8**. $\beta_0^{(ag)}$ is the two-level value of the second-order polarizability calculated from the EOAM experiments. The transition dipole moment given for **1–4** is related to the CT transition, for **5–8** only for one of the two degenerate transitions. Experimental deviations: 3–5 % for μ_g , μ_{ag} and $\Delta\mu$; 5–10 % for β .

In addition, the unusually effective conjugation in the planar systems **5**, **6**, and **8** leads to a reduction of the HOMO–LUMO distance. Only in the distorted structures **3** and **7** can the expected bathochromic shift of the dipolar 1D structure really be observed.

The changes of dipole moments $\Delta\mu$ in the CT bands detected for **1–4** by EOAM experiments are in some cases quite large; for **4** almost twice as large as for *p*NA. Together with the transition dipole moments derived from integration of the absorption signals, μ_{ag} , the strength of a donor–acceptor pair can be determined.^[1a] Especially tricyanobenzene, but also triazine, show acceptor strengths comparable to that of a nitrophenyl group. Consequently, even the 1D chromophores **2** and **4** lie close to the optimum region for second-order nonlinearities (Table 1). At 1064 nm the values of β for **2** and **4** are 6- and 56-fold larger than that of *p*NA. Even after dispersion correction (wavelength extrapolation to infinite value) to give β_0 values and standardization to the molecular mass of *p*NA, an NLO figure of merit β_0/M for **4** is obtained which is almost six times larger than that of *p*NA. The second-order polarizabilities calculated from μ_{ag} and $\Delta\mu$ on the basis of the two-level model are quite close to the data from HRS measurements. Greater deviations are only observed for **4**, and these are possibly caused by multilevel contributions.

Even greater values for the second-order polarizabilities are observed for the threefold-donor-substituted compounds **6** and **8**. The measured β value of **8** is 100 times and the figure of merit six times larger than the corresponding value of *p*NA. This is the largest value ever obtained for nondipolar NLO chromophores with a threefold symmetry axis. In contrast, the second-order polarizabilities of the sterically hindered systems **3** and **7**, with drastically reduced transition dipole moments, are clearly smaller and below that of *p*NA.

Figure 2 proves a clear correlation between the NLO figures of merits of the 1D and 2D NLO chromophores. For the optimization of β_{zzz} of dipolar and nondipolar NLO

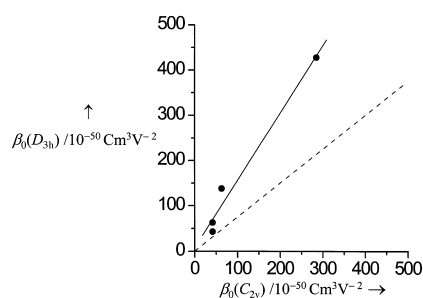


Figure 2. Correlation of β_0 for the one-dimensional and the analogous two-dimensional NLO phores with threefold symmetry (—). The slope expected for three independent subchromophores is 0.75 (---).

chromophores with a threefold symmetry axis, similar design criteria have to be used—at least for the systems shown here. This result, which is at first surprising, has recently been theoretically predicted by us on the basis of a simple two-electron, three–center system.^[1a]

In conclusion, the new structural types offer an important contribution to the optimization of nonlinear optical chromophores with threefold symmetry. In contrast to the often

expressed opinion that dipolar two-level contributions are unimportant in these compounds lacking dipole moments, a clear correlation between the second-order polarizabilities β of threefold-acceptor-substituted nonpolar chromophores with D_{3h} symmetry and the analogous C_{2v} -symmetric dipolar chromophores with substitution by a single acceptor has been proven experimentally. Even after corrections with respect to absorption and molecular mass, compound **8**, with a carefully adjusted donor–acceptor strength and minimized steric hindrance, is several times more active than the NLO prototype *p*NA and therefore gives a new upper limit for this type of NLO-active compound.

Experimental Section

Purities of the compound samples used for measurements were secured by NMR spectroscopy (Bruker, 300 MHz for ^1H NMR; CDCl_3 as solvent, unless noted otherwise) and elemental analysis (deviations of less than 0.2% C, H, N).

1-Chloro-3,5-diphenyl-2,4,6-tricyanobenzene (11): Compound **10**^[13] (1026 mg, 4.000 mmol), $[\text{Pd}(\text{PPh}_3)_4]$ (116 mg, 0.100 mmol), and CuO (278 mg, 3.50 mmol) in DMF^[14] (20 mL) were stirred at 50 °C for 30 min. After the addition of tributylphenyltin^[15] (1285 mg, 3.500 mmol), heating was continued at 90 °C for 90 min. Dilution with CH_2Cl_2 (100 mL), extraction with a 10% solution of KF, treatment with water (8 ×), drying over MgSO_4 , and chromatography (silica gel, toluene) yielded starting material (16%), 1,3-dichloro-5-phenyl-2,4,6-tricyanobenzene (45%, m.p. 258–259 °C from heptane/toluene), and **11** (210 mg, 0.620 mmol, 35%), m.p. 235 °C (colorless prisms from heptane/toluene). ^1H NMR: δ = 7.51–7.56 (m, 4H), 7.57–7.62 (m, 6H); ^{13}C NMR: δ = 112.74, 113.94, 114.33, 115.70, 128.79, 129.29, 131.45, 133.13, 144.82, 154.27.

2-(4-*N,N*-Diethylaminophenyl)-4,6-diphenyl-1,3,5-triazine (1): *t*BuLi (1.7 M in *n*-pentane, 1.3 mL, 2.2 mmol) was added at –78 °C to a solution of 4-iodo-*N,N*-diethylaniline^[16] (550 mg, 2.00 mmol) in THF (10 mL). The temperature was raised to –45 °C and then lowered again to –78 °C to give a colorless suspension. Over 20 min, a solution of **9**^[17] (502 mg, 2.00 mmol) in THF (25 mL) was added; a yellow color formed immediately. The mixture was allowed to warm to room temperature, and the suspension gave a clear, yellow solution. Addition of diethyl ether (100 mL), extraction with half-concentrated NaCl, drying over MgSO_4 , chromatography (silica gel, CH_2Cl_2 /light petroleum 1/4), and concentration of the product fraction yielded **1** as yellow needles (235 mg, 0.618 mmol, 31%), m.p. 165 °C. ^1H NMR: δ = 1.23 (t, ^3J = 7.0 Hz, 6H), 3.46 (q, ^3J = 7.0 Hz, 4H), 6.77 (pseudo d, J = 9.2 Hz, 2H), 7.52–7.61 (m, 6H), 8.63 (pseudo d, J = 9.2 Hz, 2H), 8.74–8.77 (m, 4H); ^{13}C NMR δ = 12.62, 44.57, 110.80, 122.53, 128.44, 128.78, 130.91, 131.94, 136.89, 151.06, 170.93, 171.37.

2-(4-*N,N*-Diethylaminophenylethynyl)-4,6-diphenyl-1,3,5-triazine (2): *n*BuLi (1.6 M, 1.5 mL, 2.4 mmol) was added at –78 °C to a solution of 4-*N,N*-diethylaminophenylacetylene^[18] (433 mg, 2.50 mmol) in THF (25 mL). The temperature was then raised to 0 °C and lowered again to –78 °C. A solution of **9**^[17] (502 mg, 2.00 mmol) in THF (25 mL) was added, and an intensive orange-yellow color developed. The mixture was allowed to warm to room temperature, and Et_2O (100 mL) was added. The resulting solution was extracted with half-saturated solutions of NaCl, dried with MgSO_4 , filtered, and purified by chromatography over aluminum oxide (neutral, activity II; CH_2Cl_2 /light petroleum 1/4). Concentration gave **2** as bright yellow platelets (525 mg, 1.30 mmol, 65%), m.p. 184–186 °C. ^1H NMR: δ = 1.18 (t, ^3J = 7.1 Hz, 6H), 3.38 (q, ^3J = 7.1 Hz, 4H), 6.63 (pseudo d, J = 9.5 Hz, 2H), 7.50–7.64 (m, 8H), 8.65–8.69 (m, 4H); ^{13}C NMR: δ = 12.49, 44.38, 87.56, 95.14, 105.71, 110.95, 128.57, 129.01, 132.56, 135.10, 135.65, 149.05, 161.45, 171.32.

1-(4-*N,N*-Diethylaminophenyl)-3,5-diphenyl-2,4,6-tricyanobenzene (3): Prepared from **11** (235 mg, 0.692 mmol) in analogy to the synthesis of **7**. Chromatography (CH_2Cl_2 /light petroleum 7/3) gave pure **3** (226 mg, 0.499 mmol, 72%); orange-yellow needles from heptane/toluene (130 mg), m.p. 237–238 °C. ^1H NMR: δ = 1.23 (t, J = 7.1 Hz, 6H), 3.40 (q, J = 7.1 Hz, 4H), 6.78 (pseudo d, 2H), 7.53 (pseudo d, 2H), 7.59 (brs, 10H);

^{13}C NMR: $\delta = 12.49, 44.28, 110.92, 112.89, 114.01, 114.84, 115.45, 119.22, 128.88, 128.96, 130.63, 131.09, 134.48, 149.66, 153.72$.

1-(4-*N,N*-Diethylaminophenylethynyl)-3,5-diphenyl-2,4,6-tricyanobenzene (**4**): Prepared from **11** (221 mg, 0.650 mmol) in analogy to the synthesis of **8**; orange microneedles (215 mg, 0.451 mmol, 69%), m.p. 273–275 °C (formation of a deep red polymorph at ca. 266 °C). ^1H NMR: $\delta = 1.18$ (t, $^3J = 7.0$ Hz, 6H), 3.40 (q, $^3J = 7.0$ Hz, 4H), 6.61 (pseudo d, $J = 9.2$ Hz, 2H), 7.51–7.58 (m, 12H); ^{13}C NMR: $\delta = 12.49, 44.56, 85.07, 105.24, 111.23, 111.62, 112.89, 114.69, 114.81, 114.94, 128.88, 129.08, 130.82, 134.04, 135.20, 136.15, 149.82, 152.92$.

1,3,5-Tricyano-2,4,6-tris(4-*N,N*-diethylaminophenyl)benzene (**7**): A suspension of **10** (256 mg, 1.00 mmol), $[\text{Pd}(\text{PPh}_3)_4]$ (162 mg, 0.140 mmol), and CuO (254 mg, 3.20 mmol) in DMF (15 mL) was heated for 10 min to 80 °C and then cooled to room temperature. 4-*N,N*-Diethylaminophenyltributyltin^[9] (1403 mg, 3.200 mmol) in DMF (8 mL) was added, and the mixture heated again to 85 °C for 8 h. After cooling, the mixture was diluted with CH_2Cl_2 (100 mL). It was extracted with a 10% solution of KF ($3 \times$) and water ($5 \times$) and then dried (MgSO_4). Chromatography (silica gel, CH_2Cl_2) gave a yellow product (395 mg), which was dissolved in CH_2Cl_2 /light petroleum (1/4). The solution was filtered and concentrated to provide yellow needles (295 mg, 0.496 mmol, 50%), m.p. 280–284 °C. ^1H NMR: $\delta = 1.20$ (t, $^3J = 7.1$ Hz, 18H), 3.40 (q, $^3J = 7.1$ Hz, 12H), 6.74 (pseudo d, $J = 9.0$ Hz, 6H), 7.47 (pseudo d, $J = 9.0$ Hz, 6H); ^{13}C NMR: $\delta = 12.57, 44.25, 110.84, 111.99, 116.71, 120.41, 130.98, 149.32, 154.34$.

1,3,5-Tricyano-2,4,6-tris(4-*N,N*-diethylaminophenylethynyl)benzene (**8**): A solution of **10** (256 mg, 1.00 mmol), 4-*N,N*-diethylaminophenylacetylene (693 mg, 4.00 mmol), $[\text{Pd}(\text{PPh}_3)_4]$ (116 mg, 0.100 mmol), and CuI^[18] (19 mg, 0.10 mmol) in NEt_3 (3 mL) was heated to 85 °C for 6 h. Formation of red crystals began after about 30 min, and a viscous, deep red suspension was formed. Chromatography on neutral alumina (activity II; CH_2Cl_2 /light petroleum 1/1) yielded **8** (535 mg, 0.802 mmol, 80%); red prisms from heptane/toluene (375 mg, 0.562 mmol, 56%), m.p. > 230 °C (decomp). ^1H NMR (CD_2Cl_2): $\delta = 1.20$ (t, $^3J = 7.2$ Hz, 18H), 3.43 (q, $^3J = 7.2$ Hz, 12H), 6.67 (pseudo d, $J = 8.9$ Hz, 6H), 7.54 (pseudo d, $J = 8.9$ Hz, 6H); ^{13}C NMR (CD_2Cl_2): $\delta = 12.66, 44.94, 84.39, 105.56, 111.01, 111.68, 112.73, 115.64, 135.11, 150.18$. One signal expected on the basis of the structure could not be detected.

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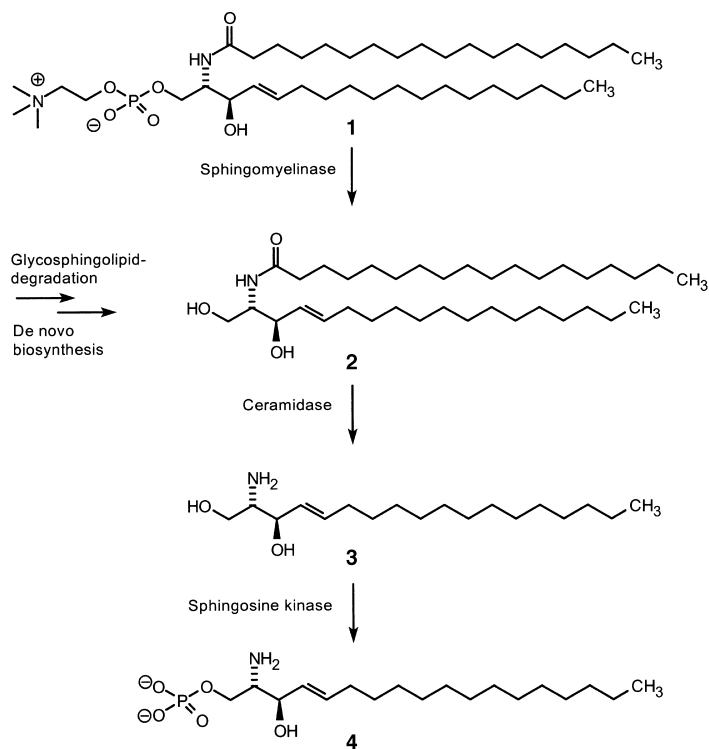
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- $$\beta_{zzz}^{(ag)}(-2\omega; \omega, \omega) = \beta_{zzz}^{(ag)}(0) \frac{\omega_a^4}{(\omega_a^2 - \omega^2)(\omega_a^2 - 4\omega^2)} \quad (1)$$
- $$\beta_{zzz}^{(ag)}(0) = \lim_{\omega \rightarrow 0} (-2\omega; \omega, \omega) = \frac{6\Delta\mu_z^{ag}(\mu_z^{ag})^2}{(\hbar\omega_a)^2} \quad (2)$$
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Synthesis of the First Selective Irreversible Inhibitor of Neutral Sphingomyelinase**

Christoph Arenz and Athanassios Giannis*

Sphingomyelin (**1**, Scheme 1) is a ubiquitous constituent of cell membranes.^[1] In vertebrates, it accounts for up to 25 % of the total amount of membrane lipids, depending on the cell type. The catabolites of sphingomyelin, which are ceramide

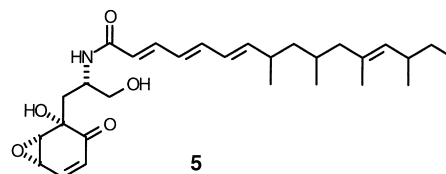


Scheme 1. Sphingomyelin and catabolites.

(**2**), sphingosine (**3**), and sphingosine-1-phosphate (**4**), have become a focus of extensive research due to their possible role as secondary messengers.^[1–4] The primary sphingomyelin catabolite, ceramide, is generated in the so-called sphingomyelin cycle^[5, 6] through the action of either a lysosomal acid sphingomyelinase (A-SMase) or a membrane-bound neutral sphingomyelinase (N-SMase). Ceramide is believed to play a vital role in cell regulation, in modulation of inflammatory processes, and also in programmed cell death (apoptosis).^[1, 2, 5–7] Many experiments suggest that various cytokines (such as TNF- α , Interleukin-1 β , Interferon- γ), as well as radiation, heat, oxidative agents, and vitamin D₃ are all able to activate sphingomyelinases. Nonetheless, various aspects of ceramide-mediated signal transduction, particularly its role in

apoptosis, are controversial.^[8, 9] Certainly, the biological outcome of ceramide action is not uniform and depends on the cell-type, the topology of ceramide within the cell, and on the crosstalk (interaction) with other signals pathways. Additionally, the question regarding which of the sphingomyelinases is important for stimulus-induced ceramide production is still a point of controversy.^[5, 8–11] The membrane-located N-SMase underlies physiological regulation through substances like glutathione or arachidonic acid^[12] and is believed to play an important role in signal transduction.

Selective inhibitors of the different sphingomyelinase-types can contribute to a better understanding of the precise roles of these enzymes and ceramide in signal transduction. While several modest inhibitors are known for A-SMase,^[1] the natural product scyphostatin (**5**)^[13, 14] was only recently

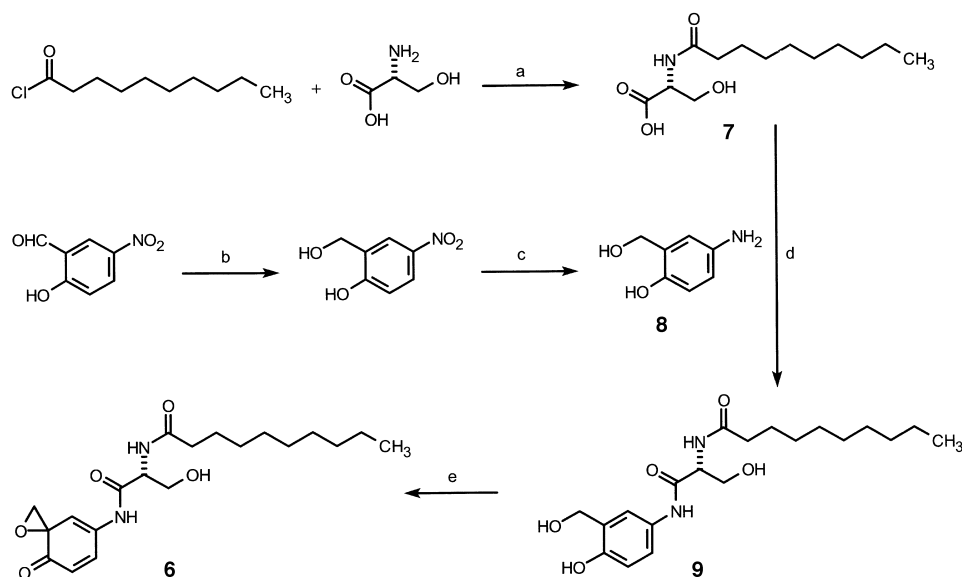


isolated and found to be a potent competitive inhibitor of N-SMase ($IC_{50} = 1.0 \mu M$). However, this compound inhibits A-SMase as well ($IC_{50} = 49.3 \mu M$).^[15]

Herein we report the synthesis of the first selective irreversible inhibitor of N-SMase. Preliminary studies in our laboratory revealed that short-chain ceramide analogues, such as 2-*N*-lauroylamido-1,3-propanediol, weakly inhibit N-SMase. Moreover we supposed that N-SMase—in analogy with other phosphodiesterases^[16]—may contain nucleophilic groups (for example, amino acid side chains such as arginine, serine, or cysteine) in its active site, which are able to react with suitable electrophiles within the head group of prospective ceramide analogues. We expected that the compound **6** would fulfil these requirements; in comparison to scyphostatin, it contains a more reactive epoxide group.^[17] Reaction of *D*-serine with decanoylchloride under Schotten–Baumann conditions afforded *N*-decanoyl-*D*-serine (**7**, Scheme 2). Coupling of 5-amino-2-hydroxybenzyl alcohol (**8**, obtained by a two-step reaction sequence) with **7**, which was activated with dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole (HOBT), afforded compound **9**. After subsequent reaction with sodium periodate, the spiroepoxide **6** was obtained as a 53:47 mixture of diastereomers.^[18] In the enzyme assay, compound **6** was revealed to be a covalent inhibitor of N-SMase (Figure 1). Furthermore increased concentrations of sphingomyelin decreased the inhibitory effect of the epoxide **6** (Figure 2), suggesting that the inhibitor binds to the active site of the N-SMase. Under the assay conditions, the epoxide **6** showed no inhibition of A-SMase even at a concentration of $500 \mu M$ (Figure 3). To examine the influence of the amino acid configuration, the enantiomeric derivative *ent*-**6** was synthesized from *L*-serine. This compound showed a similar time-dependent inactivation of N-SMase whereas the enzymatic activity of A-SMase was not affected (data not shown).

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Scheme 2. Synthesis of the spiroepoxide **6**. Reagents and conditions: a) H_2O , THF, 3 equiv. Na_2CO_3 , 3 h, 68%; b) NaBH_4 , EtOH, 1 d, 99%; c) In , NH_4Cl , EtOH, 90°C , 3 h, 91%; d) DCC, HOBT, DMF, 16 h, 61%; e) NaIO_4 , MeOH/ H_2O , 3 h, 20°C , 70%.

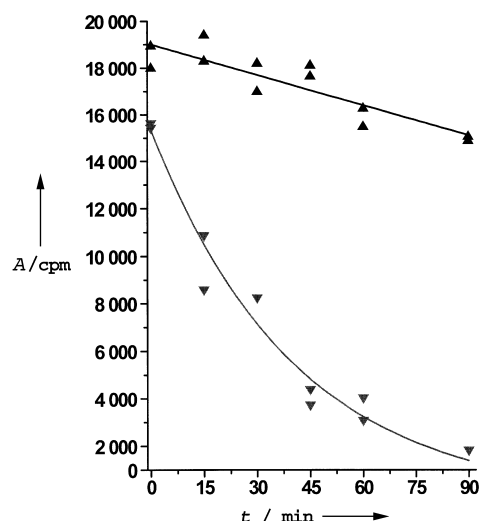


Figure 1. Time dependence of the inhibition of N-SMase by compound **6** ($200\text{ }\mu\text{M}$ in preincubation buffer). With inhibitor **6**: ▼, control: ▲. A = activity, t = preincubation time.

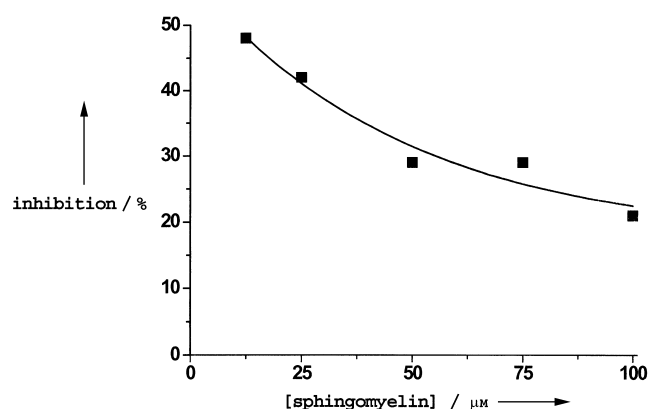


Figure 2. Inhibition of the N-SMase at different concentrations of sphingomyelin (average of two results, at a concentration of $100\text{ }\mu\text{M}$ of **6**, without preincubation).

Due to its interesting biochemical behaviour, compound **6** appears to be a valuable tool for the elucidation of the biological role of N-SMase and ceramide concerning signal transduction processes. Moreover, this compound could be used to label the active site of N-SMase and gain some insight into the enzyme mechanism which is currently unknown.^[19] In addition, our results could be helpful for the development of further inhibitors of N-SMase, as the synthetic pathway allows the incorporation of various fatty acids, amino acids, and functionalized aniline derivatives. The fact that scyphostatin shows remarkable anti-inflammatory

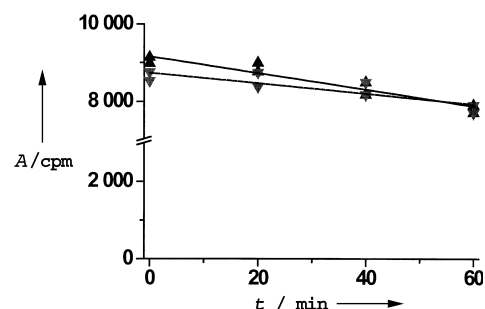


Figure 3. Effect of the compound **6** ($200\text{ }\mu\text{M}$ in the preincubation buffer) on A-SMase. With inhibitor **6**: ▼, control: ▲. A = activity, t = preincubation time.

effects justifies the development of such inhibitors and makes N-SMase an interesting target for the experimental therapy of inflammatory diseases, including disorders of the central nervous system with an autoimmune component, such as multiple sclerosis.^[20, 21]

Experimental Section

Partial purification of sphingomyelinases was carried out following the method described by Hannun et al.^[22] Four rats were decapitated and the brains were homogenised in a 25 mM tris(hydroxymethyl)aminomethane (TRIS)/HCl buffer (pH 7.4), which contained 20 mg L^{-1} each of leupeptine, chymostatin, antipain, and pestatin, as well as 1 mM phenylmethylsulfonyl-fluoride (PMSF), 2 mM ethylenediaminetetraacetic acid (EDTA) and 5 mM 1,2-di(2-aminoethoxy)ethane- N,N,N',N' -tetraacetic acid (EGTA). The mixture was centrifuged for 1 h at $100\,000\text{ g}$, the supernatant was removed, and the pellet was dissolved in the above-mentioned buffer, containing an additional 1% Triton X-100. The solution was loaded through a sterile filter onto an anion exchange column (POROS 20HQ, PerSeptive Biosystems Inc.). After equilibration with a solution of 20 mM TRIS/HCl buffer (pH 7.4), which contained 1 mM each of EDTA, EGTA, PMSF, and a change to 1 M sodium chloride in the same buffer, the sphingomyelinases were eluted with a gradient from 0 to 1% Triton X-100 in the equilibration buffer.

For the determination of the N-Smase activity, the inhibitor (diastereomeric mixture) was dissolved in chloroform. An aliquot of 10 nmol was

dried under a nitrogen stream, redissolved in 40 μL 75 mM TRIS/HCl buffer (pH 7.4), which contained 0.05 % Triton X-100 and 2.5 mM MgCl_2 , and mixed with 10 μL of enzyme preparation. Together with control experiments, the probes were preincubated for 90, 60, 45, 30 and 15 min at 37 °C. After addition of 10 nmol ^{14}C -sphingomyelin (ca. 40000 cpm (counts per minute)) in 50 μL of the same buffer, the reaction was incubated for another 30 min. The reaction was stopped by the addition of 750 μL chloroform/methanol (1/1). After addition of 200 μL water, the lipids were extracted and the radioactivity of the polar upper phase, which contained ^{14}C -phosphorylcholine, was determined by scintillation counting.

The determination of A-SMase proceeded analogously, with use of an Mg^{2+} -free sodium acetate buffer (pH 4.5).

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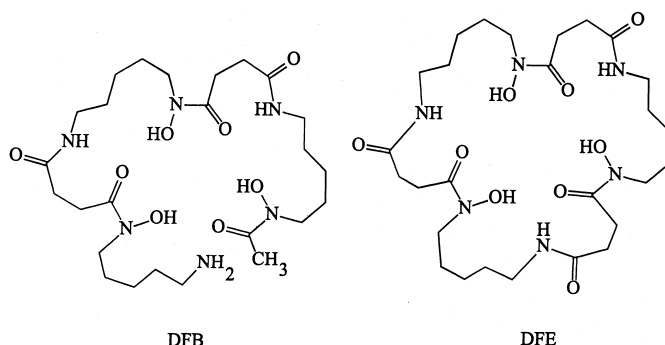
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Structural Characterization of a Plutonium(IV) Siderophore Complex: Single-Crystal Structure of Pu-Desferrioxamine E**

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In order to acquire sufficient essential iron, most micro-organisms produce very powerful, low molecular weight chelating agents that can deliver iron into cells via active transport systems. Ferrioxamine siderophores are linear or cyclic hydroxamates that contain 1-amino-5-hydroxyamino-pentane as a building block.^[1] Desferrioxamine E (DFE) and



D_2 (DFD_2) are the cyclic compounds of this group; the linear compound desferrioxamine B (DFB)^[2] has become the drug of choice for iron and aluminum overload by transfusion.^[3] Desferrioxamines (DFOs) bind Fe^{III} over a wide pH range (1–12), while showing very little affinity for iron(II) ($\text{DFB-Fe}^{\text{II}}$: $\log\beta_{110} = 30.6$; $\text{DFB-Fe}^{\text{III}}$: $\log\beta_{110} = 7.2$).^[4] The hexadentate, hard oxygen-donor DFO ligands also strongly bind other hard metal ions.

We are studying the complexation and solubilization of plutonium by siderophores. While plutonium does not occur

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naturally, six tons of plutonium have been released into the biosphere since 1941.^[5] In addition, numerous U.S. Department of Energy sites have significant plutonium-contamination problems due to accidental releases and past waste-handling practices.^[6] Plutonium most likely enters into soils as plutonium(IV) hydroxides and oxides.^[7] These forms of plutonium are thought to pose little risk for contaminating ground water and/or becoming bioavailable because they have very low solubility and uncomplexed plutonium(IV) strongly sorbs to mineral surfaces. However, compounds that solubilize the plutonium significantly increase its environmental migration and thereby also increase its bioavailability. Ferrioxamines are estimated to be present at 0.01–0.1 μM concentrations in soils,^[8] and the stability constant for a Pu^{IV} –DFB species is about $\log \beta_{110} = 30.8$.^[9]

We have prepared $^{239}\text{Pu}^{\text{IV}}$ –DFO complexes by reacting Pu^{III} , Pu^{IV} , Pu^{V} , or Pu^{VI} ions with the free ligand. In all cases a Pu^{IV} –DFO species formed. To minimize Pu^{IV} hydrolysis and multiple species formation, the title complex was best prepared by reacting one equivalent of H_4DFE with Pu^{III} in 2M trifluoromethanesulfonic acid. Following adjustment of the solution to pH 2 with 0.01M Al in 1M NaOH, a Pu^{III} –DFE complex formed, which quickly oxidized in air to Pu^{IV} –DFE. The solution was concentrated and crystals formed within a week on storing the solution at 7°C. An X-ray crystal structure analysis reveals the product to be $[\text{Al}(\text{H}_2\text{O})_6][\text{Pu}(\text{DFE})(\text{H}_2\text{O})_3]_2(\text{CF}_3\text{SO}_3)_5 \cdot 14\text{H}_2\text{O}$, **1**.^[10] This is the first plutonium–siderophore complex to be structurally characterized.

The asymmetric unit contains the $[\text{Pu}(\text{DFE})(\text{H}_2\text{O})_3]^+$ ion (Figure 1), a hexaaquoaluminum(III) ion, four trifluoromethanesulfonate groups and seven water molecules. The nine

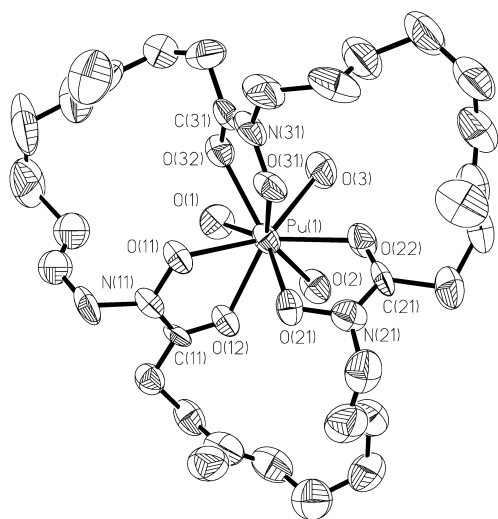


Figure 1. Thermal ellipsoid plot of the Pu cation in **1**. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Pu–O(1) 2.461(12), Pu–O(2) 2.472(11), Pu–O(3) 2.456(12), Pu–O(11) 2.315(10), Pu–O(12) 2.361(10), Pu–O(21) 2.296(11), Pu–O(22) 2.341(11), Pu–O(31) 2.303(11), Pu–O(32) 2.386(12); O(1)–Pu–O(2) 74.5(4), O(1)–Pu–O(11) 85.3(4), O(1)–Pu–O(12) 71.0(4).

-coordinate plutonium atom is bound by DFE in approximately one hemisphere and three water molecules in the other. The polytopal geometry of the plutonium coordination sphere (Figure 2) is slightly distorted tricapped-trigonal prism

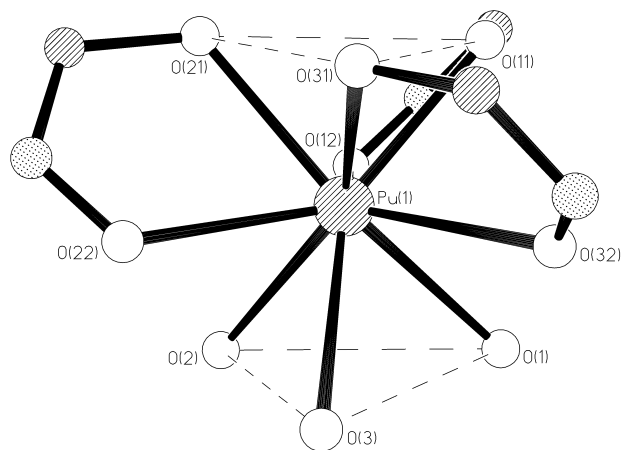


Figure 2. Drawing showing the tricapped trigonal-prismatic geometry.

(a twist angle of 10.1° relates the two trigonal planes), in which three water molecules and three oximate oxygen atoms form trigonal planes and three carbonyl oxygen atoms cap the prismatic faces. The four trifluoromethanesulfonate groups form a hydrogen-bonding network with the interstitial water molecules.

Characterization of plutonium complexes is scarce; for the most common oxidation state, plutonium(IV), only a few complexes with mono- and bidentate ligands have been characterized by single-crystal X-ray diffraction. Most plutonium(IV) complexes characterized by X-ray diffraction are eight-, ten-, or twelve-coordinate and contain several bidentate ligands arranged in a square-antiprismatic, dodecahedral, or icosahedral geometry, for example, in the oxalato, nitrate, carbonate, and sulfonate complexes.^[11] Compound **1** is the first discrete molecule containing a nine-coordinate plutonium(IV) ion.

The free DFE ligand and its complex with Fe^{III} have been structurally characterized.^[12] An overlay of the $[\text{Fe}^{\text{III}}(\text{DFE})]$ and $[\text{Pu}^{\text{IV}}(\text{DFE})]$ complexes is shown in Figure 3. Remarkably, the DFE molecule spans the same diameter in both

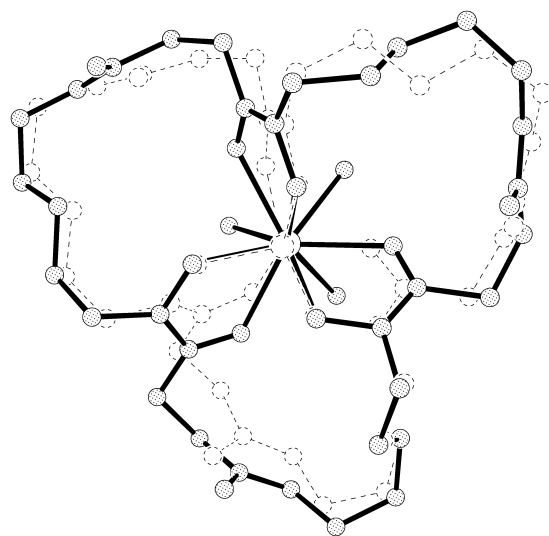


Figure 3. Overlay of Ferrioxamine E (dashed line) and the plutonium cation in **1** (solid line).

complexes, yet has the flexibility to twist the hydroxamate groups roughly 20° relative to the [Fe^{III}(DFE)] structure to accommodate the three coordinated water molecules in **1**. This has the effect of making the oxygen atoms that were *trans* (about 180°) in the iron complex to lie in the plutonium complex 140.8(4)° (O(11)–Pu–O(22)), 136.5(4)° (O(21)–Pu–O(32)), and 135.7(4)° (O(12)–Pu–O(31)) apart. This rotation and the larger size of the plutonium atom allows the DFE ligand to span only one half of the atom as compared to fully encapsulating the iron center. The larger plutonium(IV) ion also increases the metal–hydroxamate bonds from 1.938(4)–2.089(3) Å in the iron complex to 2.303–2.375 Å in the plutonium complex, which in turn decreases the average bite angles from 79.1° to 65.6°. The structure has three distinct Pu–O bonds: a Pu–O (water) mean length of 2.463(12) Å and two different Pu–O (hydroxamate) lengths, reflecting a negative charge localized on the oximate oxygen atom. On average, the Pu–O_N distances are 0.06 Å shorter than the Pu–O_C lengths. This is a smaller difference than those reported for other M^{IV}–hydroxamate complexes (range from 0.105–0.142 Å).^[13]

The *cis-cis* configuration of the oximate oxygen atoms of the DFE molecule relative to one another is the same as that in its iron complex. A correct designation of *trans* or *cis* configuration of the nine-coordinate plutonium is impossible; however, a “pseudo designation” can be inferred from the angles. This configuration may be a result of the hydrogen bonding interactions of the oximate oxygen atoms and the hydrated aluminum cation. The aluminum cation is on an inversion center between two [Pu(DFE)] units. The water molecules from the hydrated Al^{III} ion form strong hydrogen bonds to all three oximate oxygens of the DFE hydroxamate groups (O(21)–O(70) 2.63(5), O(11)–O(72) 2.62(5), O(31)–O(71) 2.61(4) Å).

The DFO ligand has shown extraordinary ability to coordinate a much larger and structurally diverse metal center than that of iron. The unique properties of this ligand, specifically the lipophilic pentane groups and hydrophilic polar carbonyl and hydroxamate groups, appear to dictate a specific molecular structure upon metal complexation. All three polar peptide carbonyl groups lie on the same side of the molecule in both [Pu^{IV}(DFE)] and [Fe^{III}(DFE)], not the case in the free ligand. This change in molecular conformation may provide a microorganism with a mechanism by which metal complexes are recognized and transported into the cell. Initial studies of the aqueous speciation of plutonium(IV) in the presence of DFB and DFE show the formation of similar products as a function of pH: one at lower pH (<4) and additional species at higher pH (4–10). Studies of the solution properties of **1** and other [Pu^{IV}(DFO)] complexes and the bacterial uptake of plutonium in the presence of DFB are in progress.

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Towards Detection of a Long-lived Protonated Metal Cation: Generation of GeH^{2+} Using High-Energy Collisions**

Phillip Jackson, Martin Diefenbach, Ragampeta Srinivas, Detlef Schröder, and Helmut Schwarz*

*Dedicated to Rolf Huisgen
on the occasion of his 80th birthday*

Multiply charged ions are a topic of interest in biochemistry and chemical physics.^[1, 2] Recently, thermochemically stable diatomic trications have been synthesized by using the technique of charge-stripping mass spectrometry.^[3, 4] For a diatomic di- or trication AB^{n+} to be classified as thermochemically stable, the polycationic minimum must lie below the asymptotes of the charged separated products $\text{A}^{(n-1)+} + \text{B}^+$; otherwise electronic rearrangement can lead to repulsive dissociation via the Coulomb asymptote. Metastable dications, in which this latter situation holds, may survive long enough to be detected in microsecond time scale (or shorter) experiments. To date, most of the diatomic trications synthesized possess halogen ligands;^[1–7] electrostatic complexes of multiply charged metals with rare gas ligands should also be feasible,^[8, 9] but only few of them, for example VHe^{3+} , have been reported.^[10]

Considerable controversy surrounds the proposed detection of CH^{2+} ,^[11–15] and very recent experiments refute its existence.^[16] Calculations do however suggest that long-lived $^2\Sigma^+ \text{CH}^{2+}$ may be detectable, provided it is possible to generate this ion at all, as poor Franck–Condon factors render its generation from CH^+ in charge-stripping experiments almost impossible. Another problem associated with the detection of CH^{2+} is the non-negligible abundance of ^{13}C , and in some reports this source of artefact has not been adequately addressed. Similar problems were encountered during the characterization of $^{28}\text{SiH}^{2+}$ ^[17] as this ion is isobaric with the ^{29}Si isotope.

In this study, we present the first unambiguous evidence for the existence of GeH^{2+} , a metastable, protonated metalloid cation.^[18] To characterize the bonding and stability of this

particular ion, calculations at the CCSD(T)/cc-pVTZ level of theory have been used to map the potential-energy surface.^[19] On the basis of similar theoretical results, the previously suggested^[17, 20] existence of metastable SiH^{2+} is also confirmed.

The charge-stripping mass spectrum of $^{70}\text{GeH}_2^+$ (m/z 10 to m/z 69) is presented in Figure 1. The overwhelmingly abundant singly charged dissociation products m/z 70 and 71

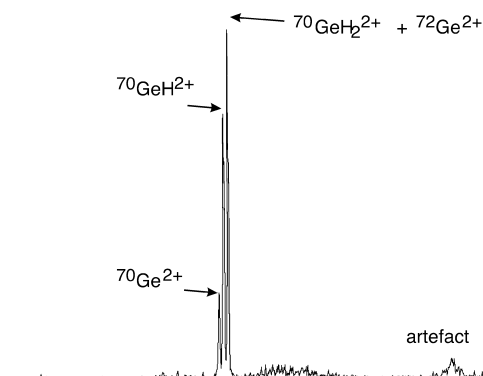


Figure 1. Charge-stripping mass spectrum of $^{70}\text{GeH}_2^+$, containing some $^{72}\text{Ge}^+$, with O_2 as the target gas.

(loss of H_n , $n = 1, 2$) were not recorded. The peak at m/z 35 is due to $^{70}\text{Ge}^{2+}$, while the peak at m/z 36 could be a mixture of isobaric $^{72}\text{Ge}^{2+}$ and $^{70}\text{GeH}_2^{2+}$. Except the contribution of ^{72}Ge , no other isobaric impurities were observed, in particular, as there exists no ^{71}Ge isotope, the peak at m/z 35.5 is unequivocally $^{70}\text{GeH}^{2+}$. On the basis of this spectrum, GeH^{2+} is stable at least on a microsecond time scale.

Modeling of the $[\text{GeH}_2]^+$ potential-energy surfaces, to be reported in greater detail in a follow-up publication,^[21] provides a simple rationale for the generation of GeH^{2+} from this precursor in collision experiments. The reason becomes clear on inspection of the bond lengths calculated by density functional theory (DFT) (Table 1). The bond lengths of the diatomics GeH^+ and GeH_2^+ differ substantially (41.8 pm). While charge stripping of the GeH^+ monocation affords a tiny

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Table 1. Energy E , Ge–H distance R_e , H–Ge–H angle θ_{HGeH} , and vibrational frequency ω_e of small neutral and ionic germanium hydride species calculated at the B3LYP/6-311++G(d,p) level. The normal mode symmetry is given in parentheses.

	E [Hartree]	R_e [pm]	θ_{HGeH} [°]	ω_e [cm ^{−1}]
$^2\Pi \text{GeH}^{[a]}$	−2077.52295	159.8		1812
$^1\Sigma^+ \text{GeH}^{+[a]}$	−2077.25461	159.2		1944
$^3\Pi \text{GeH}^{+[a]}$	−2077.16816	169.5		1267
$^2B_2 \text{Ge}(\text{H}_2)^+$	−2077.81284	218.5	20.3	406 (a ₁) 625 (b ₁) 3994 (a ₁)
$^2A_1 \text{HGeH}^+$	−2077.81096	154.8	120.3	817 (a ₁) 2021 (a ₁) 2109 (b ₁)
$^2\Sigma^+ \text{GeH}^{2+}$	−2076.58479	201.0		606

[a] Values taken from ref. [37]. The frequencies were evaluated by using a valence basis set of double-zeta plus quality and effective core potential (ECP).^[38, 39]

dication signal due to GeH^{2+} , vertical ionization might therefore cause dissociation of the dication. In contrast, the Ge–H bond lengths of the $[\text{Ge}_2\text{H}_2]^+$ global minimum, ${}^2\text{B}_2$ $\text{Ge}(\text{H}_2)^+$, are much closer to the calculated dication value. It is then possible to envisage formation of GeH^{2+} as a concerted charge-stripping/bond-fission event resulting from a small-impact parameter, impulsive collision between the target gas and $\text{Ge}(\text{H}_2)^+$ generated in the ion source. The low dication yields compared with singly charged collisional-activation products suggest that interactions with electrophilic dioxygen at 8 kV result primarily in simple bond cleavages, and collisions yielding the dications are disfavored (small cross-section).

The results from the coupled-cluster investigations of XH^{2+} , $\text{X} = \text{Si}, \text{Ge}$, are presented in Table 2 and Figure 2. Except for the Ge–H bond lengths in the dication, the CCSD(T) and

Table 2. CCSD(T)/cc-pVTZ results for H , X^{n+} , $n = 0-2$, and XH^{n+} , $n = 1, 2$, $\text{X} = \text{Si}, \text{Ge}$ (T_e = term energy).

	Term	E [Hartree]	R_e [pm]	T_e [eV]
H	${}^2\text{S}$	– 0.499810		
Si	${}^3\text{P}$	– 288.986846		
Si^+	${}^2\text{P}$	– 288.689336		
Si^{2+}	${}^1\text{S}$	– 288.093388		
SiH^+	${}^1\Sigma^+$	– 289.313174	150.9	0.0000
SiH^{2+}	${}^2\Sigma^+ (3p_z)$	– 288.637650	174.3	18.3821
	${}^2\Pi (3p_x)$	– 288.496015	183.1	22.2362
	${}^4\Pi (3sp, p_x)$	– 288.405045	209.9	24.7116
Ge	${}^3\text{P}$	– 2075.549500		
Ge^+	${}^2\text{P}$	– 2075.259788		
Ge^{2+}	${}^1\text{S}$	– 2074.683559		
GeH^+	${}^1\Sigma^+$	– 2075.877059	156.8	0.0000
GeH^{2+}	${}^2\Sigma^+ (4p_z)$	– 2075.219026	189.3	17.9061
	${}^2\Pi (4p_x)$	– 2075.062057	191.9	22.1775
	${}^4\Pi (4sp, p_x)$	– 2074.962485	216.1	24.8870
$\text{SiH}^+ \rightarrow \text{Si}^+ + \text{H}$			3.3750 ^[a]	
$\text{SiH}^{2+} \rightarrow \text{Si}^{2+} + \text{H}$			1.2096 ^[a]	
$\text{SiH}^{2+} \rightarrow \text{Si}^+ + \text{H}^+$			– 1.4065 ^[a]	
$\text{GeH}^+ \rightarrow \text{Ge}^+ + \text{H}$			3.1963 ^[a]	
$\text{GeH}^{2+} \rightarrow \text{Ge}^{2+} + \text{H}$			0.9703 ^[a]	
$\text{GeH}^{2+} \rightarrow \text{Ge}^+ + \text{H}^+$			– 1.1092 ^[a]	

[a] Zero Kelvin reaction enthalpy in eV.

B3LYP data agree quite well. Inspection of the heats of reaction reveals the Coulomb explosion asymptotes, $\text{X}^+ + \text{H}^+$, are below the stationary points located for the dications, indicating the XH^{2+} dications are metastable for both elements. The zero-point corrected bond strength $D(\text{Si}^{2+}\text{—H})$ is 1.16 eV (26.9 kcal mol^{–1}),^[22] whereas for Ge the $\text{Ge}^{2+}\text{—H}$ bond is slightly weaker at 0.93 eV (21.7 kcal mol^{–1}). For both dications, the ground states are ${}^2\Sigma^+$, and the bonds between X and H can be described as one-electron sigma bonds, with hydrogen the principal electron donor. At the B3LYP level,^[23] the Mulliken atomic charges are +1.68 (Si) and +0.32 (H) and +1.70 (Ge) and +0.30 (H), which supports a localized bonding model $\text{X}^{2+}(4s^2 4p^0)\text{—H}(1s^1)$. The B3LYP spin densities, +0.49 (Si) and +0.51 (H) and +0.37 (Ge) and +0.63 (H), infer a much larger degree of HOMO polarization towards the H atom for GeH^{2+} , but both spin distributions implicate H-electron donation to the superacid X^{2+} as the source of molecular stabilization.

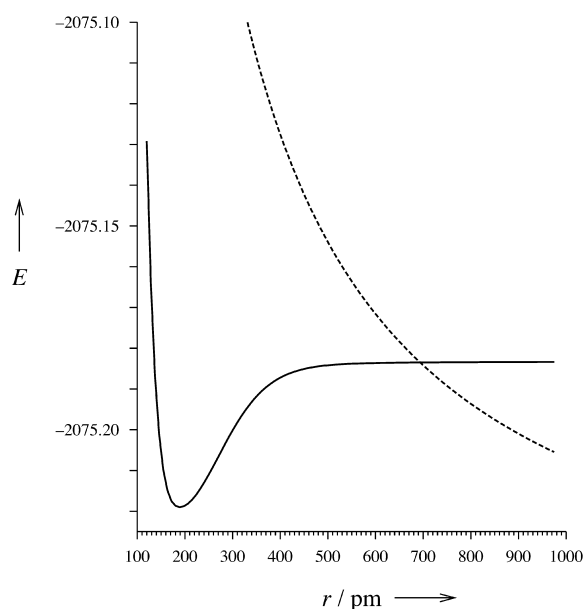


Figure 2. Potential-energy surface scan of GeH^{2+} (solid line). Absolute CCSD(T)-Energy E is given in Hartree. Dashed line represents Coulomb repulsion, $E(r) = E(\text{Ge}^+) + E(\text{H}^+) + 1/r$.

Spin-orbit corrections for the bond strengths of the dications are zero, as all the species involved are either closed-shell or $m_l = 0$; the only exception is the ${}^2\text{X}^+ + {}^1\text{H}^+$ asymptote, for which empirical spin-orbit-weighted-average corrections of 0.55 kcal mol^{–1}^[24] and 3.37 kcal mol^{–1}^[25] can be used to adjust the surfaces for ${}^2\text{P}_{1/2}/{}^2\text{P}_{3/2} \text{X}^+$, $\text{X} = \text{Si}, \text{Ge}$, respectively.

We present the uncorrected and spin-orbit-corrected atomic ionization energies (first and second for Si and Ge) calculated at the B3LYP/6-311++G(d,p) and CCSD(T)/cc-pVTZ levels of theory in Table 3. We have also tabulated the

Table 3. Atomic ionization energies (IE) in eV calculated at the B3LYP/6-311++G(d,p) and CCSD(T)/cc-pVTZ level. The numbers in parentheses are spin-orbit corrected according to the values in Table 4. The final row gives the mean variance^[a] in the experimental and theoretical ionization energies.

	Atom	B3LYP	CCSD(T)	Exp.
IE(X) ^[b]	H	13.667	13.601	13.598 ^[d]
	Si	8.113 (8.108)	8.096 (8.091)	8.152 ^[e]
	Ge	7.831 (7.805)	7.884 (7.858)	7.899 ^[f]
IE(X ⁺) ^[c]	Si	16.397 (16.421)	16.217 (16.241)	16.345 ^[e]
	Ge	15.424 (15.570)	15.680 (15.826)	15.934 ^[f]
mean variance ^[a]		0.104 (0.078)	0.058 (0.033)	

[a] Calculated as $(\sum(\text{IE}_{\text{calcd}} - \text{IE}_{\text{exp}})^2)^{1/2}/N$. [b] For $\text{X} = \text{H}$, the transition is ${}^2\text{S} \text{H} \rightarrow {}^1\text{S} \text{H}^+$; for $\text{X} = \text{Si}, \text{Ge}$, ${}^3\text{P} \text{X} \rightarrow {}^2\text{P} \text{X}^+$. [c] The transition is ${}^2\text{P} \text{X}^+ \rightarrow {}^1\text{S} \text{X}^{2+}$; $\text{X} = \text{Si}, \text{Ge}$. [d] Ref. [40]. [e] Ref. [24]. [f] Ref. [25].

experimental values for comparison; the energy levels for the ground state terms of Si^0/Si^+ and Ge^0/Ge^+ are given in Table 4. The coupled-cluster results are clearly superior, but this may be attributable to the saturated nature of the larger basis set used in these calculations, so B3LYP with a modest triple-zeta basis set performs adequately in this regard.

To conclude, it is quite remarkable that GeH^{2+} was even detected in our experiments, given that the ionization energy

Table 4. J -level energies (E_J) and corresponding weighted average^[a] in eV for Si atoms and Si⁺ ions^[24] as well as for Ge atoms and Ge⁺ ions.^[25]

Level	Si	Ge	Level	Si ⁺	Ge ⁺
³ P ₀	0.00000	0.00000	² P _{1/2}	0.00000	0.00000
³ P ₁	0.00956	0.06908	² P _{3/2}	0.03561	0.21912
³ P ₂	0.02767	0.17481			
weighted average ^[a]	0.01856	0.12014		0.02374	0.14608

[a] Weighted average, calculated as
$$\frac{\sum_{J_{\min}}^{J_{\max}} (2J+1)E_J}{(2L+1)(2S+1)}$$

of hydrogen is 2.34 eV less than the second ionization energy of Ge (²P Ge⁺ → ¹S Ge²⁺); this implies that exothermic internal conversion and dissociation via ²Ge⁺ + ¹H⁺ must be significantly barrier-hindered (Figure 2), as the ion has sufficient time for many thousands of vibrations after formation. Our results for SiH²⁺ also support the previous assignments and $Q_{\min}$ value ($Q_{\min}$ = kinetic energy loss in CS) measured by Porter et al.;^[20] the lower experimental value reported by Koch et al.^[17] appears to be due to interfering ²⁹Si⁺. Compared to GeH²⁺, the silicon hydride dication will be shorter lived on account of the greater covalency of the SiH²⁺ bond. The greater covalency of the Si²⁺–H bond entails the hydrogen electron residing closer to the Si²⁺ fragment. Thus, the Si⁺ + H⁺ configuration must make a greater contribution to the ground-state wavefunction. A natural consequence of this will be that internal conversion must be more probable for this ion.

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- [18] The charge-stripping of ⁷⁰GeH₂⁺, generated by the chemical ionization of GeH₄, was performed using an instrument of BEBE configuration (B represents magnetic and E electric sector) which has been described in detail in a number of articles.^[26, 27] The experiments were conducted as follows: ⁷⁰GeH₂⁺ was mass-selected by using B(1)E(1) at a mass resolution of $m/\Delta m \approx 3000$, and collided with stationary O₂ molecules at 8 kV. The O₂ pressure was maintained so that the ions traversing the collision cell undergo an average of 1.0–1.2 collisions.^[28] This results in both collisional dissociation and charge-stripping events, leading to the generation of small amounts of ⁷⁰GeH²⁺ (m/z 35.5). Fortunately, there is no ⁷¹Ge isotope, however we are left to speculate about the existence of ⁷⁰GeH₂²⁺ because of isobaric interference from ⁷²Ge²⁺ (see below).
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The structure of IF₃**

Sevim Hoyer and Konrad Seppelt*

Iodine forms four stable, binary, and neutral fluorides, IF₇, IF₅, IF₃ and IF; this is the largest number at least among nonmetal fluorides. Our knowledge of these species differs. The structure of IF₇ has been assumed pentagonal-bipyramidal for a long time but has been precisely established only recently.^[1] The heptafluoride shows weak intermolecular interaction in the crystal. The most thoroughly investigated species is IF₅ and is a square pyramid with the iodine atom slightly above the basal plane defined by the four fluorine atoms.^[2] A plethora of intermolecular interactions are found in the crystal, which, however, do not significantly affect the molecular structure.^[3] Both compounds are thermally stable and are textbook examples of various structure–bonding models and theories.

Much less is known about IF₃ and IF. The trifluoride is the least stable binary fluoride of iodine, with a decomposition temperature of –28 °C, as established by differential thermogravimetry (IF decomposes at –14 °C).^[4] This instability is in contrast also to the stability of its homologues ClF₃ and BrF₃.

If iodine is treated with diluted elemental fluorine at low temperatures, IF₃ is obtained free of IF₅.^[5] The yellow solid is either insoluble in all conventional solvents, or it reacts with them. Thus information about its structure is restricted to vibrational spectroscopy.^[6]

It is known that anhydrous HF dissolves traces of IF₃, as noted by a slight yellow color. Addition of small amounts of water increases the solubility and a deep brownish-yellow color results.^[6] All other halogen fluorides are known to react with water under hydrolysis; this has also been described for IF₃.^[6] We presume that water in small amounts acts as a base [Eq. (1)].



Enough IF₃ may go into solution to make material transport and recrystallization possible. The IF₃ is obtained in form of very thin, yellow platelets. A single crystal X-ray structure determination shows a polymeric structure (Figure 1), from which a planar T-shaped molecule can be derived on considering only the shortest I–F bonds (187.2(4), 2 × 198.3(3) pm). This structure for IF₃ is expected, as is the fact that the two I–F bonds, which have a bond angle of 160.3(2)° with each other, are longer than the middle I–F bond, and that all fluorine atoms of the planar molecule are positioned within one hemisphere. Remarkable are, however, the intermolecular I–F···I bridges of 276.9(3) pm. These fluorine atoms

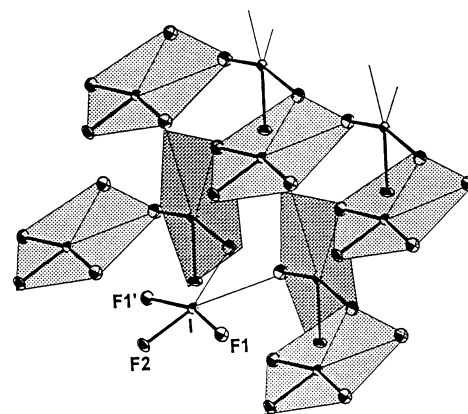


Figure 1. Section of the crystalline structure of IF₃ (ORTEP representation). Bond lengths [pm] and angles [°]: I–F1 198.3(3), I–F2 187.2(4), I···F1 276.9(3); F1–I–F2 80.2(1), F1–I–F1' 160.3(2), F1···I···F1' 59.5(1).

belong to the coordination sphere of two iodine atoms. It is not surprising that only the two weaker bound fluorine atoms make such bridges. Surprisingly, the resulting coordination polyhedron around the iodine atom is a planar pentagon. This is in contrast to the structure of solid BrF₃, in which the coordination of this T-shaped molecule is increased to a planar quadrilateral by one fluorine bridge.^[7]

Whereas solid ClF₃ is best described as a pure molecular lattice,^[8] and the structure of BrF₃ seems to contain the structure of anionic BrF₄[–], the structure of IF₃ is reminiscent of the IF₅^{2–} structure. The latter has indeed a regular planar-pentagonal structure, according to the analysis of the vibrational spectra and theoretical calculations.^[9] For isoelectronic XeF₅[–] this structure has been shown by crystallography.^[10] A square-planar structure for IF₄[–] is also known.^[11]

Furthermore, IF₃ also differs from I₂Cl₆, which is known to form a double chlorine-bridged planar dimer. The transition to CF₃ICl₂, which has recently been prepared in a pure state and structurally characterized,^[12] may be interesting. The CF₃ICl₂ forms planar layers with weak chlorine bridges. The resulting coordination at the iodine atom is either tetragonal planar or pentagonal planar, depending on how many chlorine contacts are taken into consideration.

A pentagonal-planar coordination as a building unit was possibly first found among Te^{IV} compounds such as CH₃TeI[S₂CN(C₂H₅)₂]₂.^[13] These can be considered isoelectronic to IF₃ in a widest sense.

In many respects, OTeF₅ is the ligand most similar to a fluorine atom, if its reduced tendency to form bridged structures is overlooked.^[14] For I(OTeF₅)₃, the T-shaped molecular structure is increased to a planar tetragon by only one, and also weaker, I···F–Te contact, just as it is found also in solid Br(OTeF₅)₃^[15] (Figure 2).

Experimental Section

IF₃: An Ar/F₂ (10/1) mixture was bubbled slowly into a suspension of I₂ in CFCl₃ in a poly-perfluoro-ether tetrafluoroethene (PFA) tube at –45 °C until the I₂ disappeared completely. A yellow solid was formed in quantitative yield. Raman spectra: (cryst., –130 °C): 631 (23), 620 (73), 487 (100), 427 (14), 328 (15), 211 (45) cm^{–1}; see also ref. [6]. After the solvent had been evaporated, anhydrous HF was condensed into the tube. When the tube was opened at –50 °C, H₂O was allowed to condense into it

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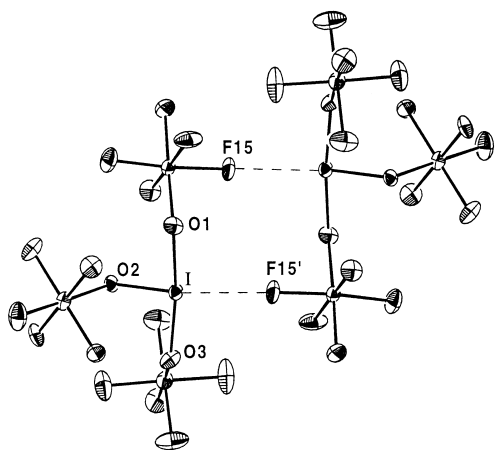


Figure 2. Crystalline structure of $\text{I}(\text{OTeF}_5)_3$ (ORTEP representation). Bond lengths [pm] and angles [°]: I–O1 208.3(5), I–O2 193.5(5), I–O3 203.3(6), I...F15 283.3(5), Te–O 183.9(5)–190.8(5), Te–F 180.8(5)–184.4(5) (F15); O1–I–O2 86.8(2), O1–I–O3 170.6(2), O2–I–O3 88.2(2) $\text{O}_2\text{---I---F15'}$ 171.2(2).

until the IF_3 dissolved largely or totally on shaking and the HF solution was a yellow-brown color. Warming to -30°C and slow cooling to -78°C yielded IF_3 as light-yellow platelets. With an especially designed apparatus^[16] a suitable crystal was mounted on a Bruker SMART CCD 1000 TM diffractometer. Crystal structure analysis: orthorhombic, space group $Pcmn$, $a = 465.0(1)$, $b = 665.5(1)$, $c = 875.5(1)$ pm, $V = 270.9 \times 10^6 \text{ pm}^3$, $T = -135^\circ\text{C}$, $Z = 4$, $\text{MoK}\alpha$ radiation, graphite monochromator, scan width of $0-3\omega$, illumination time 10 s per frame, 3279 measured, 465 independent reflections, 23 parameters, $R(F \geq 4\sigma(F)) = 0.031$, $wR_2 = 0.058$. After semi-empirical absorption correction (SADABS) the structure was solved and refined by the SHELX programs.^[17]

$\text{I}(\text{OTeF}_5)_3$:^[18] In a quartz vessel CFCl_3 (20 mL), IF_5 (1.65 g, 7.5 mmol) and $\text{B}(\text{OTeF}_5)_3$ (9.13 g, 12.5 mmol) are condensed on 635 mg (2.5 mmol) iodine at -196°C . After the mixture had been stirred at room temperature for 2 h all volatile materials were removed under vacuum. An orange-red liquid residue slowly crystallized; the yield was almost quantitative. ^{19}F NMR ($n\text{-C}_6\text{F}_{14}$): AB_4 spectrum, $\delta_A = -48.21$, $\delta_B = -45.55$, $J(\text{AB}) = 175 \text{ Hz}$, $J(^{125}\text{Te}, \text{F}) = 3699 \text{ Hz}$; Raman spectrum (cryst., -150°C): 807 (20), 760 (16), 750 (8), 738 (15, sh), 730 (22), 719 (57), 713 (32, sh), 700 (62), 689 (60), 666 (97), 642 (15, sh), 635 (35), 596 (42), 492 (60), 470 (100), 449 (65), 390 (12), 346 (15), 326 (32), 314 (22, sh), 298 (25), 254 (37), 235 (59), 228 (31, sh), 215 (11), 201 (12), 177 (49), 162 (22), 130 (85), 109 (16), see also ref. [18]. Crystal structure analysis: monoclinic, space group $P2_1/c$, $a = 1447.8(1)$, $b = 973.4(1)$, $c = 1027.4(1)$ pm, $\beta = 91.42(1)$, $V = 1447.4 \times 10^6 \text{ pm}^3$, $T = -128^\circ\text{C}$, $Z = 4$, 14936 measured, 1485 independent reflections, $R(F \geq 4\sigma(F)) = 0.049$, $wR_2 = 0.128$.

Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666, on quoting the depository numbers CSD-411036 and -411037).

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Synthesis of the N-Terminal N-Myristoylated and S-Palmitoylated Undetrigitapeptide of Endothelial NO-Synthase**

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The correct orchestration of signal transduction from the blood stream across the endothelium to the surrounding smooth muscle cells of the blood vessels is paramount to the regulation of blood pressure. A key event in this regulation is the generation and release of NO from arginine by endothelial NO-synthase (eNOS) in response to exogenous signals and the subsequent relaxation of the muscle cells.^[1,2] Furthermore eNOS is involved in vascular remodelling and angiogenesis,^[3] and contributes to the pathogenesis of blood vessel related disorders like atherosclerosis.^[4,5] The localization of eNOS to the plasma membrane and its concentration in the caveolae, membrane microdomains highly enriched in various signal transducing proteins is crucial to its correct biological functioning.^[6]

In contrast to the other isoforms of NO-synthase identified so far, the N-terminus of eNOS is N-myristoylated and twice S-palmitoylated (see Figure 1 and 1, Scheme 1).^[7] The lipid

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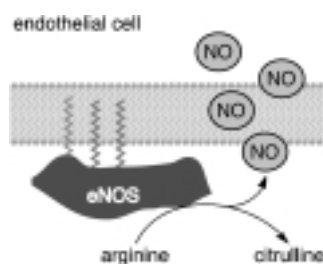
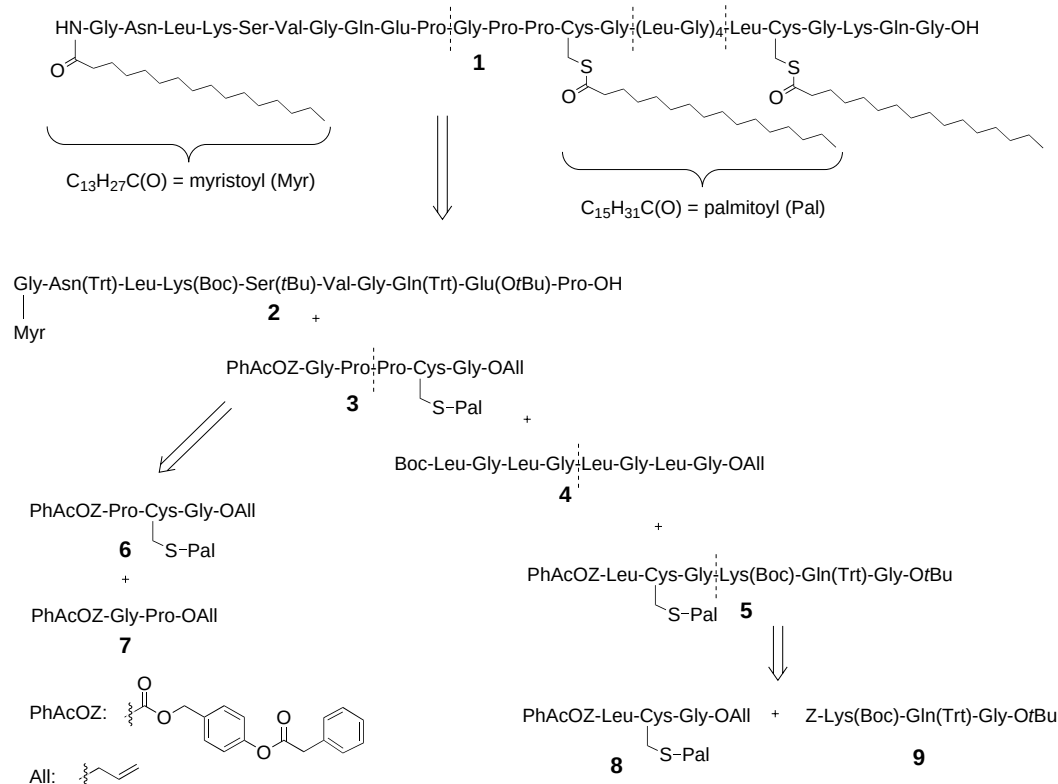


Figure 1. Membrane association and enzymatic activity of endothelial NO-synthase.



Scheme 1. Retrosynthetic analysis of the *N*-myristoylated and twice *S*-palmitoylated *N*-terminal 29mer peptide of endothelial NO-synthase. Boc = *tert*-butoxycarbonyl, Trt = trityl = triphenylmethyl, Z = benzyloxycarbonyl.

groups are required for plasma membrane localization and biological activity.^[6, 8] However, the precise biological roles fulfilled by the lipidated part of the protein are subject to various hypotheses. In particular, notions have been forwarded that the lipid groups might be responsible for selective targeting of eNOS at the plasma membrane and caveolae, for example, by mediation of protein/protein or protein/lipid interactions, and that palmitoylation/depalmitoylation might be involved in signalling through eNOS.^[5]

Lipidated peptides which embody the characteristic partial structures of their parent lipidated proteins have proven to be efficient tools for subsequent biological experiments, for example, in the case of the *Ras* proteins.^[9] For the study of the chemical biology of endothelial NO-synthase, and in particular, for the study of the factors determining its localization to the plasma membrane and caveolae, we have now developed a methodology that gives access to the correctly lipidated *N*-terminal 29mer peptide **1** of eNOS (Scheme 1).

The synthesis of lipidated peptide **1** is complicated by several parameters: 1) the palmitic acid thioesters are sensitive to bases; that is, they spontaneously hydrolyze at pH > 7 and are subject to base-induced β -elimination.^[9] Therefore, base-labile protecting groups can not be employed in the synthesis of **1**. 2) For the synthesis of *S*-palmitoylated peptides solid-phase methods are not available.^[10] 3) Peptide **1** embodies several amino acids with side-chain functional groups that require protection during the synthesis and final deprotection under conditions mild enough to guarantee that the

sensitive thioester bonds are not attacked.

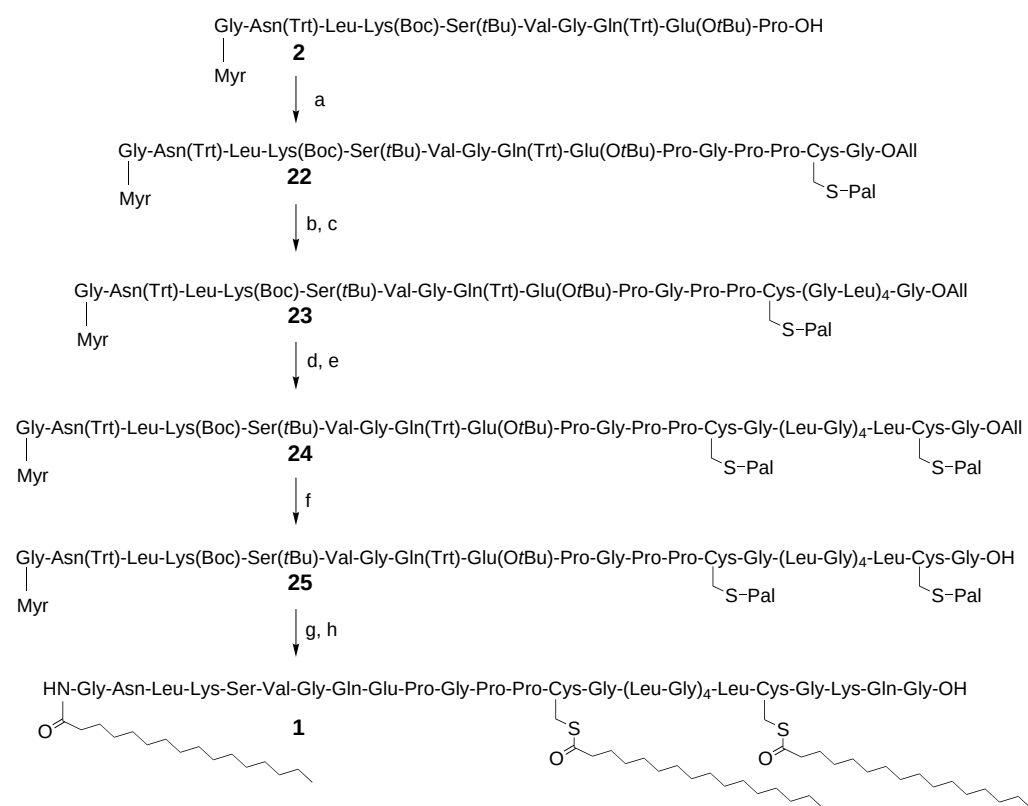
In developing a plan for the synthesis of **1** we chose a combination of enzyme-labile, acid-sensitive, and noble-metal-sensitive protecting groups and aimed to combine the use of solid-phase techniques with solution-phase fragment condensations. Thus, in a retrosynthetic sense, **1** was divided into *N*-myristoylated decapeptide **2**, *S*-palmitoylated pentapeptide **3**, octapeptide **4**, and *S*-palmitoylated hexapeptide **5** (Scheme 1). For the synthesis and selective deprotection of *S*-palmitoylated building blocks the enzyme-labile *p*-phenyl-acetoxybenzyloxycarbonyl (PhAcOZ) urethane group^[11] and the Pd⁰-labile allyl ester^[12]

were chosen as *N*- and *C*-terminal protecting functions. The side chains of Asn, Lys, Ser, Gln, and Glu were masked with acid-labile protecting groups to be cleaved off simultaneously in the final step of the synthesis. We planned to build up the *N*-terminal decapeptide on the solid phase and to assemble the entire 29mer in solution by appropriate fragment condensations. The retrosynthetic cuts were placed at the *C*-termini of glycine and proline residues to exclude epimerization during the fragment condensations.

The base labile *S*-palmitoylated building blocks required for the fragment condensations were synthesized as shown in Scheme 2. PhAcOZ-protected amino acids **10** and **11** were condensed with cystine bis(allyl ester) **12**. After cleavage of the disulfide by treatment with dithiothreitol (DTT), the liberated mercapto groups were acylated with palmitoyl chloride to yield fully masked dipeptides **13** and **14** in high overall yields. To elongate the peptide chain in the *C*-terminal direction, the allyl ester protecting group was selectively

methylene chloride (1/1/8). Peptide **2** was obtained in 98 % overall yield.

With all required and selectively unmasked building blocks in hand, the assembly of the desired 29mer eNOS peptide **1** was approached (Scheme 3). To this end, decapeptide **2** was



Scheme 3. Synthesis of the lipidated 29mer target peptide **1** by fragment condensation. a) H-Gly-Pro-Pro-Cys(Pal)-Gly-OAlI **20**, HOObt, EDC, CHCl₃/CF₃CH₂OH (3/1), 91 %; b) [Pd(PPh₃)₄], DMB, DMSO, 92 %; c) H-Leu-(Gly-Leu)₃-Gly-OAlI **21**, HOAt, NEt₃, EDC, DMSO, 72 %; d) [Pd(PPh₃)₄], DMB, DMSO, 87 %; e) H-Leu-Cys(Pal)-Gly-OAlI **18**, HOAt, EDC, NMP, 86 %; f) [Pd(PPh₃)₄], DMB, DMSO, 69 %; g) H-Lys(Boc)-Gln(Trt)-Gly-OtBu **26**, HOAt, EDC, NMP, 86 %; h) CF₃CO₂H/ethanedithiol/H₂O (95/2.5/2.5), 31 %. HOObt = 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine, NMP = *N*-methylpyrrolidine.

condensed with *S*-palmitoylated building block **20** to yield pentadecapeptide **22** in 91 % yield. From compound **22** the C-terminal allyl ester was removed with complete selectivity (92 % yield) and further chain elongation with octapeptide **21** delivered 23mer peptide **23** in high overall yield. Once more the Pd⁰-catalyzed cleavage of the allyl ester proceeded efficiently and allowed for further selective elongation of the peptide chain with *S*-palmitoylated building block **18**. The selective removal of the allyl ester from the 26mer intermediate **24** was considered to be particularly challenging since this peptide embodies two base labile thioesters and several acid-labile groups. In addition, this fully masked compound is highly hydrophobic so that formation of aggregates and poor solubility, which would render the compound poorly accessible to the Pd⁰-catalyst, had to be feared. However, to our great pleasure this deprotection could also be effected without any undesired side reaction, and C-terminally deprotected 26mer peptide **25** was obtained in high yield. Finally, the peptide chain was elongated with tripeptide **26** and, in the last step, all acid-labile side-chain protecting groups were cleaved

by treatment with trifluoroacetic acid in the presence of ethanedithiol as a cation scavenger.

The choice of the right solvents and the work-up conditions is paramount to the success of the fragment condensations (for details, see the Supporting Information). The protected

lipidated peptides **2**, **22**, **23**, **24**, and **25** are highly hydrophobic and tend to form secondary structures. Due to these properties, the peptides are only sparingly soluble in many solvents and separation of the reaction mixtures by RP-HPLC was not successful. These problems could be circumvented by running the reactions in very polar solvents and by using only a slight excess of the smaller fragments in the condensation reactions. Thus, peptide couplings were carried out with DMSO, *N*-methyl-pyrrolidinone, or CHCl₃/2,2,2-trifluoroethanol mixtures as solvents and all Pd⁰-mediated allyl ester cleavage reactions were performed in DMSO. Use of only 1.2–1.5 equivalents of the smaller building blocks in the coupling reactions gave high coupling yields and allowed for separation of excess lipopeptide by

simple washing and recrystallization due to the better solubility of the smaller monolipidated compounds.

In conclusion we have developed a highly efficient synthesis of the *N*-myristoylated and twice *S*-palmitoylated N-terminus of endothelial NO-synthase. The strategy relies on the combined use of enzyme-labile, acid-sensitive, and noble-metal-sensitive protecting groups for solution-phase synthesis of labile *S*-palmitoylated building blocks under the mildest conditions with solid-phase and fragment-condensation techniques. The results convincingly demonstrate the full capacity of the protecting group methods for the synthesis of large and multiply lipidated peptides. Together with the recently developed methods for the synthesis of entire functional proteins by a combination of organic synthesis with molecular biology,^[16] they should open up new opportunities to study the chemical biology of endothelial NO-synthase in precise molecular detail, particularly the parameters determining its localization to the plasma membrane and caveolae of endothelial cells.

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4-(*N*-Methylhydrazino)-7-nitro-2,1,3-benzooxadiazole (MNBDH): A Novel Fluorogenic Peroxidase Substrate**

Jörg Meyer, Andrea Büldt, Martin Vogel, and Uwe Karst*

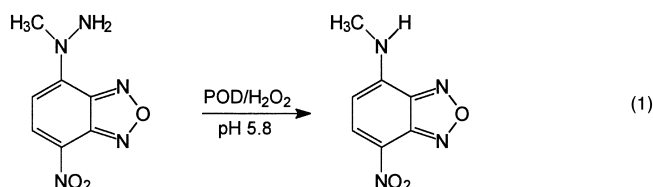
Enzymes are characterized by a range of attractive features for applications in analytical chemistry. Low analyte detection limits, even in complex matrices, are realized by their high catalytic activity and substrate selectivity. In this context, peroxidases are of special interest because of the possibility of coupling H_2O_2 detection with reactions yielding H_2O_2 . In addition to the type and activity of the peroxidase, the lower detection limit of the enzymatic reaction is influenced by the chromogenic or fluorogenic substrate used, as the properties of the detected reaction product play a crucial role. A variety of organic compounds are used as chromogenic substrates, for example, aromatic amines like *o*-phenylenediamine (OPD),^[1] 3,3'-5,5'-tetramethylbenzidine (TMB),^[2] and also 2,2'-azino-bis(3-ethylbenzothiazolin)-6-sulfonate as the diammonium salt (ABTS)^[3]. In case of the more sensitive fluorogenic methods the *p*-hydroxyphenylcarboxylic acids, especially *p*-hydroxyphenylacetic acid (pHPA), have found widespread application.^[4]

The main disadvantage of the *p*-hydroxyphenylcarboxylic acids and other fluorogenic substrates is the difference between the optimum pH for the enzymatic reaction, which lies in a moderately acidic range,^[5] and for fluorescence detection of the products, where alkaline media are required.^[4] A second drawback is the short wavelengths for the excitation maxima of the fluorophores. Furthermore, oxidation of the known fluorogenic substrates yields, in most cases, a mixture of reaction products rather than one well defined fluorophore^[6] and, in some cases, not even the exact structure of the fluorescent compounds obtained could be elucidated.

Hydrazine reagents are the most popular group of derivatising reagents for carbonyl compounds.^[7] In this work, we describe the use of a hydrazine reagent as a fluorogenic peroxidase substrate. Surprisingly, the nonfluorescent 4-(*N*-methylhydrazino)-7-nitro-2,1,3-benzooxadiazole (MNBDH), which was recently introduced as reagent for the determination of carbonyl groups^[8] and nitrite ions,^[9] is oxidized by H_2O_2 in presence of peroxidase (POD) to the intensively fluorescing 4-(*N*-methylamino)-7-nitro-2,1,3-benzooxadiazole (MNBDH) [Eq. (1)]. The identity of the reaction product was verified by NMR, UV/Vis, and fluorescence spectroscopy, mass spectrometry, and HPLC. The enzymatic reaction and fluorescence detection are carried out in a mildly

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acidic medium (pH 5.8). In case of MNBDH, similar pH optima for conversion of the substrate and detection of the product are observed. The HPLC experiments, with UV/Vis detection of the reaction mixture, show only one additional peak in the chromatogram; its retention time and UV/Vis spectrum match that of pure MNBDH. With fluorescence detection (excitation wavelength: 470 nm, emission wavelength: 547 nm) only the MNBDH peak appears in the chromatogram. No other reaction products could be observed by liquid chromatography.

For the determination of H_2O_2 , based on the procedure described below, the limit of detection (LOD) is $2.2 \times 10^{-8} \text{ M}$ and the limit of quantification (LOQ) is $7.5 \times 10^{-8} \text{ M}$. These values are superior by a factor of three compared to those obtained for pHPA. In addition, the selectivity is improved using MNBDH because of the red-shifted excitation and emission maxima.

The MNBDH method was validated by comparison with two established peroxidase substrates, ABTS^[10] and pHPA,^[11] through the determination of glucose in four different beverages. Glucose is oxidized by aerial oxygen in the presence of glucose oxidase, and forms hydrogen peroxide. The latter is detected in a peroxidase-catalyzed reaction based on one of the substrates mentioned above.

The analytical figures of merit of the three methods are listed in Table 1. The photometric method had the smallest relative standard deviation but it is an order of magnitude less sensitive than the fluorimetric techniques. The LOD and LOQ with MNBDH are lower by a factor of three compared to pHPA. Further advantages of MNBDH are the red-shifted excitation and emission maxima (see also the fluorescence spectrum depicted in Figure 1) and an improved signal stability (Figure 2). Advantages for pHPA are the better water solubility and a higher reaction rate.

The results of the determination of α -D-glucose in soft drinks are presented in Table 2. Apart from the data for cola and lemon-flavored instant tea obtained by using pHPA, all results correspond well.

The MNBDH reagent may therefore be seen as prototype of a new and powerful class of peroxidase substrates for which

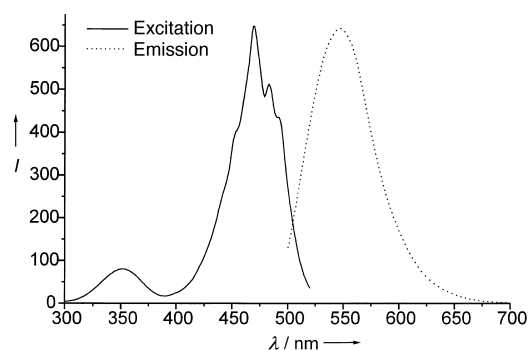


Figure 1. Fluorescence spectrum of MNBDH.

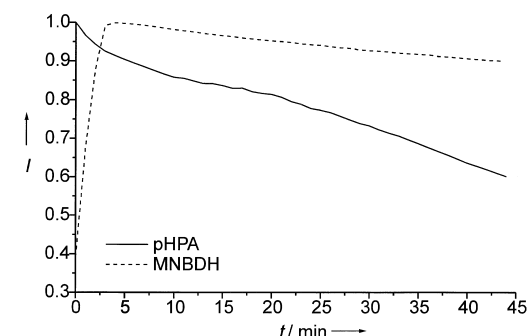


Figure 2. Time-based development for the reaction of MNBDH and pHPA with peroxidase and H_2O_2 .

Table 2. Results for the determination of glucose in soft drinks. All values refer to the content of α -D-glucose.^[a]

Method	Apple juice [g L ⁻¹]	Orange juice [g L ⁻¹]	Cola [g L ⁻¹]	Instant tea [% w w ⁻¹]
ABTS ₄₀₅	20.6 ± 0.4	25.4 ± 1.1	41.1 ± 0.6	20.6 ± 1.0
ABTS ₆₄₉	20.9 ± 0.6	26.0 ± 1.4	42.4 ± 0.8	20.6 ± 1.3
ABTS ₇₃₂	21.0 ± 0.5	26.0 ± 1.0	42.7 ± 0.6	20.3 ± 1.0
MNBDH	22.0 ± 0.4	26.4 ± 0.5	44.2 ± 2.1	20.0 ± 1.2
pHPA	20.8 ± 2.1	26.1 ± 1.4	50.0 ± 1.7	15.3 ± 1.4

[a] Deviations are calculated as the standard deviation of the mean value of eight separate determinations.

directed optimization should yield substrates with increased potential.

Experimental Section

Commercial samples investigated in this study were apple juice, orange juice, cola, and lemon-flavored instant tea. Liquid samples were diluted directly (by a factor of 10000 for detection with ABTS or pHPA, and by a

Table 1. Parameters for the determination of glucose using the peroxidase substrates ABTS, MNBDH, and pHPA.

Method	Limit of detection [M] ^[a]	Limit of quantification [M] ^[b]	Averaged standard deviation [%] ^[c]	Smallest/largest standard deviation [%] ^[d]	Linear range [M]
ABTS ₄₀₅ ^[e]	6×10^{-7}	2×10^{-6}	2.7	5.7/0.3	$2 \times 10^{-6} - 2 \times 10^{-4}$
ABTS ₆₄₉	1×10^{-6}	3×10^{-6}	2.8	7.3/0.4	$3 \times 10^{-6} - 2 \times 10^{-4}$
ABTS ₇₃₂	5×10^{-7}	2×10^{-6}	1.9	4.2/0.4	$2 \times 10^{-6} - 2 \times 10^{-4}$
MNBDH	5×10^{-8}	2×10^{-7}	3.6	5.6/2.7	$2 \times 10^{-7} - 2 \times 10^{-5}$
pHPA	2×10^{-7}	5×10^{-7}	5.3	8.8/2.7	$5 \times 10^{-7} - 2 \times 10^{-5}$

[a] Calculated as the triple standard deviation of the blank. [b] Calculated as the tenfold standard deviation of the blank. [c] Relative standard deviation of eight separate determinations, averaged for the linear range. [d] Relative standard deviation of eight separate determinations, smallest and largest value of the linear range. [e] Subscripts correspond to the wavelengths (in nanometers) used for photometric measurements.

factor of 50 000 for MNBDH). The instant tea was weighed and dissolved in bidistilled water (0.5 g in 10 mL water) and diluted in the same way.

All measurements were carried out using microplate readers.

Glucose oxidase (GOD) reaction (I): 50 μ L of a solution of GOD (15 mg) in acetate buffer (10 mL; pH=5.5; 0.01M) were added to 100 μ L of a glucose solution. After mixing thoroughly, the solution was incubated for 15 min at 37 °C.

GOD reaction (II): as I, but 20 μ L GOD solution and 40 μ L glucose solution were used.

GOD reaction (III): as I, but the GOD solution was prepared with phosphate buffer (pH 5.8; 0.01M).

Glucose determination using POD and ABTS: 50 μ L of a solution containing POD (0.5 mg) and ABTS (5.5 mg) in acetate buffer (10 mL; pH 5.5; 0.01M) were pipetted to the mixture of reaction I. After the sample had been mixed thoroughly and incubated for 10 min at room temperature, the absorbance of the samples was measured at 405, 649, and 732 nm.

Glucose determination using POD and pHPA: 50 μ L of a solution containing POD (2.5 mg) and pHPA (7.6 mg) in ammonium buffer (10 mL; pH 9.5; 0.01M) were pipetted to the mixture of reaction II. After the sample had been mixed thoroughly and incubated for 15 min at room temperature, the fluorescence of the samples was measured at excitation and emission wavelengths of 320 and 405 nm, respectively.

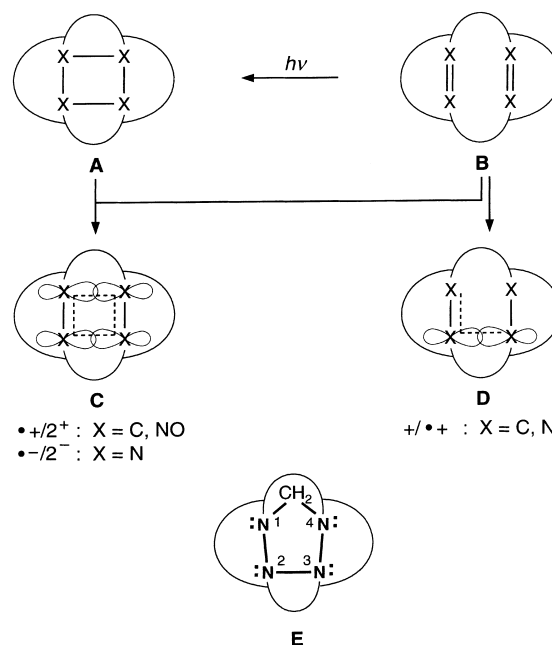
Glucose determination using POD and MNBDH: 1 mg MNBDH was dissolved in 10 mL acetonitrile. Of this solution, 1.4 mL are added to a solution containing POD (2.5 mg) in phosphate buffer (10 mL; pH 5.8; 0.01M). From this mixture, 40 μ L were pipetted into the mixture of reaction III. After the sample had been mixed thoroughly and incubated for 10 min at room temperature, the fluorescence of the samples was measured at excitation and emission wavelengths of 470 and 545 nm, respectively.

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σ -Homoconjugation in Cyclically Preoriented N4-(Radical) Cations—N...N Bond Lengths $> 2 \text{ \AA}^{**}$

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(pp) σ -Conjugation, the electron delocalization between collinear p-orbitals, is a borderline case for the theory of chemical bonding.^[1] It occurs efficiently only in compounds difficult to synthesize and with specific steric/stereoelectronic prerequisites. Making use of cage-fixed cyclobutanes **A** (X = C, (iso)pagodanes), of preoriented dienes **B** (X = C, (iso)pagodadienes/(seco)dodecahedradienes), and bisdiazenes/bisdiazenetetroxides **B** (X = N, NO), the effective σ -homoconjugation or σ -bishomoaromaticity in 3C/3(2)e cations **D** (X = C),^[2] in 4C(N)/3(2)e cations **C** (X = C, NO),^[3, 4] and in 4N/5(6)e anions **C** (X = N)^[5] have been observed. Here, we



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- [10] ABTS is oxidized to an intensely green radical cation and shows UV/Vis absorption maxima at 405, 415, 649, 732, and 815 nm.
- [11] The phenol derivative pHPA is dimerized in the peroxidase-catalyzed reaction to form the corresponding biphenol, which fluoresces in alkaline media (pH 9.5) with excitation and emission maxima of 323 and 403 nm, respectively.

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report on the σ -homoconjugation in tetraaza ions of type **D** ($X = N$), generated through the protonation and one-electron oxidation of type **E** tetrazolidines.^[6] The latter—the first of their kind^[7]—are all-*cis*-alkylated with four n-electron pairs elliptically aligned and are accessible via the bisdiazenes **B**.^[8]

The colorless tetrazolidine **2** (Figure 1; λ_{max} (relative ϵ) = 364 nm (13), 212 (100)^[9]) was quantitatively produced through the treatment of the bisdiazene **1** with CH_3I ($t_{1/2}$ = 3.5 d) followed by treatment of the yellow, thermally quite

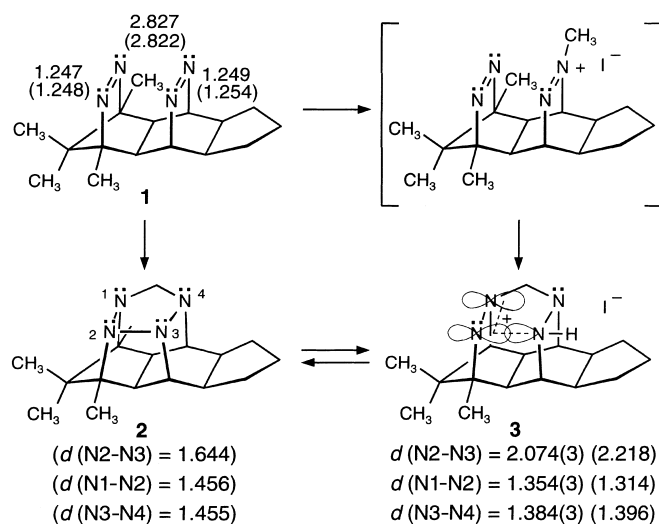


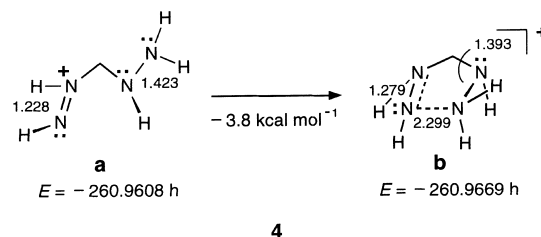
Figure 1. Selected experimental and (in parentheses) calculated (B3LYP/6-31G*) distances [Å] for **1**, **2**, and **3**.

stable salt **3** (decomp > 100 °C; λ_{max} (ϵ) in CH_3CN = 350 nm (3070), in CH_3OH = 344 nm, in CHCl_3 = 335 nm) with aqueous K_2CO_3 . Reprotonation of **2** leads back to **3**; according to calculations (B3LYP/6-31G* level) the protonation at N3 (numbering of **E**) is energetically favored.

The salt **3**, according to the X-ray structural analysis^[10] and the B3LYP/6-31G* calculations,^[11] features unusual bonding properties (Figure 1). As consequence of the strong electron repulsion in the tetraaza chain of **2**, the N2–N3 bond is considerably long ($d = 1.644$ Å), whereas the N1–N2 and N3–N4 bonds are of normal length. In the salt **3**, the N2–N3 bond is elongated by a further 0.430 Å, but the N1–N2 and N3–N4 bonds, in contrast, are shortened by 0.102 and 0.071 Å, respectively. In essence, **3** represents a diazenium ion ($\text{R}_2\text{N}^+=\text{N}^-\text{R}$), that is stabilized by σ -homoconjugation involving the n-electron pair on N3 of the hydrazine unit (N3–N4). According to an NBO analysis, the π^* orbital of the N1=N2 double bond is occupied by 0.56 electrons and the N3 electron lone pair is the main donor, providing an interaction energy of 26.96 kcal mol^{−1}; the N4 lone pair remains largely localized.

Significant through-space interaction between N1 and N4, in the sense of cyclic delocalization (**C**), is excluded by a Bader analysis.^[12] Only for the N2–N3 bond does a critical point exist, albeit with a small electron density of $\rho = 0.0537 e a_0^{-3}$. The corresponding Laplacian $\nabla^2(\rho) = +0.1488$ characterizes a donor–acceptor type bond;^[13] the color of **3** results from a charge-transfer transition. The thermodynamic

value of the N2...N3 σ -homoconjugation over a 2 Å distance has been estimated for the model compound **4**: Of the two conformers **a** and **b** the σ -homoconjugated **b** is, by B3LYP/6-31G* calculations, more stable by 3.8 kcal mol^{−1}.



How does tetrazolidine **2** respond to the loss of an electron?^[14] A B3LYP/6-31G* optimization starting from the structure of neutral **2** leads—in agreement with the nodal situation of the HOMO of **2**—with shortening of all N–N distances to the radical cation **5** (Figure 2).^[15] The calculated

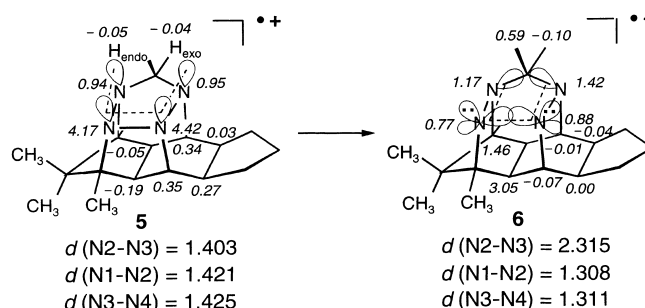


Figure 2. Calculated (B3LYP/6-31G*) hyperfine coupling constants [mT] (italics) and distances [Å] for the radical cations **5** and **6**.

isotropic hyperfine-coupling constants (hfcs) of **5** give dominant values for the four nitrogens of 4.42 and 4.17 mT for N2 and N3, and about 0.95 mT for both N1 and N4; the hfcs of the central protons, located in the nodal plane of the singly occupied molecular orbital (SOMO), are very small.

In cyclovoltammetric experiments, **2** was reversibly oxidized and the oxidation potential was surprisingly high ($E_{1/2} = 0.56$ V versus Ag/AgCl, 0.5 V s^{−1}, 281 K). The temperature dependence of the potential difference of $\Delta E_{\text{EP}} = 0.15$ V (0.079 V at 298 K) indicates significant structural changes during the charge transfer process. Chemical oxidation of **2**, using diverse methods, leads to moss-green solutions (λ_{max} (CH_2Cl_2) = 751 nm), yet this radical does not belong to the $\text{C}_{17}\text{H}_{26}\text{N}_4^{+\bullet}$ hypersurface.^[6, 16] In contrast, ionisation of **2** by γ -irradiation (^{60}Co) at 77 K (matrix $\text{CCl}_3\text{F}/\text{CF}_2\text{BrCF}_2\text{Br} = 1:1$) generated a deep-violet radical cation ($\lambda_{\text{max}} = 560$ nm). The EPR spectrum (Figure 3) proved incompatible (see Supporting Information) with the calculated spectra (B3LYP/6-31G*) of **5** and its retro[3+2]⁺ cycloadduct, yet it was in good agreement with the calculation for the N2–N3- σ -homoconjugated species **6**. The formation of the latter formally occurs by loss of an electron from the HOMO-1 of **2** (which is nearly isoenergetic with the HOMO).^[15]

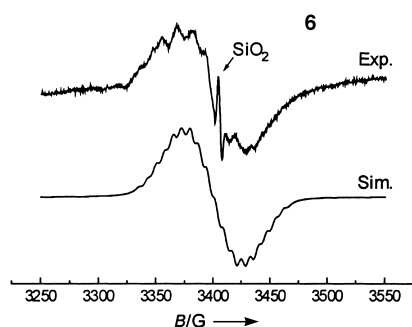


Figure 3. EPR spectra of **2** ionized at 77 K by γ -irradiation in a matrix ($\text{CCl}_3\text{F}/\text{CF}_2\text{BrCF}_2\text{Br}$ 1/1; 111 K, modulation 0.3 mT) and simulation against B3LYP/6-31G* data.

The transformation **5** $\rightarrow$ **6**, calculated to be exothermic by $10.5 \text{ kcal mol}^{-1}$, proceeds with strong elongation ($0.912 \text{ \AA}$) of the N2–N3 bond to $2.315 \text{ \AA}$ and shortening ($0.113 \text{ \AA}$) of the N1–N2 and N3–N4 bonds. Unlike in **5**, the central hydrogen atoms are no longer in the nodal plane of the SOMO (Figure 4), causing drastic changes of the (calculated) ^1H

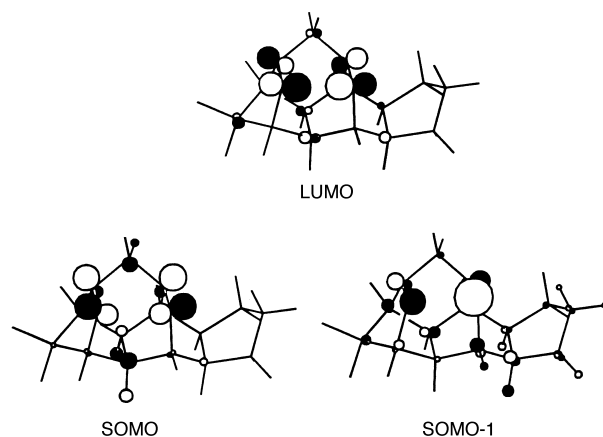


Figure 4. MOPlot^[17] representation of the frontier orbitals of **6**.

coupling constants. This assignment is supported by the UV/Vis spectra calculated (Figure 5) for the radical cations **5** and **6** (and its retro[3+2]⁺⁺ cycloadduct); only for **6** is the experimental absorption well reproduced (λ_{max} (TD-B3LYP/6-31G*)^[18] = 515 nm ($f=0.0041$), 631 nm ($f=0.0005$)). The

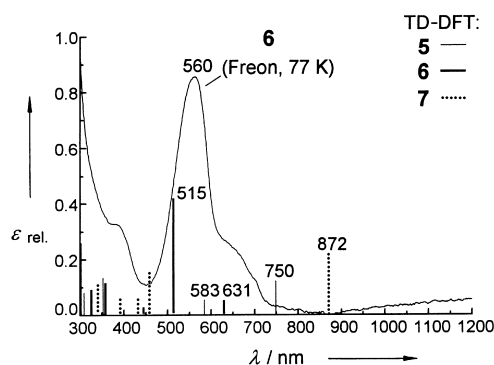


Figure 5. UV/Vis spectra of **2** ionized at 77 K by γ -irradiation (solid line) in a matrix ($\text{CCl}_3\text{F}/\text{CF}_2\text{BrCF}_2\text{Br}$ 1/1). The results of the TD B3LYP/6-31G* calculations for **5** and **6** (retro[3+2]⁺⁺ cycloadduct = **7**) are shown as vertical lines.

two longest wavelength transitions are negative (shoulder at 630 nm) and positive (band at 560 nm) combinations of the SOMO $\rightarrow$ LUMO and SOMO-1 $\rightarrow$ SOMO transitions. The transformation **5** $\rightarrow$ **6** is related to the “tight” $\rightarrow$ “extended” isomerization of the 4C/3e radical cations of the [1.1.1.1]pagodane, for which a barrier of $E_a = 2.2 \pm 0.3 \text{ kcal mol}^{-1}$ has been determined with the fast FDMR method.^[3b]

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- [15] The SOMO and SOMO-1 of the radical cation **5** correspond to the HOMO and HOMO-1 of neutral **2**. The HOMO of **2** is described as

the antibonding combination of the four nonbonding electron pairs at the nitrogen atoms.

- [16] An additional wave is observed at about 0.01 V in the backscan, which disappears at faster scan rates. The nature of the corresponding novel 4N/7e radical cation will be reported separately. K. Exner, B. Großmann, G. Gescheidt, J. Heinze, M. Keller, T. Bally, P. Bednarek, H. Prinzbach, unpublished results.
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Extremely Long, Discrete *meso*–*meso*-Coupled Porphyrin Arrays**

Naoki Aratani, Atsuhiko Osuka,* Yong Hee Kim, Dae Hong Jeong, and Dongho Kim

Considerable attention has been focused on the synthesis of monodisperse macromolecular rods of precise length and constitution in light of their potential application as molecular-scale electronics, optical devices, sensors, and for conversion of solar energy.^[1–3] Discrete molecular rods of known structure are used to position two active centers at a known distance, and the resulting assemblies are of interest as potent electronic or photonic molecular wires. Recently, the length of linear, monodisperse, π -conjugated oligomers have reached the range of approximately 10 nm.^[1, 4] Yet it still remains a great synthetic challenge to explore discrete, finite functional supramolecules with well-defined structures far beyond these achievements.

One of the most attractive building blocks for supramolecular rods are porphyrins, since they offer a variety of desirable features such as a rigid, planar geometry, high stability, an intense electronic absorption, a strong fluorescence emission, a small HOMO–LUMO energy gap, as well as flexible tunability of their optical and redox properties by appropriate metalation.^[5] Recent efforts on the preparation of

supramolecular porphyrin arrays have become increasingly focused on the realization of various molecular devices.^[5, 6] However, these studies are often hampered by poor solubility, difficult separations, and demanding characterizations. Therefore, high solubilities, easy separations, and reliable characterizations of the arrays are of prime importance in devising a larger molecular system.

Recently we found that the Ag^I-promoted *meso*–*meso*-coupling reaction of Zn^{II} 5,15-diarylporphyrins has several advantages;^[7, 8] 1) the regioselectivity of the *meso*–*meso* coupling is quite high, 2) the porphyrin arrays have essentially the same linear rodlike shape, 3) the porphyrin arrays are highly soluble, presumably because of orthogonal conformations arising from steric hindrance around the *meso*–*meso* linkage, 4) the separation of the coupling products is easy by recycling preparative GPC-HPLC chromatography as a result of large differences in molecular weight, and finally 5) the long coupling products still bear two free *meso* positions that are available for the next reaction.

Here we report the synthesis and characterization of *meso*–*meso*-coupled porphyrin oligomers up to 128-mer, which is, to the best of our knowledge, the longest (ca. 106 nm) monodisperse, rodlike molecule prepared so far. Previously we employed Zn^{II} 3,5-di-*tert*-butylphenylporphyrin as a building block, but we encountered a serious solubility problem at the stage of the porphyrin 8-mer. In order to circumvent the solubility problem, we employed the more soluble Zn^{II} 3,5-dioctyloxyphenylporphyrin **Z1** (here we denote the *meso*–*meso*-coupled Zn^{II} porphyrin arrays as **Zn** where *n* represents the number of porphyrins; Ar = 3,5-dioctyloxyphenyl). Chain elongation can be achieved quite simply by repeating the dimerization reactions from **Z1** to **Z2**, **Z2** to **Z4**, **Z4** to **Z8**, **Z8** to **Z16**, and **Z16** to **Z32**. The yields of the dimerization products were commonly 20–30% together with the recovery of starting materials (55–60%). Finally the coupling reaction of **Z32** afforded **Z64**, **Z96**, and **Z128** in yields of 25, 19, and 5%, respectively, all in a discrete state. The longest porphyrin array **Z128** isolated from the reaction of **Z32** was identical to the product obtained from the dimerization of **Z64**. During these repeated preparations we also isolated **Z3**, **Z5**, **Z7**, **Z10**, **Z12**, **Z20**, **Z24**, **Z40**, and **Z48**. The use of pure CHCl₃ as the solvent and strictly controlling the reaction temperature to 30 °C were crucial to avoid polymerization of the Zn^{II} porphyrin, which was enhanced particularly in the presence of small amounts (0.5–3%) of *N,N*-dimethylacetamide (DMA) or upon slight heating.^[9] Also equally important was the use of recycling GPC-HPLC for product separation. Figure 1 shows GPC-HPLC chromatographs of the reactions of **Z16** and **Z32**. The coupling products were nicely separated by GPC-HPLC in both cases owing to the large differences in molecular weight of the products. The molecular weights of these porphyrin arrays were determined by matrix-assisted laser desorption ionization (MALDI-TOF) mass spectrometry (Table 1).^[10]

Figure 2 shows the ¹H NMR spectra of **Z1**, **Z2**, **Z4**, **Z8**, **Z16**, **Z32**, **Z64**, and **Z128** taken in CDCl₃ at room temperature. To our surprise the longer arrays **Z64** and **Z128** display relatively well-resolved spectra similarly to those of the shorter arrays. The assignments were performed through comprehensive

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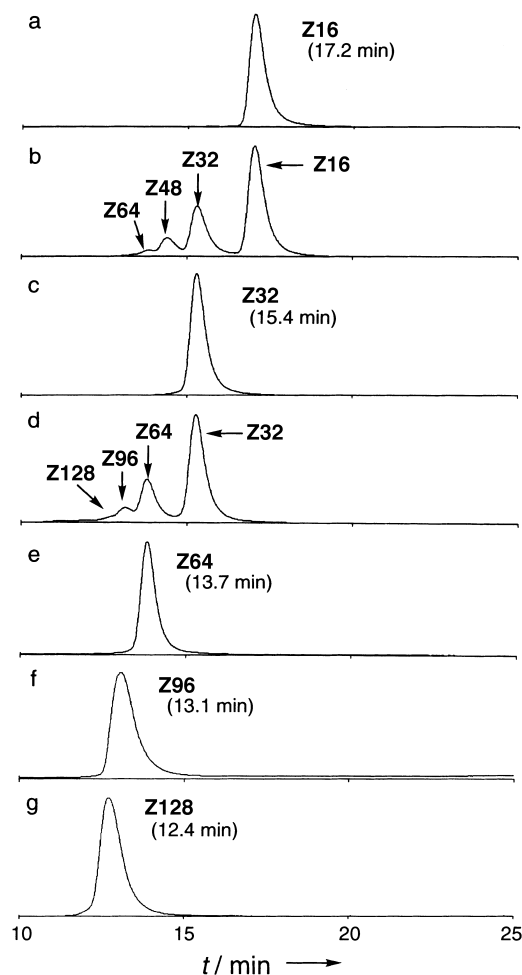


Figure 1. Analytical GPC-HPLC chromatograms of the reactions of **Z16** (a–c) and **Z32** (c–g): a) the starting **Z16**, b) the reaction mixture of **Z16** with 0.8 equiv AgPF_6 after 9 h, c) purified **Z32**, d) the reaction mixture of **Z32** with 2.0 equiv AgPF_6 after 9 h, e) purified **Z64**, f) purified **Z96**, and g) purified **Z128**.

Table 1. Molecular weights and retention times of the porphyrin arrays.

Compound number	Molecular formula	$M_c^{[a]}$	$M_o^{[b]}$	t_R [min] ^[c]
Z1	$\text{C}_{64}\text{H}_{84}\text{N}_4\text{O}_4\text{Zn}$	1037	1036	22.4
Z2	$\text{C}_{128}\text{H}_{166}\text{N}_8\text{O}_8\text{Zn}_2$	2075	2076	21.4
Z3	$\text{C}_{196}\text{H}_{248}\text{N}_{12}\text{O}_{12}\text{Zn}_3$	3114	3112	20.7
Z4	$\text{C}_{256}\text{H}_{330}\text{N}_{16}\text{O}_{16}\text{Zn}_4$	4146	4145	20.3
Z5	$\text{C}_{320}\text{H}_{412}\text{N}_{20}\text{O}_{20}\text{Zn}_5$	5186	5183	19.9
Z6	$\text{C}_{384}\text{H}_{494}\text{N}_{24}\text{O}_{24}\text{Zn}_6$	6222	6214	19.4
Z7	$\text{C}_{448}\text{H}_{576}\text{N}_{28}\text{O}_{28}\text{Zn}_7$	7259	7253	19.1
Z8	$\text{C}_{512}\text{H}_{658}\text{N}_{32}\text{O}_{32}\text{Zn}_8$	8296	8286	18.8
Z10	$\text{C}_{640}\text{H}_{822}\text{N}_{40}\text{O}_{40}\text{Zn}_{10}$	10369	10351	18.3
Z12	$\text{C}_{768}\text{H}_{986}\text{N}_{48}\text{O}_{48}\text{Zn}_{12}$	12443	12416	17.9
Z16	$\text{C}_{1024}\text{H}_{1314}\text{N}_{64}\text{O}_{64}\text{Zn}_{16}$	16590	16566	17.2
Z20	$\text{C}_{1280}\text{H}_{1642}\text{N}_{80}\text{O}_{80}\text{Zn}_{20}$	20736	20769	16.6
Z24	$\text{C}_{1536}\text{H}_{1970}\text{N}_{96}\text{O}_{96}\text{Zn}_{24}$	24884	24465	16.0
Z32	$\text{C}_{2048}\text{H}_{2626}\text{N}_{128}\text{O}_{128}\text{Zn}_{32}$	33178	33292	15.4
Z40	$\text{C}_{2560}\text{H}_{3282}\text{N}_{160}\text{O}_{160}\text{Zn}_{40}$	41470	41177	14.8
Z48	$\text{C}_{3072}\text{H}_{3938}\text{N}_{192}\text{O}_{192}\text{Zn}_{48}$	49764	49497	14.3
Z64	$\text{C}_{4096}\text{H}_{5250}\text{N}_{256}\text{O}_{256}\text{Zn}_{64}$	66350	66323	13.7
Z96	$\text{C}_{6144}\text{H}_{7874}\text{N}_{384}\text{O}_{384}\text{Zn}_{96}$	99527	99050	13.1
Z128	$\text{C}_{8192}\text{H}_{10498}\text{N}_{512}\text{O}_{512}\text{Zn}_{128}$	132702	130295	12.4

[a] Calculated molecular weight. [b] Molecular weight determined by MALDI-TOF mass spectrometry. [c] Retention time determined by GPC-HPLC analysis.

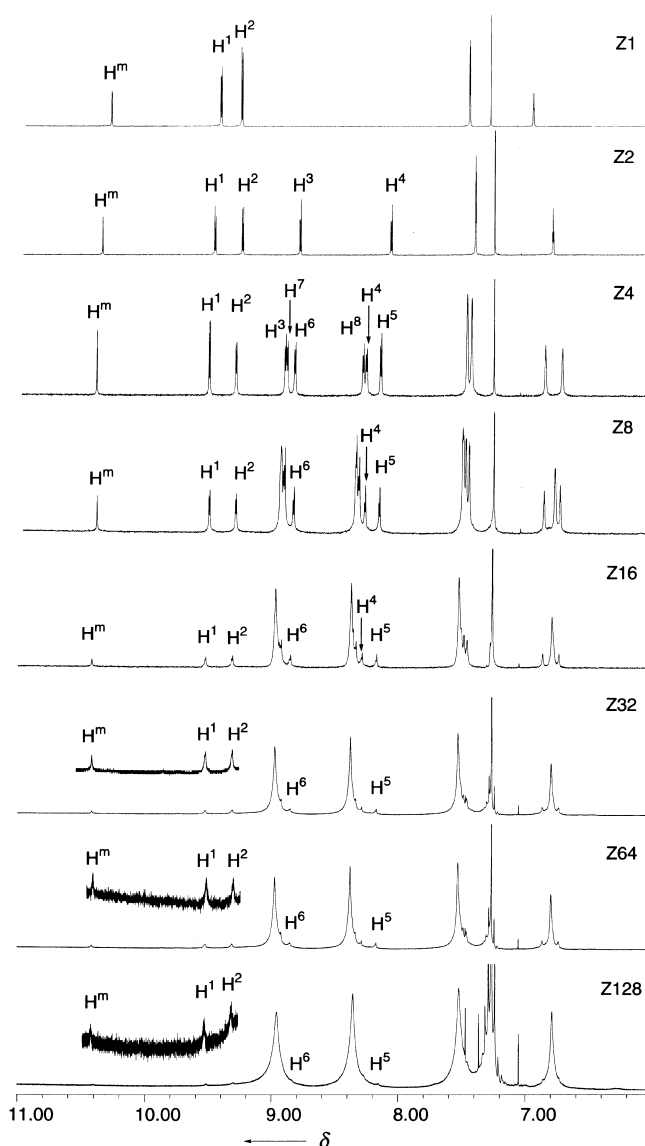


Figure 2. 500 MHz ^1H NMR spectra of the porphyrin arrays taken in CDCl_3 . Assignments are shown in the structure of **Z8**.

ROESY experiments (the designation of the protons is shown for **Z8**; Ar = 3,5-dioctyloxyphenyl). It is noteworthy that the *meso*-protons (H^m), outer β -protons (H^1 and H^2), and many inner β -protons (H^3 – H^8 , etc.) appear at nearly the same chemical shifts for all the arrays, which indicates that no significant aggregation of the arrays occurs under these conditions.

The absorption spectra normalized at approximately 413 nm are shown in Figure 3a. As reported previously,^[7, 8] the *meso*–*meso*-coupled arrays exhibit split Soret bands as a result of exciton coupling. As the number of porphyrins increases the low-energy Soret band is shifted to longer wavelength, while the high-energy Soret band remains at nearly the same wavelength (413 nm), which results in a progressive increase in the splitting energy. The systematic spectral changes can be explained by the simple point–dipole exciton coupling theory developed by Kasha et al.^[11] The Soret band of a Zn^{II} porphyrin has two perpendicular components B_x and B_y . In a simple monomer, they are

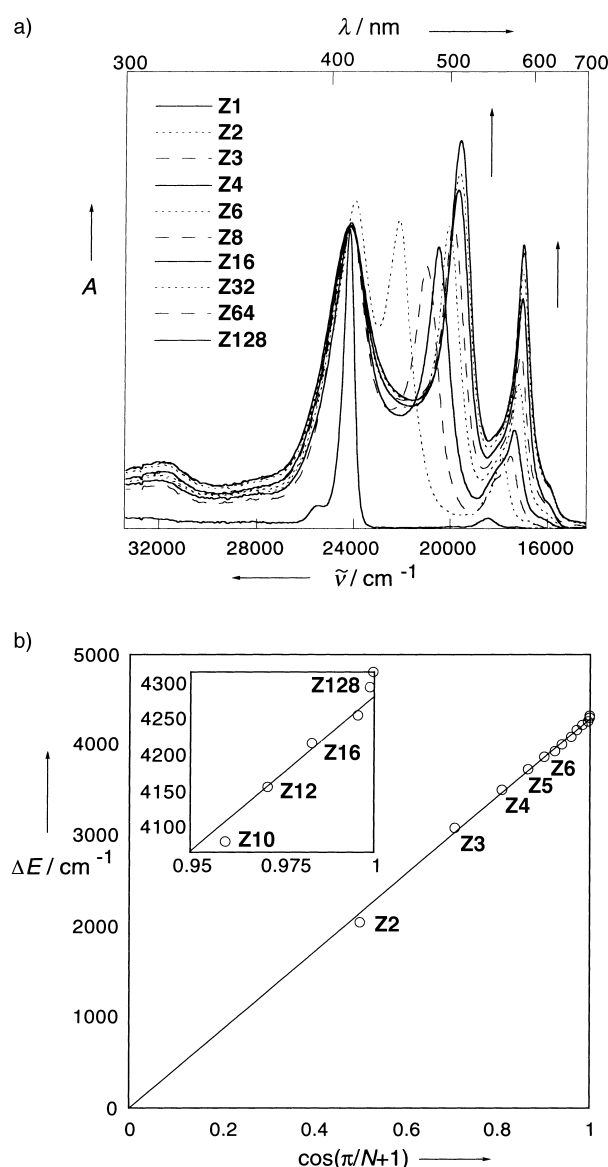
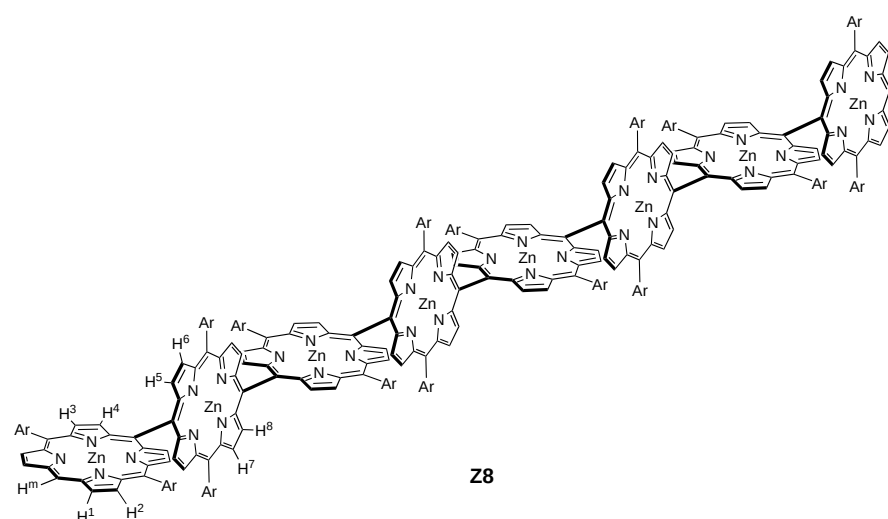


Figure 3. a) The UV/Vis absorption spectra of **Z1**–**Z4**, **Z6**, **Z8**, **Z16**, **Z32**, **Z64**, and **Z128** taken in THF. The absorbances at approximately 413 nm were normalized. b) Plot of ΔE versus $\cos[\pi/(N+1)]$.

degenerate, but in a porphyrin dimer they couple differently. In the case of **Z2**, only B_x transitions along the *meso*–*meso* bond are parallel, which results in a red shift of the band in the spectrum, while the other dipole interactions should be canceled out as a consequence of the perpendicular conformation between neighboring porphyrins. The unperturbed Soret transitions at about 413 nm for all the arrays suggest the averaged perpendicular conformation. This feature was also confirmed from the polarization fluorescence excitation spectra of the arrays, which exhibited different absorption transition dipole alignments for the long arrays and unperturbed Soret transitions.^[12] According to the

exciton-coupling theory the splitting energy (ΔE) for larger arrays should be given by Equation (1), where N represents the number of chromophores and ΔE_0 represents the splitting energy of neighboring porphyrins.^[11]

$$\Delta E = \Delta E_0 \cos[\pi/(N+1)] \quad (1)$$

When ΔE data were plotted according to Equation (1), we obtained a straight line with a slope of $E_0 = 4300 \text{ cm}^{-1}$ (Figure 3b).^[13] The linear relationship observed indicates that the spectral shapes of the absorption bands are actually influenced by the number of porphyrins and that the constituent porphyrins are regularly aligned in the same linear arrangement, though some deviation from linearity is observed for the longer arrays. On this basis, these arrays are believed to consist of repeating individual chromophores that have substantial electronic interactions in the ground state.

The exciton delocalization length (coherent length) has been the central issue in the natural light-harvesting systems^[14, 15] as well as J-aggregates of synthetic pigments.^[16] We thus attempted to estimate the coherent length of our arrays. The steady-state fluorescence spectra of the arrays are shown in Figure 4. Array **Z1** exhibits a two-peak emission (584 and 633 nm) characteristic of Zn^{II} porphyrin and **Z2** displays a red-shifted and broader fluorescence spectrum. The fluorescence spectra of the larger arrays (**Z3**–**Z128**) are observed in nearly the same region, with two bands around 15600 cm^{-1} (640 nm) and 15000 cm^{-1} (667 nm). Figure 5 shows the relative intensities of these two fluorescence bands are plotted against the number of porphyrins. The fluorescence quantum yields determined with respect to $\Phi_F = 0.03$ for Zn tetraphenylporphyrin (ZnTPP)^[17] increase up to **Z16** and then decrease as the number of porphyrins increases. By using the fluorescence lifetimes (τ_F) obtained by the time-correlated single-photon counting technique,^[18] we calculated the natural radiative rate (k_F) according to Equation (2).

$$k_F = \Phi_F / \tau_F \quad (2)$$

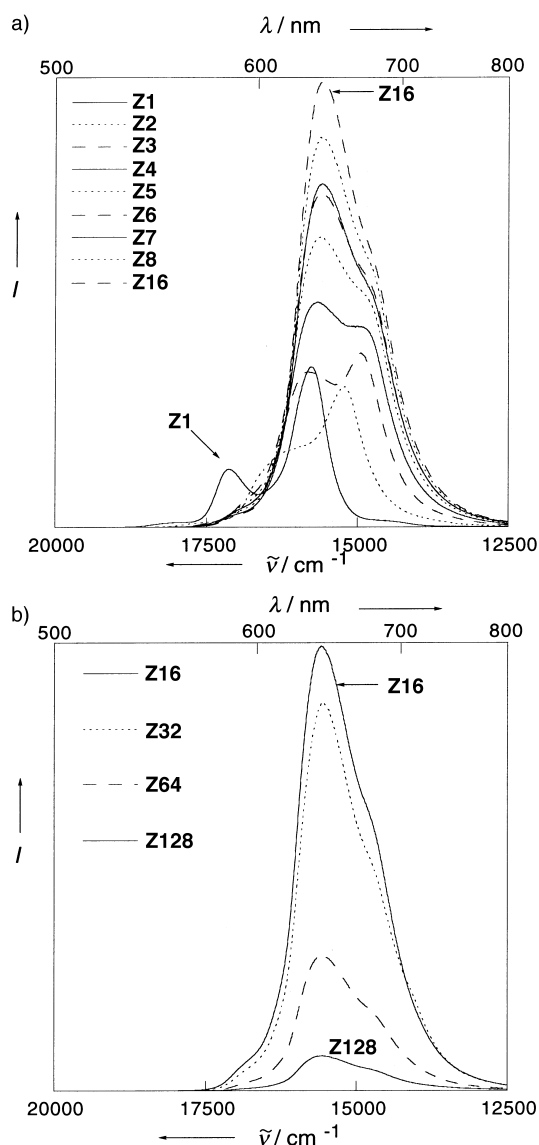


Figure 4. The fluorescence spectra of the arrays taken after excitation of a THF solution at 413 nm with the absorbance at 413 nm adjusted at 0.20. a) **Z1–Z8**, and **Z16**. b) **Z16**, **Z32**, **Z64**, and **Z128**.

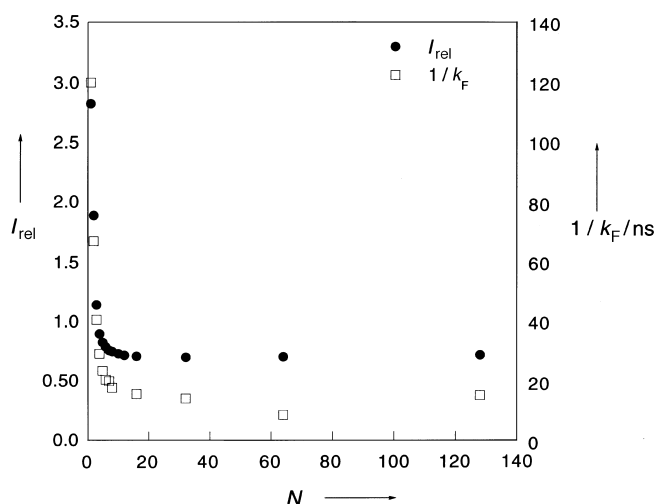


Figure 5. Plots of the inverse of k_F (□) and the relative fluorescence intensity (●) of 640 nm to 667 nm versus the number N of porphyrins.

Figure 5 also shows the plots of the inverse of k_F versus the number of porphyrins in the array. It is apparent that the radiative rate increases steadily from **Z1** to **Z6–Z8** and becomes rather constant for the arrays larger than **Z6–Z8**. The plot of the relative fluorescence intensity also reveals a similar trend, with the fluorescence shape becoming rather constant at **Z6–Z8**. Since the natural radiative rate is closely related to the exciton delocalization length,^[15] these results suggest a coherent length of 6–8 porphyrin units for S_1 states of these *meso–meso*-coupled Zn^{II} porphyrin arrays over which the exciton is delocalized.^[19]

In summary, the Ag^I -promoted *meso–meso*-coupling reaction has been demonstrated to be particularly effective for the preparation of extremely long, discrete porphyrin arrays. The regularly arranged arrays with ample electronic interactions will be promising as a light-harvesting photonic wire by the transmission of singlet excitation energy rapidly over the array. This possibility may be supported by observations that the extended linear conformation precludes the formation of any stacked energy sink and the electronic interactions are considerably enhanced in the excited states.

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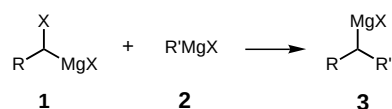
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 [18] The fluorescence decays of shorter arrays obey a single exponential function but those of longer arrays (**Z32**, **Z64**, and **Z128**) can be fit only with a biexponential function and thus we used the averaged lifetimes.
 [19] The estimated coherent length of 6–8 is in accordance with other extensive measurements including excitation-wavelength- and porphyrin-number-dependent resonance Raman and laser-intensity dependent decay.^[12]

Formation of Rearranged Grignard Reagents by Carbenoid-C-H Insertion**

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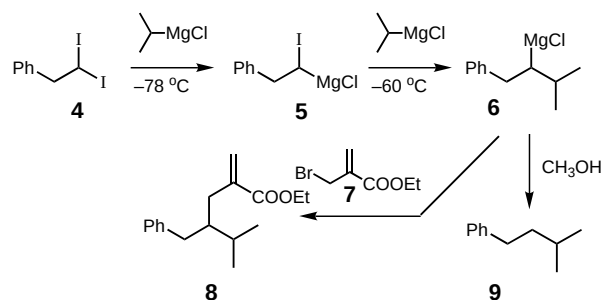
Grignard compounds are standard carbanion reagents of classical organic synthesis. Most methods to generate Grignard reagents rely on the reaction of metallic magnesium with alkyl or aryl halides and are, hence, prone to the intermediate generation of free radicals and to side reactions caused by the latter. There are only few routes to alkylmagnesium reagents that are devoid of this risk.^[1] One is the carbenoid-homologation reaction,^[2] in which an α -haloalkylmetal Grignard reagent **1** is treated with another organometallic reagent, for example, a second Grignard reagent **2**, to generate a new Grignard reagent **3** by C–C bond formation.



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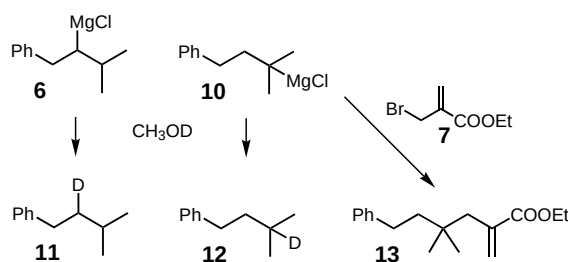
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During model studies on this reaction we made some unexpected findings, which we report here. At first, the reaction of the diiodoalkane **4** with 3 equivalents of isopropylmagnesium chloride proceeded uneventfully in THF: The first equivalent of the Grignard reagent generated over one hour^[3] the α -iodoalkylmagnesium compound **5**, which reacted slowly at -78°C and rapidly at temperatures up to -60°C with a further equivalent of isopropylmagnesium chloride to give the desired Grignard reagent **6**. The latter may be



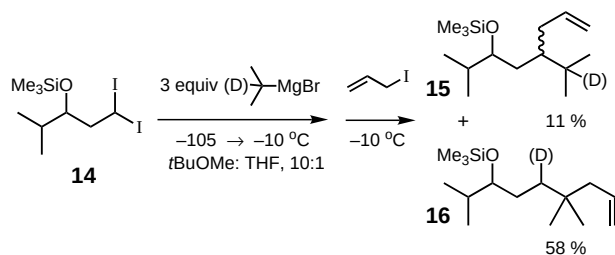
trapped, for example, by the α -bromomethylacrylate **7** at -90 to -78°C over 30 min to give the adduct **8** in 79% yield (accompanied by 12% of a side product later identified as **13**). Protonation of the Grignard reagent **6** with methanol led to the hydrocarbon **9** in 92% yield.

Trapping of **6** with CH_3OD was therefore expected to give the deuterated hydrocarbon **11**. Inspection of the product by ^2D -NMR spectroscopy revealed, however, the presence of the isotopomer **12** in about 10% yield. This pointed to the formation of the tertiary Grignard reagent **10** as the immediate precursor of **12**.



This “side reaction” surprisingly became the main process when the reaction was carried out in diisopropyl ether or in diethyl ether as solvent (see Table 1). When the overall reaction was carried out in diethyl ether the “rearranged” Grignard reagent **10** could indeed be trapped by the α -bromomethylacrylate **7** to give **13** in 79% yield alongside **8** in 12% yield.

Similar observations were made when the diiodo compound **14** was treated with three equivalents of isopropylmagnesium bromide followed by trapping with allyl iodide. While when the reaction was carried out in THF as solvent the product **15** predominated over **16** by 10:1 (55% yield), the “rearranged” product (**16**) was again the main product (58%



yield) using a solvent mixture rich in *tert*-butyl methyl ether (*t*BuOMe/THF = 10/1). When this reaction was repeated with $(\text{CH}_3)_2\text{CDMgBr}$ the deuterium atom could be shown by ^{13}C NMR spectroscopy to be located at the indicated position in **16**. At first glance, this looks like a rearrangement of a secondary Grignard reagent of the type **6** to a tertiary Grignard reagent of the type **10**, a process, in which the magnesium and a hydrogen atom swap places. This process, on the other hand, appeared highly unlikely since it is energetically unfavorable! Indeed, when a solution rich in secondary Grignard reagent **6** was generated in THF and the solvent was changed to diethyl ether the amount of the “rearranged” tertiary Grignard did not increase. Vice versa, when a solution rich in **10** was generated in diethyl ether, the Grignard reagent **10** was not converted to **6** on change of the solvent to THF. Therefore the Grignard reagents **6** and **10** do not interconvert, rather it appears that the Grignard reagents **6** and **10** are formed from the α -iodoalkyl Grignard reagent **5** and isopropylmagnesium chloride by two independent and concurring pathways, which show a different solvent dependence of the reaction rate.

Further experiments show that the tendency to form the “rearranged” Grignard reagent **10** depends not only on the solvent, but also on the nature of the halogen in the α -haloalkyl Grignard reagents **1** and on the nature of the second Grignard reagent **2** (Table 1). Changing the halogen in **1** from

Table 1. Formation of rearranged Grignard reagents.

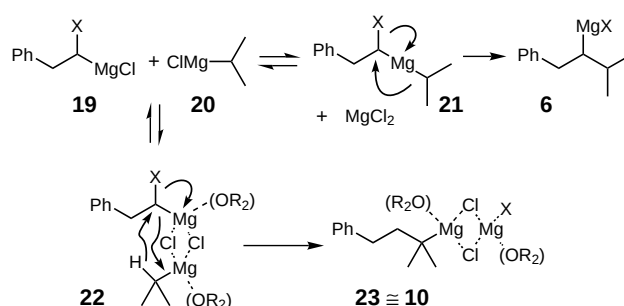
X	R ¹	Solvent	17:18 ^[a]	Yield [%] of deuterated hydrocarbons
I	Me	THF	90:10	92
		MeOCMe ₃	31:69	82
		Et ₂ O	25:75	91
		<i>i</i> Pr ₂ O	19:81	93
Br	Me	THF	18:82	85
		Et ₂ O	34:66	65
Cl	Me	THF	23:77	95
		Et ₂ O	35:65	81
I	H	THF	100:0	72
		Et ₂ O	100:0	71
Br	H	THF	89:11	74
		Et ₂ O	85:15	72
Cl	H	THF	97:3	76
		Et ₂ O	94:6	81

[a] Ratio determined by ^2H NMR spectroscopy after quenching with CH_3OD .

iodine to bromine or chlorine increases the amount of the unexpected product **12**. The more electrophilic (reactive) the carbenoid **1**, the higher the proportion of **12** that is formed. Regarding the Grignard reagent **2** used to initiate the reaction, the tendency to form the unexpected product **12** is clearly higher with isopropyl than with ethyl Grignard as the reaction partner.

For the formation of the “expected” Grignard reagent **6** a conventional mechanism can be proposed, for example similar to the reaction of α -haloalkyl-boronates with Grignard reagents,^[4] involving a dialkylmagnesium intermediate **21**. When the dialkylmagnesium species **21** was generated in diethyl ether from the α -iodoalkylmagnesium compound **5** and two equivalents of isopropyllithium,^[5] only the regular substitution product **6** was formed (70%).

It is therefore unlikely that the dialkylmagnesium compound **21** is a precursor of the unexpected product **12**. We rather propose that the tertiary Grignard product **10** is derived from a mixed aggregate **22** that is formed from the



two Grignard reagents **19** and **20**. The formation of such a halide-bridged aggregate should be favored in less coordinating solvents such as diethyl ether or *tert*-butyl methyl ether.^[1] Moreover, it is known that lithium carbenoids $\text{R}-\text{CHX}-\text{Li}$ are stabilized by THF, whereas they decompose much more rapidly in diethyl ether.^[6] The tendency to generate carbenes or at least the electrophilic reactivity of carbenoids is apparently increased in these nonpolar solvents. We therefore propose that the carbenoid moiety in **22** undergoes an intra-aggregate C–H insertion (direct or indirect) into the α -C–H bond of the second Grignard reagent **20** to generate the product aggregate **23**, that is the tertiary Grignard reagent **10**.

This proposed mechanism is in line with the finding that the tertiary α -C–H bond in the isopropyl Grignard reagent should be more reactive towards electrophilic attack than the secondary α -C–H bond in an ethyl Grignard reagent. Furthermore, it is in accord with the effect exerted by the halogen atom in the α -haloalkyl Grignard reagent **1**, that is the iodo compounds are less inclined to undergo carbenoid insertion reactions than the other halo compounds.

While these mechanistic speculations may be superseded by other explanations, we have nevertheless established that the carbenoid homologation reaction may be diverted to a novel process that leads to a “rearranged” Grignard reagent.

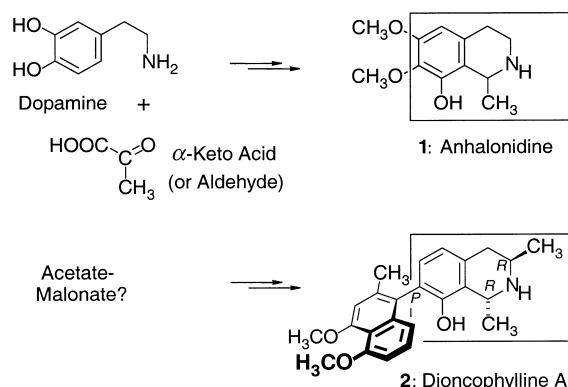
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A New Biosynthetic Pathway to Alkaloids in Plants: Acetogenic Isoquinolines**

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Tetrahydroisoquinoline alkaloids constitute a large family of more than 2500 known,^[1] mostly pharmacologically important, secondary plant metabolites—from simple 1-alkylisoquinolines like anhalonidine^[2] (**1**, Scheme 1) to complex



Scheme 1. Known biogenetic origin of tetrahydroisoquinolines such as anhalonidine (**1**) by Pictet–Spengler condensation^[2] and the proposed novel pathway to dioncophylline A (**2**).

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polycyclic benzyloisoquinolines like the analgesic morphine.^[3] Until now, it has been generally assumed that they are all derived from aromatic amino acids such as tyrosine through a common biosynthetic key step, the Pictet–Spengler condensation of 2-arylethylamines, like dopamine, with aldehydes (or α -keto acids). The ultimate structural diversity of isoquinolines found in nature^[4] originates from the variation of the aldehyde precursor and subsequent transformations of the tetrahydroisoquinoline initially formed.

The structures of dioncophylline A (**2**, Scheme 1) and other naphthylisoquinoline alkaloids,^[5] however, do not fit into this, hitherto, generally applicable biosynthetic scheme. In this paper, we report the discovery of a fundamentally different biosynthetic pathway to 1,2,3,4-tetrahydroisoquinoline alkaloids in higher plants; the entire carbon skeleton of dioncophylline A from *Triphyophyllum peltatum* (Dioncophyllaceae)^[6] is unambiguously demonstrated to be synthesized by an acetate–polymalonate pathway.

Hints at the chemical plausibility of an acetogenic origin for naphthylisoquinoline alkaloids had already been obtained from early biomimetic polyketide cyclization reactions,^[7] which had led to the efficient synthesis of both molecular parts from identical precursors and, thus, to first total syntheses of these compounds.^[6]

Direct-feeding experiments with addition of [^{14}C]- and [^{13}C]-labelled acetate and malonate to cultivated or wild plants of the Ancistrocladaceae family did not yield significant incorporation rates. Cell cultures of *Ancistrocladus heyneanus* (Ancistrocladaceae) produced large amounts of naphthoquinones and tetralones^[8] related to the naphthalene part of the alkaloids, but not the alkaloids themselves in sufficient quantities. More recently, we succeeded in establishing cell cultures of *T. peltatum* for the first time.^[9] These proved to be capable of forming both naphthoquinones and naphthylisoquinolines, predominantly dioncophylline A (**2**).

The presumed precursor acetate was fed to these cultures in [$^{13}\text{C}_2$]-labelled form. After a previously optimized incubation time, **2** was isolated and investigated by high-field NMR spectroscopy.^[10] The ^1H -decoupled ^{13}C NMR spectrum recorded on a 600 MHz system showed complex signal patterns. Due to overlapping signals and baseline noise obscuring the ^{13}C satellites, however, it was not possible to draw final conclusions. We addressed these problems by using the 2D INADEQUATE^[11] experiment for the identification of direct C–C connectivities.^[12] The signal-to-noise ratio was substantially improved by acquiring the data with a cryoprobe^[13] on a 500 MHz NMR spectrometer.

The obtained spectrum (Figure 1) only displays clear pairwise C–C correlations which originate from the acetate units incorporated intact, without bond cleavage, into dioncophylline A (**2**).^[14] Closer examination led to the conclusion that the entire carbon skeletons of both molecular halves of **2** are derived from acetate and that they exhibit an identical polyketide folding pattern with respect to the corresponding isocyclic rings. Furthermore, it is obvious that in both molecular halves decarboxylations occur at homologous positions, leaving the ultimate 1-methyl carbon atom and 3'-C.^[15] These findings unambiguously prove our biosynthetic postulate^[6] of the acetogenic origin of these alkaloids.

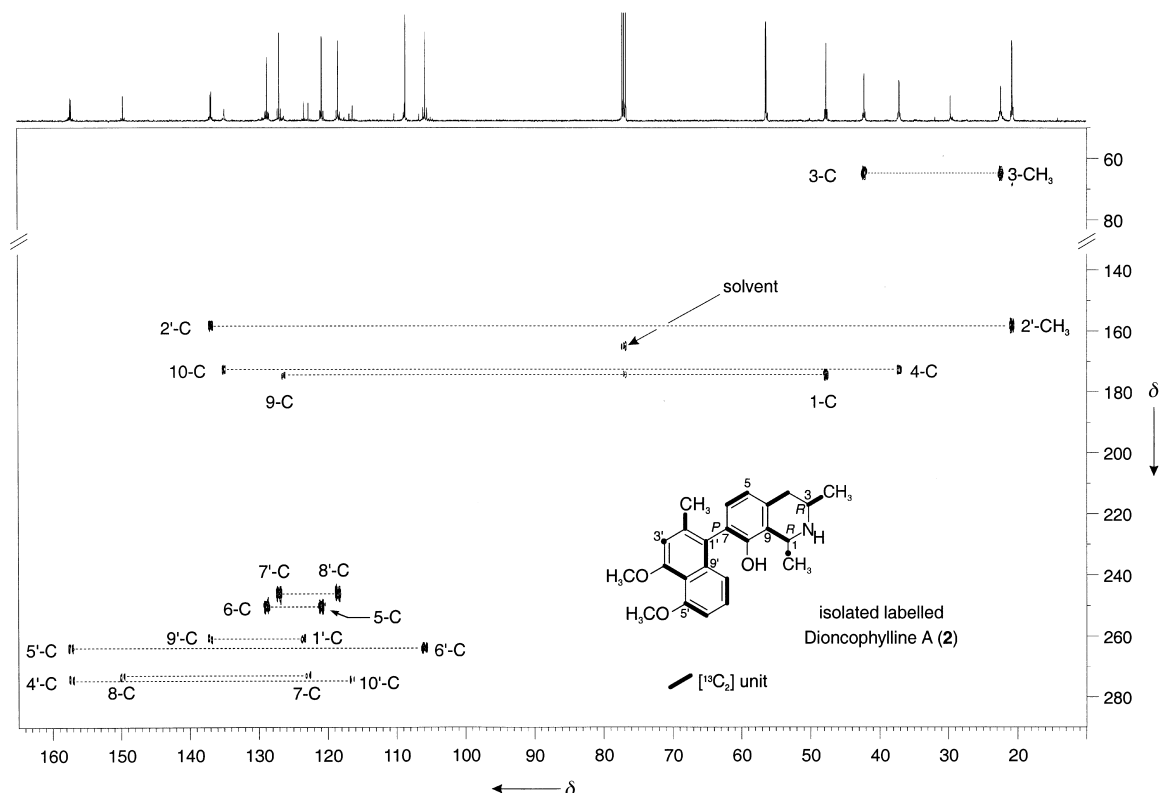
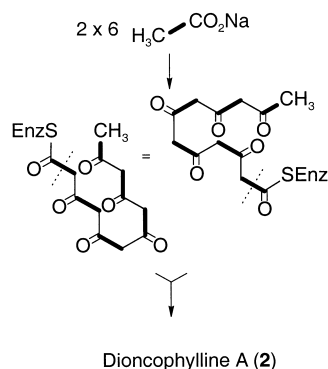


Figure 1. 2D-INADEQUATE NMR spectrum ($[\text{H}]\text{CHCl}_3$, 30 °C) of dioncophylline A (**2**) from bond-labeling experiments with sodium $[\text{C}_2]^{13}\text{C}$ acetate; the pairwise ^{13}C - ^{13}C correlations of incorporated $[\text{C}_2]^{13}\text{C}$ units are visible.

Accordingly, starting from six acetate units each, through identical intermediate β -polycarbonyl precursors, both the naphthalene and the isoquinoline halves of dioncophylline A are formed divergently by cyclization and, in the case of the isoquinoline moiety, nitrogen incorporation. The resulting two molecular halves are then joined together convergently to give the full alkaloid, dioncophylline A (Scheme 2). Further



Scheme 2. The new biosynthetic pathway to isoquinolines involving purely acetogenic precursors.

metabolic steps such as reductions, oxidations, or methylations result in the known multitude of structures,^[6] all based on common precursors.

The now successfully established biogenetic origin of the naphthylisoquinoline alkaloid dioncophylline A (**2**) by the acetate–polymalonate pathway paves the way for further studies on key steps of this interesting biosynthesis and the corresponding enzymes. It furthermore emphasizes the great

importance of polyketide metabolism,^[16] which is well-known in microorganisms,^[17] but has so far been underestimated in higher plants.

Experimental Section

$[1,2\text{-}^{13}\text{C}_2]\text{NaOAc}$ (99% isotopic enrichment) was purchased from Promochem (Wesel, Germany). A sterile-filtered solution of 0.05 M labelled NaOAc in distilled water, adjusted to pH 5.8, was used for the feeding experiments.

Callus cultures of *T. peltatum* were established as previously reported.^[9] For feeding experiments, they were cultivated on the same solid medium as used for general maintenance. During a period of two months, 250 mg of labelled NaOAc were administered in total to 832 mg (dry weight) of callus.

The lyophilized callus material was extracted with MeOH and 1% 0.1 N HCl (v/v). The methanolic extract was diluted with an equal amount of water, neutralized with NH_3 , and reextracted with CH_2Cl_2 . After evaporation of the solvent the organic phase was purified by reverse-phase MPLC (Lobar C-18, MeOH/ H_2O (70/30) and 0.1% TFA (v/v)), normal-phase MPLC (Lobar Si-60, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9/1) and 1% NEt_3 (v/v)), and preparative HPLC on a chiral-phase column (Chiralcel OD, hexane/*i*PrOH (8/2) and 1% NEt_3 (v/v)) to yield 1.7 mg dioncophylline A (**2**). Unlabelled **2**, (2.5 mg) isolated from root material of *T. peltatum*,^[18] was added to this sample. The final purification step by column chromatography (deactivated silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (80/1)) gave 4.0 mg of **2**.

For the assignment of the ^1H and ^{13}C signals, NMR spectra of an unlabelled sample in $[\text{H}]\text{CHCl}_3$ were recorded on a Bruker DMX600 spectrometer, using standard 1D as well as 2D HMQC, HMBC, COSY, TOCSY, and ROESY experiments. To establish C–C connectivities, a 2D INADEQUATE^[19] spectrum (optimized for $1J(^{13}\text{C},^{13}\text{C}) = 50$ Hz) of the labelled dioncophylline A was acquired at 125.7 MHz on a Bruker DRX500 spectrometer within a measurement time of 39 h. For this experiment, a prototype of a 5 mm ^{13}C cryoprobe with a ^1H decoupling coil was used with the coils and the preamplifier was cooled to 20 K.

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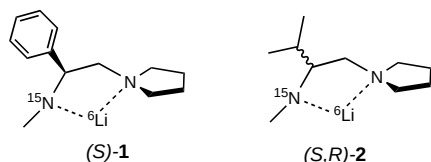
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⁶Li and ¹⁵N NMR Data as a Probe for the Influence of Solvent and Intramolecular Solvation on the Solution-State Structures of Chiral Lithium Amides**

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The molecular design of chiral auxiliaries and ligands for use in asymmetric synthesis is of outmost importance in modern organic chemistry. A large variety of chiral ligands has been designed for catalytic or stoichiometric chirality transfer in various reactions.^[1] Much effort has been put into ligand optimization since the degree of asymmetric induction obtained in a particular system is often critically dependent upon the structure of the organic ligand. Regardless of whether the ligand structure has been optimized through trial and error, through a combinatorial approach, or through computational modeling of a known transition-state structure, is it vital to know the exact composition and structure of the reagent in use. However, the reagent taking part in the reaction is not necessarily the simple monomeric ligand itself. More often, the reagent is composed of aggregated species.^[2] This is especially true for organometallic reagents.

Here we report multinuclear and multidimensional NMR spectroscopic studies on enantiomerically pure lithium (*S*)-methyl(1-phenyl-2-pyrrolidinoethyl)[¹⁵N]amide (**1**) and racemic, as well as the enantiomerically pure, lithium (1-isopropyl-2-pyrrolidinoethyl)methyl[¹⁵N]amide (**2**). These lithium amides display a large diversity of aggregation and coordination abilities.



The ⁶Li NMR spectrum of the chiral lithium amide **1**, in diethyl ether ([D₁₀]DEE) at –90 °C, displays three groups of signals (Figure 1a). Two triplets, appearing in a 1:1 ratio, are observed at δ = 2.15 (*J*_{Li,¹⁵N} = 3.7 Hz) and δ = 2.32 (*J*_{Li,¹⁵N} = 6.1). Another, less intense triplet is observed at δ = 1.63 (*J*_{Li,¹⁵N} = 4.5 Hz). The *T*₁ values and the linewidths of the signals at δ = 2.15 and 2.32 are notably different: 6.1 s and 0.98 Hz (δ = 2.15), 2.5 s and 2.33 Hz (δ = 2.32). These variations in *T*₁ and linewidth are in accordance with previous studies of chiral lithium amide dimers reporting a difference in solvation of the two lithium cations. The results indicate that the lithium ion at δ = 2.15 is tetracoordinated and the lithium ion at δ = 2.32 is tricoordinated.^[3] The splitting pattern

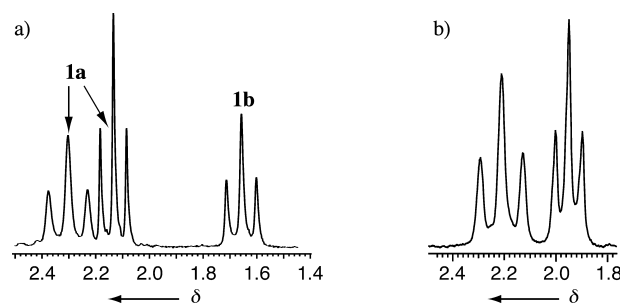
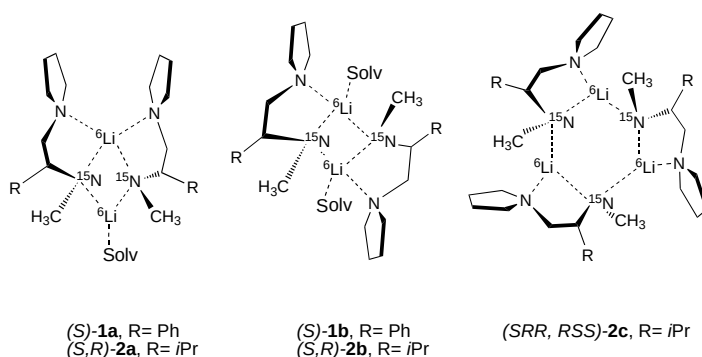


Figure 1. ⁶Li NMR spectra of a) **1** at *T* = –90 °C in [D₁₀]DEE, isotopic enrichment ¹⁵N [>98 %] and ⁶Li [95 %], b) **2** at *T* = –70 °C in [D₁₀]DEE, isotopic enrichment ¹⁵N [98 %] and ⁶Li [95 %].

and linewidths, together with a temperature-independent 1:1 integral ratio of the two lithium signals at δ = 2.15 and 2.32, reveal that these signals originate from an unsymmetrically solvated dimer, that is **1a** in Scheme 1. Unsymmetrically



Scheme 1. Structures of the lithium amides **1** and **2** identified in solution. Solv = solvating ligand.

solvated dimers containing two lithium atoms with different chemical surroundings and coordination have previously been described by us and by others.^[4] The triplet at δ = 1.63 was found to increase in intensity with decreasing temperature at the expense of the two other signals. The splitting pattern and the temperature dependence, together with the titration studies presented below, confirm that this resonance originates from a symmetrically solvated dimer, that is **1b** in Scheme 1.

The integrals of the ⁶Li NMR signals of **1**, at –90 °C in [D₁₀]DEE, show that the unsymmetrically coordinated dimer **1a** is slightly favored over the symmetrically coordinated dimer **1b** under these conditions (integral ratio 70:30; [**1**]_{tot} = 0.65 m). Upon addition of THF, the chemical shifts of the resonances originating from **1a** were unaffected; however, the lithium signal of **1b** shifted slightly downfield to about δ = 1.70 and increased in intensity. The intensity of the ⁶Li NMR signals of **1a** continued to decrease when more THF was added. When one equivalent of THF had been added, only the symmetrically coordinated dimer **1b** could be observed. Addition of TMEDA to this solvent mixture did not alter the ⁶Li NMR chemical shifts or ⁶Li,¹⁵N coupling constants to any extent—surprisingly, no monomers were formed. Titration of a solution of **1** in DEE at –90 °C with cyclohexene

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oxide, the substrate commonly used to evaluate the efficiency of chiral lithium amide bases in enantioselective rearrangement reactions, showed the same behavior as described above. Only the symmetrically solvated dimer was obtained with a signal around $\delta = 1.70$.

In contrast to **1**, the lithium amide **2** in $[D_{10}]DEE$ at $-70^\circ C$ displayed only two triplets at $\delta = 1.95$ ($J_{6Li,15N} = 3.8$ Hz) and $\delta = 2.22$ ($J_{6Li,15N} = 6.2$ Hz) (Figure 1b). These signals appeared in a 1:1 integral ratio at all temperatures studied. The ^{15}N NMR spectrum of **2** in $[D_{10}]DEE$ at $-70^\circ C$ showed only one signal at $\delta = -77.5$, indicating the presence of only one species in solution. Thus, this lithium amide forms an unsymmetrically coordinated dimer in DEE (**2a** in Scheme 1). The signal of the tetracoordinated lithium ion appears at $\delta = 1.95$ ($T_1 = 7.0$ s, linewidth 1.1 Hz), that of the tricoordinated ion at $\delta = 2.22$ ($T_1 = 2.0$ s, linewidth 1.7 Hz). The ^6Li resonances of the DEE-solvated **2a** decreased upon titration with THF, and a new ^6Li NMR signal appeared at $\delta = 1.61$ ($J_{6Li,15N} = 4.5$ Hz). This signal was assigned to a symmetrically solvated species (see above).

The ^6Li resonances for the unsymmetrically solvated dimer **2a** show similar differences in T_1 , linewidth, and coupling constants as for **1a**. The difference in coupling constants between the tetracoordinated lithium ions ($J_{6Li,15N} \approx 4$ Hz) and the tricoordinated lithium ions ($J_{6Li,15N} \approx 6$ Hz) is in good agreement with the results of computational studies by Kikuchi and co-workers.^[5] This suggests that not only the aggregation state, but also the coordination number at the lithium ion strongly affects the magnitude of the coupling constant. Collum and co-workers have also observed differences in the $^6Li,^{15}N$ coupling constants upon changes in solvation of symmetrically solvated lithium amides. However, these differences were assigned to a distortion in the dimer core and not to electronic factors.^[6] In the unsymmetrically solvated lithium amides reported here, we may directly probe the electronic effects associated with increased or decreased coordination at the lithium atom using $^6Li,^{15}N$ coupling constants. These data show that increased coordination at the lithium ion reduces the magnitude of the $^6Li,^{15}N$ coupling constant.

The $^6Li,^{15}N$ coupling constants of 4.5 Hz observed for the symmetrically coordinated dimers indicate that the lithium atoms in such dimers are mainly tetracoordinated. This conclusion is supported by the temperature dependence of the equilibrium between **1a** and **1b**, as well as the titration studies with THF; in other words, the more solvated dimers **1b** and **2b** are favored at low temperatures and in solvents with a high propensity to coordinate lithium.

A solution of **2** in $[D_8]$ toluene at $-70^\circ C$ displayed three ^6Li NMR signals of equal intensity at $\delta = 2.47$ ($J_{6Li,15N} = 5.9$ Hz), 2.60 ($J_{6Li,15N} = 5.5$ Hz), and 2.71 ($J_{6Li,15N} = 5.5$ Hz). The ^{15}N NMR spectrum of this solution also displayed three signals at $\delta = -68.5$, -74.0 , and -77.0 . These signals were assigned using a $^6Li,^{15}N$ -HMQC 2D NMR experiment (Figure 2a). The coupling pattern clearly indicates that the ^6Li NMR signals originate from one complex, as they show coupling to all ^{15}N nuclei. Consequently, **2** forms a cyclic trimer (**2c** in Scheme 1) in $[D_8]$ toluene. The magnitude of the $^6Li,^{15}N$ coupling constant was almost the same (ca. 5.5 Hz) for all lithium ions in the cyclic trimer. This suggests tricoordination; that is each

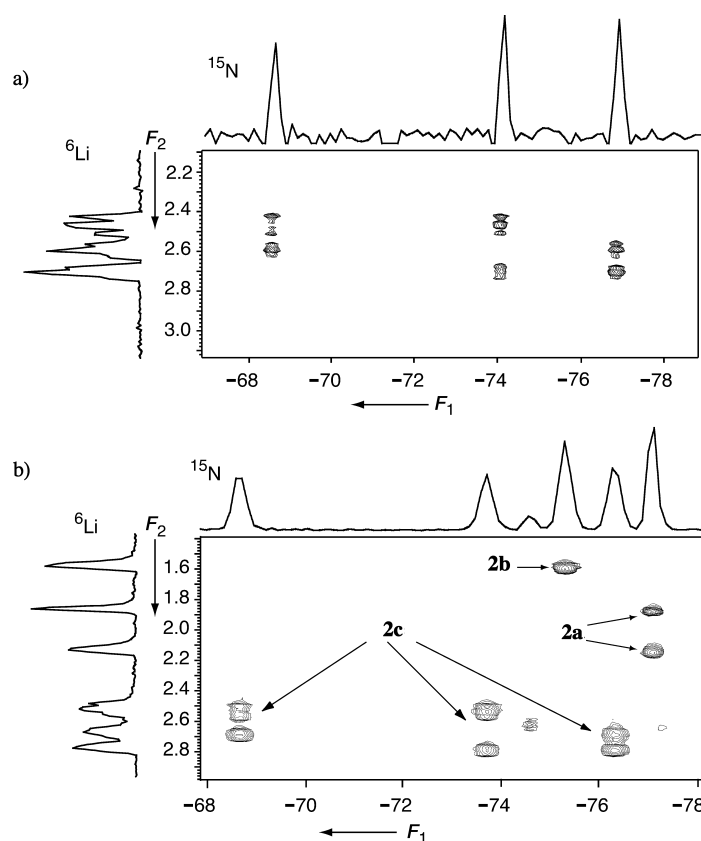


Figure 2. $^6Li,^{15}N$ -HMQC 2D NMR spectra of a) **2** at $-70^\circ C$ in $[D_8]$ toluene, b) **2** at $-70^\circ C$ in $[D_8]$ toluene, with 4.0 equiv of $[D_{10}]DEE$ and 0.6 equiv of $[D_8]THF$ added; the spectrum shows signals of the aggregates **2a**, **2b**, and **2c** present under these conditions.

pyrrolidine ring coordinates to one lithium atom. Thus, it appears that only one of the possible chelatomers^[7] exists under these conditions. Surprisingly, the chiral lithium amide **1** displayed only two main triplets in $[D_8]$ toluene at $-70^\circ C$. This unexpected result led us to investigate a sample of enantiomerically pure (*R*)-**2**, however *without* ^{15}N labeling.

As shown in Figure 3a, enantiomerically pure (*R*)-**2** also displays only two main signals, probably originating from an unsymmetrical dimer or from a homochiral trimeric species. However, addition of small amounts of the enantiomer (*S*)-**2** to this solution results in the immediate appearance of the three signals originally seen for racemic **2** (Figure 3b). Further addition of (*S*)-**2**, up to two equivalents, only results in more trimer formation. Addition of more than two equivalents of (*S*)-**2** again leads to the homochiral species (Figure 3c–e). Thus in $[D_8]$ toluene, these chiral lithium amides display a large tendency to form heterochiral trimers, that is cyclic trimers (*S,R,R*)-**2** or (*R,S,S*)-**2**. The nitrogen atoms in these aggregates are also stereogenic centers. They may undergo rapid inversion or, more likely, the configuration at the nitrogen centers could result from “transfer of chirality” induced by the proximal stereogenic carbon centers.^[8] Apparently, one of the possible diastereomers is more stable than the others since only one set of signals results.

A careful titration of the original toluene solution of racemic, ^{15}N -labeled **2** with DEE, THF, and finally TMEDA allowed us to simultaneously prepare all the previously

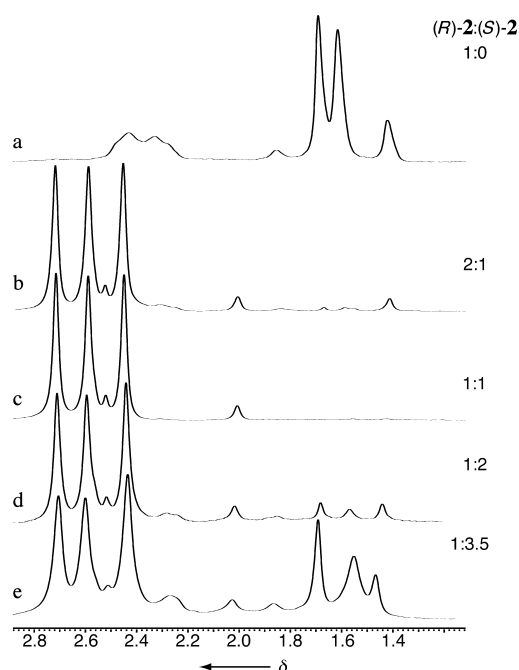


Figure 3. ^6Li NMR spectra of **2** without ^{15}N labeling at -90°C in $[\text{D}_8]\text{toluene}$. a) Enantiomerically pure (*R*)-**2**, b–e) (*R*)-**2** with increasing amounts of (*S*)-**2** added.

described species (Figure 4). The $^6\text{Li},^{15}\text{N}$ -HMQC 2D experiment of this mixture, prior to addition of TMEDA, is shown in Figure 2b. This spectrum clearly shows the presence of all species described in Scheme 1: the cyclic trimer **2c**, the symmetrically solvated dimer **2b**, and the unsymmetrically solvated dimer **2a**.

To conclude, the lithium amides **1** and **2** form trimers as well as symmetrically and unsymmetrically solvated dimers depending on the solvent used. Trimers are observed for **1** and **2** in hydrocarbon solvents like toluene, at least when an enantiomerically impure reagent is used. The lithium amide **2** forms unsymmetrically solvated dimers in DEE but symmetrically solvated dimers in THF, whereas the lithium amide **1** gives both unsymmetrically and symmetrically solvated dimers in DEE. The temperature-dependent equilibrium between **1a** and **1b** suggests that one additional molecule of DEE is required to form the symmetrically coordinated dimer **1b**. Thus, the different ability of **1** and **2** to form unsymmetrically solvated dimers in DEE is probably a result of the different spacial congestion by the isopropyl and the phenyl group.

Furthermore, we have demonstrated that the coordination number at the lithium ions in **1** and **2** can be monitored by NMR linewidths and T_1 values as well as by the magnitude of the $^6\text{Li},^{15}\text{N}$ coupling constants. We conclude that the magnitude of the coupling constant is a very sensitive tool for probing changes in the coordination number of lithium ions and, we believe, more reliable than T_1 or the linewidth for determining the coordination number of a lithium ion; T_1 relaxation rates are very sensitive to the aggregation state, whereas effects of aggregation upon $^6\text{Li},^{15}\text{N}$ coupling constants are less significant.^[9]

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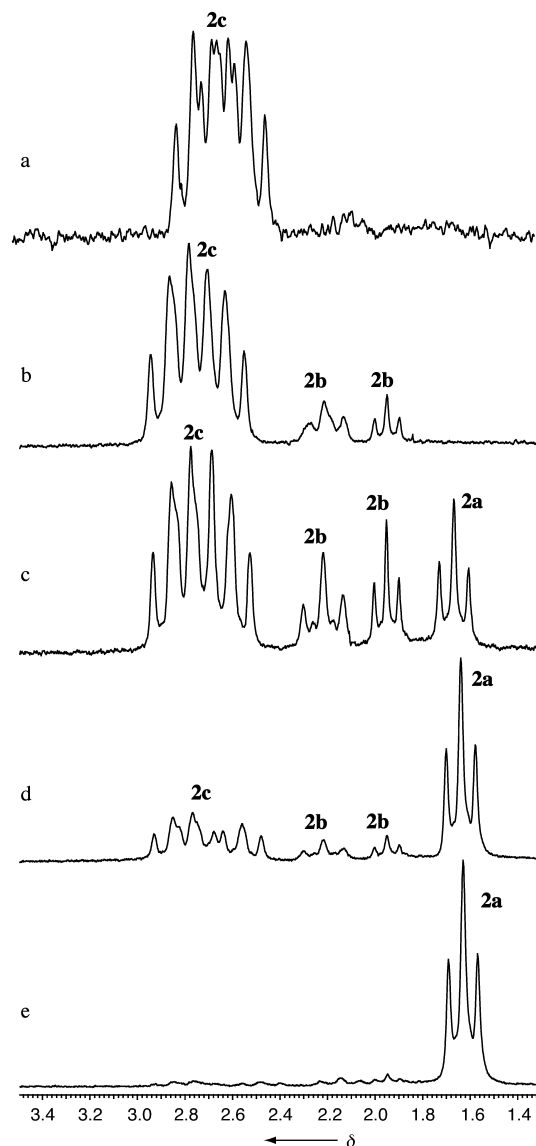


Figure 4. ^6Li NMR spectra of **2** at -70°C in a) $[\text{D}_8]\text{toluene}$ titrated with b) $[\text{D}_{10}]\text{DEE}$, c) $[\text{D}_8]\text{THF}$, and d, e) TMEDA.

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Low-Temperature, Catalyzed Growth of Indium Nitride Fibers from Azido-Indium Precursors**

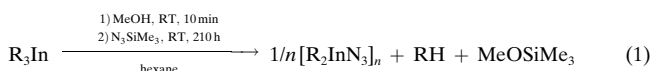
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We have achieved low-temperature synthesis and crystallization of InN through precursor design and crystal-growth catalysis. The group III nitrides GaN, InN, $\text{In}_n\text{Ga}_{1-n}\text{N}$, and $\text{Al}_n\text{Ga}_{1-n}\text{N}$ have recently acquired technological importance for blue/violet LED and laser diode applications.^[1] However, InN begins decomposing with loss of N_2 at low temperatures (427–550°C),^[2,3] which makes the growth of crystalline InN-containing materials challenging. We now report, to our knowledge, the lowest-temperature synthesis of crystalline

InN, at 203°C, well below its decomposition range. The work demonstrates that catalysis effectively lowers crystallization barriers, allowing InN synthesis under the mild conditions of conventional, solution-phase chemistry. Catalyzed growth may thus offer new strategies for the preparation of crystalline, thermally unstable materials.

Typical chemical vapor deposition (CVD)^[2] and melt^[3] syntheses of InN and InN-containing alloys require temperatures within or above the InN decomposition range, and proceed with difficulty. Recently, crystalline InN has been grown by single-source CVD at the surprisingly low temperature of 350°C.^[4] Efforts to prepare covalent, nonmolecular solids like InN at such low temperatures generally produce only amorphous products, due to the lack of active crystal-growth mechanisms.^[5] We now report that InN crystal growth is activated at 203°C by a process in which nanometer-sized metal droplets serve as catalytic sites for crystalline fiber formation. The growth process appears to be directly analogous to the previously reported solution–liquid–solid (SLS) mechanism (see below).^[5,6]

Azido precursor compounds have been previously used for CVD of group III nitrides;^[2a,b,4,7] we have developed appropriate analogs for low-temperature, solution-phase growth of InN. The precursors $i\text{Pr}_2\text{InN}_3$ (**1a**) and $t\text{Bu}_2\text{InN}_3$ (**1b**) were prepared in one-pot procedures from the corresponding trialkylindanes via dialkylmethoxyindane intermediates [Eq. (1); R = *i*Pr (**1a**), *t*Bu (**1b**); 85–95% yields]. The



products are effectively insoluble in hydrocarbons at room temperature, but dissolve in Lewis-basic solvents such as pyridine and acetone. In the solid state, **1a** and **1b** are isostructural, ladderlike polymers (Figure 1).^[8]

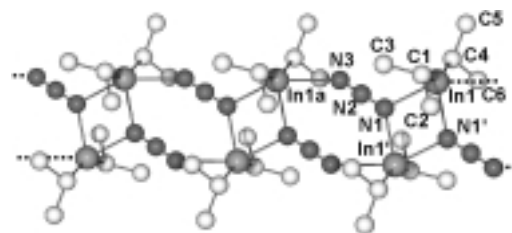


Figure 1. Ball-and-stick representation of the crystal structure of $[i\text{Pr}_2\text{InN}_3]_n$ (**1a**).^[8] Selected bond distances [Å] and angles [°]: In1–C1 2.166(2), In1–N1 2.296(2), In1–N1' 2.433(1), In1a–N3 2.655(3), N1–N2 1.194(2), N2–N3 1.138(3); C4–In1–C1 147.26(8), C1–In1–N1 105.21(7), C1–In1–N1' 99.07(7), In1–N1–In1' 107.66(6), C5–C4–In1 112.55(18), C4–In1–N1' 97.82(7), N1–In1–N1' 72.34(6), N3–N2–N1 178.9(2).

Reactions of the precursors **1a** or **1b** with the mild reductant^[9] 1,1-dimethylhydrazine, H_2NNMe_2 , produced crystalline InN. Thermolysis of **1a** in refluxing diisopropylbenzene (203°C) without H_2NNMe_2 gave a gray-black precipitate with a broad powder X-ray diffraction (XRD) pattern (Figure 2a), indicating an amorphous structure. However, thermolysis of **1a** under the same conditions but with H_2NNMe_2 gave black InN having an average XRD coherence length (approximate

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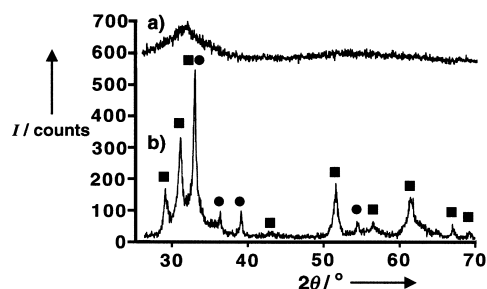
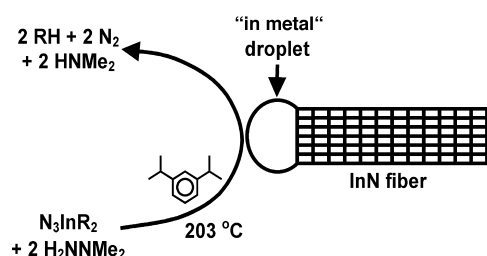


Figure 2. Powder X-ray diffraction patterns of InN formed by solution-state thermolysis of **1a** at 203 °C a) in the absence of and b) in the presence of 1,1-dimethylhydrazine. ■ InN reflections, ● In reflections.

crystallite dimension) of 18 nm (Figure 2b), as determined by the Scherrer equation.^[10] Refined lattice parameters $a = 3.551(6)$ Å and $b = 5.754(12)$ Å were extracted from the XRD data, which compared well to the literature values of $a = 3.537$ Å and $b = 5.704$ Å for InN.^[11] Reflections for metallic indium were also evident in the XRD pattern; elemental analysis established a InN:In molar ratio of 80:20. Thermolysis of **1b** with H_2NNMe_2 gave similar results. Thermolysis of **1b** without H_2NNMe_2 also gave crystalline InN, although the XRD coherence length was smaller (12 nm versus 7 nm, with and without H_2NNMe_2), and the crystallite morphologies of the two samples were very different (see below). Monitoring of the H_2NNMe_2 reactions by NMR and GC-MS, which detected the alkane and HNMe_2 byproducts, suggested the process shown in Scheme 1.



Scheme 1. Proposed solution-liquid-solid (SLS) growth mechanism for InN synthesis from the dialkyl(azido)indane precursors N_3InR_2 **1a** or **1b**.

Polycrystalline InN fibers, of diameters around 20 nm and lengths in the range 100–1000 nm, predominated transmission electron microscope (TEM) images of the materials produced in the H_2NNMe_2 reactions, as is evident in Figure 3. The fiber diameters were consistent with the coherence lengths from the XRD. No features suggestive of amorphous byproducts were found in the images. Each InN fiber exhibited a metallic indium droplet attached to its tip. Energy dispersive X-ray spectroscopy on the fiber in Figure 3c gave In:N ratios of 60(5):40(5) and 45(5):54(5) at two locations along the fiber length; only indium was detected in the droplet attached to the fiber tip (see arrow in Figure 3c; nitrogen detection limit was ca. 5%). In contrast, the dominant morphology obtained from thermolysis of **1b** without 1,1-dimethylhydrazine was small (< 10 nm), equidimensional InN nanocrystallites; only a very small fraction (< 2%) of stunted InN fibers with indium droplets was present.

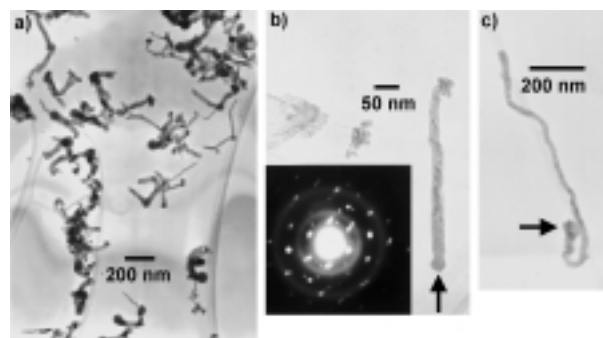


Figure 3. Representative TEM images of InN produced according to Scheme 1 show that fibrous morphologies are formed almost exclusively: a) and b) from precursor **1a**; c) from precursor **1b**. The inset in b) is an electron-diffraction pattern collected from the fiber in image b); the intense spots index to the (033) zone of InN and indicate the whisker axis aligns with the (210) direction of this primary crystal grain. Faint spots due to secondary, misaligned InN crystal grains are also evident. The rings in the inset index to reflections of randomly oriented metallic indium. Arrows indicate metallic indium droplets attached to InN fiber tips; many such droplets are also evident in image a).

A primary role of H_2NNMe_2 (Scheme 1) was as a stoichiometric hydrogen-atom donor to assist alkane elimination. Other potential hydrogen donors PhSH , Me_2NH , and PhNH_2 were not effective in promoting InN fiber growth. Note that the N–N bond in H_2NNMe_2 was cleaved and N_2 was generated, which is likely to provide a driving force for hydrogen donation. Because N_2 and/or N were generated, one must consider that 1,1-dimethylhydrazine may also serve as a nitrogen atom donor to InN. However, reactions of $t\text{Bu}_3\text{In}$ and H_2NNMe_2 under these conditions gave only amorphous products and metallic indium, strongly suggesting that H_2NNMe_2 was not a primary nitrogen donor. Thus, the N_3 ligand was implicated as the nitrogen source. 1,1-Dimethylhydrazine also induced metallic indium generation, discussed below.

Fiber growth was observed only when indium was also generated. Indium droplets were observed to form in the presence of H_2NNMe_2 , but not in the absence of a hydrogen-atom donating coreactant. Thus, H_2NNMe_2 is a sufficiently strong reductant^[9] to convert some of **1a** or **1b** to metallic indium under the reaction conditions. If indium formation had occurred in a process subsequent and unrelated to fiber growth, then the droplets would have been indiscriminately distributed on and about the fibers. Since the indium droplets were found *only* at the fiber tips and not in other configurations, these observations strongly suggest that the indium droplets formed in an adventitious side reaction preceding InN fiber growth,^[6b] and performed a catalytic role in fiber growth.

Metal droplets catalyze whisker and fiber growth under higher-temperature CVD conditions in a process known as the vapor-liquid-solid (VLS) mechanism.^[12] A solution-phase analog of the VLS mechanism, the SLS mechanism, was recently elucidated.^[6a] In both VLS and SLS growth, the catalytic droplets promote both precursor decomposition and crystal-lattice construction as shown in Scheme 1.^[5, 6] The principal requirements established for the catalytic metal is that it be molten under the reaction conditions and that at

least one constituent of the product has a limited solubility in it. Under our reaction conditions, indium metal (m.p. 157°C) is indeed molten and dissolves less than 0.001 atomic % nitrogen.^[13] The most obvious characteristics of the VLS^[12] and SLS^[5, 6] mechanisms—one-dimensional fiber or whisker growth morphologies and attached metal-catalyst particles—were clearly evident in the InN samples produced. Consequently, all the key indicators of the SLS growth mechanism were present.

The SLS growth process has been previously demonstrated for group III element phosphides and arsenides,^[5, 6] which are thermally stable at conventional growth temperatures. However, indium nitride is not. The SLS mechanism operates at very low temperatures in comparison to conventional materials-synthesis methods, presumably because it is catalytic and lowers energy barriers for both precursor decomposition and the interfacial steps required for nonmolecular crystal growth (crystal lattice assembly). SLS synthesis of other thermally unstable compounds and crystal structures should be possible.

Experimental Section

Compounds $t\text{Bu}_3\text{In}^{[14]}$ and $i\text{Pr}_3\text{In}^{[15]}$ were prepared according to the literature. The synthesis of $t\text{Bu}_3\text{InN}_3$ (**1b**) is described here; $i\text{Pr}_3\text{InN}_3$ (**1a**) was prepared similarly. MeOH (225 μL , 0.178 g, 5.55 mmol) was added to a dry, O_2 -free solution of $t\text{Bu}_3\text{In}$ (1.61 g, 5.63 mmol) in hexane (20 mL) at 25°C. The mixture was stirred for 10 min and then N_3SiMe_3 (0.800 mL, 0.660 g, 5.73 mmol) was added, instantly generating a fine white precipitate. The slurry was stirred for 2 h. Precursor **1b** was then collected by filtration and washed with 2×5 mL of hexane (yield: 1.39 g, 5.12 mmol, 91 %). Analytical data for **1b**: m.p. 210°C (dec.); elemental analysis calcd for $\text{C}_8\text{H}_{18}\text{InN}_3$: C 35.45, H 6.69, N 15.50; found: C 35.74, H 6.46, N 15.44; ^1H NMR ($[\text{D}_6]\text{acetone}$): $\delta = 1.29$ (s, 18H); IR (KBr): $\tilde{\nu} = 2087\text{ cm}^{-1}$ (asym. N_3). Analytical data for **1a**: m.p. 181°C; ^1H NMR ($[\text{D}_5]\text{pyridine}$): $\delta = 1.34$ (d, 12H, $J = 6.6\text{ Hz}$), 1.45 (m, 2H); IR (KBr): $\tilde{\nu} = 2075\text{ cm}^{-1}$ (asym. N_3). In a typical InN synthesis, **1a** or **1b** (1.5 mmol) and 1,1-dimethylhydrazine (3.0 mmol) were combined in dry, O_2 -free 1,3-diisopropylbenzene (10 mL) at 25°C. The mixture was stirred for 2 h, then heated to reflux at 203°C (in a sand bath under an efficient condenser) for 20 h. The resulting, air-stable InN/In product was collected by filtration and washed with 2×10 mL of pentane (yield: 90–95 %). Elemental analysis calcd for InN: C 0, H 0, N 10.88, In 89.13; found (from **1a**): C 1.87, H 0.12, N 7.31, In 84.1; found (from **1b**): C 2.05, H 0.19, N 8.39, In 81.6.

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Oxidation–Reduction and Photochemical Reactions of Metalladecaborane Clusters: The Interconversion of *hypercloso*- $[(\eta^6\text{-C}_6\text{Me}_6)\text{RuB}_9\text{H}_9]$ and *closo*- $[(\eta^6\text{-C}_6\text{Me}_6)\text{RuB}_9\text{H}_9]^{2-}$

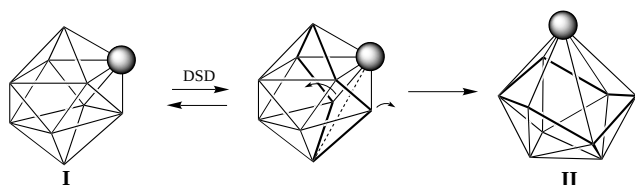
Ralf Littger, Ulrich Englisch, Karin Ruhlandt-Senge, and James T. Spencer*

The most common structure for a 10-vertex polyhedral cluster with a $2n+2$ skeletal electron count (where n is the number of vertices) is the bicapped square antiprism (**I**; Scheme 1).^[1] In one of the two known isomeric forms of these

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Scheme 1. Structural relationship between *closo*-2-metalladecaborane (**I**) and *hypercloso*-1-metalladecaborane (**II**) clusters.

closo-monometalladecaborane clusters, the metal center occupies a polar in the other a tropical position. However, the alternative *hypercloso* deltahedral structure **II** was observed for some monometalladecaborane clusters. The two structural types **I** and **II** are proposed to be related by a single diamond-square-diamond (DSD) process (Scheme 1).^[2c]

In our studies on the photochemistry of nonaborane organometallic derivatives of manganese, rhodium, and rhenium, we found that *nido*-borate **1**[−],^[3] upon irradiation, was converted in high yield into cage-unsubstituted *hypercloso*-borate **2**[−], with structure **II**, by the loss of two equivalents of molecular hydrogen (Figure 1).^[4] The synthesis and characterization of the two similar, albeit cage-substituted, *hypercloso* complexes **4** and **5** by different pathways was also reported previously.^[2] Underivatized compounds such as **2**[−] and [1-(η^6 -C₆Me₆)Rh-*hypercloso*-B₉H₉]^[5] provide insights into the relationship between structures **I** and **II** for cage-unsubstituted 10-vertex clusters.^[6, 7] Fundamental questions remain, however, concerning the description of compounds **2–5** as either *hypercloso* 2*n* electron systems^[6, 8] or as isomers of *closo* (*isocloso*) 2*n*+2 electron systems which apparently violate Wade's rules.^[7]

Extended Hückel MO calculations on the model system [(CO)₃RhB₉H₉]^{+/−}[(CO)₃RhB₉H₉]^{−/+} showed that the bicapped square antiprismatic structure **I** is preferred for the 2*n*+2 skeletal electron count (*closo*), while the C_{3v} structure **II** is favored for 2*n* electron systems (*hypercloso*).^[8] The only

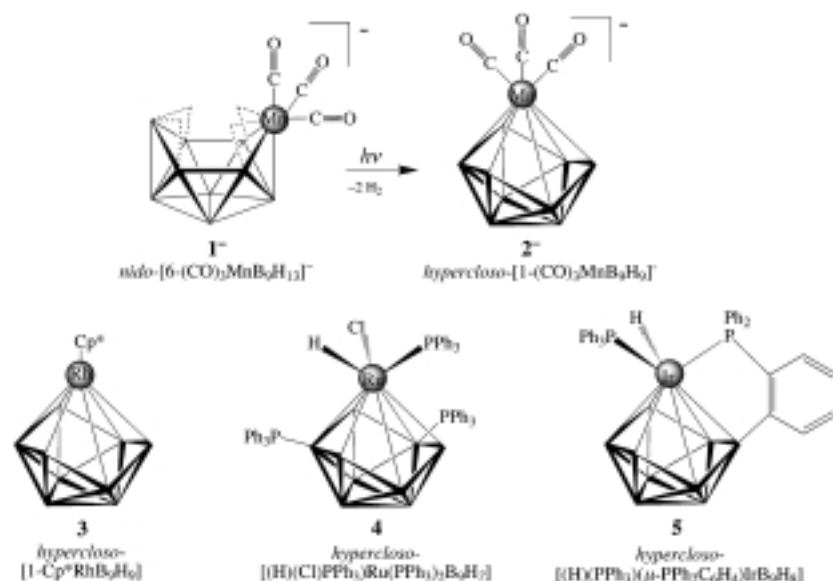
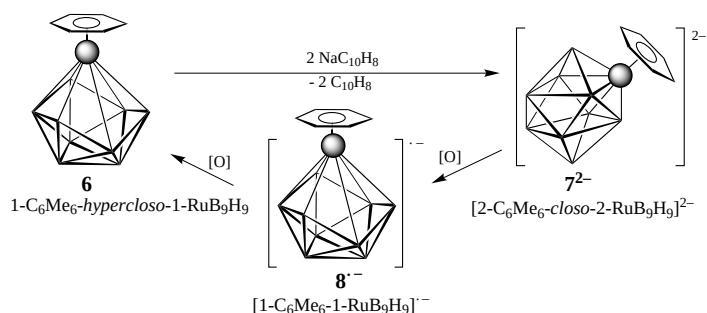


Figure 1. Photochemical generation of **2**[−] and structures of known *hypercloso*-nonaborane complexes (terminal hydrogen atoms omitted for clarity).

example of a *closo* to *hypercloso* conversion was reported for the reaction of **5** with CS₂ to yield the cage-substituted cluster [10-(PPh₃)-2,6:2,9-(μ -S₂CH)₂-2-(*o*- μ -PPh₂C₆H₄)-*closo*-2-IrB₉H₉][−].^[9] An equilibrium between the *hypercloso* and *closo* forms was proposed by Hawthorne et al. for the [6-(PET₃)₃-*closo*-6,2,3-RuC₂B₇H₉]/[1-(PET₃)₂-*hypercloso*-1,2,3-RuC₂B₇H₉] system.^[10] While a simple two-electron redox process should interconvert these structures, this has never been experimentally shown for underivatized metalladecaborane species.

Here we report the first reversible and quantitative interconversion of an unsubstituted *hypercloso*-metalladecaborane (C_{3v} structure **II**) into the corresponding bicapped square-antiprismatic *closo*-2-metalladecaborane (structure **I**) by a simple chemical redox process (Scheme 2). The starting material **6**^[5] was cleanly reduced by two equivalents of sodium



Scheme 2. Interconversion of **6** and **7**^{2−} and the proposed intermediate radical anion species **8**^{2−} (terminal hydrogen atoms omitted for clarity).

dihydronaphthylide to form the cage-unsubstituted complex **7**^{2−}. This dianion was isolated in 86 % yield as pale yellow, air-sensitive disodium salts [Na(dme)]₂[**7**] and [Na(thf)]₂[**7**]. These compounds were characterized by NMR spectroscopy^[11] and an X-ray crystal structure analysis for [Na(thf)]₂[**7**].

The intensities of the signals in the one-dimensional ¹¹B NMR spectrum and the ¹¹B–¹¹B COSY NMR correlations of **7**^{2−} were consistent with a bicapped square-antiprismatic structure in which the metal atom occupies a tropical 2-position (C_s). In addition, the NMR data of **7**^{2−} are very similar to those reported for structurally characterized *closo*-2-metalladecaborane clusters. The ¹¹B NMR spectrum of **7** consists of six proton-coupled doublets at δ = 35.1, −0.1, −6.1, −9.5, −26.3, and −27.9 in a 1:1:2:1:2:2 ratio. The ¹¹B chemical shift of the B(1) atom had the characteristic low-field value of δ = +35.1, as is often observed for low-connectivity cage vertices, especially when they are adjacent to a metal center.^[9]

The molecular structure of **7**^{2−}, determined by an X-ray single-crystal analysis of [Na(thf)]₂[**7**], was consistent with a structure based upon a 22-electron ten-vertex *closo*-RuB₉ cluster in which the metal atom occu-

pies a tropical site of a bicapped Archimedean square antiprism. The boron–boron and boron–metal distances of 7^{2-} are quite typical for polyhedral *closo*-metallaboranes. The B_9Ru cage consists of a distorted square antiprismatic framework, while the ruthenium atom displays a pseudooctahedral geometry. The dianion 7^{2-} is one of very few crystallographically characterized *closo*-metalladecaborane clusters and the only example that bears the same charge as the parent *closo*- $B_{10}H_{10}^{2-}$ cluster. The other related, albeit cage-substituted, examples are $[2-(C_5H_5)-3,10-(PMe_2Ph)_2-closo-2-RhB_9H_7]$,^[11] a subcluster in $[(C_5Me_5)RhB_9(SMe_2)H_{10}RhB_9H_7(SMe_2)]$,^[2a] $[2,2-(PH_3)_2-10-(PPh_3)-2-(o-\mu-PPh_2C_6H_4)-closo-2-IrB_9H_7]^-$,^[2b] and the analogous $[2,10-(PPh_3)_2-2,6;2,9-(\mu-S_2CH)_2-closo-2-IrB_9H_6]$ and $[10-(PPh_3)_2-2,6;2,9-(\mu-S_2CH)_2-2-(o-\mu-PPh_2C_6H_4)-closo-2-IrB_9H_6]^-$.^[9] Also related are heterometallic clusters such as *closo*- $[2,2,2-(PMe_3)_2H-2,1-IrSB_8H_8]$.^[12]

Interestingly, the relatively stable radical anion intermediate $8^{\cdot-}$ was observed on one-electron oxidation of 7^{2-} . The ^{11}B NMR spectrum of $8^{\cdot-}$ consists of proton-coupled doublets at $\delta = 90.0$, 21.5, and -14.2 in a 1:1:1 ratio. On the basis of spectroscopic data, $8^{\cdot-}$ is believed to have a C_{3v} structure related to that of the *hypercloso*-cluster **6**. The complex also displayed a broad, unresolved signal in the EPR spectrum. Further oxidation of $8^{\cdot-}$ converted it quantitatively into the *hypercloso*-complex **6**.

This is the first example of a chemically reversible *hypercloso*–*closo*–*hypercloso* redox interconversion and further represents the first *hypercloso*–*closo* process of a noncage substituted compound. We are currently exploring the structure and chemistry of the radical anion intermediate $8^{\cdot-}$.

Experimental Section

$[Na(dme)_2][7]$: Under a nitrogen atmosphere, a dry, degassed 0.10 M solution of sodium dihydronaphthylide in dimethoxyethane (DME) was slowly added to a suspension of **6**^[5] (130 mg, 0.35 mmol) in dry, degassed DME (20 mL) at $-40^\circ C$, during which time **6** completely dissolved. Addition of the reducing agent was stopped when its dark green color persisted in solution (approximately 7 mL). ^{11}B NMR spectroscopy showed complete conversion of **6** to $[Na(dme)_2][7]$. The solution was then slowly warmed to room temperature, during which time a precipitate was formed, and stored overnight at $15^\circ C$. The solid was filtered off, washed with 2 mL of dry, degassed DME and dried in vacuo. $[Na(dme)_2][7]$ was obtained as a pale yellow, air-sensitive solid (180 mg, 86.4% yield). The salt is only slightly soluble in THF and DME, more soluble in CH_3CN , and very soluble in water (degassed). ^{11}B NMR (96.3 MHz, CD_3CN): $\delta = 35.1$ (d, $^1J_{BH} = 137$ Hz, 1B, B(1)), -0.1 (d, $^1J_{BH} = 138$ Hz, 1B, B(10)), -6.1 (d, $^1J_{BH} = 107$ Hz, 2B, B(6,7)), -9.5 (d, $^1J_{BH} = 116$ Hz, 1B, B(4)), -26.3 (d, $^1J_{BH} = 110$ Hz, 2B, B(3,5)), -27.9 (d, $^1J_{BH} = 126$ Hz, 2B, B(8,9)); ^{11}B – ^{11}B COSY NMR correlations: 1 (4, 3, 5), 10 (6, 7, 8, 9), 6, 7 (10, 3, 5), 4 (1, 8, 9), 3, 5 (1, 6, 7), 8, 9 (10, 4); ^1H [^{11}B] NMR (300.1 MHz, CD_3CN): $\delta = 4.97$ (s, BH_{exo}), 3.47 (s, 8H, H_3COCH_2), 3.29 (s, 12H, H_3COCH_2), 1.88 (s, 18H, $C_6(CH_3)_6$), 3.01 (s, BH_{exo}), -0.99 (s, BH_{exo}), -1.16 (s, BH_{exo}). X-ray structure analysis of $[Na(thf)_2][7]$:^[13] Siemens SMART CCD diffractometer, MoK_α radiation, $C_{28}H_{39}B_9Na_2O_4Ru$ ($M_r = 704.09$), monoclinic, space group $P2_1/c$, $a = 19.2595(1)$, $b = 13.8368(1)$, $c = 13.7534(2)$ Å, $\beta = 90.244(1)^\circ$, $V = 3665.08(6)$ Å³, $Z = 4$, $\rho_{calcd} = 1.276$ g cm⁻³.

$[Na(thf)_2][7]$ was prepared in an identical fashion to $[Na(dme)_2][7]$, except that THF was substituted for DME. The THF-solvated compound was employed here since it was more soluble in ether solvents and gave superior crystals. Pale yellow crystals of $[Na(thf)_2][7]$ were grown from a saturated solution in THF/hexane at $-15^\circ C$. The crystals were removed from the Schlenk tube under a stream of inert gas and immediately covered with a layer of viscous hydrocarbon oil. A suitable crystal was selected under the

microscope, attached to a glass fiber and immediately placed in the low-temperature nitrogen stream of the diffractometer.^[13, 14] The data collection covered over a hemisphere of reciprocal space by a combination of three sets of exposures. Each exposure covered 0.3° in ω . Crystal decay was monitored by repeating the initial frames at the end of data collection and analyzing the duplicate reflections. No decay was observed. $T = 150(2)$ K, $2.12 \leq 2\theta \leq 56.40$; 29272 reflections measured, of which 8590 were unique and 7485 observed ($I > 2\sigma(I)$). Solution: direct methods. Full-matrix refinement on F_o^2 (SHELXL93); empirical absorption correction applied (SADABS). Four THF solvent molecules and the hydrogen atoms of the boron cage were located in the difference map and were refined with free coordinates and displacement parameters; 453 parameters, $wR_2 = 0.0731$ for all data, $R_1 = 0.0292$ ($I > 2\sigma(I)$). 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-138294. 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).

Oxidation of $[Na(dme)_2][7]$: Under an inert atmosphere, a sample of the complex in dry, degassed CD_3CN was exposed to the air by removal of the stopper for 1 s. The tube was then resealed. The initial pale yellow color of 7^{2-} turned red. The ^{11}B NMR spectrum of this solution showed, besides signals for **6** and 7^{2-} , three new signals at $\delta = 90.0$, 21.5, and -14.2 (1:1:1). Upon further exposure to the air, the ^{11}B NMR spectrum showed signals only for the completely oxidized complex **6** ($\delta = 94.6$, 27.9, and -12.3).

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Study of the Configuration Stability of the Carbon–Zinc Bond, Direct Measurement of Enantiomeric Ratios, and Tentative Assignment of the Absolute Configuration in Secondary Organozinc Halides**

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The determination of the stereochemical features of reactions involving organometallic species is a long-standing issue, which is still to be appropriately addressed. The study of the stereochemistry of products after a reaction of an organometallic species with a suitable electrophile has been the most commonly used strategy,^[1] and often the only possible approach.^[2] However the term “suitable electrophile” is intrinsically imprecise. The reaction of an organometallic reagent with an electrophile is always a possible source of interference when the goal is to study the organometallic compound itself. The degree of retention/inversion/loss of stereochemical integrity is highly specific for each organometallic–electrophile pair and is therefore not available in many cases. Different electrophiles can give rise to a different distribution of products with partial (or complete) retention (or inversion) of their configurations.^[3] Even though retention of configuration is the most common reaction pathway, the exact behavior of each particular system is, at the present time, simply unpredictable.^[4, 5]

Among the different organometallic reagents utilized in organic chemistry, organozinc compounds occupy an intermediate position in terms of the electronegativity of the metal and hence reactivity. As a general trend for organometallic reagents devoid of functionality, the more covalently bonded species are those which display high energy barriers to inversion of the carbon center (or topoisomerization barriers),^[6] and vice versa. Thus, activation energies for inversion in primary organometallic compounds of the type R_nM increase in the order $M = Li < Mg < Zn$, and the inversion of Al and Hg compounds is slow on the NMR time scale.^[7a,b] In general, NMR spectrometers are designed to operate between 200 °C and –100 °C or less, which allows the study of a wide range of systems with activation energies ranging from approximately 5 to 25 kcal mol^{–1}.^[8] When the experimental conditions permit the observation of coalescence the information obtained is very valuable.^[7a–c] However, in the cases in which the inversion is slow on the NMR time scale, the

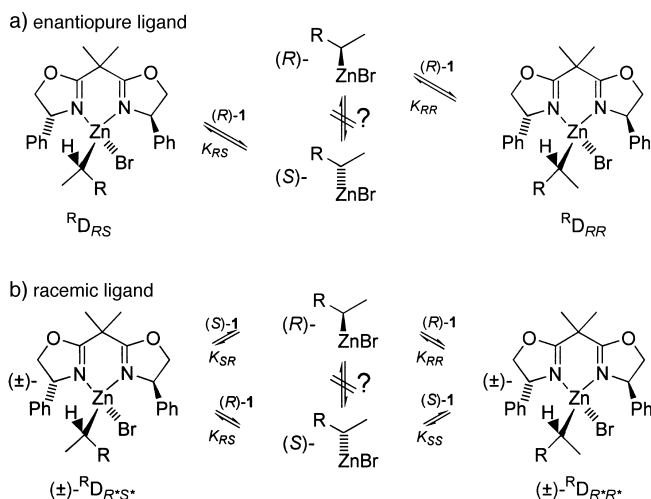
ultimate question about the preservation of the configurational integrity of the organometallic species on a macroscopic time scale remains unanswered. This is the case for most secondary organometallic compounds, which are, otherwise, far more interesting than primary ones for possible synthetic applications. It is not surprising that secondary organozinc bromides invert slowly under the conditions of the experiment (200 MHz ¹H NMR, 1.5 M in THF, 150 °C) since the inversion rates for secondary organolithium or Grignard reagents could not be obtained in this way.^[7fg] Stereocontrolled preparation and reaction of organozinc compounds is, however, a very active field of research. Diastereomeric cyclic secondary organozinc halides were prepared as mixtures of isomers that appear to be configurationally stable under the experimental reaction conditions used ($RZnI$; $E^+ = I_2$, Bu_3SnCl).^[9] The distribution of products was found to be dependent on the electrophile E^+ . Other cyclic and acyclic diastereomerically enriched mixed diorganozinc species have also been prepared and their stereochemistry studied after reaction with electrophiles ($RZnPr$; $E^+ = D_2O$, $CuCN \cdot 2LiBr$ + allyl bromide).^[10] In other studies, benzylic secondary organozinc halides were found to be labile at ambient temperature under the reported reaction conditions ($RZnX$; $E^+ = D_2O$).^[11]

We have attempted to observe the configuration of organozinc halides directly by NMR spectroscopy by employing chiral solvating agents.^[12, 13] After a survey of different chiral ligands (including mono- and diamines, protected diols and binaphthols, diphosphanes, boranes, and alkaloids) some chiral bis(oxazoline) ligands (box-ligands) were identified that displayed two sets of signals in the ¹H NMR spectrum of complexed 2-butylzinc bromide. This organozinc substrate was chosen for its simplicity, with the aim of developing a general method applicable to the measure of enantiomeric excesses in more complex systems. Several 2,2'-bis(oxazoline) and methylene, isopropylidene, and 2-indanylidene 2,2'-bis(oxazoline) ligands, all C_2 symmetrically substituted (for example, 4,4'-Ph₂, -Bn₂, -tBu₂, or 4,4',5,5'-Ph₄) were tested. Among them, (+)-2,2'-isopropylidene-bis((*R*)-4-phenyloxazoline) ((*R*)-**1** or (+)-**1**) gave the best results in terms of $\Delta\Delta\delta$ values. The dynamic behavior of organometallic compounds in solution involves inversion at the carbon atom bonded to the metal center, carbon–metal exchange, and ligand–metal coordination exchange. A fast dynamic equilibrium in solution, a product of these last two processes, generates surprisingly simple NMR spectra at room temperature (Scheme 1a, Figure 1a–c). The fact that two sets of signals occur, which correspond to the two enantiomers of the organozinc reagent (1:1 ratio), indicates by itself that inversion of configuration is slow on the NMR time scale. This observation has little significance from a synthetic point of view,^[14] and could be inferred from data in the literature.^[7] The search for a different test to determine the limits of the configurational robustness of the C–Zn bond in organozinc bromides was undertaken. Under fast equilibrium conditions two racemic reagents will generate only one set of signals, even though two pairs of diastereomers are formed. Indeed, the use of a racemic ligand afforded a single set of signals, as expected for a fast complexation equilibrium (Figure 1d and

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Scheme 1. Complexation equilibria of 2-butylzinc bromide ($R = \text{Et}$) or (1-phenylprop-2-yl)zinc bromide ($R = \text{Bn}$) with: a) (R)-**1**; b) (R S)-**1**. $K_{RS} = K_{SR} = K_{RS^*} = K_{RR} = K_{SS} = K_{RR^*} = K_{SS^*}$. The ratio of the concentration of both diastereomers, measured in the racemic system, is the equilibrium constant between these diastereomers (${}^R D_{RS} \rightleftharpoons {}^R D_{RR}$); ${}^R K = K_{RR}/K_{RS} = [{}^R D_{RR^*}]/[{}^R D_{RS^*}]$.

e). The equilibrium can be frozen at -50°C and two sets of signals, analogous to those observed using an enantiopure ligand but in the appropriate ratio, are again observed in the NMR spectrum (Figure 1 f). The ratio now corresponds to the thermodynamic equilibrium constant, which depends on the relative stabilities of both diastereomeric complexes, and is in general $\neq 1:1$. This ratio is ${}^{\text{Et}}K = K_{RR}/K_{RS} = 1.01:1$ for 2-butylzinc bromide at -50°C ($R = \text{ethyl}$, Scheme 1 b, Figure 1 f), which is right at the limit of the sensitivity of the integration.^[15]

Differences in steric hindrance between Me and Et are not large and results in the equilibrium constant for ${}^{\text{Et}}D_{RR} \rightleftharpoons {}^{\text{Et}}D_{RS}$ (${}^{\text{Et}}K$) being close to 1. Substitution of Et by Bn modifies the final equilibrium composition, with ${}^{\text{Bn}}K = 2.70$ ($R = \text{benzyl}$, Scheme 1, Figure 2 f) at -30°C . The rate of inversion of the secondary C-Zn bond could be measured using this last organozinc bromide. The spectrum of (1-phenylprop-2-yl)zinc bromide in the presence of one equivalent of (R)-**1** showed two sets of signals in a 1:1 ratio (Figure 2 b). This is not a steady state. The rate at which the composition of the diastereomeric/enantiomeric mixture will spontaneously evolve from 1:1 to approximately 2.70:1, that is reach the thermodynamic equilibrium, will depend on the rate of inversion of the C-Zn bond.^[16] In other words, the presence of a chiral ligand shifts the composition of the initial racemic mixture of the organozinc bromide from 1:1 to another value corresponding to the new thermodynamic equilibrium in that chiral medium. A good estimate of this new equilibrium is obtainable using the racemic ligand approach. From the rate laws of interconversion of both enantiomers, represented by Equation (a), the equations that describe the exponential approach to the final equilibrium can be easily deduced [Eqs. (b) and (c)]. In the simplest approximation to the

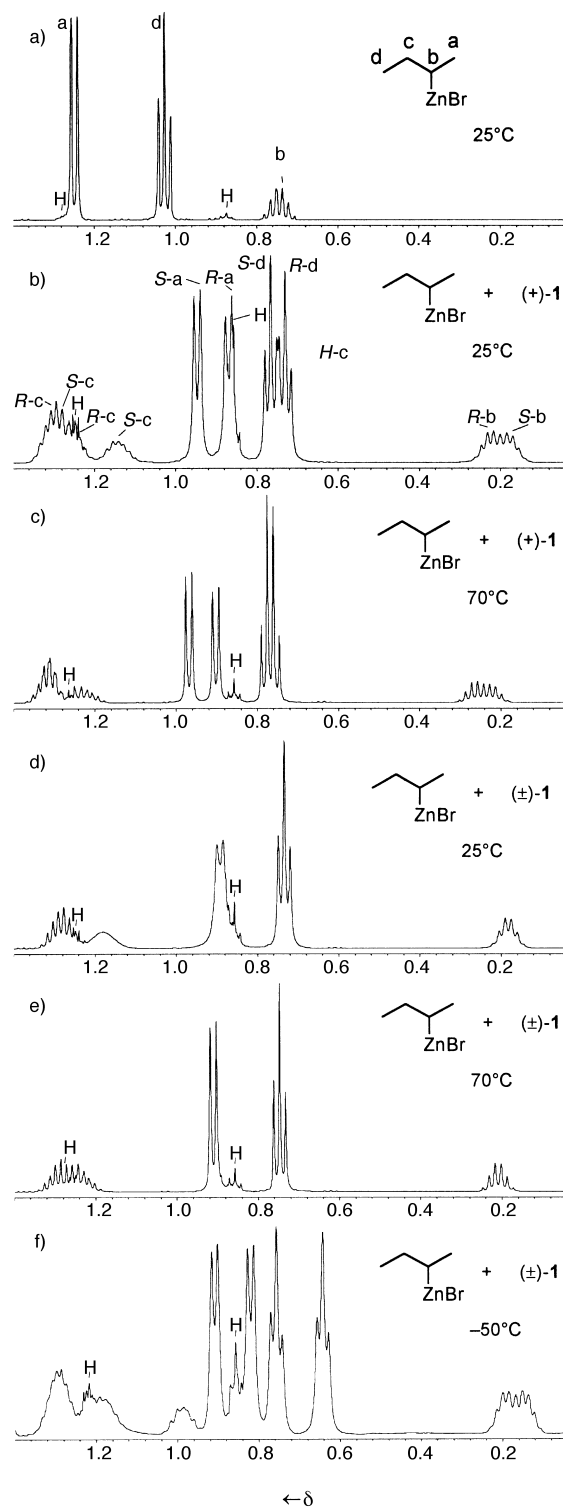


Figure 1. Partial 500 MHz ${}^1\text{H}$ NMR spectra of 2-butylzinc bromide (a) in the presence of one equivalent of (R)-**1** (b, c) or its racemic counterpart (RS)-**1** (d–f) at several temperatures. The butane side product is represented by H. The peaks of the methylene protons c are not shown in spectrum (a) because they overlap with the solvent peak. Assignments of the absolute configurations were made on the basis of predicted anisotropic effects, and are illustrated in spectrum (b).

$$(1 + K)[D_{RR}] - 1 = \frac{K - 1}{2} e^{-(k_1 + k_{-1})t} \quad (\text{b})$$

$$K - (1 + K)[D_{RS}] = \frac{K - 1}{2} e^{-(k_1 + k_{-1})t} \quad (\text{c})$$

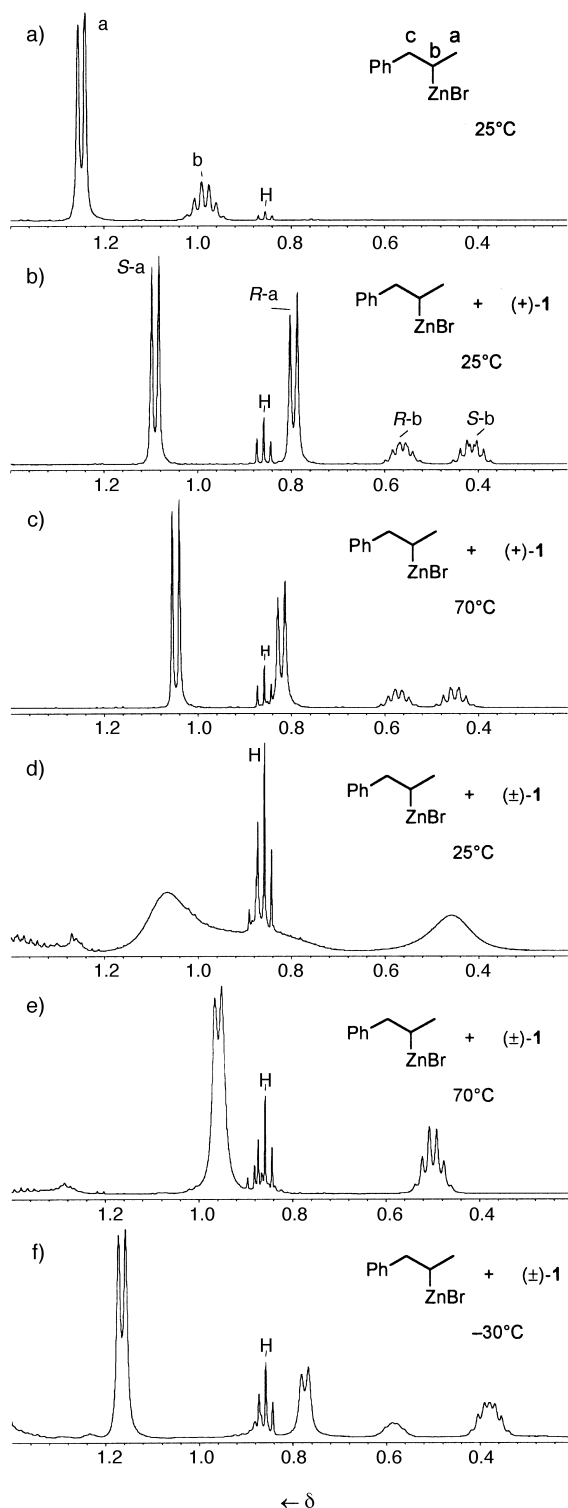


Figure 2. Partial 500 MHz ^1H NMR spectra of (1-phenylprop-2-yl)zinc bromide (a) in the presence of one equivalent of (*R*)-**1** (b, c) or (*RS*)-**1** (d–f) at several temperatures. The 1-phenylpropane side product is represented by H. Methylene protons (c: 2.75–2.95 (2H, m, CH_2) in spectrum (a) are not shown. Assignments of the absolute configurations were made on the basis of both free-energy criteria and predicted anisotropic effects, and are illustrated in spectrum (b).

mechanism of inversion, a monomolecular transition state is assumed.^[7a] D corresponds to the averaged signal of the actual diastereomer and the free organozinc reagent in fast equilibrium, as observed by NMR spectroscopy. A sample of

$\text{BnCH}(\text{ZnBr})\text{Me} + (\text{R})\text{-1}$ was monitored by ^1H NMR spectroscopy over nine days. The evolution of both diastereomers was slow, but perceptible, as they grew towards the predicted ratio ($^{\text{Bn}}K$ varies only slightly with temperature).^[16] The results, plotted as a function of Equations (b) or (c) are represented in Figure 3. From the slope, $k_1 + k_{-1} = 0.00024 \text{ h}^{-1}$, a half-life of $t_{1/2} = 4.0$ months is obtained for

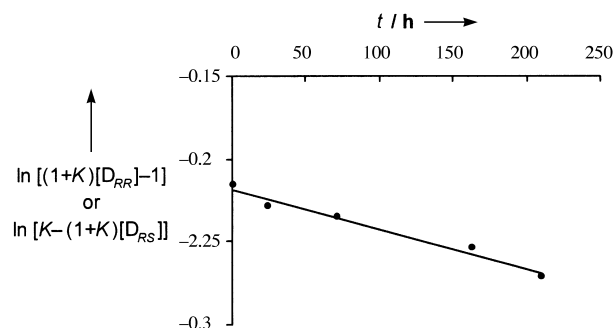


Figure 3. Kinetic plot showing the evolution of a mixture of ($\pm$)- $\text{PhCH}_2\text{CH}(\text{ZnBr})\text{CH}_3 + (\text{R})\text{-1}$ towards the thermodynamic equilibrium, according to Equations (b) and (c). Slope: $k_1 + k_{-1} = 2.42 \times 10^{-4} \text{ h}^{-1}$, ordinate origin: $\ln[(K-1)/2] = -0.22$, correlation coefficient = 0.98. The concentration of both diastereomers was obtained by averaging the Me and $\alpha\text{-H}$ signals. An approximately constant amount of phenylpropene was corrected for by normalizing the overall $\text{D}_{\text{RR}} + \text{D}_{\text{RS}}$ concentration to 1. The lifetime of the inversion process at 25°C is 4130 h.

the inversion of the secondary carbon atom. This value corresponds to a free energy of activation $\Delta G^\ddagger = 27.2 \text{ kcal mol}^{-1}$ at 25°C . The data collected represents only the early stages of the system in reaching equilibrium. However, it also carries information about the final equilibrium. From the ordinate value at $t = 0$, we can also obtain a perhaps better determination of $^{\text{Bn}}K$ at room temperature as $^{\text{Bn}}K_{25^\circ\text{C}} = 2.60$.

The scenario depicted so far requires an empirical model to perform NMR assignments of the absolute configuration in these organometallic compounds. Unfortunately no NOE could be observed at low temperature in this dynamic system, and other NMR experiments were also unsuccessful. Both inductive effects from the chelated Zn center and anisotropic effects from the phenyl group in the ligand explain the large upfield shifts observed. However, only the latter is responsible for the differences in the chemical shifts between the two diastereomers. The intrinsic geometric character of the anisotropic effect may certainly render some structural insights, provided that previous knowledge about the conformations involved is available. Conformational analyses on $^{\text{Et}}\text{D}$ and $^{\text{Bn}}\text{D}$ were best accomplished using PM3 semiempirical calculations.^[17] These not only provided a reliable picture of the conformational equilibrium for each diastereomer, but also an excellent way to analyze differences in the energies in these organometallic complexes. The ligand (*R*)-**1** was used in all the analyses. Most of the structure in the complex is rigid, which limits considerably the number of degrees of freedom in the final conformational equilibrium and hence facilitates the analysis.

A rather simple scenario is found, which describes the geometry of the final set of conformers on the basis of two

main characteristics: a) the metallacyclic subunit is slightly twisted from a flat conformation, with an approximately tetrahedral Zn atom. For (*R*)-**1**, only the (*P*)-twist (or (*R*)-twist, since the twist is a chiral conformation) is an energy minimum; b) three main conformations are observed, which correspond to the three rotamers of the α -carbon atom relative to the zinc center: C_H (H *anti* to Br, as in Scheme 1), C_{Me} (Me *anti* to Br), and C_{Et/Bn} (Et or Bn *anti* to Br; Figure 4,

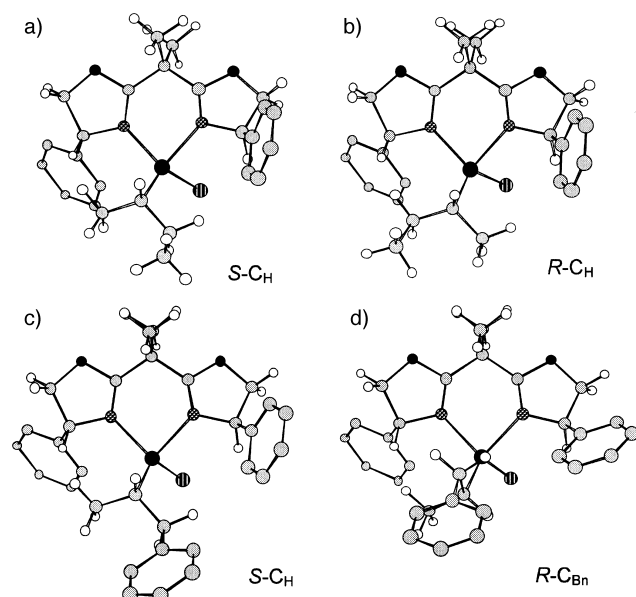


Figure 4. Major conformers of each diastereomer as obtained from PM3 calculations. Hydrogen atoms on the phenyl rings are omitted for clarity. Other conformations in Table 2 can be approximated by rotation of the α -C–Zn bond. Conformations without an α -hydrogen atom on the phenyl side are always high energy and other metallacyclic conformations may occur. In structure (d) the natural orientation of the phenyl ring is altered by the presence of the benzyl group.

Table 1). The conformations of the remaining bonds are mostly trivial. In general, these geometric patterns match those actually observed in the crystal structure of [(*S*)-**1**·ZnCl₂].^[18] Table 1 shows the thermodynamic description of the complexation process, as obtained from PM3 calculations. We include enthalpies $\Delta H^\circ = \sum_i n_i \Delta H_{i, \text{form}}^\circ$, and from them, calculated populations (n), entropies of mixing^[19] ($S_{\text{mix}} = -R \sum_i n_i \ln n_i$), free energy ($\Delta G^\circ = \Delta H^\circ - T \Delta S^\circ$), and predicted $K_{25^\circ\text{C}}$ for the given equilibrium. The assignment of the NMR signals for R = Bn to nuclei in the *R* and *S* enantiomers was made on the basis of both free energy criteria and expected anisotropic effects. Energetic criteria are not applicable to 2-butylzinc bromide since the ratio of signals falls within the experimental error of the integration. On the other hand, anisotropic effects are more reliable for 2-butylzinc bromide since interferences from an intramolecular aromatic group (Bn) are not present. In general, the shielding provoked by the (*R*)-5-phenyl substituent, relative to the nonchiral complexation, is expected to be more intense in the group *anti* to the bromide ion in the first place, then in the β -group facing the phenyl ring, and, finally, weaker still in the β -group opposite to the phenyl ring (for example, $\alpha\text{-H} > \beta\text{-CH}_2 > \beta\text{-CH}_3$ for C_H of ^{Et}D_{RS}, Figure 4a). Table 2 summarizes the

Table 1. Thermodynamic description of the organozinc–ligand complexation at 25 °C based on PM3 energies.^[a]

ZnBr·(<i>R</i>)- 1 Conformer	^{Et} D _{RR} (major)			^{Et} D _{RS} (minor)		
	C _H	C _{Me} ^[b]	C _{Et}	C _H	C _{Me}	C _{Et} ^[b]
$\Delta H_{\text{form}}^\circ$ ^[c]	−25.02	−23.93	−24.74	−25.09	−24.58	−23.90
n ^[d]	0.560	0.090	0.349	0.640	0.273	0.087
$\Delta H^\circ = 0.026 \text{ kcal mol}^{-1}$; $\Delta S^\circ = 0.11 \text{ cal mol}^{-1} \text{ K}^{-1}$						
$\Delta G^\circ = -0.008 \text{ kcal mol}^{-1}$; ${}^{\text{Et}}K_{25^\circ\text{C}} = 1.01$						
${}^{\text{Et}}D_{RS} \rightleftharpoons {}^{\text{Et}}D_{RR}$						
ZnBr·(<i>R</i>)- 1 Conformer	^{Bn} D _{RS} (major)			^{Bn} D _{RR} (minor)		
	C _H	C _{Me}	C _{Bn} ^[b]	C _H	C _{Me}	C _{Bn}
$\Delta H_{\text{form}}^\circ$ ^[c]	6.62	8.24	8.49	8.10	8.38	7.36
n ^[d]	0.903	0.058	0.039	0.194	0.122	0.684
$\Delta H^\circ = -0.84 \text{ kcal mol}^{-1}$; $\Delta S^\circ = -0.90 \text{ cal mol}^{-1} \text{ K}^{-1}$						
$\Delta G^\circ = -0.57 \text{ kcal mol}^{-1}$; ${}^{\text{Bn}}K_{25^\circ\text{C}} = 2.61$						
${}^{\text{Bn}}D_{RR} \rightleftharpoons {}^{\text{Bn}}D_{RS}$						

[a] Corresponding to isolated molecules. [b] In highly congested conformations, boatlike deviation geometries were found to have energies close to those of the twist ones, which only affects the thermodynamic parameters marginally. [c] Fully optimized $\Delta H_{\text{form}}^\circ$ [kcal mol^{−1}] values were obtained after an exhaustive search for minima in the energy surfaces. [d] Populations based on a Boltzmann distribution.

Table 2. Predicted relative anisotropic chemical shifts.^[a]

Configuration ^[b]	^{Et} D _R		^{Bn} D _R	
	<i>S</i>	<i>R</i>	<i>S</i>	<i>R</i>
$\alpha\text{-H}$	up	up	up	down ^[c]
$\beta\text{-CH}_3$	weak	up	weak	up ^[d]
$\beta\text{-CH}_2$	up	weak	up ^[e]	down ^[c, f]
$\gamma\text{-CH}_3$	down ^[g]	up ^[g]	—	—
model	4a	4b	4c	4d

[a] Based on the major conformation for each diastereomer, which are represented in Figure 4. Up = upfield. [b] Configuration of the organozinc; the ligand is always *R*. [c] Downfield anisotropic chemical shift resulting from a group approximately coplanar to the phenyl ring. [d] Tentatively assigned to intramolecular shielding from the benzyl group. [e] Not shown: 1.84 (1 H, dd, $J = 12.2, 10.4 \text{ Hz}$, PhCHH) and 2.24 (1 H, dd, $J = 12.2, 6.7 \text{ Hz}$, PhCHH). [f] Not shown: 2.02 (1 H, dd, $J = 13.3, 9.1 \text{ Hz}$, PhCHH) and 2.49 (1 H, dd, $J = 13.3, 5.3 \text{ Hz}$, PhCHH). [g] Groups further than the β position do not seem to obey a simple scheme of anisotropic effects.

predicted relative anisotropic chemical shifts for the major conformation of each diastereomer displayed in Figure 4. The observed chemical shifts matched the predictions for α - and β -hydrogen atoms and allowed interpretation of the spectra in terms of absolute configurations. Indeed, this was confirmed by a COSY experiment performed at -50°C , which revealed the expected correlation between the signals. Their absolute configuration assignments are indicated in Figures 1 b and 2 b.

The procedure reported herein constitutes a straightforward way to measure enantiomeric ratios of reactive organometallic species directly by NMR spectroscopy^[20] by using a chiral solvating reagent, as well as an easy way of testing for racemization in carbon–metal bonds without having to prepare an enantiomerically enriched organometallic reagent. Kinetic parameters for the inversion in the presence of the ligand can be calculated. The chemical shift of the α -hydrogen atom is conveniently separated from the main areas of solvent and other resonances; typical $\Delta\Delta\delta$ values for these and other

signals range from 0.1–0.3 and increase as the temperature lowers. Finally, an empirical model based on PM3 conformational analysis permits a tentative assignment of configurations at the carbon atom α to the metal, relative ligand on the basis of both anisotropic effects and free energy criteria. Structural studies aimed at finding definitive proof for the assignment of the absolute configuration as well as studies of other organometallic species are underway.

Experimental Section

Organozinc bromides were obtained by reaction of active zinc with the corresponding bromides, previously distilled over P_2O_5 , in dry THF at RT in an Ar atmosphere.^[21] (*R*)-**1** and (*S*)-**1** were purified by precipitation with $ZnCl_2$ (THF), extraction (0.2 M aqueous NaCN in $CHCl_3$), and vacuum distillation. (*RS*)-**1** ($[\alpha]_D^{25} = 0.0$) was prepared by mixing equal amounts of the former reagents. The concentration in all the NMR experiments was 0.5 M in THF/ C_6D_6 (1/1), except for those performed at 150 °C in which it was 1.5 M in THF/ $[D_8]THF$ (4/1). TMS was added as an internal standard.

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Electrochemical Oxidation of Water to Dioxygen Catalyzed by the Oxidized Form of the Bis(ruthenium–hydroxo) Complex in H_2O^{**}

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Much attention has been paid to the oxidation of water to dioxygen by homogeneous catalysts. Of particular interest are di- and tetranuclear transition metal complexes, since extended X-ray absorption fine structure studies have indicated that the O_2 -evolving center (OEC) in photosystem II is composed of a tetranuclear Mn cluster with dimeric di- μ -oxo Mn units.^[1] A variety of di- and tetranuclear metal complexes have been prepared as structural models of the OEC, and four-electron oxidation of water has been attained with only a few dinuclear metal (Mn, Ru) complexes.^[2–4] The key intermediates for O_2 evolution in the OEC is thought to be high-valent metal–oxo complexes derived from aqua

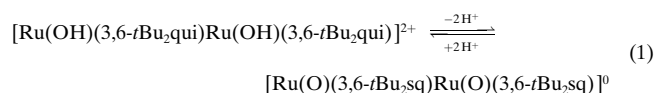
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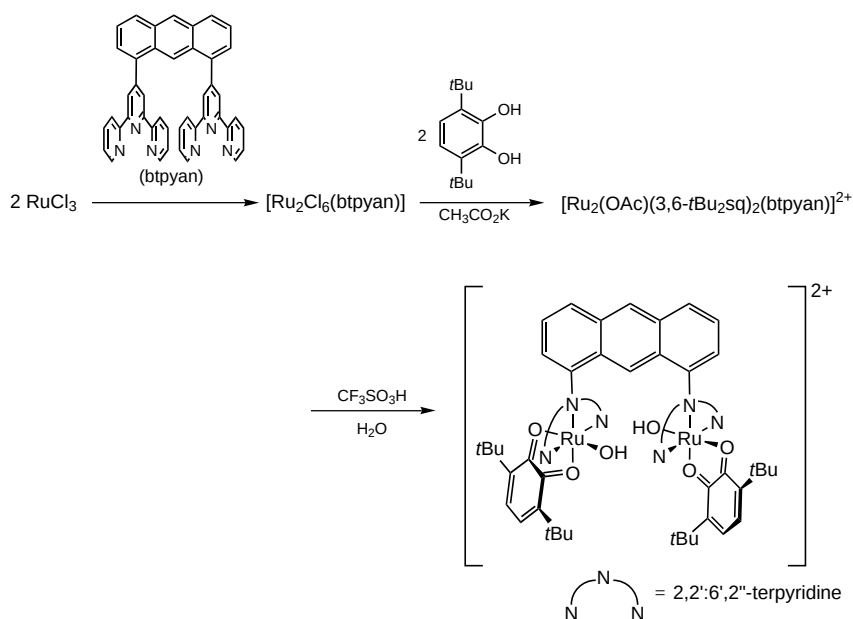
complexes.^[5] We have reported that, depending on the pH of the media, the aqua ligand of $[\text{Ru}(\text{OH}_2)(\text{quinone})(\text{terpy})]^{2+}$ (terpy = 2,2':6',2''-terpyridine) leads to dissociation of protons without formation of a μ -oxo dimer.^[6] The dinuclear complex $[\text{Ru}_2^{\text{II}}(\text{OH})_2(3,6\text{-}t\text{Bu}_2\text{qui})_2(\text{btpyan})](\text{SbF}_6)_2$ (3,6- $t\text{Bu}_2\text{qui}$ = 3,6-di(*tert*-butyl)-1,2-benzocquinone, btpyan = 1,8-bis[(2,2':6',2'')-terpyridyl]anthracene) was thus prepared, with the aim of converting two H_2O molecules into oxo ligands at a vicinal position in the complex to form the O–O bond. Herein we report an effective oxidation of water that is catalyzed by the indium-tin-oxide (ITO) electrode modified with the bis(ruthenium–hydroxo) complex in water.

The bis(ruthenium–hydroxo) complex was prepared by three reactions as shown in Scheme 1. $[\text{Ru}_2\text{Cl}_6(\text{btpyan})]$, prepared by the reaction of RuCl_3 with 1,8-bis(terpyridyl)anthracene (btpyan) in MeOH, was treated with 3,6-di(*tert*-butyl)-1,2-benzocathechole in the presence of potassium acetate in MeOH. The resulting μ -acetato complex $[\text{Ru}_2^{\text{II}}(\text{OAc})(3,6\text{-}t\text{Bu}_2\text{sq})_2(\text{btpyan})]^+$ (3,6- $t\text{Bu}_2\text{sq}$ = 3,6-di(*tert*-butyl)-1,2-semiquinone)^[7] was treated with triflic acid in MeOH containing water, and then sodium hexafluoroantimonate was added to the reaction mixture to give the bis(ruthenium–hydroxo) complex.^[8] The total yield over three steps was 29% based on the amount of RuCl_3 used.

The electronic absorption spectra of the bis(ruthenium–hydroxo) complex in MeOH showed a strong band at 576 nm. The addition of two equivalents of $t\text{BuOK}$ to the solution resulted in the loss of the band at 576 nm and the appearance of a new band at 850 nm in the spectrum. Moreover, acidification of the solution by the addition of two equivalents of HClO_4 completely restored the band at 576 nm and the 850 nm band disappeared. On the basis of the electronic absorption spectra of the mononuclear ruthenium(II)–quinone complex^[6, 9] the bands at 576 nm and 850 nm are reasonably assigned to the metal-to-ligand charge-transfer (MLCT) bands of ruthenium(II)–quinone and ruthenium(II)–semiquinone complexes, respectively. The acid–base equilibrium of the OH_2 group of $[\text{Ru}(\text{OH}_2)(\text{Q})(\text{terpy})]^{2+}$ has been shown to be coupled with the reduction of the quinone (Q) to the semiquinone (SQ).^[6] The change in the electronic absorption spectra in the present study is therefore ascribed to the acid–base equilibrium between $[\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}$ and $[\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{sq})\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{sq})]^0$ coupled with the ligand-localized redox reaction [Eq. (1)]. The rest potential of the solution of

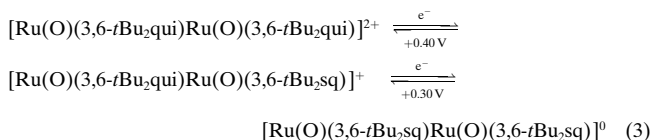
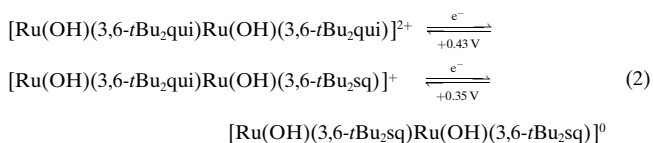


$[\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}$ in MeOH was +0.49 V (versus Ag/AgCl).^[10] The cyclic voltammogram of the complex showed two redox couples at $E_{1/2} = +0.43$ and



Scheme 1. Synthesis of the bis(ruthenium–hydroxo) complex.

+0.35 V in MeOH [Eq. (2)]. The conversion of $[\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}$ into $[\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{sq})\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{sq})]^0$ by the addition of two equivalents of $t\text{BuOK}$ to the MeOH solution [Eq. (1)] shifted the rest potential of the solution to –0.12 V. The redox process of the resultant oxo complex also displayed two nearly reversible redox couples at $E_{1/2} = +0.40$ and +0.30 V [Eq. (3)].



However, further oxidation of $[\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}$ and $[\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}$ was not detected in MeOH and acetone as a result of decomposition of the solvent. The present bis(ruthenium–hydroxo) complex was not soluble in water. We used an ITO electrode modified with the complex to study the redox behavior of the complex in water.^[11] The electronic absorption spectra of the complex on a glass plate in water at pH 2.0 also showed the strong MLCT band at 578 nm. The intensity of the 578 nm band decreased and the band at 850 nm emerged with increasing pH. The ratio of the absorbances at 578/850 nm reached about 3/2 at pH 3.0, and became constant at higher pH values. This observation is explained by the reasoning that only the complex located in the vicinity of the surface of the modified electrode reversibly releases a proton from the aqua ligand, and is dependent on the pH value of the aqueous phase [Eq. (1)].

Figure 1 shows the cyclic voltammogram of the bis(ruthenium–hydroxo) complex modified on an ITO electrode (1.2×10^{-8} mol per 2.0 cm^2) in water (pH 4.0). The complex on the ITO electrode exhibited a broad redox couple

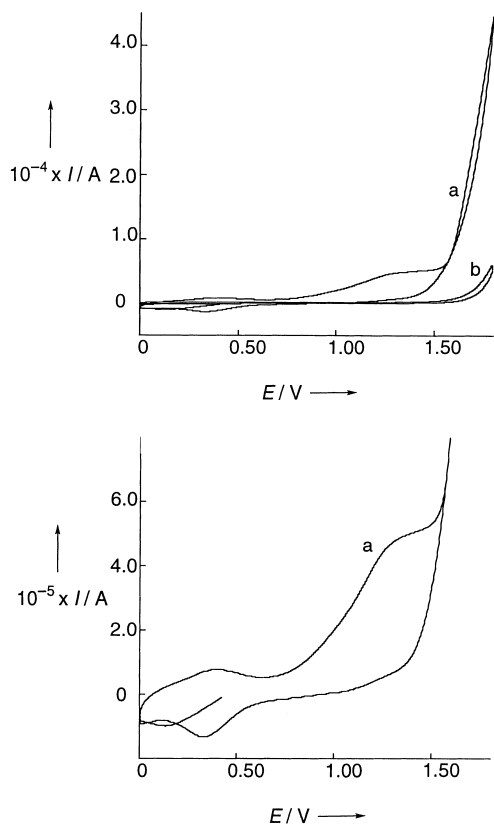


Figure 1. Cyclic voltammograms (versus Ag/AgCl) of the ITO electrode modified with the bis(ruthenium–hydroxo) complex (1.2×10^{-8} mol per 2.0 cm^2) (a) and an ITO electrode (b) in aqueous $\text{H}_3\text{PO}_4/\text{KOH}$ solution (0.5M) at pH 4.0.

centered at +0.40 V (versus Ag/AgCl), an irreversible anodic wave at +1.20 V, and a strong anodic current at potentials more positive than +1.5 V.^[12] On the basis of the redox behavior of the complex in MeOH and the electronic absorption spectra of the complex on a glass plate, the broad anodic and cathodic waves centered at +0.40 V is reasonably assigned to the $[\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}/[\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{sq})\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{sq})]^0$ and $[\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}/[\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{sq})\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{sq})]^0$ redox reactions [Eqs. (2), (3)]. The irreversible anodic wave at +1.20 V is associated with two-electron oxidations of $[\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}$ and $[\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}$ that afford $[\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{OH})(3,6\text{-}t\text{Bu}_2\text{qui})]^{4+}$ and $[\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})]^{4+}$, respectively. The strong anodic current at potentials more positive than +1.5 V is apparently caused by the oxidation of water to dioxygen.

Indeed, when a controlled-potential electrolysis of the bis(ruthenium–hydroxo) complex on an ITO electrode was conducted at +1.70 V (versus Ag/AgCl) in water (pH 4.0) 1.1 mL of O_2 evolved after 20.2 coulombs had passed in the

electrolysis.^[13] The current efficiency for O_2 evolution was 95 % and the turnover number was 500 based on the complex. The current density of the electrode was 0.12 mA cm^{-2} in the initial stage. The current gradually decreased with a decrease in the pH of the aqueous phase and almost stopped at pH 1.2. The current density of the electrode for the oxidation of water recovered when the pH of the water was readjusted to 4.0 by the addition of aqueous KOH to the aqueous phase. The oxidation of water by the ITO electrode modified with the bis(ruthenium–hydroxo) complex finally evolved 15.0 mL of O_2 (turnover 6730) before the evolution completely stopped after 40 h.^[14]

In contrast to the catalytic activity of the dinuclear complex toward the oxidation of water, the cyclic voltammogram of the mononuclear complex $[\text{Ru}(\text{OH}_2)(3,5\text{-}t\text{Bu}_2\text{qui})(\text{terpy})](\text{ClO}_4)_2$ displayed no catalytic current of water oxidation in H_2O at pH 4.0. This result indicates that the two ruthenium–hydroxo units in the bis(ruthenium–hydroxo) complex play the key role in the oxidation of water. Two hydroxo groups in the present bis(ruthenium–hydroxo) complex must be placed adjacently inside the cavity formed by two terpyridyl and two bulky 3,6-di(*tert*-butyl)-1,2-benzoquinone ligands. The formation of the O–O bond in the catalytic evolution of O_2 probably results from the intramolecular coupling of the two oxo ligands of the dinuclear oxo complex derived from the bis(ruthenium–hydroxo) complex. The two-electron oxidation of $[\text{Ru}^{\text{II}}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}^{\text{II}}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})]^{2+}$ produces $[\text{Ru}^{\text{III}}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}^{\text{III}}(\text{O})(3,6\text{-}t\text{Bu}_2\text{qui})]^{4+}$. The electronic structure of the latter species would be expressed as a resonance hybrid between $[(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}^{\text{III}}\text{O}-\text{ORu}^{\text{III}}(3,6\text{-}t\text{Bu}_2\text{qui})]^{4+}$ and $[(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}^{\text{II}}\text{O}=\text{ORu}^{\text{II}}(3,6\text{-}t\text{Bu}_2\text{qui})]^{4+}$. We, therefore, propose that O_2 evolution is caused by the replacement of the O_2 unit in $[(3,6\text{-}t\text{Bu}_2\text{qui})\text{Ru}^{\text{II}}\text{O}=\text{ORu}^{\text{II}}(3,6\text{-}t\text{Bu}_2\text{qui})]^{4+}$ with two molecules of H_2O . In this mechanism the two $\text{Ru}^{\text{II/III}}$ and two quinone/semiquinone redox couples must also contribute to oxidize two water molecules with four electrons.

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- [7] The acetato complex showed no signal in the usual paramagnetic region of the ^1H NMR spectra. The electronic spectra of the acetato complex in MeOH exhibited the strong band at 845 nm attributed to an MLCT band of the Ru^{II} -semiquinone complex. The electronic

structure of the acetato complex is consistent with the formula $[\text{Ru}_2(\text{OAc})(3,6\text{-tBu}_2\text{sq})_2(\text{btpyan})]^+$.

- [8] The bis(ruthenium–hydroxo) complex was prepared as follows: triflic acid (100 μL) was added to a solution of $[\text{Ru}_2(\text{OAc})(3,6\text{-tBu}_2\text{sq})_2(\text{btpyan})](\text{OAc})$ (150 mg, 0.11 mmol) in MeOH (10 mL), and the solution was stirred for 4 d at room temperature. After the addition of NaSbF_6 , the solution was concentrated to 5 mL to give $[\text{Ru}_2(\text{OH})_2(3,6\text{-tBu}_2\text{sq})_2(\text{btpyan})](\text{SbF}_6)_2$ as a violet powder (57% yield). ESI-MS: m/z : 659(M^{2+}); elemental analysis calcd for $\text{C}_{72}\text{H}_{72}\text{N}_6\text{O}_6\text{F}_{12}\text{Ru}_2\text{Sb}_2$: C 48.34, H 3.94, N 4.70; found: C 48.39, H 3.85, N 4.64; UV/Vis-NIR (in MeOH): $\lambda_{\text{max}} = 576 \text{ nm}$ ($\epsilon = 5700 \text{ M}^{-1} \text{ cm}^{-1}$). The oxidation of the semiquinone ligand of $[\text{Ru}_2(\text{OAc})(3,6\text{-tBu}_2\text{sq})_2(\text{btpyan})]^+$ to the quinone ligand of $[\text{Ru}_2(\text{OH})_2(3,6\text{-tBu}_2\text{sq})_2(\text{btpyan})]^{2+}$ during the reaction may be caused by O_2 .
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- [11] A solution of the bis(ruthenium–hydroxo) complex in acetone was dropped on an ITO electrode by microsyringe, and dried at room temperature.
- [12] The cyclic voltammogram was measured at 10 mV s^{-1} in an $\text{H}_3\text{PO}_4/\text{KOH}$ buffer solution (0.5 M) using an ITO electrode modified with the bis(ruthenium–hydroxo) complex ($1.2 \times 10^{-8} \text{ mol per } 2.0 \text{ cm}^2$) as the working electrode, a platinum wire as the counter electrode, and an Ag/AgCl reference electrode.
- [13] Two compartment cells separated by a Nafion membrane were filled with an $\text{H}_3\text{PO}_4/\text{KOH}$ buffer solution (1.0 M, 60 mL) and He gas was bubbled into the solution to remove O_2 from the aqueous phase. Controlled-potential electrolysis was performed with the ITO electrode modified with the bis(ruthenium–hydroxo) complex ($1.0 \times 10^{-7} \text{ mol per } 10 \text{ cm}^2$) as the working electrode, a platinum plate (2.0 cm^2) as the counter electrode, and an Ag/AgCl reference electrode. Evolved dioxygen was determined by GC measurement.
- [14] The complex was completely detached from the ITO electrode in 40 h under the controlled-potential electrolysis conditions at +1.7 V in H_2O .

Designing a Helical Polymer that Reverses its Handedness at a Selected, Continuously Variable, Temperature**

Kap Soo Cheon, Jonathan V. Selinger,* and Mark M. Green*

A new kind of stereochemical experiment only accessible with cooperative helical arrays has been designed by enforcing a competition between two *structurally different* non-racemic chiral molecules to control the helical sense of a polymer. The experiment, which has been analyzed by a statistical physical theory, allows the optical activity of the polymer, as a function of the composition of the competing units, to be set to zero at any temperature and then increases in magnitude, in a positive or negative direction, as the temperature deviates from the chosen value.

Since the polyisocyanates^[1] have served as models for other helical systems,^[2] a conformational state of considerable interest,^[3] we have applied this idea by synthesizing the polymer from structurally different chiral units, which compete with each other favoring the left- and right-handed helical senses. Since the strength of the chiral biases of the competing units for their favored helical sense are different, they compensate each other at some relative proportion away from 50/50. Moreover, since the competing chiral biases depend on temperature in different ways, this compensation point also depends on temperature. Hence, a polymer of fixed composition can pass through the compensation point as a function of temperature, with its dominant helical sense switching between left- and right-handed. This phenomenon can be described theoretically by a variation of the one-dimensional random-field Ising model.^[4]

Three monomer units (**1**–**3**) were used in this study.^[5] Homopolymers synthesized entirely from the *R* enantiomers of **1**, **2**, and **3** show identical circular dichroism spectra in sign and form, thereby demonstrating a preference for the same helical sense.^[6] This corresponds to a negative rotation at the sodium D line.^[1, 5, 6]

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The competition for helical sense was designed through the synthesis of copolymers with various compositions of the following pairs: (*R*)-1 and (*S*)-3; (*R*)-2 and (*S*)-1. Figures 1 and 2 show the optical activity $[\alpha]$ as a function of temperature for the two sets of variable-composition copolymers.^[7] In each of these cases, the optical activity is zero at a temperature ("compensation temperature") dependant upon the composition of the polymer; this is consistent with the reversal of the helical sense.^[6] Although it is apparent from the data that the

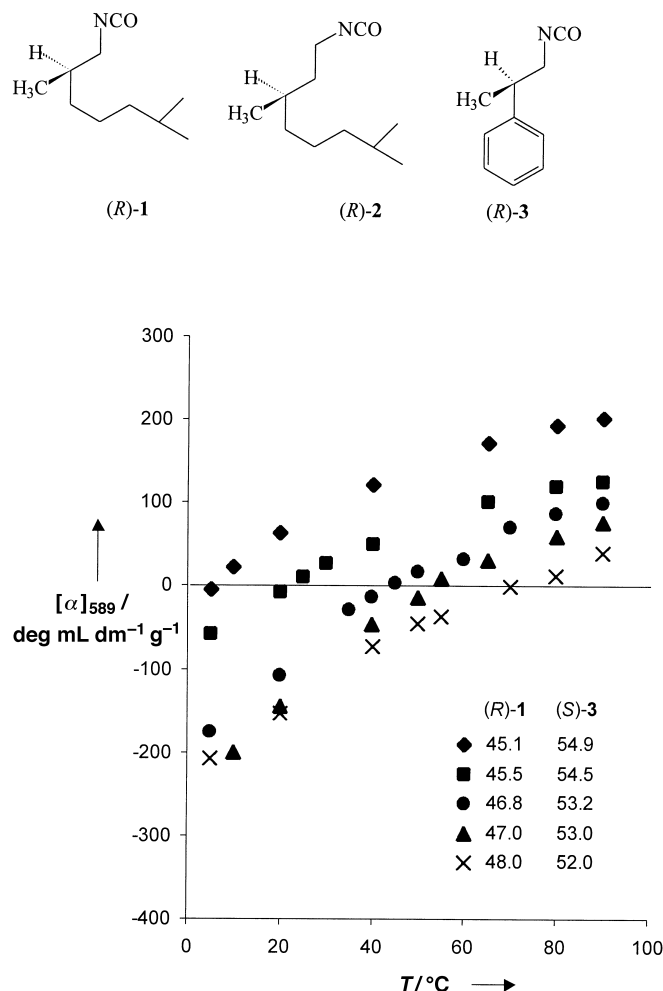


Figure 1. Optical activity $[\alpha]$ (at 589 nm) in a dilute toluene solution of the (*R*)-1/(*S*)-3 copolymer as a function of temperature. ◆: $M_w = 48200$, polydispersity $\rho = 1.7$; ■: $M_w = 46800$, $\rho = 1.9$; ●: $M_w = 42300$, $\rho = 1.9$; ▲: $M_w = 219000$, $\rho = 2.4$; ×: $M_w = 45100$, $\rho = 2.0$. Measurements are described in ref. [7].

compensation point can be varied by simply changing the proportions of the competing chiral units in each polymer, the detailed response of the optical activity to composition and temperature differs greatly between the two systems. This difference can be understood in terms of the statistical physical theory discussed below.

The copolymers are described by adapting a random-field Ising model previously developed for copolymers synthesized from nearly racemic monomers.^[4, 8, 9] This random field takes the values of $+\Delta G_{h1}$ for one type of chiral unit along the chain, $-\Delta G_{h2}$ for the competing chiral unit, and zero for any

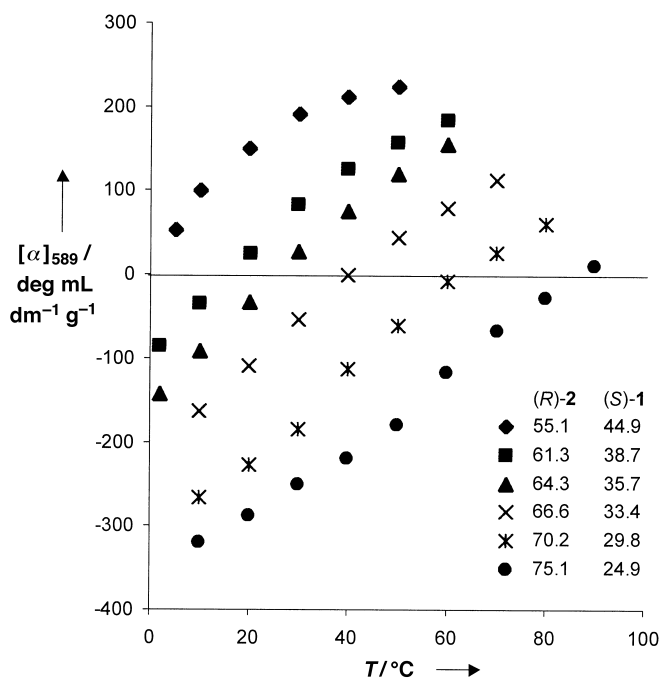


Figure 2. Optical activity $[\alpha]$ (at 589 nm) in dilute solution, in hexane for the four lowest temperatures and in octane for the two highest temperatures, of the (*R*)-2/(*S*)-1 copolymer as a function of temperature. ◆: $M_w = 346000$, $\rho = 2.9$; ■: $M_w = 269000$, $\rho = 2.8$; ▲: $M_w = 282000$, $\rho = 2.6$; ×: $M_w = 236000$, $\rho = 2.5$; ✱: $M_w = 300000$, $\rho = 2.7$; ●: $M_w = 290000$, $\rho = 2.5$. Measurements are described in ref. [7].

achiral units. The predictions of the theory can be derived by an approximate analytic solution that is a straightforward generalization of the solution for polymers with mirror-image units.^[4, 8]

Let r be the fraction of all monomer units that are chiral, and let p be the fraction of chiral units that are of type 1. The optical activity is then predicted by Equation (1), where $[\alpha]_{\max}$ is the optical activity of a polymer with a single helical sense, erf is the standard error function of statistics, L is the helical domain size or correlation length along the chain, and p^* is given by Equation (2).

$$[\alpha] = [\alpha]_{\max} \text{erf} \left[\sqrt{\frac{Lr}{2p^*(1-p^*)}} (p-p^*) \right] \quad (1)$$

$$p^* = \frac{\Delta G_{h2}}{\Delta G_{h1} + \Delta G_{h2}} \quad (2)$$

In deriving this prediction, we assume that the sequence of units along the chain is random (see below) and that the statistical disorder in the random field exceeds the thermal energy, $(\Delta G_{h1} + \Delta G_{h2})\sqrt{2Lrp^*(1-p^*)} \gg RT$. Both of these assumptions are justified in the systems studied earlier, and we expect them to apply in this case.

In the prediction of Equations (1) and (2), note that $p = p^*$ defines the compensation point at which the contributions of the competing chiral monomers cancel and the optical activity equals zero. For a polymer composed of mirror-image *R* and *S* units, we have $\Delta G_{h1} = \Delta G_{h2}$ by symmetry and hence $p^* = 1/2$ independent of temperature. However, for a polymer composed of competing chiral units that are not mirror images, p^*

is not $\frac{1}{2}$. Moreover, the two chiral biases ΔG_{h1} and ΔG_{h2} will generally vary as functions of temperature and hence p^* will also vary as a function of temperature, $p^*(T)$. Therefore, the optical activity will vanish as a function of temperature when $p^*(T)$ passes through p , the fraction of chiral units that are of type 1. The compensation temperature can therefore be tuned continuously by varying the composition of the polymer, as seen in the experimental data in Figures 1 and 2.

The theory yields further insight into the experimental results. Consider the relationship between compensation temperature and composition shown in Figure 3.

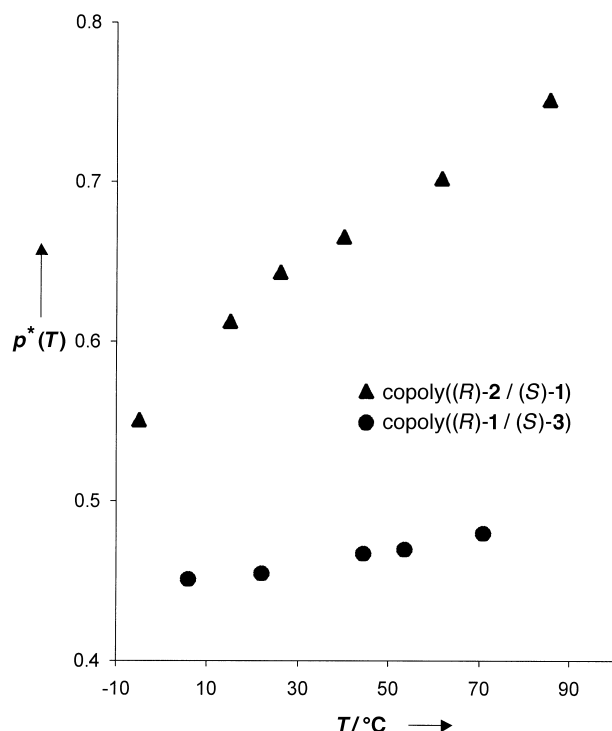


Figure 3. Relationship between composition and temperature at the compensation point for all the copolymers exhibited in Figures 1 and 2.

Equation (2) shows that changes in $p^*(T)$ with temperature correspond to changes in the ratio of the temperature-dependant chiral-bias free energies $\Delta G_{h1}(T)$ and $\Delta G_{h2}(T)$. If this ratio of free energies changes rapidly with temperature, then $p^*(T)$ also changes rapidly too, and hence a small change in compensation temperature will correspond to a large change in composition. Conversely, if this ratio of free energies changes slowly as a function of temperature, then a large change in compensation temperature will correspond to a small change in composition. The free energy dependence on temperature is primarily associated with entropy, which is linked to the flexibility of the chiral units. This is consistent with the greater slope of the data shown in Figure 3 with copolymers with **2** rather than **3**.^[10]

Another feature of the experimental data is in $d[\alpha]/dT$ around the compensation temperature. The theory predicts Equation (3).

$$\frac{d[\alpha]}{dT} [p = p^*(T)] = -[\alpha]_{\max} \sqrt{\frac{2Lr}{\pi p^*(1-p^*)}} \frac{dp^*}{dT} \quad (3)$$

This equation implies that the slope $d[\alpha]/dT$ is proportional to the slope dp^*/dT , with a proportionality constant that depends on the cooperative length scale L . A comparison of the slopes found in Figures 1 and 2 with Figure 3 confirms that the slopes are correlated. However, the observed slope $d[\alpha]/dT$ is not quite as large as predicted by the theory. For example, consider the copolymer (R)-**2**/(S)-**1**. With the chiral fraction $r=1$, the maximum optical activity is approximately $[\alpha]_{\max} \approx -500^\circ \text{ mL dm}^{-1} \text{ g}^{-1}$,^[11] and the slope in Figure 3 is approximately $dp^*/dT \approx 0.002 \text{ K}^{-1}$. Based on earlier experiments with copolymers of mirror-image chiral units, we expect the helical domain size to be at least $L=100$. To test this expectation, we have used gel-permeation chromatography to fractionate one of these copolymers into a number of narrow molecular mass samples.^[11] Figure 4 confirms that the molar ellipticity θ of the fractionated samples depends on chain

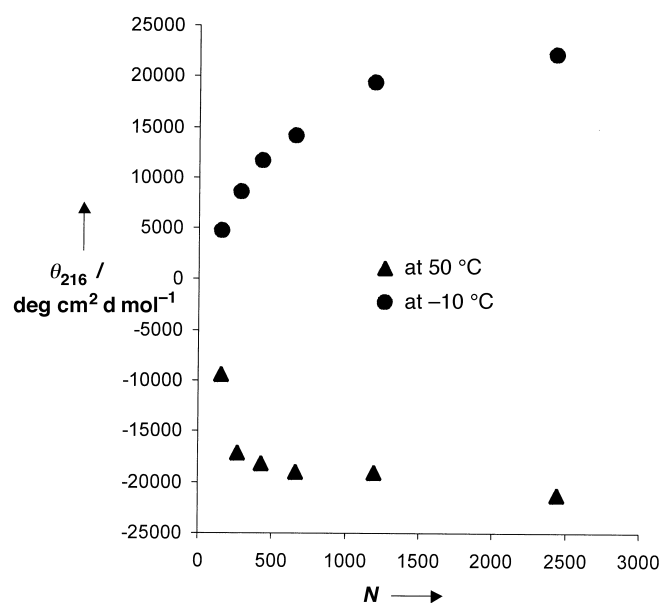


Figure 4. Molar ellipticity θ (at 216 nm) as a function of the degree of polymerization N (chain length) for the fractionated copolymer (R)-**2**/(S)-**1**.

length for a degree of polymerization N of up to several hundred monomer units, which is consistent with L of order at least 100. Hence, the slope $d[\alpha]/dT$ should be at least $16^\circ \text{ mL dm}^{-1} \text{ g}^{-1} \text{ K}^{-1}$ [Eq. (3)]. However, the experimental slopes around the compensation temperature in Figure 2 are only $d[\alpha]/dT \approx 5.7^\circ \text{ mL dm}^{-1} \text{ g}^{-1} \text{ K}^{-1}$.

Since any deviation from randomness^[12] in the copolymerization could lead to a reduction in $d[\alpha]/dT$,^[8] we have studied this factor by degrading one composition of each copolymer to trimers. The composition of trimer population, determined by NMR, can reveal the microstructure, as has been described.^[12a] The data show the copolymerizations to be so near to random as to exclude this as an explanation for the discrepancy in compared slopes noted above.^[13]

Figures 1 and 2 also show the optical activity is more sensitive to temperature below, rather than above, the

compensation point. This can be understood since the helical domain size L , on which the optical activity depends [Eq. (1)], itself depends on temperature.^[1] Indeed, Figure 4 shows explicitly that the optical activity saturates for shorter chain length at 50 °C than at –10 °C, confirming that L is shorter at high temperature than at low temperature.

In conclusion, we have designed a polymer in which structurally different chiral units compete to control the helical sense of the polymer chain. This competition leads to thermal switching of the helical sense at a compensation point that depends continuously and predictably on the composition of the polymer. This model effect,^[14] potentially applicable to other macromolecular and supramolecular helical systems, and which can be understood in terms of a theory of cooperative helical order, may offer new materials based on liquid crystals^[15] in which the changes in the chiral characteristics of the polymer can translate into conversions between a nematic state and cholesteric states of opposite sense.

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Piezoelectricity in Polar Supramolecular Materials**

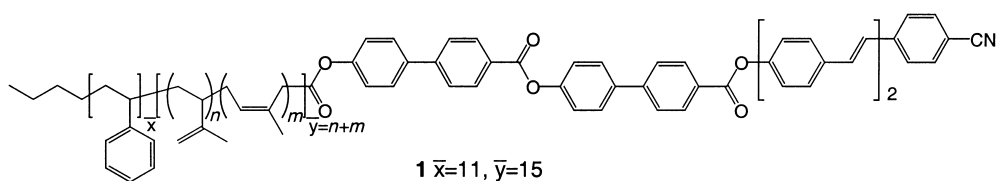
Martin U. Pralle, Kenji Urayama, Gregory N. Tew, Dieter Neher, Gerhard Wegner, and Samuel I. Stupp*

The great potential of supramolecular materials is the possible discovery of properties that are characteristic of molecular clusters and not of individual molecules. Simple changes in the chemistry of building blocks in such clusters enhance further our ability to target specific properties in supramolecular materials. Designing for polar order in organic systems has long been a goal in materials chemistry because of its implications in surface properties, nonlinear optics, piezo-, ferro-, and pyroelectricity. The approaches to polar organic materials include the poling of host–guest systems^[1] self-assembled host–guest systems,^[2] the poling of polymer films,^[3] Langmuir–Blodgett film multilayers,^[4–6] grafted polymer brushes,^[7] multilayer growth,^[8] or the spontaneous assembly of triblock rodcoil molecules into polar supramolecular films^[9] discovered in our laboratory.

This spontaneous polar self-assembly provides potentially a direct pathway to the creation of polar domains with a minimum number of processing steps.^[9] These hierarchical structures begin with the aggregation of rodcoil molecules into a mushroom-shaped nanostructure lacking a center of inversion. This structure forms as a result of the crystallization of identical rodlike segments but long-range order is disrupted in the system by steric and entropic effects involving the oligomeric coils grafted to rod segments. The supramolecular objects arrange parallel to each other and form sheets and their head-to-tail stacking leads to polar three-dimensional (3D) domains. The self-assembly of these domains on a substrate generates a macroscopic material with net polarization.^[9] Recent work has shown that this polar structure is not highly specific to a certain chemical composition of rodcoil molecules. Instead, the structure seems to be a direct consequence of molecular architecture.^[10] This finding implies

that many rodcoil molecules could be synthesized to target specific properties.

We reported previously on the synthesis of **1** in a stepwise fashion starting with the sequential anionic polymerization of styrene and isoprene and continuing with esterification steps



to build the rod segment.^[10] The cyano-substituted phenylene vinylene chromophore imparts fluorescent properties^[10] to these molecules and increases drastically their dipole moment.^[11] Our previous characterization of this family of molecules has included fluorescence studies, nonlinear optical experiments, small-angle X-ray scattering, as well as transmission electron microscopy (TEM) and electron diffraction.^[10–12] We showed that these materials form mushroom-shaped supramolecular aggregates consistent with previous work on triblock rodcoil molecules. Triblock structure **1**, with an average of 11 units of styrene and 15 units of isoprene, forms the most regular nanostructures of this particular family of molecules. Furthermore, we have observed in this family of molecules the polar stacking of molecular layers by cross-sectional TEM.^[12]

In this work we have measured piezoelectricity and electrostriction in films of **1** using interferometric experiments described elsewhere.^[1, 7, 13] Piezoelectricity is an electromechanical transduction observed exclusively in polar materials, thus resulting in electrical signals as a consequence of a mechanical deformation. Electrostriction, on the other hand, is observed in all materials and refers to deformation in materials as a result of an applied electric field. Samples were prepared on glass substrates coated with a 30-nm aluminum electrode. The films of **1** were deposited from a 2.5 wt. % toluene solution by dip coating at a controlled rate (ca. 1 cm s^{−1}) resulting in films with a uniform thickness of 110 nm. The dip-coating process left a droplet of solution at the bottom edge of the substrate, leading to a thicker region near that edge. However, care was taken to ensure measurements were carried out within the film regions that had uniform thickness. Films were annealed above their relaxation temperature^[14] ($T \approx 100^\circ\text{C}$) for 2 h and then a top aluminum electrode was deposited by evaporation to a thickness of 50 nm. Leads were silver painted to the aluminum in such a way as to prevent the shorting of the device.

The sample configuration described above can be considered as a dielectric in a parallel plate capacitor and therefore it can be shown that Equation (1) holds^[1] and for an alternating current Equation (2) is valid, where h is the film thickness, a and d are the electrostriction and piezoelectric tensors, respectively, and E is the applied electric field. In this sample configuration the tensor notation can be suppressed and using a lock-in amplifier a and d are measured independently.

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$$h(E) = h_0(1 + dE + aE^2 + \dots) \quad (1)$$

$$\frac{\Delta h(E)}{h_0} = \left(\frac{1}{2} a E_0 + d E_0 \cos \omega t + \frac{1}{2} a E_0^2 \cos 2 \omega t + \dots \right) \quad (2)$$

Figure 1 is a plot of the piezoelectric response as a function of voltage. The data points are an average of multiple scans to ensure that the observed response is reproducible and not due

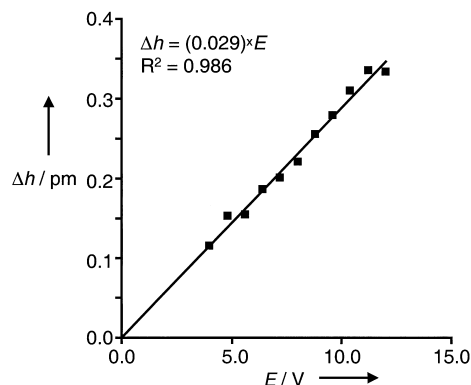


Figure 1. Plot of the piezoelectric response of an annealed film of **1**; the piezoelectric coefficient is equal to 0.029 C N⁻¹.

to thermal fluctuations.^[1, 7, 13] The field-induced extensions observed yield a piezoelectric coefficient of $d = 0.029 \text{ C N}^{-1}$. Figure 2 shows a plot of polarization in self-assembled films as a function of temperature. This sample was not annealed prior to the experiment such that changes in the film could be

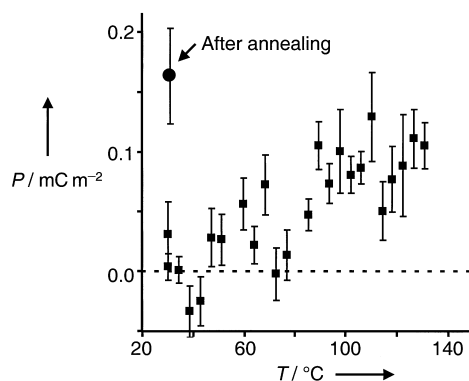


Figure 2. A net polarization develops during annealing of a film of molecules **1**. The circular data point (●) represents the stable net polarization remaining after cooling to room temperature.

observed during the annealing process. In order to obtain these data, the sample was sequentially heated to various temperatures for 30 min before recording piezoelectric and electrostrictive responses. The polarization, P , at each temperature was calculated using Equations (3) and (4),^[1] where β is the plate compliance for uniaxial compression normal to the

$$d = -\beta P \frac{\epsilon + 2}{3} \left(\frac{\epsilon + 2}{3} \right) \quad (3)$$

$$a = \frac{-\beta \epsilon_0}{2} \left(\epsilon + \frac{(\epsilon + 2)(\epsilon - 1)}{3} \right) \quad (4)$$

layer^[1] and ϵ is the dielectric constant. Specifically a , d , and ϵ were measured at each temperature, and the above system of equations was solved for P . A measurable polarization is not detected in as-cast samples, but above the relaxation temperature of 80 °C a positive polarization is observed. Further increments in temperature result in higher polarization, and most importantly when samples are cooled to room temperature the net polarization is retained. The scatter in data is a consequence of compounded errors associated with each experimentally measured value, however, the error bars clearly demonstrate the statistically significant change after annealing. This thermally activated reorganization demonstrates that a polar structure is indeed stable in this material. Polar order was previously suggested by second harmonic generation experiments and these piezoelectricity measurements confirm a net polar arrangement in the self-assembled films. Furthermore, the samples with piezoelectric activity had been annealed above their relaxation temperature ($T \approx 100^\circ\text{C}$) without an applied field prior to the measurements. This should have allowed the system to equilibrate indicating that the spontaneous polarization is an inherent characteristic of the material.

A poled sample was prepared by applying a DC field of 45 MV m⁻¹ to the sample at temperatures above the relaxation temperature for 30 min and cooling it to room temperature under an applied field. Then, the sample was heated and the piezoelectric response in the absence of the poling field was monitored with increasing temperature. Plotting piezoelectric coefficient and plate compressibility versus temperature one can observe the decay of the piezoelectric response down to the nominal value for the unpoled sample. At the same time the softening of the material is observed (Figure 3). We note

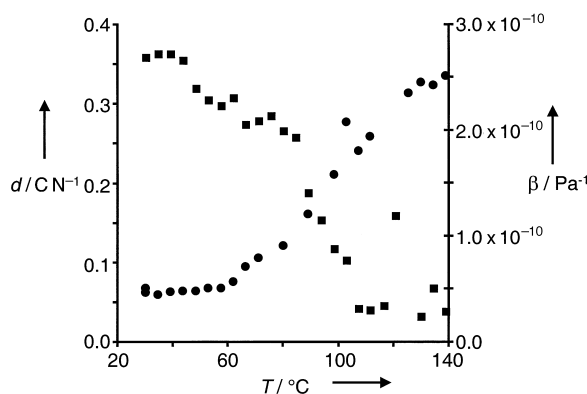


Figure 3. Loss of piezoelectric response, d , (■, left axis) in a poled sample with increasing temperature, and corresponding increase in plate compliance, β , (●, right axis).

the values of β at low and high temperatures are comparable to those measured for amorphous polymers below and above the glass transition temperature, respectively. This suggests the observed changes in the self-assembled films must be controlled by the glass-forming oligostyrene block.^[13] The fact that the piezoelectric signal returns to a value similar to that measured in a film annealed but never exposed to a poling field offers support for the possibility that net polarization in these systems is thermodynamically stable.

The calculated maximum value of polarization one would expect if all nanostructures were perfectly aligned would be $P = 3.2 \text{ mCm}^{-2}$,^[15] an order of magnitude larger than the maximum value measured. This discrepancy is presumably due to the fact that polar grains point in different directions and also to the existence of inverted stacks of polar layers. However, unlike conventional ferroelectric materials where the global spontaneous polarization is canceled by polydomains, here macroscopic net polarization can be simply achieved by casting and annealing without the use of an external electric field. It is possible that the substrate on which the material is cast as well as the air/solid interface on top align nanostructures in a preferred direction thus generating net polarization in the film.

It was suggested above that the discrepancy between theoretical and observed polarization was due to inversions in the system. The poled sample, however, should eliminate these inversions and, as expected, the polarization of this sample was 1.46 mCm^{-2} , much larger than that of the unpoled sample. A value of 3.2 mCm^{-2} is not achieved in the sample because of the aligning field used (45 mVm^{-1} is not large enough). A maximum value of 3.19 mCm^{-2} can be obtained at higher poling fields from these materials (see Figure 4). This poling experiment strongly supports our hypothesis that a polydomain structure prevails in the as-cast film. The value of the piezoelectric coefficient for this soft self-assembling films is on the order of that observed for quartz. The system studied here contains oligostyrene and oligoisoprene segments which obviously dilute the overall dipole density of the system. Since we have shown that it is not the specific chemistry that is critical for the observed self-organization of triblock molecules,^[10] it should be possible in principle to design systems to maximize the piezoelectric character. This of course requires both mechanical as well as polar design of the system and may require combinatorial approaches for optimization.

Figure 4 is a plot of polarization versus electric field for both positive and negative bias. The saturation values of polarization lie in the range expected for complete alignment of dipolar species. This observation is strong evidence for the polar nature of domains in this self-assembled material. Interestingly, the data show a slight hysteresis with a remnant polarization similar to that observed just after annealing the

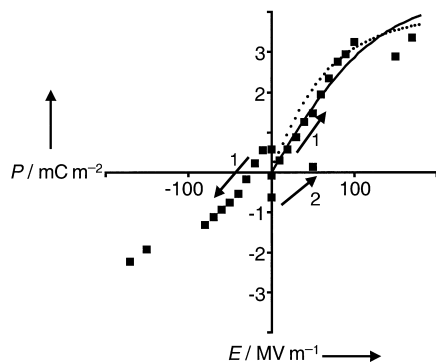


Figure 4. Plot of polarization versus electric field (■) showing a small hysteresis. The fitted curves correspond to a two-state model (solid curve) and a Langevin model (dotted curve). The arrows indicate the E -field path during cycle 1 and cycle 2.

film without an applied field. This suggests that the polar order is stabilized in the self-assembled state, similar to what is observed in ferroelectric materials.^[16] It is of course an open question whether these self-assembling systems indeed fall within the broader class of materials known as ferroelectrics. The fitted curves on the graph were calculated based on different models for dipoles in an applied field. One is a simplistic two-state model (solid curve), allowing only two antiparallel molecular orientations, and the other is a Langevin model (dotted curve) where dipoles orient with some average angle relative to the field orientation. The mathematical expression for the two-state model is given in Equation (5) where $x = \mu E/kT$, and for the Langevin model it is given in Equation (6).

$$P = \frac{N}{V} \mu \tanh x \quad (5)$$

$$P = \frac{N}{V} \mu \left(\coth x - \frac{1}{x} \right) \quad (6)$$

Given the error bars in Figure 2, it is clear that the error bars in Figure 4 are comparable to the size of the data points in this graph and therefore not visible. Neither of these models accurately describes the system but might provide upper and lower boundaries for estimating the dipole moments of the system's components. In fact, as revealed by the graph, the data do not precisely agree with either model but rather appear to have characteristics of both. Remarkably, both models yield an effective dipole which is larger than that of a single rodcoil molecule. The two-state model yields a μ_{eff} value of 8.5 D, while the Langevin model yields a μ_{eff} value of 33 D. Since the dipole of one molecule is roughly 4.2 D, both models suggest cooperative dipole interactions and thus imply that groups of molecules rather than single molecules realign in the applied field. The data suggest that at elevated temperatures supramolecular entities remain in the system. Our laboratory has obtained other evidence for this by showing that it is possible to thermally crosslink the interior of mushroom-shaped aggregates containing oligobutadiene segments without forming gels at temperatures as high as 250°C .^[17] This can only be possible if the reactive sites in supramolecular nanostructures are spatially isolated within one aggregate at such temperatures. We have also observed a small-angle X-ray peak that appears to correspond to the characteristic size of nanostructures at elevated temperature.^[10] These observations and the data presented here would support the retention of supramolecular structure in the molten state.

Interestingly, a discrepancy is observed when a sample is poled in the opposite direction under the same conditions for the same amount of time. The piezoelectric constant of the reverse-poled sample is only 60 % of the value of the forward-poled sample. The reason for this difference can be attributed to the resistance of the material to reorganize at the substrate/material interface. As was mentioned earlier, the films formed by rodcoil molecules must order with the substrate during solvent casting and subsequent annealing. The reverse field might thus be forcing the mushroom-shaped nanostructures to reorder in a thermodynamically unfavorable orientation with respect to the substrate.

We have shown here that supramolecular films composed of dipolar rodcoil molecules self-organize into polar macroscopic materials showing piezoelectric activity. Most importantly, the state with net polarization appears to have thermodynamic stability and to involve interactions between polar domains in the film and the substrate. Furthermore, our experiments strongly suggest that molecular aggregates present in these materials are important for the observed properties. This observation supports the concept that great potential exists in the supramolecular design of materials.

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Unusual Smectic Ordering of Unlocked Copper Bis-(terpyridine) Complexes**

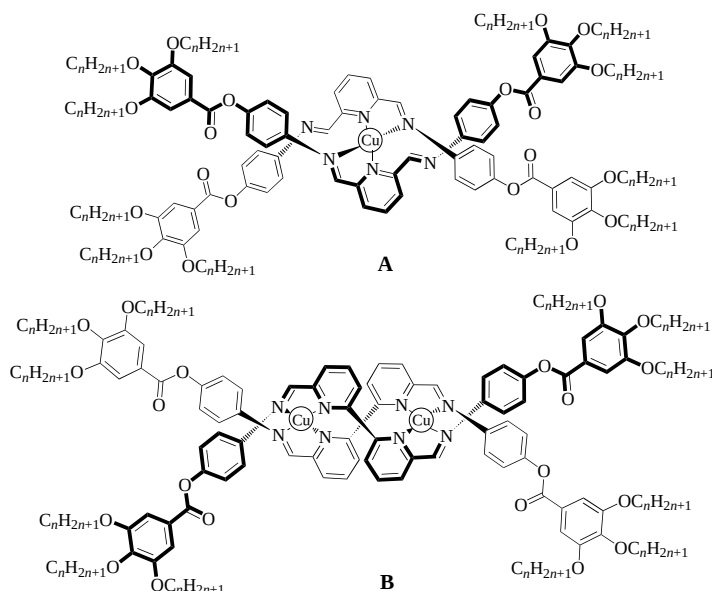
Raymond Ziessel,* Laurent Douce, Abdelkrim El-ghayoury, Anthony Harriman, and Antoine Skoulios

Supramolecular liquid crystals have now been engineered by way of hydrogen bonding, donor-acceptor interactions, or by cation complexation; the latter leading to the formation of metallomesogens.^[1] Individual molecules within these organized networks act cooperatively to fulfill a useful function, such as thermochromism, ferroelectricity, nonlinear optical effects, or gelation. The anticipation that such structures might be used to construct molecular devices has been augmented by many examples of complex supramolecular architectures, such as discrete and infinite helices, hydrogen-bonded or π - π interacting networks, three-dimensional assemblies with defined channels, cucurbituril and similar molecules, highly symmetric coordination clusters, and organometallic polymers.^[2] Increasing the extent of molecular ordering, however, to form organized macroscopic structures has proven difficult. Two important examples include silver complexes, constructed from polycatenar scaffolds, forming columnar liquid-crystalline mesophases,^[3] and the description of the macroscopic ordering of a metallo-helicate (**B**).^[4] It has also been shown that various pyridino-functionalized Schiff-base ligands coordinated to a tetrahedral copper(II) center assemble into columnar liquid-crystalline materials (**A**).^[5] These latter structures, being rather rigid, appear to lack useful physical or catalytic properties.

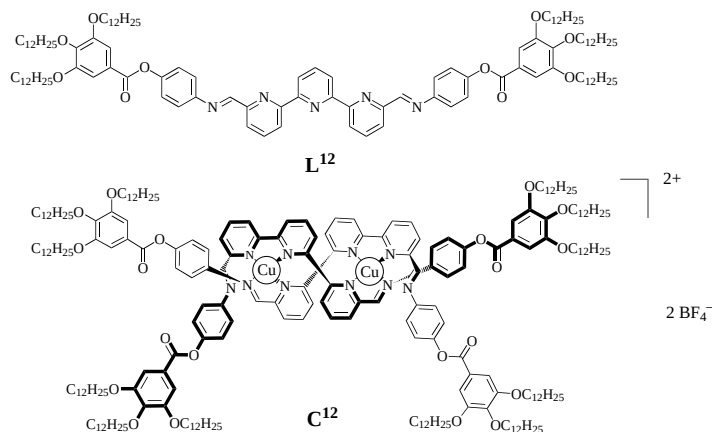
We have sought to improve this situation by introducing more flexibility into the supermolecular structure but without detracting from its ability to assemble into organized networks. This delicate operation can be achieved by using a central core constructed from a terpyridine (terpy) ligand bearing two imino appendages equipped with phasmidic tails (long chains bound to the ends of a rodlike core). Complexation to copper(II) cations gives the first thermotropic terpy-based metallomesogens. Metallomesogens formed from tridentate ligands are rare, but lyotropic mesophases have been generated from ruthenium(II)-terpy complexes,^[6] while the related terdentate (C,N,N) ligands cyclometalated to palladium(II) centers^[7] are known to display a monotropic nematic phase.

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Ligands **Lⁿ** ($n=8, 12, 16$) were synthesized in excellent yield by an acid-catalyzed reaction of the pivotal 6,6''-diformyl-2,2':6',6''-terpyridine^[8] with the appropriate polyfunctionalized aniline. The ligands self-associate in the presence of $[\text{Cu}(\text{CH}_3\text{CN})_4][\text{BF}_4]$ to afford dark-brown, air-stable, binuclear metallohelicates **Cⁿ** in almost quantitative yield. All new compounds were fully characterized by NMR spectroscopy and by electrospray mass spectrometry (ES-MS); for example, the ES-MS spectrum of **C¹²** exhibits peaks at m/z 3785.3 [**C¹²** – BF_4]⁺ and 1849.1 [**C¹²** – 2BF_4]²⁺.



Complexation of copper(I) by **L¹²** induces an upfield shift of about 0.31 ppm for the ^1H NMR signal of the imine proton while the wavenumber of the $\nu_{\text{N}=\text{C}}$ stretching vibration increases by circa 40 cm^{-1} . Cation binding also affects other regions of the ^1H NMR spectra, the most notable being the upfield shifts of the three doublets belonging to those protons attached to the pyridine rings *ortho* to the imine group ($\Delta\delta = 0.78$) and to the exocyclic C–C bond ($\Delta\delta = 0.66$ (terminal rings) and 0.43 (central ring)). Furthermore, the AB quartet belonging to the bridging N-phenyl-O moiety is shifted upfield by 0.48 ppm. These various spectral perturbations,

together with the ES-MS results, are consistent with two polytopic ligands wrapping around two copper(I) cations in such a way that each metal center is coordinated to three pyridine nitrogen atoms and one imino nitrogen atom, leaving a vacant imine group on each ligand. This arrangement forces the above-mentioned protons to reside within the shielding region exerted by the complementary ligand. Only a single imine resonance is observed in solution, however, such that the complex must be in a state of dynamic fluctuation whereby the two coordinated terpy ligands glide across the metal centers.^[9] This internal flexibility might be of extreme importance in controlling the morphology of the metal complex and we note that recent studies have established that certain conformationally unlocked complexes form chiral microdomains within columnar mesophases.^[10] Indeed, the binuclear copper(I) complexes, being equipped with a chiral helical shell and extended paraffinic tails, possess the necessary functionalities by which to assemble into mesophases. Ligands **L⁸** and **L¹⁶** also formed helicoidal dinuclear copper(I) complexes featuring similar spectroscopic behaviour.

The unique coordination of these intricate complexes was unambiguously confirmed by a crystallographic structural determination of the parent complex, in which the trialkoxybenzoate termini are replaced by methoxy groups (Figure 1a). The packing of this compound, projected along the xy plane, has the molecules aligned in parallel rows and arranged in single layers of thickness $b/2 = 11.5\text{ \AA}$ surrounded by the methoxy groups and separated by the BF_4^- ions (Figures 1b and 1c). Evidently, this packing is auspicious for the formation of lamellar mesophases when alkyl chains are inserted between the layers, provided here by judicious tailoring of the ligands.

The thermotropic polymorphism of **C¹²** was analyzed by differential scanning calorimetry (DSC) and polarizing optical microscopy (POM). The DSC profiles, recorded on heating from 0 to 200°C , show two peaks, each corresponding to a first-order phase transition. The crystal melts at 115°C ^[11] into a liquid-crystalline material and transforms to an isotropic liquid at 187°C ($\Delta H = 2.6\text{ J g}^{-1}$). The liquid-crystalline phase does not revert back to the crystal upon cooling to room temperature. Optical textures, observed on slow cooling from the isotropic melt (crossed droplets turning into micellar rods and coalescing into a fine Schlieren texture), indicate that the liquid crystal has a biaxial smectic structure.

Definitive structural information for the liquid-crystalline phase was sought from X-ray diffraction (XRD) studies. The observed patterns (Figure 2) indicate an unusual macroscopic organization wherein individual molecules align to form a columnar liquid crystal with a lamellar morphology, similar to what we found for an *ortho*-metallated palladium complex.^[12] Hints of such supramolecular organization have been suggested by Levelut et al.^[13] and Lattermann et al.^[14] for charge transfer assemblies and azamacrocyclic compounds, respectively. Four notable aspects of the structure are as follows. a) The diffuse band at $4.5\text{ \AA}$ (marked A in Figure 2) confirms that the alkyl chains are segregated from the aromatic cores and have a liquidlike conformation. b) The presence of two sharp equidistant reflections, indexed as (001) and (002), shows the molecules to be arranged in regularly spaced layers

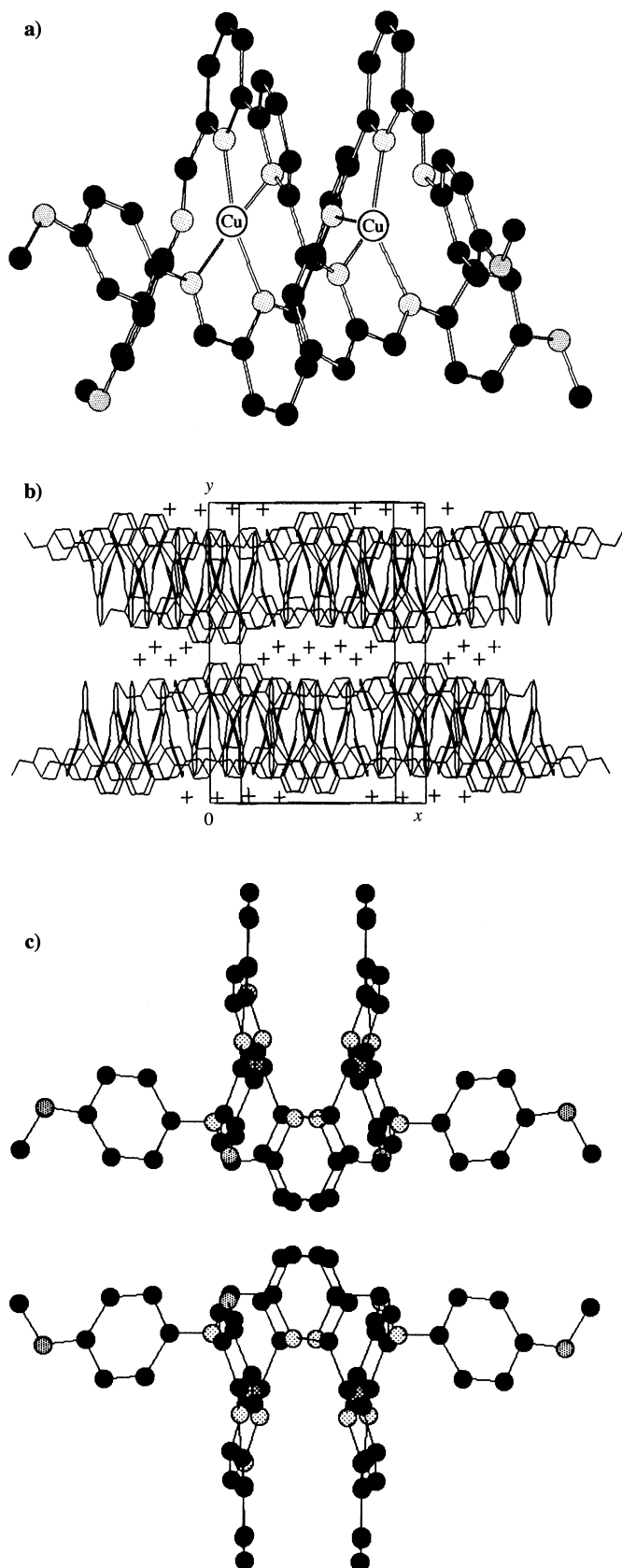


Figure 1. a) X-ray crystal structure of the copper(I) terpyridine helicite prepared from a terpy-anisole ligand^[9]; b) crystal packing of the same dinuclear copper(I) complex projected along the xy plane. For the sake of clarity the BF_4^- ions are represented as +; c) view of two molecules of this complex projected along the xy plane. The BF_4^- ions located between these molecules have been omitted for clarity.

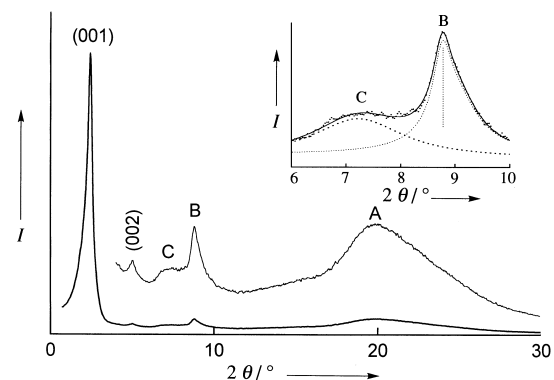


Figure 2. Powder X-ray diffraction pattern of complex **C**¹² in the liquid-crystal state ($T = 100^\circ\text{C}$). For clarity, the intensity at Bragg angles $2\theta > 3^\circ$ is multiplied tenfold. The intensity I is reported in arbitrary units. Inset: expanded representation of peaks B and C.

for which the lamellar period $d = 35.5 \text{ \AA}$ corresponds to the length of one individual helicite (Figure 3). c) The bands B and C (Figure 2) are related to the internal structure of the aromatic sublayers with the respective spacings of 10.1 and 12.2 $\text{\AA}$ due to the lateral dimensions of the helicite core. The sharpness of B ($\Delta(2\theta) \approx 0.4^\circ$) shows that the lateral packing of

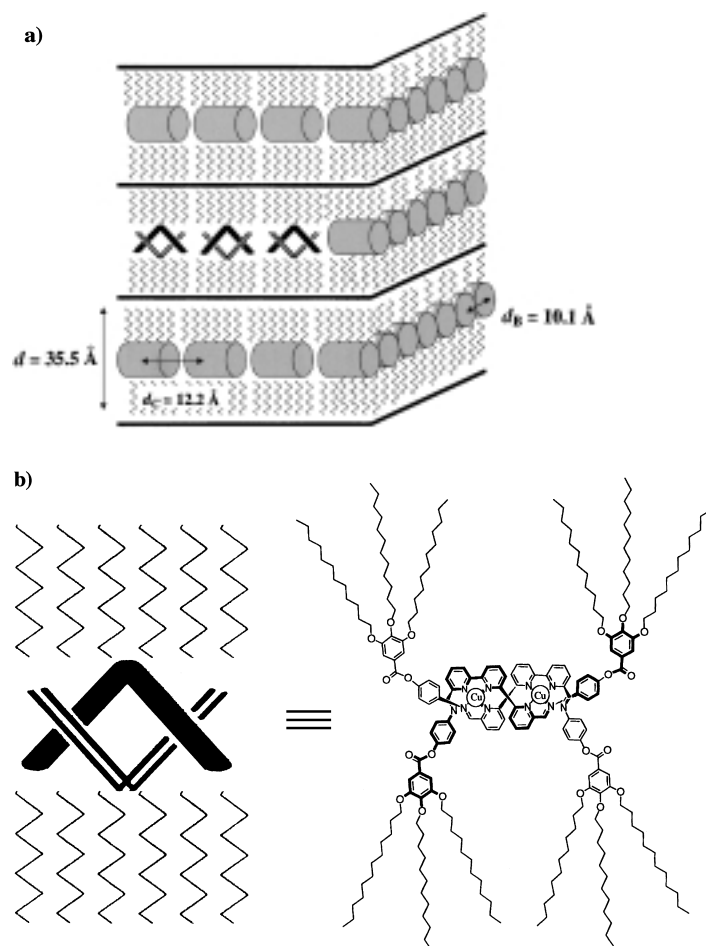


Figure 3. a) Schematic front and lateral view of the smectic layering. The rigid helicite cores (shown schematically (see b) and as gray cylinders) are arranged in single layers separated by the molten alkyl chains (wavy lines). b) Schematic representation of the terpy-based metallohelicite.

molecular rows inside the aromatic sublayers extends over some 22 rows whereas the width of C ($\Delta(2\theta) \approx 2.0^\circ$) indicates loose packing inside the rows that is restricted to 3.5 repeat units. d) The absence of (10l) reflections and, significantly, the presence of a wide-angle wing to band B show that the layers are not positionally correlated in three-dimensional space. Therefore, the liquid-crystalline phase has a genuine smectic structure (Figure 3) and resembles that of linear DNA stretched across a lipid bilayer.^[15] In fact, the structural similarity between the smectic liquid-crystalline phase and the oriented DNA molecule is striking. From the one-dimensional positional order inside the layers and long-range orientational order of the rows across the layers, as revealed by the optical texture, the structure can be categorized into the class of hexatic smectic liquid crystals.^[16] We consider that local segregation of the polar helicate from the paraffinic chains creates an interface that facilitates adoption of a nondiscoidal liquid-crystalline phase. This seems to be viable to obtain new types of self-organized assemblies of nanoscopic dimensions.

Chemical oxidation of **C**¹² with ferrocenium cations forms a mixed-valence complex **C**^{12m} which was unambiguously characterized by its ES-MS spectrum (pseudomolecular peaks at m/z 1892.7 [**C**^{12m} – 2BF₄]²⁺ and 1233.0 [**C**^{12m} – 3BF₄]³⁺), its EPR spectrum,^[17,18] and a Gaussian-shaped intervalence charge transfer (IVCT) absorption band^[19] centered at 1435 nm ($\epsilon_{\text{max}} = 48 \pm 10 \text{ M}^{-1} \text{ cm}^{-1}$). Observation of this IVCT band indicates that the metal centers possess very similar coordination shells in the mixed-valence complex, while the EPR spectrum is consistent with the copper(II) center being five coordinate. These realizations are made possible by the availability of ancillary imino functions adjacent to each metal center that can coordinate to the emergent copper(II) cation and thereby stabilize the higher-valence state. Remarkably, the mixed-valence complex remains liquid crystalline over a wide temperature range but, because of the increased electronic charge, the morphology differs significantly from that described for the binuclear copper(I) complex. Indeed, the XRD studies reveal a single sharp peak at 51 Å (indicative of macroscopic order) together with a diffuse band at about 4.5 Å confirming that the alkyl chains are conformationally disordered. The absence of supplementary reflection peaks limits, at the present time, further description of the morphology of this liquid-crystalline material.

In summary, we have described an example of a liquid-crystalline metallohelicate which resists recrystallization from the melt and which forms a liquid-crystalline, mixed-valence complex. This is clear indication that multicharged (di- and tricationic) helicates can be organized under ambient conditions into large scale macroscopic arrays that retain redox activity. It should be noted that there is a precedent for forming a liquid-crystalline material from a mixed-valence Ru^{II}/Ru^{III} complex.^[20] While the mesophase obtained with the Cu-terpy helicate is smectic, that of the corresponding 2,2'-bipyridine complex^[4] is columnar. The two major structural differences between these polypyridine complexes might account for this structural variation: a) The extended length of the aromatic core stretches the molecule into a calamitic shape that favors a smectic arrangement; and b) fluxional motion inherent to the terpy-based metallohelicate increases

the entropy of the system and favours the formation of the mesophase. It is this local fluctuation that establishes microdomains sustaining liquid-crystalline behavior at room temperature. Furthermore, the **C**ⁿ helicate forms a highly unusual, smectic mesophase comprising layers of metallohelicates arranged in equidistant columns but without a third-dimensional correlation of the layers (Figure 3). Such structures are made possible by combining internal flexibility of the coordinated polytopic ligands, ancillary coordination sites to stabilize emerging redox centers, and multiple flexible side-chains. The unique properties of these liquid-crystalline complexes arise from the combination of order and mobility at the molecular level and from an adequate mismatch between the central helicoidal shell and the flexible swallow-tail-shape paraffinic tails. The principles elucidated here may certainly be applicable to other classes of molecules as well and suggest that introduction of flexible coils in self-assembled supramolecular structures might provide a novel strategy to construct multidimensional nanostructures.

Experimental Section

Ligand L¹²: A Schlenk tube was successively charged with 6,6''-diformyl-2,2':6',6''-terpyridine (0.035 g, 0.120 mmol), 4-[3,4,5-tri(dodecyloxy)benzoyloxy]aniline (0.186 g, 0.243 mmol), EtOH (10 mL) and acetic acid (1 drop). At 80 °C, complete solubilisation occurs and the solution was heated for 4 h. After cooling to room temperature, the precipitate was filtered, washed with EtOH (3 × 10 mL) and afforded 0.172 g of **L**¹² (80 % yield). M.p. 77–79 °C; UV/Vis (CH₂Cl₂): λ_{max} (ϵ) = 300 nm (62 400 M^{−1} cm^{−1}); ¹H NMR (200.1 MHz, CDCl₃, 25 °C): δ = 8.78 (s, 2H, H-imine), 8.73 (d, ³J(H,H) = 7.7 Hz, 2H), 8.62 (d, ³J(H,H) = 8.0 Hz, 2H), 8.31 (d, ³J(H,H) = 8.0 Hz, 2H), 8.03 (m, 3H), 7.37 (q_{AB} + s, 12H), 4.07 (m, 12H, OCH₂), 1.8 (m, 12H, CH₂), 1.5 (m, 12H, CH₂), 1.27 (brs, 96H, CH₂), 0.88 (m, 18H, CH₃); ¹³C{¹H} NMR (50.3 MHz, CDCl₃, 25 °C): δ = 165.17 (C=O), 161.32 (C=N), 156.17, 155.08, 154.23, 153.09, 149.89, 148.74, 143.21, 138.14, 137.61, 123.91, 122.63, 122.31, 121.72, 121.46, 115.76, 108.71 (aromatic), 73.69 (OCH₂), 69.39 (OCH₂), 32.03 (CH₂), 30.45 (CH₂), 29.80 (CH₂), 29.74 (CH₂), 29.68 (CH₂), 29.50 (CH₂), 29.47 (CH₂), 29.42 (CH₂), 26.19 (CH₂), 22.80 (CH₂), 14.20 (CH₃); IR (KBr): $\tilde{\nu}$ = 2925 (s), 2855 (w), 1732 (m, ester), 1629 (w, imine), 1576 (m), 1500 (m), 1464 (w), 1432 (m), 1385 (w), 1338 (s), 1192 (s), 1116 (s), 1003 (w), 958 (w), 863 cm^{−1} (w); FAB⁺-MS (*meta*-nitrobenzylalcohol matrix): m/z [%]: 1785 (80) [**M**+H]⁺, 1022 (20) [**M** – NC₆H₄OCOC₆H₂(OC₁₂H₂₅)₃], 259 (25) [**M** – 2(NC₆H₄OCOC₆H₂(OC₁₂H₂₅)₃)]]; elemental analysis calcd for C₁₁₅H₁₇₃N₅O₁₀ (M_r = 1785.689): C 77.35, H 9.77, N 3.92; found: C 77.10, H 9.45, N 3.62.

Dicopper(I) complex C¹²: A solution of [Cu(CH₃CN)₄][BF₄] (0.022 g, 0.069 mmol) in anhydrous CH₃CN (10 mL) was transferred by cannula to a stirred solution of **L**¹² (0.120 g, 0.067 mmol) in anhydrous CH₂Cl₂ (15 mL) at 20 °C. The solution was kept under an atmosphere of argon. After stirring for 2 h the solution was filtered over celite and evaporated to dryness. The residue was recrystallized from CH₂Cl₂/MeOH giving 0.125 g (97 % yield) of a dark-brown powder. UV/Vis (CH₂Cl₂): λ_{max} (ϵ) = 278 (115 200), 450 (6600), 500 nm (5600 M^{−1} cm^{−1}); ¹H NMR (200 MHz, CDCl₃, 25 °C): δ = 8.45 (s, 4H, H-imine), 7.93 (m, 18H), 7.37 (s, 8H), 6.92 (q_{AB}, J_{AB} = 8.9 Hz, 16H), 4.06 (m, 24H), 1.80 (m, 24H), 1.49 (m, 24H), 1.26 (brs, 192H), 0.87 (m, 36H); ¹³C{¹H} NMR (50.3 MHz, CDCl₃, 25 °C): δ = 165.05 (C=O), 156.47 (C=N), 153.07, 152.52, 152.04, 151.42, 150.65, 144.39, 143.39, 139.50, 127.01, 125.85, 124.18, 123.15, 122.91, 108.63 (aromatic), 73.61 (OCH₂), 69.34 (OCH₂), 31.90 (CH₂), 30.36 (CH₂), 29.63 (CH₂), 29.36 (CH₂), 29.13 (CH₂), 26.13 (CH₂), 26.07 (CH₂), 22.67 (CH₂), 14.07 (CH₃); IR (KBr): $\tilde{\nu}$ = 2925 (s), 2855 (s), 1731 (m, ester), 1588 (m, imine), 1501 (m), 1463 (w), 1433 (m), 1384 (w), 1336 (s), 1190 (s), 1112 (s), 952 (w), 866 cm^{−1} (w); ES-MS (CH₂Cl₂): m/z : 3785.3 [**M** – BF₄]⁺, 1849.1 [**M** – 2BF₄]²⁺; elemental analysis calcd for C₂₃₀H₃₄₆N₁₀O₂₀Cu₂B₂F₈ (M_r = 3872.078): C 71.35, H 9.01, N 3.62; found: C 71.19, H 8.68, N 3.44.

Cu^I/Cu^{II} mixed-valence complex **C**^{12m}: A solution of ferrocenium (BF₄ salt) (0.003 g, 0.01 mmol) in CH₂Cl₂ (5 mL) was added to a stirred solution of **C**¹² (0.04 g, 0.01 mmol) in anhydrous CH₂Cl₂ (10 mL) at 20 °C. After stirring for 2 h, the solvent was removed. Crystallisation from hexane afforded 0.035 g (88% yield) of a dark-brown powder. UV/Vis (CH₂Cl₂): λ_{max} (ε): 279 (137000), 450 (6700), 500 nm (4600 M⁻¹ cm⁻¹); IR (KBr): ν̄ = 2925 (s), 2855 (s), 1731 (m, ester), 1590 (m, imine), 1500 (m), 1465 (w), 1433 (m), 1385 (w), 1336 (s), 1190 (s), 1113 (s), 862 cm⁻¹ (w); ES-MS (CH₂Cl₂): m/z: 1892.7 [M - 2BF₄]²⁺, 1233.0 [M - 3BF₄]³⁺; elemental analysis calcd for C₂₃₀H₃₄₆N₁₀O₂₀Cu₂B₃F₁₂·CH₂Cl₂ (M_r = 3958.882 + 84.933): C 68.61, H 8.67, N 3.46; found: C 68.22, H 8.41, N 3.08.

The synthesis and characterization of additional ligands and complexes, as well as their mesomorphic behavior, will be reported in full elsewhere. Equipment used: DSC: Perkin-Elmer DSC 7, heating/cooling rate 10 K min⁻¹; POM: Leitz Orthoplan, Mettler FP 82 hot stage; XRD: Guinier focusing camera, Cu_{Kα1} radiation, powder samples in Lindemann capillaries, INSTEC hot-stage, INEL CPS-120 curved position-sensitive detector.

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structure. A nonsymmetrical structure requires the reduction potentials of the metal centers to differ by 0.22 eV but this redox disparity is too large to sustain an IVCT absorption band.

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An Expedient Total Synthesis of the Natural Stereomeric Mixture of Stenusine Following a Possible Biogenetic Pathway**

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Dedicated to Professor Pierre Potier
on the occasion of his 65th birthday

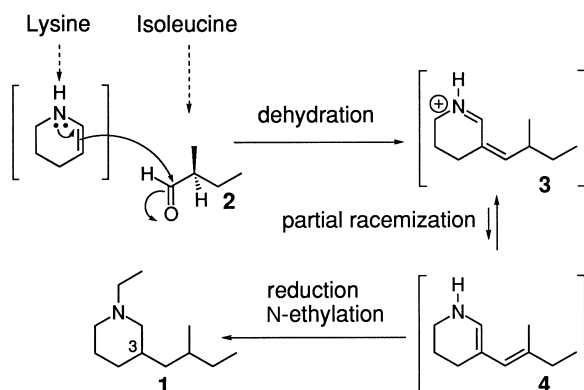
Stenus comma (Coleoptera, Staphylinidae) is a familiar beetle encountered on the sandy banks of stagnant ponds and sluggishly flowing rivers in Eastern and Central Europe. The beetle propels itself over the water surface by an unusual biological phenomenon in which it expels an oily substance with a high spreading capacity onto the aqueous surface. Since the isolation and structure elucidation of stenusine **1** (see Scheme 1; [α]₃₆₅²⁰ = +5.8, c = 0.115 in EtOH) as the main component of the propulsion fluid and a toxic chemical substance by Schildknecht et al.,^[1] numerous preparations have been developed based on racemic^[2] and asymmetric^[1a, 3] strategies. Finally the enantioselective syntheses of isomeric (2*S*,3*S*)-1-ethyl-3-(2-methylbutyl)piperidine and (2*S*,3*R*)-1-ethyl-3-(2-methylbutyl)piperidine by Enders, De Kimpe et al.^[3a] accompanied by chiral GC for both synthetic and natural samples helped to establish that natural stenusine is a mixture of the four possible stereoisomers in a ratio of 43:40:13:4 = (*S*,*S*):(*S*,*R*):(*R*,*R*):(*R*,*S*) with predominance (83:17) of the two epimers with *S* configuration on the side chain.

It is unusual that an organism produces a natural compound as a mixture of two pairs of enantiomers in a particular ratio. This intriguing observation led us to reflect on the biogenetic origin of the compound. Although Schildknecht et al.^[1a] suggested a terpenoid origin, the biosynthesis of stenusine has not yet been elucidated by incorporation experiments. In continuation of our research on the biomimetic synthesis of piperidine alkaloids,^[4] we sought a rapid access to natural stenusine. The essence of our biogenetic postulate and strategy for synthesis is that structure **1** derives most likely from lysine and isoleucine and could be considered as the biological condensation of their metabolites, 1,2,3,4-tetrahydropyridine and aldehyde (–)-**2** (Scheme 1). The inter-

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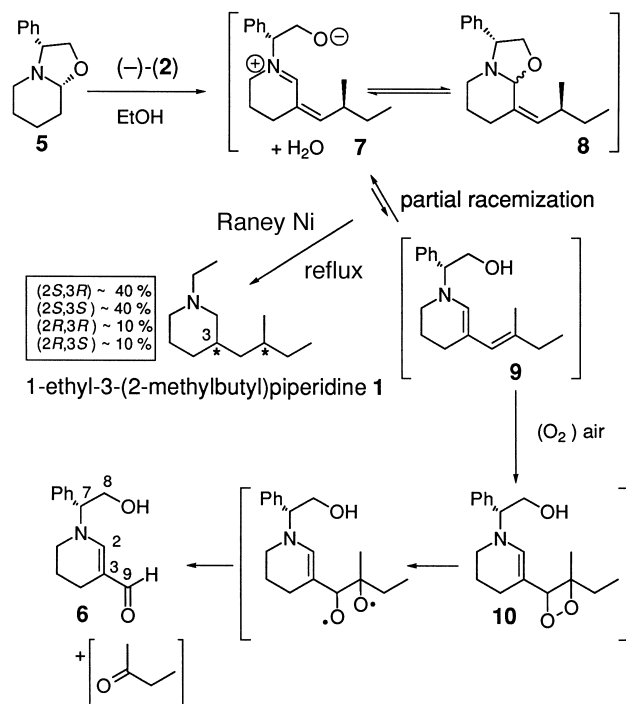


Scheme 1. Possible biogenetic pathway for the synthesis of **1**.

mediates **3** and **4** resulting from the iminium–enamine equilibrium (Scheme 1) could explain the formation of enantiomers at the stereogenic center C-3 and the partial racemization on the side chain leading to the natural stereomeric mixture.

To test the chemical basis of the hypothesis outlined in Scheme 1, we decided to use a stable surrogate of 1,2,3,4-tetrahydropyridine as starting material. We chose compound **5**,^[5] which is easily obtained from (*R*)-(-)-phenylglycinol as chiral nitrogen source and glutaraldehyde as C₅ unit biogenetically derived from lysine. The potential enamine functionality of **5** through the oxazolidine/alcohol–enamine equilibrium in protic media was revealed by its ability to react with electrophiles such as aldehydes.

Reaction of **5** with an excess of (*S*)-(-)-2-methylbutyraldehyde ((-)-**2**)^[6] in ethanol at room temperature led to the total consumption of the starting material (monitored by TLC) and isolation of only small quantities of compound **6** (Scheme 2) instead of the expected oxazolidine **8**. A modification of the



Scheme 2. Synthesis of **1**.

reaction conditions (refluxing in EtOH in the presence of air/molecular sieves) afforded **6** in 60% yield. The formation of this new compound provides strong support for the sequence depicted in Schemes 1 and 2, in which the intermediate conjugate iminium ion **7** (synthetic equivalent of **3**) is in equilibrium with tautomeric dienamine **9** (synthetic equivalent of **4**). The unexpected oxidative degradation of dienamine **9** can be rationalized by the formation of a dioxetane **10**, which produces two carbonyl fragments by a stepwise mechanism in which a 1,4-diradical^[7] is formed by cleavage of the oxygen bond, followed by double β -cleavage. This sequence leads to aldehyde **6**, an optically active synthetic equivalent of 1,4,5,6-tetrahydronicotinaldehyde,^[8] and butan-2-one (not isolated).^[9]

To synthesize stenusine **1**, it was necessary to perform the reaction in the total absence of oxygen. Moreover, for stenusine bearing an ethyl chain at the nitrogen atom the chiral appendage of phenylglycinol had to be properly exchanged. We have shown that the phenylethanol moiety of phenylglycinol can be replaced easily by an alkyl chain under hydrogenolytic conditions by treatment with the corresponding primary alcohol in the presence of Raney nickel.^[4b, 10] Thus, in a one-pot procedure, addition of Raney nickel to the reaction mixture of (-)-**2** and **5** in EtOH under argon (Scheme 2) afforded directly stenusine **1** ($[\alpha]_{365}^{20} = +5$ ($c = 0.115$ in EtOH), 51%). It is noteworthy that a series of eight steps is performed in a single operation: oxazolidine ring opening, condensation, dehydration, reduction, debenzyla-tion, oxidation of ethanol to ethanal, Schiff base formation, and reduction to give an *N*-ethyl group.

Our initial hypothesis gained further support when we measured an optical rotation for **1** identical to that reported by Schildknecht^[11] for natural stenusine. We thus decided to investigate more accurately the diastereomeric ratio of our mixture by NMR spectroscopy, taking advantage of the easy formation of a chloroform-soluble salt after addition of Mosher acid to synthetic stenusine **1** in a 1:1 ratio. This chiral solvating agent has been already used to induce nonequivalence in the ¹H NMR spectra of several racemic tertiary amines, usually in the signals of the protons adjacent to the amino group.^[11] While no significant information could be deduced from the ¹H NMR spectrum, an excellent resolution of several signals was displayed by the ¹³C NMR spectrum. Interestingly, those two resonances corresponding to C-2^[12] were split into four signals of different intensity. Quantitative evaluation of the stereomeric composition of mixtures by ¹³C NMR spectroscopy is a known technique.^[13] To this end, racemic stenusine ($\pm$)-**1** was prepared by the same one-pot procedure by using **5** and racemic 2-methylbutyraldehyde. After addition of one equivalent of Mosher acid to a 0.01 mM solution of ($\pm$)-**1** in CDCl₃, a ¹³C NMR spectrum was recorded. As expected, the resonances of C-2 were split into four signals of equal intensity.

The spin-lattice relaxation time T_1 of each signal was measured by the inversion–recovery method^[13] and was shown to be identical (0.6 s) under the experimental conditions. Taking into account the identical value of T_1 for the four C-2 signals in ($\pm$)-**1**, a comparison of the peak areas of these signals gave a 25/26/25/24 ratio for the diastereomers in

the racemic stenusine and a 9/36/43/12 ratio in the compound derived from (–)-**2**. Although these values were obtained with moderate accuracy (percentage error $\pm 2\%$) as expected for ^{13}C NMR spectroscopy, they are in good agreement with the data for natural stenusine. These results indicated that the synthesis afforded no stereochemical control at one center and partial control at the other. The starting material being (–)-**2**, one might expect total absence of control at the stereogenic center C-3 and partial racemization at the chiral carbon atom of the 2-methylbutyl moiety during the reaction (Scheme 2). Thus, the major diastereomers should be (2*S*,3*S*)-**1** and (2*S*,3*R*)-**1** as observed by Enders, De Kimpe et al.^[3a] in the natural stenusine.

In conclusion, racemic stenusine, (±)-**1**, could be synthesized in a one-pot procedure using simple reagents—the shortest synthesis hitherto of (±)-**1**. Moreover, the same strategy using (*S*)-(–)-2-methylbutyraldehyde afforded a disproportionate mixture of the four stereoisomers in a ratio analogous to that of natural stenusine as demonstrated by optical rotation and NMR studies. The efficiency and shortness of this first synthesis of the natural stenusine mixture might confirm the likelihood of our biogenetic hypothesis. The latter is also supported by the isolation of the new conjugated aldehyde **6**.

Experimental Section

5: To a solution of (*R*)-(–)-phenylglycinol (200 mg, 1.45 mmol) in methanol (10 mL) cooled to -5°C was added dropwise over 10 min under vigorous stirring glutaraldehyde (25% aqueous solution, 0.6 mL, 1.45 mmol) diluted in methanol (3 mL). The mixture was stirred for another 10 min before it was cooled to -50°C . Sodium borohydride (26 mg, 0.619 mmol) was added gradually over 2 h. Then a saturated aqueous solution of sodium hydrogencarbonate was added and the mixture was extracted with CH_2Cl_2 ($3 \times$). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The oily residue (290 mg) was purified by flash chromatography on silica gel (90/10 cyclohexane/diethyl ether). Crystallization from cyclohexane afforded **5** (147 mg, 50%) as colorless crystals. M.p. $38-41^\circ\text{C}$; $[\alpha]_D^{20} = -103$ ($c = 1$, in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 1.30-1.45$ (m, 1H; H-4), $1.48-1.61$ (m, 3H), $1.85-1.89$ (m, 1H), $1.97-2.05$ (m, 2H), 2.85 (br d, $^3J(\text{H,H}) = 10.5$ Hz, 1H; H-6), 3.53 (t, $^3J(\text{H,H}) = 8$ Hz, 1H; H-7), 3.65 (t, $^3J(\text{H,H}) = 8$, $^3J(\text{H,H}) = 8$ Hz, 1H; H-8), 3.68 (dt, $^3J(\text{H,H}) = 3$, $^3J(\text{H,H}) = 9$ Hz, 1H; H-2), 4.17 (t, $^3J(\text{H,H}) = 8$, $^3J(\text{H,H}) = 8$ Hz, 1H; H-8), $7.26-7.40$ (m, 5H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 22.5$, 24.8 , 30.3 , 47.8 , 67.1 , 72.9 , 94.6 , 127.6 , 127.7 , 128.4 , 138.9 ; MS: m/z : 204 [$M^+ + 1$]; elemental analysis for $\text{C}_{15}\text{H}_{17}\text{NO}$: calcd: C 76.81, H 8.43, N 6.89; found: C 76.75, H 8.15, N 6.96.

1: Compound **5** (600 mg, 2.95 mmol) was dissolved in ethanol (50 mL). The resulting solution was degassed with argon and (–)-**2** was added (29.5 mmol, 3.16 mL). The mixture was stirred at room temperature in darkness for 5 d. Raney nickel (W2, 50% slurry in water, 11 g) was added and the suspension refluxed for 24 h before being filtered over celite. After addition of a saturated solution of sodium hydrogencarbonate, the cloudy solution was extracted with dichloromethane ($3 \times$). The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum to give an oily residue. Purification by flash chromatography over silica gel (dichloromethane/methanol, 92/8) followed by ion-exchange chromatography (amberlyst OH^-) led to **1**^[1, 2, 3] as a colorless oil (108 mg, 20%). When the reaction was performed in EtOH/ H_2O (3/1) followed by extraction (Et_2O), evaporation and dissolving in EtOH before treatment with Raney nickel, compound **1** was obtained in 51% yield. ^{13}C NMR (75 MHz, CDCl_3 , 0.01 M solution of **1** and Mosher acid, 25°C) C-2: $\delta = 57.8$ (9%), 57.7 (36%), 57.5 (43%), 57.4 (12%).

6: Compound **5** (400 mg, 1.97 mmol) and (±)-**2** (10 equiv, 19.7 mmol, 2.11 mL) were dissolved in dry ethanol (30 mL). Molecular sieves ($3 \text{ \AA}$, 1 g)

were added and the mixture was refluxed for 48 h under air bubbling. Filtration and concentration gave a yellowish oil which was submitted to flash chromatography (dichloromethane/methanol, 95/5). Compound **6** was obtained from trituration in diethyl ether as white crystals (273 mg, 60%). M.p. $116-118^\circ\text{C}$; $[\alpha]_D^{20} = 52$ ($c = 1$, in CHCl_3); IR (CHCl_3 , film): $\tilde{\nu}$ [cm^{-1}] = 1578 (CHO); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 1.69-1.77$ (m, 2H; H-5), $2.22-2.29$ (m, 2H; H-4), $3.06-3.29$ (m, 2H; H-6), $4.10-4.14$ (m, 2H; H-8), $4.49-4.54$ (bt, $^3J(\text{H,H}) = 8.5$ Hz, 1H; H-7), $7.20-7.40$ (m, 6H; H_{ar} , H-2), 8.71 (s, 1H; H-9); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 18.0$ (C-5), 20.3 (C-4), 44.9 (C-6), 61.3 (C-8), 70.1 (C-7), 110.6 (C-3), 126.9 (HC_{ar}), 128.3 (HC_{ar}), 128.8 (HC_{ar}), 136.2 (C_{ar}), 156.5 (C-2), 186.9 (C-9); MS (EI): m/z : 231 [M^+]; HRMS (EI): m/z : [M^+] for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: calcd: 231.1259 ; found: 231.1255 .

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From Large Furan-Based Calixarenes to Calixpyrroles and Calix[*n*]furan[*m*]pyrroles: Syntheses and Structures**

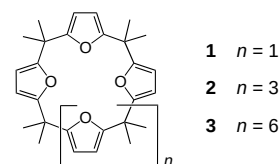
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Giovanna L. La Torre, Andrew J. P. White, and
David J. Williams

Calixarenes have for many decades been the subject of intense research. These cyclophanes can be considered as "benzene based" since they are made up of a number of phenolic residues that are linked by a one-carbon-atom bridge to form a macrocyclic system.^[1] Their heterocyclic analogues, on the other hand, especially those containing more than four aromatic units, have received considerably less attention.^[2]

As part of our continuing research^[3] on the functionalization of the furan-based analogues of the calixarenes **1** and **2**, obtained by the acid-promoted condensation of furan and

acetone,^[4] we have substantially improved both the yield and synthesis of the cyclic hexamer **2**, and also developed the first synthesis of the nonamer **3**.^[5]

Thus, with large quantities of **2** and **3** at our disposal, we were able to explore their potential as precursors for other hetero-



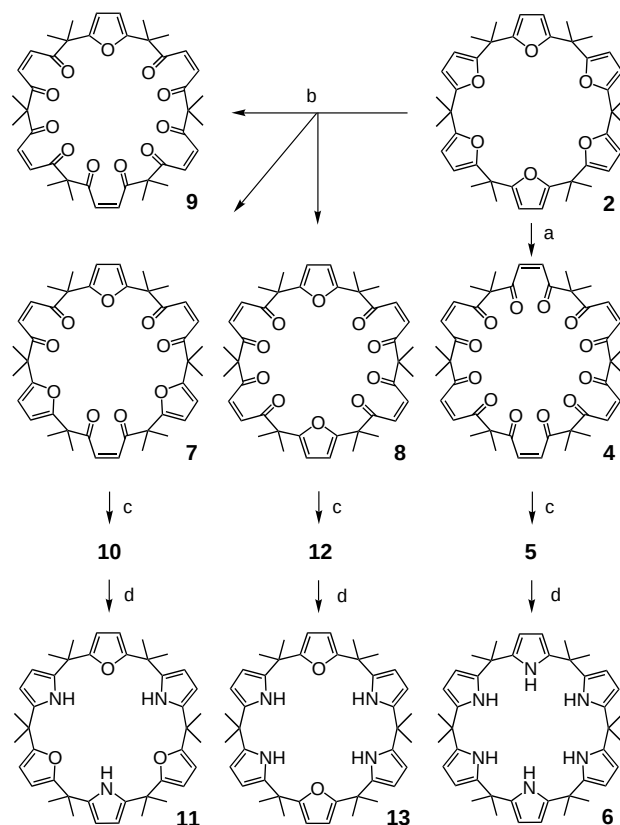
calixarenes through the conversion of all (or just some) of the furan rings into pyrrole, thiophene, or other heterocyclic units.^[6] The homologation of the furan units of **2** and **3** into pyrroles^[6a] appeared a particularly attractive target since calix[4]pyrroles^[7] have recently been shown to bind both anions and neutral molecules,^[8] and also to form a number of transition metal complexes that exhibit interesting redox properties.^[9] Moreover, calix[*n*]pyrroles with *n* > 4 are far less accessible than calix[4]pyrroles because the direct condensation of ketones with pyrrole yields complex mixtures with the tetramer being by far the major component.^[8b] A recent synthesis of a calix[6]pyrrole system^[10] relies on the use of intermediate 1:2 condensation products of aryl ketones and pyrrole. The synthesis of a calix[5]pyrrole (as part of a larger molecule and which uses a calix[5]arene as template) has also been reported.^[11]

Herein we describe a) the conversion of the calix[6]furan **2** into the corresponding calix[6]pyrrole **6**, b) its use as a precursor for the mixed heterocyclic systems calix[3]furan[3]pyrrole **11** and calix[2]furan[4]pyrrole **13** (Scheme 1), and c) the X-ray crystal structures of **6** and **11**.

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Scheme 1. The conversion of calix[6]furan **2** into calix[6]pyrrole **6**, calix[3]furan[3]pyrrole **11** and calix[2]furan[4]pyrrole **13**. a) MCPBA (6.2 mol), CHCl₃; b) MCPBA (4 mol), CHCl₃; c) Zn/CH₃COOH (reduction of the olefinic double bonds to -CH₂-CH₂- units); d) CH₃COONH₄/EtOH.

The key compound in the synthesis of **6** is the dodecaketone **5** which was obtained by the method described by Williams and Le Goff.^[12, 13] This compound was treated with ammonium acetate in ethanol to give **6** in 42% yield. Using our improved synthesis of **2**^[5] the preparation of **6** involves five simple steps (from acetone and furan) and does not require the use of chromatography.

The X-ray crystal structure of **6**^[14] (Figure 1) showed the crystals to be solvated with both water and ethanol. The macrocycle adopts a tennis-ball-seam conformation with three of the N-H bonds oriented outwards whilst the other three are directed towards the center of the cavity within which the water molecule is trapped (the ethanol molecule is positioned on the periphery of the macrocycle and is disordered). The binding of the water molecule is in accord with that predicted theoretically^[15a] and demonstrated experimentally^[15b] for the solvation of water by pyrrole. In the present structure the water molecule is involved in no fewer than six hydrogen-bonding interactions with the hexapyrrole: three N-H...O and three O-H...π interactions (Figure 1).

Encouraged by the successful synthesis of **6**, we turned our attention to the possibility of converting only some of the furan rings of **2** into pyrroles. The oxidative ring-opening of only three or four of the furan units in **2** can only produce, in each case, three regioisomers, which differ with respect to the regiochemistry of the newly formed 1,4-eneketone units.

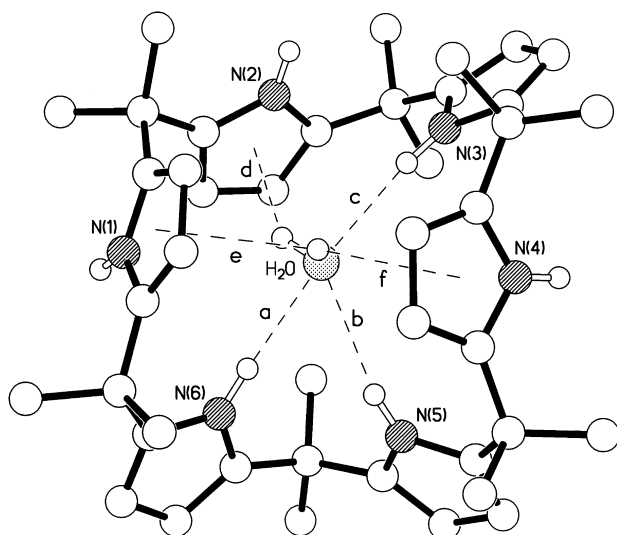


Figure 1. The X-ray crystal structure of **6**. The H-bonding geometries are: a) N $\cdots$ O 3.07, H $\cdots$ O 2.18 Å, N–H $\cdots$ O 174°; b) N $\cdots$ O 3.21, H $\cdots$ O 2.38 Å, N–H $\cdots$ O 152°; c) N $\cdots$ O 3.15, H $\cdots$ O 2.25 Å, N–H $\cdots$ O 173°; d) H $\cdots$ π 2.36 Å, O–H $\cdots$ π 145°; e) H $\cdots$ π 2.75 Å, O–H $\cdots$ π 109°; f) H $\cdots$ π 2.70 Å, O–H $\cdots$ π 113°.

However, treatment of **2** with four moles of *meta*-chloroperbenzoic acid gave (after chromatography on SiO₂, hexane: EtOAc 7:3) only the eneketones **7** (24%) and **8** (52%), which are derived from the opening of furan units at the 1,3,5 and 1,2,4,5 positions within the macrocyclic ring respectively. A small amount of the pentaoxidation product—the decaenketone **9** (14%)—was also obtained. Thus this oxidation process appears to take place with considerable regioselectivity; the mechanism and/or the origin of this selectivity has not yet been investigated. The reduction of the olefinic bonds in **7** and **8** was best achieved with Zn/AcOH, catalytic hydrogenation with Pd/C in EtOAc at 1.5 atm did not proceed to completion. Treatment of the saturated ketones **10** and **12** with CH₃COONH₄ as described for **5** gave the calix[3]furan[3]pyrrole **11** and the calix[2]furan[4]pyrrole **13**, respectively. The ¹H and ¹³C NMR spectra of **7**, **10**, **11** and **8**, **12**, **13** are consistent with the “averaged” D_{3h} and D_{2h} symmetries of the two sets of compounds respectively, thus indicating the regiochemistry of the chemical transformation sequences.

Single crystals of **11**^[16] were obtained from EtOH. The X-ray structure shows that the desired alternating pattern of furan and pyrrole rings has indeed been achieved (Figure 2) as expected on the basis of the NMR spectroscopic data. Here, unlike in **6**, the crystals are free from included solvent, though the conformation of the macrocycle is similar, again having a tennis-ball-seam geometry. This conformation is in part stabilized by an intramolecular N–H $\cdots$ O hydrogen bond between the N(4) pyrrole and O(3) furan ring atoms. Surprisingly, there are no hydrogen-bonding interactions involving either the N(2) or N(6) pyrrole hydrogen atoms. In the absence of included water the conformation is virtually self-filling, though there is a small cleft between the O(1) and O(5) furan rings, which are separated by approximately 5.4 Å. This cleft is partially filled by the edge of the O(1) furan ring of a centrosymmetrically related molecule.

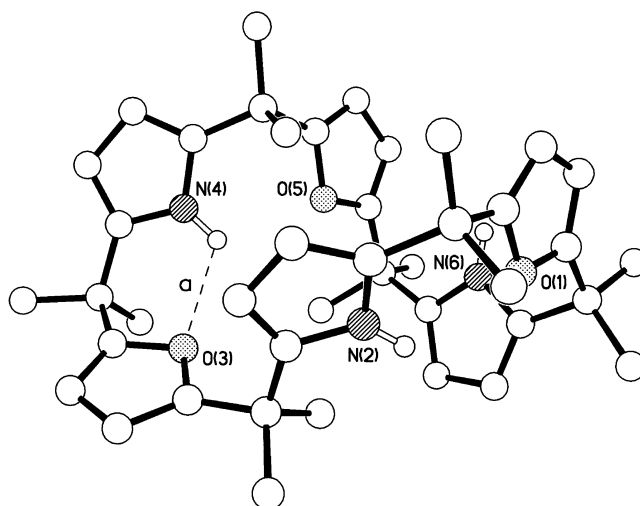


Figure 2. The X-ray crystal structure of **11**. The N–H $\cdots$ O hydrogen bond (a) has N $\cdots$ O 2.80, H $\cdots$ O 2.25 Å, and N–H $\cdots$ O 119°.

The anion binding by calix[4]pyrroles proceeds by a perching geometry that utilizes N–H $\cdots$ anion hydrogen bonds^[8a] rather than by encapsulation since the cavity of the macrocycle is in general too small. In contrast, the “hexameric” mixed furan/pyrrole ring systems **6**, **11**, and **13** have larger cavities and thus have the potential to bind anions though inclusion^[17] and thus discriminate by size^[18] more effectively than the calix[4]pyrroles. The mixed systems **11** and **13** also provide arrays of pyrrole units which should be especially suited for the recognition of nonspherical anions. Furthermore, the ready access to these mixed systems provided by the above synthetic protocols, conjures up the prospect of the formation of novel metal complexes of deprotonated **6**, **11**, and **13**, and the exploration of enticing new areas of chemistry. In addition, the availability^[5] of calix[9]furan **3** provides the opportunity for an extension of this current research to this larger system.

Experimental Section

General: Column chromatography was conducted on silica gel (230–400 mesh, 60 Å, from Aldrich). ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Varian Gemini 300 spectrometer at 300 and 75 MHz, respectively. Mass spectra were measured by electron impact (EI) on a Finnigan Mat 90 spectrometer. Melting points were determined on a Kofler hot stage apparatus, and are not corrected. Abbreviations: py = pyrrole, fr = furan.

Preparation of **6**, **11**, and **13** from **5**, **10**, and **12** respectively: CH₃COONH₄ (1.5 mol per mol of 1,4-diketone units in the macrocycles) was added to the polyketones in absolute EtOH (50 mg mL^{−1}). The mixture was heated at reflux for 30 h under N₂, concentrated in vacuo, and dissolved in a mixture of CHCl₃ and H₂O. The organic phase was dried (MgSO₄), concentrated, then treated as indicated below for each compound.

6: The crude product was dissolved in a mixture of hexane and EtOAc and quickly filtered through SiO₂. The filtrate was concentrated and crystallized from EtOH: 41%, m.p. 232–234 °C. ¹H NMR: δ = 1.53 (s, 36H, CH₃), 5.85 (d, 12H, py-H β), 7.95 (brs, 6H, NH); ¹³C NMR: δ = 29.4 (CH₃), 35.5 (C(CH₃)₂), 103.3 (CH), 138.5 (Cq); EI-MS: *m/z*: 642 [*M*⁺].

11: The crude product was crystallized from EtOH (86 mg). An additional amount (50 mg) was obtained from the mother liquor by column chromatography (hexane:EtOAc 9:1). Total yield 39%, m.p. 162–164 °C from EtOH. ¹H NMR: δ = 1.50 (s, 36H, CH₃), 5.71 (d, 6H, py-H β), 5.85 (s, 6H, fr), 7.95 (brs, 3H, NH); ¹³C NMR: δ = 27.6 (CH₃), 36.0 (C(CH₃)₂),

102.5 and 103.7 (fr-CH and py-CH), 136.8 (py-Cq), 159.8 (fr-Cq); EI-MS: m/z : 646 [(M+H)⁺].

13: The residue was subjected to column chromatography (hexane:EtOAc 9:1) to give **13** as the first eluted fraction: 17%, m.p. 170–171 °C from EtOH. ¹H NMR: δ = 1.48 (s, 24H, CH₃ next to frs), 1.55 (s, 12H, CH₃ between pys), 5.72 (d, 4H, fr), 5.76–5.78 and 5.84–5.86 (2 × m, 2 × 4H, py-H_β), 7.78 (brs, 4H, NH); ¹³C NMR: δ = 27.7 (fr-C(CH₃)₂-py), 29.5 (py-C(CH₃)₂-py), 35.5 (py-C(CH₃)₂-py), 36.1 (fr-C(CH₃)₂-py), 103.0, 103.1 and 103.7 (fr and py-CH), 136.9 and 138.2 (py-Cq), 159.7 (fr-Cq); EI-MS: m/z : 644 [M⁺].

Partial oxidation of calix[6]furan: A solution of *meta*-chloroperbenzoic acid (1.168 g, 6.8 mmol) in CHCl₃ (10 mL) was added over a few minutes to a solution of **2** (1.0 g, 1.5 mmol) in CHCl₃ (50 mL) at 0 °C. The mixture was stirred for 18 h while allowing it to reach room temperature, washed (NaHCO₃ aq), dried (MgSO₄), and concentrated. Column chromatography (hexane:EtOAc 7:3) of the residue afforded, in order of elution: **7**: 250 mg, 24%, m.p. 148–149 °C from EtOH. ¹H NMR: δ = 1.48 (s, 36H, CH₃), 6.12 and 6.23 (2 × s, 2 × 6H, olefin and fr); ¹³C NMR: δ = 22.8 (CH₃), 48.2 (C(CH₃)₂), 107.0 (fr-CH), 134.8 (olefin), 156.6 (fr-Cq), 202.7 (CO); EI-MS: m/z : 697 [M⁺]. **8**: 554 mg, 52%, m.p. 154–156 °C from EtOH. ¹H NMR: δ = 1.42 (s, 12H, COC(CH₃)₂CO), 1.46 (s, 24H, COC(CH₃)₂-fr), 6.16 (s, 4H, fr), 6.39 and 6.44 (AB system, J_{AB} = 12 Hz, 8H, olefin); ¹³C NMR: δ = 20.8 (COC(CH₃)₂CO), 22.6 (COC(CH₃)₂-fr), 48.1 (COC(CH₃)₂-fr), 61.1 (COC(CH₃)₂CO), 107.0 (fr-CH), 133.3 and 137.3 (olefin), 156.7 (fr-Cq), 201.4 and 202.5 (CO); EI-MS: m/z : 712 [M⁺]. **9**: 155 mg, 14%, m.p. 128–130 °C from EtOH. ¹H NMR: δ = 1.33 (brs, 24H, CH₃), 1.40 (brs, 12H, CH₃), 6.10 (s, 2H, fr), 6.29 and 6.33 (AB system, J_{AB} = 12.1 Hz, 4H, olefin), 6.51 (brs, 6H, olefin); EI-MS: m/z : 728 [M⁺].

Reduction of the eneketones **4**, **7**, **8**: An excess of Zn powder was added to a warm solution of the eneketones in glacial acetic acid (ca. 30 mg mL⁻¹). After cooling, the mixture was filtered, diluted with water, and extracted with CHCl₃. The combined organic extracts were washed (NaHCO₃ aq), dried (MgSO₄), and concentrated to give the saturated ketones in quantitative yield.

10: m.p. 200–201 °C from EtOH. ¹H NMR: δ = 1.42 (s, 36H, CH₃), 2.43 (s, 24H, CH₂), 6.17 (d, 6H, fr); ¹³C NMR: δ = 23.4 (CH₃), 31.8 (CH₂), 48.1 (C(CH₃)₂), 106.8 (CH(fr)), 157.4 (Cq(fr)), 210.0 (CO); EI-MS: m/z : 702 [M⁺].

8: m.p. 151–152 °C from EtOH. ¹H NMR: δ = 1.37 (s, 12H, COC(CH₃)₂CO), 1.43 (s, 24H, COC(CH₃)₂-fr), 2.52–2.67 (m, 16H, CH₂), 6.19 (fr); ¹³C NMR: δ = 21.5 (COC(CH₃)₂CO-), 23.3 (COC(CH₃)₂-fr), 31.9 and 32.0 (CH₂), 48.6 (COC(CH₃)₂-fr), 62.0 (COC(CH₃)₂CO-), 106.6 (CH(fr)), 157.6 (Cq(fr)), 209.8 (CO); EI-MS: m/z : 720 [M⁺].

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AlITQ-6 and TiITQ-6: Synthesis, Characterization, and Catalytic Activity**

Avelino Corma,* Urbano Diaz, Marcelo E. Domine, and Vicente Fornés

The catalytic processes involving ever-larger molecules in the fields of oil refining and the production of fine chemicals have pushed the development of catalytic zeolites towards structures with larger pore diameters.^[1–3] The MS-14 molecular sieves, of which MCM-41 is an example, can be used for some catalytic applications with bulky reactants.^[4] However, these materials do not show short range order and, from this point of view, are more similar to amorphous than zeolitic materials.

Recently, a new approach for to use zeolites to catalyze the reactions of larger molecules has been undertaken.^[5] This approach involves preparation of lamellar zeolites, whose structure is subsequently delaminated, to make accessible all the potentially catalytically active sites.^[6] The main difference between this type of material and the mesoporous MCM-41 type materials is that the delaminated zeolites have a short range order and the active sites are, as a consequence, of a zeolitic nature.

Up to now, the only delaminated material reported has been ITQ-2, which shows outstanding adsorption and catalytic properties as an acid catalyst for larger molecules.^[5–7] Unfortunately, although the external surface area of ITQ-2 was above 700 m² g^{−1}, not all acid sites were accessible from this surface since a system of ten-membered ring (10MR) sinusoidal pores remained. Furthermore, the introduction of transition metals by direct synthesis was unsuccessful and redox catalysts were produced only by anchoring titanium on the external silanol groups through a secondary synthesis.^[8] The resultant material was active and selective towards the epoxidation of olefin with organic peroxides but not when the more desirable oxidant H₂O₂ was used.

We have now developed a delaminated zeolite (ITQ-6) as a silicoaluminate (AlITQ-6) and as a silicotitanate (TiITQ-6). The acid and redox-active sites were introduced by direct synthesis and are accessible from the external surface. Herein, we present the synthesis, characterization, and

catalytic activity of ITQ-6 systems towards acid and epoxidation reactions using H₂O₂ as oxidant. All results referring to ITQ-6 are as the aluminate form AlITQ-6 unless otherwise specified.

The X-ray diffraction (XRD) patterns of ferrierite (FER)^[9] (Figure 1d) and ITQ-6^[10] (Figure 1c) show, on comparison, that the intensity of the reflections corresponding to planes

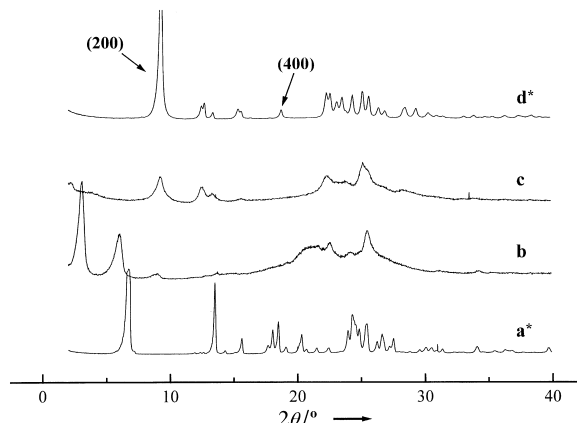
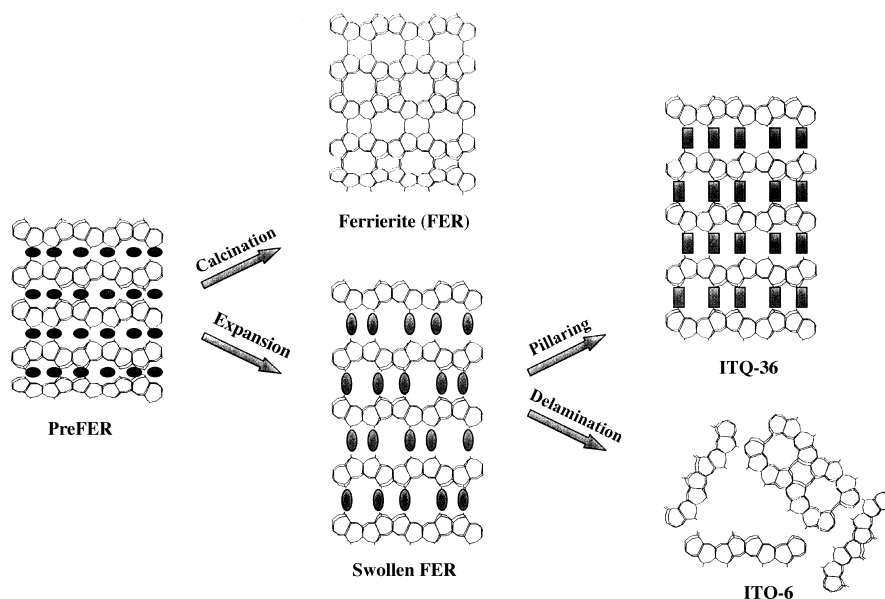


Figure 1. XRD patterns of: a) PreFER, the lamellar precursor of ferrierite; b) PreITQ-6, the expanded material; c) ITQ-6, a delaminated zeolite; d) FER, a ferrierite zeolite obtained after calcination of PreFER at 853 K. Spectra marked * are reduced by a third for comparative purposes.

(0kl) are basically identical, whereas reflections corresponding to planes (h00) are strongly diminished in ITQ-6, indicating a remarkable loss of order along the *a* axis. If true, it indicates a delaminated structure and the resultant ITQ-6 material consists mostly of monolayers of the lamellar precursor PreFER, as illustrated in Scheme 1. Calcination of PreFER yields FER, whereas the swollen material can be pillared to give ITQ-36^[11] or delaminated to produce ITQ-6. In agreement with the delaminated structure, no 10MR pores



Scheme 1. Schematic representation of the different materials arising from the lamellar ferrierite precursor PreFER.

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are detected in ITQ-6, as measured by argon adsorption. From nitrogen adsorption isotherms, the external surface areas were calculated for ITQ-6 and FER. The results (Table 1) show that the external surface area ($S_{\text{ext}} = S_{\text{tot}} - S_{\text{micro}}$) has increased by a factor of about 10 after delamination.

Table 1. Specific surface areas (S [$\text{m}^2 \text{g}^{-1}$]) determined from nitrogen adsorption isotherms.

Sample	S_{total} (BET)	S_{micro} (t-plot)
FER	270	210
ITQ-6	618	< 10

It is evident from Scheme 1 that the ITQ-6 material should present a high ratio of Q_3/Q_4 type silicon atoms in where the Q_3 atoms would mainly correspond to terminal SiOH groups oriented towards the external surface of the monolayer. This is indeed seen in Figure 2, in which the ^{29}Si MAS NMR

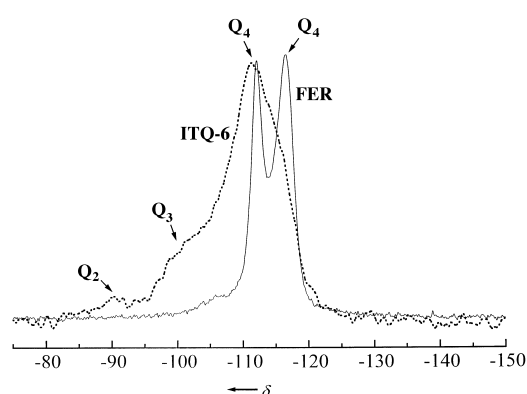


Figure 2. ^{29}Si MAS NMR spectra of FER (calcined PreFER) and ITQ-6 (delaminated PreFER).

spectra of ITQ-6 and FER are compared. The formation of Q_3 and Q_2 geminal silicon atoms during delamination is also consistent with the large amount of silanol groups detected by IR spectroscopy in ITQ-6 (at 3740 and ca. 960 cm^{-1} ; spectra not shown).

It is important to note that the structure of ITQ-6 is stable after calcination at 823 K and a significant amount of the aluminum is still present in the tetrahedral zeolite framework positions, as demonstrated by ^{27}Al MAS NMR spectroscopy (spectra not shown). These aluminum atoms generate strongly acidic sites, as shown by the adsorption–desorption of pyridine (Py) (Table 2). During the delamination process some dealumination has also occurred resulting in a lower concentration of Brønsted acid sites in ITQ-6 (Table 2). However, although the total number of acid sites is somewhat

lower for ITQ-6, they become more accessible to bulky molecules than in FER. This feature is demonstrated by measuring the adsorption of 2,6-bis(1,1-dimethylethyl)pyridine (DTBPy, Table 2), which cannot penetrate into the 10MR pores of FER^[12].

Differences in the total acidity and the number of accessible Brønsted-acid sites should be reflected in the catalytic activity for cracking *n*-decane and 1,3,5-tris(isopropyl)benzene (TIPB). The comparatively higher activity of ITQ-6 for cracking the sterically bulky TIPB (Table 3) confirms that, through delamination, we have generated a new zeolitic

Table 3. Catalytic activity^[a] (rate of hydrocarbon cracking) of ITQ-6 and FER.

Sample	k [$\times 10^2 \text{ s}^{-1}$]	
	<i>n</i> -decane	TIPB
FER	0.25	3.5
ITQ-6	0.21	14.0

[a] Reaction conditions are: 773 K, time on stream (TOS) = 60 s, 1 bar of hydrocarbon.

material in which the acid sites in the structure are accessible to larger molecules owing to its very high external surface area. It would be of interest to expand the possibilities of this material by introducing, through direct synthesis, other framework catalytic functions.

Thus far, the only titanium-rich zeolites prepared by direct synthesis and which show good catalytic performance for oxidation reactions are TS-1, TS-2, and Ti-Beta.^[13–15] Although Ti-ZSM-48 was also prepared, it showed no catalytic activity due to pore size constraints.^[16] Recently,^[17] it has been proposed that the presence of titanium(IV) ions impedes or lowers the nucleation rates in the organothermal synthesis of a titanium-ferrierite system but it was possible to prepare a titanium-containing analogue by seeding with a silicon ferrierite. Unfortunately, the sample had no detectable catalytic activity.^[17] In our case, we succeeded in synthesizing directly, without adding seeds, the laminar Ti-PreFER,^[11] following the same procedure used for Al-PreFER. The UV/Vis spectrum of the sample shows a single absorption band centered at $\lambda \sim 210 \text{ nm}$ corresponding to an isolated framework of tetrahedrally coordinated titanium atoms. This band remained after calcination (TiFER) as well as after delamination and calcination (TiITQ-6). However, as with AlITQ-6, we observed a degree of titanium extraction from TiITQ-6 during delamination. Nevertheless, we have prepared samples of TiFER and TiITQ-6 with a similar titanium content (1.3 and 1.0 wt %, respectively). The samples were used as catalysts for the epoxidation of 1-hexene with H_2O_2

Table 2. Surface acidity measurements determined by the adsorption–desorption of Py and DTBPy as quantified^[a] by IR spectroscopy.

Sample	Total acidity [$\mu\text{mol g}^{-1}$ of Py]						Surface-accessible acid sites (DTBPy adsorption)	
	523 K		623 K		673 K		intensity (3365 cm^{-1})	accessibility [%]
	Lewis	Brønsted	Lewis	Brønsted	Lewis	Brønsted		
FER	2.7	19.3	2.7	16.9	1.4	5.6	< 0.05	< 5
ITQ-6	8.5	9.0	6.4	6.0	5.6	5.4	1.6	90

[a] The integrated molar extinction coefficients of adsorbed pyridine are taken from Emeis.^[18]

and the results (Table 4) show that TiITQ-6 is an active and selective olefin epoxidation catalyst with H_2O_2 as an oxidizing agent. Moreover, its activity is much higher than that of TiFER, owing to the higher accessibility of titanium sites, and very similar to the activity of Ti-Beta.

Table 4. Catalytic activity^[a] of titanium-containing zeolites for the epoxidation of 1-hexene with hydrogen peroxide.

Sample	$X_{\text{hexene}}^{[b]}$ [%]	Selectivity [%] ^[c] to epoxide	TON
TiFER	3.2	85.2	23
TiITQ-6	19.7	95.5	73
Ti-Beta	18.0	97.2	77

[a] Reaction conditions are: 16.5 mmol of olefin, 11.8 g acetonitrile, 4.5 mmol H_2O_2 , 300 mg catalyst, 323 K, 5 hours. [b] Consumption of 1-hexene relative to the maximum possible. [c] Selectivity values scaled against the maximum possible.

In conclusion, a new zeolitic material, ITQ-6, has been prepared by delamination of a layered precursor of ferrierite. This zeolitic material is stable upon calcination and zeolitic acid sites can be generated. It presents a very high external surface area for reactant accessibility. A novel introduction of titanium into the framework of the ferrierite precursor gives titanium ferrierite and, by direct synthesis, the active and selective epoxidation catalyst TiITQ-6.

Experimental Section

ITQ-6: Silica (10 g, Aerosil 200, Degussa), alumina (2.3 g, as boehmite, Catapal B), NH_4F (9.2 g, Aldrich, 98 %), HF (3.1 g, Aldrich, 49.8 %), (R)-4-amino-2,2,6,6-tetramethylpiperidine (26 g, Fluka, 98 % purity), and Milli-Q water (27.9 g) were mixed in an autoclave and left at 448 K for five days. The resulting product (PreFER,^[9] Si:Al = 30:1) was filtered, washed with water, and dried at 333 K (XRD in Figure 1a). The PreFER was expanded to PreITQ-6 through a 16 hours reflux at 368 K as a suspension in an aqueous cetyltrimethylammonium bromide/tetrapropylammonium hydroxide ($\text{CTMA}^+\text{Br}^-/\text{TPA}^+\text{OH}^-$) solution (XRD in Figure 1b). Delamination was performed by placing the PreITQ-6 slurry in an ultrasound bath (50 W, 40 kHz) for one hour, maintaining a pH of 12.5 and a temperature of 323 K. The solid phase was washed thoroughly with water, dried at 373 K (Si:Al = 30:1), and calcined at 853 K for 7 hours yielding ITQ-6 (Si:Al > 40:1; XRD in Figure 1c). A portion of PreFER was calcined at 853 K without previous treatment to yield FER (XRD in Figure 1d).

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Ligand-Directed Structural Modification of Imidotin(II) Cubanes: The Mixed Oxidation State Double-Cubanes $[\text{Sn}_7\{2\text{-NR}\}_8] \cdot n\text{THF}$ ($\text{R} = \text{Pyrimidinyl}$, 5-Methylpyridinyl)**

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In memory of Ron Snaith

Imidotin(II) cubanes of general formula $[\{\text{SnNR}\}_4]$ are the prototypical imidotin(II) compounds. Previous studies have shown that these species are accessible using a variety of synthetic strategies. In certain cases nucleophilic substitution of $\text{SnCl}_2^{[1]}$ or $\text{SnCp}_2^{[2]}$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$) with RN^{2-} or RNH^- can be employed. However, acid–base reactions of the Sn^{II} reagents $[\{\text{Me}_2\text{Si}(\text{NMe}_2)_2\text{Sn}\}]^{[3]}$, $[\text{Sn}\{\text{N}(\text{SiMe}_3)_2\}_2]^{[4]}$ and $[\text{Sn}(\text{NMe}_2)_2]^{[5]}$ with primary amines (RNH_2), hydrazines (H_2NNR), and borylamines (R_2BNH_2) provide more general approaches to these species. Of particular interest to us has been reactions involving $[\text{Sn}(\text{NMe}_2)_2]$ which have the advantages that they give clean formation of the cubanes for a broad range of amines at low temperatures.^[5] The isolation of intermediates of the type $[\{\text{Sn}(\text{NR})_2\}(\text{SnNMe}_2)_2]$ from the

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reactions of $[\text{Sn}(\text{NMe}_2)_2]$ with sterically demanding amines, such as DippNH_2 ($\text{Dipp} = 2,6\text{-iPr}_2\text{C}_6\text{H}_3$),^[6] suggests that cubane formation involving acid–base reactions occurs by a common stepwise process, rather than through the aggregation of discrete $[\text{SnNR}]$ monomers.

On the basis of the extensive synthetic investigations previously undertaken and the overwhelming propensity for imidotin(II) complexes of this type to aggregate into cubanes,^[1–5] we anticipated no structural or chemical variations would result from the reactions of 2-aminopyrimidine $[2\text{-H}_2\text{N}(\text{pm})]$ and 2-amino-5-methylpyridine $[2\text{-H}_2\text{N}(5\text{-MePy})]$ with $[\text{Sn}(\text{NMe}_2)_2]$. However, surprisingly these reactions (in THF as the solvent) do not lead to the anticipated cubanes of the type $[\text{Sn}(\text{NR})]_4$ but to unique mixed oxidation state $\text{Sn}^{\text{II}}/\text{Sn}^{\text{IV}}$ complexes of the formula $[\text{Sn}_7(\text{NR})_8]$ (**1**: $\text{R} = \text{pyrimidinyl}$; **2**: $\text{R} = 5\text{-methylpyridinyl}$),^[7] together with finely divided Sn metal (see Experimental Section). Although the precise mechanism of formation of the complexes is uncertain, clearly the presence of the heterocyclic substituent directly bonded to the imidonitrogen center is key to this process. This is highlighted by the fact that discrete cubane structures are sustained for both Ph^{I} and $\text{CH}_2(2\text{-pyridine})^{\text{II}}$ substituents. Evidence that substituents can have a direct effect on the electrochemistry of imido cubanes is provided by cyclic voltammetry of $[\{\text{Sn}(\text{NtBu})\}_4]$ and $[\{\text{Sn}(\text{NPh})\}_4]$ (in MeCN). Although complicated by unidentified reduction processes, the cyclic voltammogram of $[\{\text{Sn}(\text{NtBu})\}_4]$ exhibits one irreversible oxidation wave at about 1.00 V (vs. Fe/Fe^{2+}), which we attribute to a $\text{Sn}^{\text{II}}/\text{Sn}^{\text{IV}}$ oxidation. However, this irreversible oxidation process is significantly more favorable in $[\{\text{Sn}(\text{NPh})\}_4]$, now occurring at 0.63 V (vs. Fe/Fe^{2+}).

The low-temperature X-ray crystal structures of **1** (Figure 1) and **2** (see Supporting Information)^[8] show that both consist of similar, centrosymmetric molecules, composed of two interlocked Sn_4N_4 imido cubane fragments which share a common Sn^{IV} apex (located at the crystallographic centers of symmetry). In addition, there are two THF and 0.33 THF molecules per formula unit in the lattices of **1** and **2**, respectively. The N–Sn–N angles and Sn–N bond lengths associated with the Sn^{II} centers ($\text{Sn}(2)$, $\text{Sn}(3)$, and $\text{Sn}(4)$), and the Sn–N–Sn angles within the cubane units of **1** and **2** are similar to those observed in the structurally characterized cubanes $[\{\text{SnNR}\}_4]$ (mean Sn–N–Sn 98.4° , N–Sn–N 81.9° ; Sn–N range $2.15(1)–2.34(2)$ Å^[1–5]). It therefore appears that there is comparatively little strain resulting from the incorporation of the Sn^{IV} center ($\text{Sn}(1)$) into the cubane frameworks, despite the presence of significantly shorter Sn–N bonds at the Sn^{IV} centers of **1** and **2** (range $2.157(3)–2.177(5)$ Å). The compression in the internal N–Sn–N angles at the Sn^{IV} centers in both complexes (cf. ca. 99° for those between the cubane units) gives pseudo-octahedral metal geometries which are similar to that observed in the $[\text{Sn}(\text{NHCy})_6]^{2-}$ amido dianion of $[\text{THF} \cdot \text{Li}(\mu\text{-NHCy})_3\text{Sn}(\mu\text{-NHCy})_3\text{Li} \cdot \text{THF}]$ ($\text{Cy} = \text{cyclohexyl}$).^[8] A further interesting feature present in the structures of **1** and **2** are the relatively short $\text{Sn} \cdots \text{N}$ interactions which span the two cubane halves of the molecules ($2.807(3)–2.935(3)$ in **1**, $2.761–2.784(5)$ Å in **2**). In addition to the electrochemical influence of the substituents, these interactions (which are similar to those found in $[\{\text{SnN}[\text{CH}_2(2\text{-pyridine})\}_4]$ ($2.86–2.92$ Å)^[9]) may play a role in promoting the stability of the double-cubane cage arrangements of the complexes.^[10]

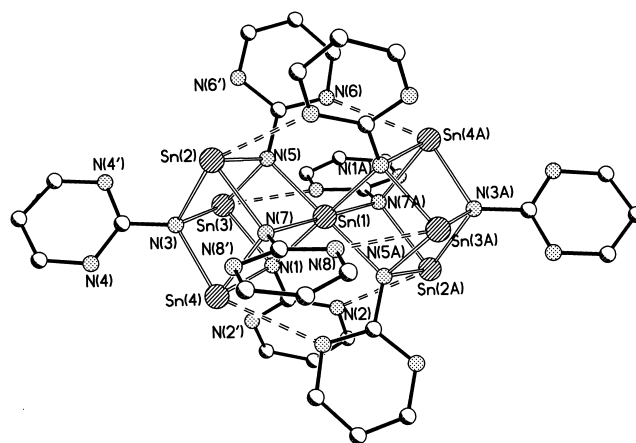


Figure 1. Molecular structure of **1** (hydrogen atoms and the disordered THF molecule in the lattice are omitted for clarity). The core structure of **2** is identical (see Supporting Information). Key bond lengths [Å] and angles [$^\circ$]: for **1**: $\text{Sn}(1)\text{--N}(1)$ 2.157(3), $\text{Sn}(1)\text{--N}(5)$ 2.161(3), $\text{Sn}(1)\text{--N}(7)$ 2.157(3), $\text{Sn}(2)\text{--N}(3)$ 2.295(3), $\text{Sn}(2)\text{--N}(5)$ 2.200(3), $\text{Sn}(2)\text{--N}(7)$ 2.333(3), $\text{Sn}(3)\text{--N}(1)$ 2.236(4), $\text{Sn}(3)\text{--N}(3)$ 2.236(4), $\text{Sn}(3)\text{--N}(5)$ 2.225(3), $\text{Sn}(4)\text{--N}(1)$ 2.273(3), $\text{Sn}(4)\text{--N}(3)$ 2.190(3), $\text{Sn}(4)\text{--N}(7)$ 2.237(3), range $\text{N}(2,6,8) \cdots \text{Sn}(2\text{A},3\text{A},4\text{A})$ $2.807(3)–2.935(3)$, range $\text{N--Sn}(2,3,4)\text{--N}$ $76.6(1)–80.7(1)$ (mean 78.8), range $\text{Sn--N}(1,3,5,7)\text{--Sn}$ $96.9(1)–101.6(1)$ (mean 99.7), $\text{N--Sn}(1)\text{--N}$ range $80.8(1)–99.3(1)$; for **2**: $\text{Sn}(1)\text{--N}(1)$ 2.166(5), $\text{Sn}(1)\text{--N}(5)$ 2.169(5), $\text{Sn}(1)\text{--N}(7)$ 2.177(5), $\text{Sn}(2)\text{--N}(1)$ 2.247(5), $\text{Sn}(2)\text{--N}(3)$ 2.261(5), $\text{Sn}(2)\text{--N}(7)$ 2.212(5), $\text{Sn}(3)\text{--N}(1)$ 2.222(5), $\text{Sn}(3)\text{--N}(3)$ 2.240(6), $\text{Sn}(3)\text{--N}(5)$ 2.212(5), $\text{Sn}(4)\text{--N}(3)$ 2.266(5), $\text{Sn}(4)\text{--N}(5)$ 2.225(5), $\text{Sn}(4)\text{--N}(7)$ 2.191(5), $\text{N}(2,6,8) \cdots \text{Sn}(2\text{A},3\text{A},4\text{A})$ $2.761–2.784(5)$, range $\text{N--Sn}(2,3,4)\text{--N}$ $78.1(2)–80.9(2)$ (mean 79.5), range $\text{Sn--N}(1,2,3,4)\text{--Sn}$ $96.3(2)–101.9(2)$ (mean 99.1), $\text{N--Sn}(1)\text{--N}$ range $81.0(2)–99.0(2)$.

pyridine))₄] ($2.86–2.92$ Å)^[9] may play a role in promoting the stability of the double-cubane cage arrangements of the complexes.^[10]

A survey of the literature reveals that, although rare compared to discrete cubanes, molecular double-cubane structures related to **1** and **2** have been identified for a range of transition metal and main group metal complexes.^[11] However, this arrangement has only been observed for species containing alkoxide, sulfide, or halide bridges. The closest relative to **1** and **2** is the Sn^{IV} complex $[\{\text{nBuSn--S}(\text{O}_2\text{PPh}_2)\}_3]_2\text{Sn}$,^[11c] composed of two interlocked Sn_4OS_3 cubane units which share a Sn center. Complexes **1** and **2** are the first imido complexes having this design and the only mixed oxidation state $\text{Sn}^{\text{II}}/\text{Sn}^{\text{IV}}$ imido complexes to be structurally characterized. Their structures can be viewed alternatively as composed of two tripodal $[\text{Sn}_3(\text{NR})_4]^{2-}$ ligands which coordinate the central Sn^{4+} ions. Such a tripodal ligand has been observed in the anion $[\text{tBuNSn}_3(\text{Nnaph})_3\text{Li}]^-$ ($\text{naph} = 1\text{-naphthalene}$).^[12]

This study has revealed that organic substituents have an unforeseen and dramatic effect on the structures of simple imidotin(II) cubanes. Similar structural effects and underlying electrochemistry may well be worthy of study in related main group metal compounds.

Experimental Section

1, 2: $\text{Sn}(\text{NMe}_2)_2$ (0.52 g, 2.5 mmol) in THF (25 mL) was added dropwise to a solution of 2-aminopyrimidine (0.24 g, 2.5 mmol, for **1**) or 2-amino-5-methylpyridine (0.27 g, 2.5 mmol, for **2**) in THF (30 mL) at -78°C . The reaction mixture was allowed to warm to about 0°C and then stored

immediately in the dark at room temperature (12 h). Crystals form as small lemon-yellow cubes in the case of **1** and as colorless cubes in the case of **2**. Elemental analysis and spectroscopic investigations were complicated by the presence of finely dispersed Sn metal in samples of the complexes and by their sparing solubility in organic solvents. For **1**: Yield 0.10 g, 19% (on the basis of 2-aminopyrimidine). Decomposition occurred at about 250°C to give a brown solid. IR (Nujol, NaCl): no N–H str; ^{119}Sn MAS-NMR (relative to $\text{SnCl}_2/\text{D}_2\text{O}$, 148.99 MHz, 8 KHz spin speed); $\delta = 353.7$ (Sn^{VI} , $\text{Sn}(1)$), -180.4 (Sn^{II} , $\text{Sn}(2,3,4)$); elemental analysis: calcd: C 27.9, H 2.3, N 19.6; found: C 25.5, H 2.2, N 17.3. For **2**: Yield 0.10 g, 19% (on the basis of 2-amino-5-methylpyridine). Decomposition occurred at about 150°C to give a brown solid. IR (Nujol, NaCl): no N–H str; elemental analysis: calcd: C 34.3, H 2.8, N 13.3; found: C 33.7, H 3.1, N 12.3.

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- [8] a) X-ray crystal structure data for **1**: $\text{C}_{40}\text{H}_{40}\text{N}_{24}\text{O}_2\text{Sn}_7$, $M_r = 1719.79$, monoclinic, space group $P2_1/c$, $Z = 2$, $a = 13.9577(5)$, $b = 12.7540(5)$, $c = 14.8385(5)$ Å, $\beta = 107.182(2)^\circ$, $V = 2523.6(2)$ Å³, $\mu(\text{MoK}\alpha) = 3.470 \text{ mm}^{-1}$, $T = 180(2)$ K. Data were collected on a Nonius Kappa CCD diffractometer. Of a total of 5231 reflections collected, 3156 were independent ($R_{\text{int}} = 0.044$). All of the O and C atoms of the THF molecule in the lattice are disordered over two 50:50 sites. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 . Final $R1 = 0.032$ [$I > 2\sigma(I)$] and $wR2 = 0.073$ (all data).^[8c13] b) X-ray crystal structure data for **2**: $\text{C}_{49.33}\text{H}_{50.67}\text{N}_{16}\text{O}_{0.33}\text{Sn}_7$, $M_r = 1703.89$, trigonal, space group $R\bar{3}$, $Z = 9$, $a = b = 20.8640(8)$, $c = 34.147(2)$ Å, $V = 12872.9(11)$ Å³, $\mu(\text{MoK}\alpha) = 3.055 \text{ mm}^{-1}$, $T = 180(2)$ K. Data were collected on a Nonius Kappa CCD diffractometer. Of a total of 7095 reflections collected, 4527 were independent ($R_{\text{int}} = 0.033$). The lattice-bound THF molecule (one for every three molecules of **2**) is disordered about a threefold axis. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 . Final $R1 = 0.038$ [$I > 2\sigma(I)$] and $wR2 = 0.086$ (all data).^[8c13] c) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-137024 (**1**) and 137025 (**2**). 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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How Important is the Inert Matrix of Supported Enantiomeric Catalysts? Reversal of Topicity with Two Polystyrene Backbones**

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The development of efficient polymer-supported chiral reagents and catalysts has become an important research topic.^[1,2] This is a result of the advantages of heterogeneous systems for large-scale reactions and of the availability of new materials and methods provided by the advances in combinatorial chemistry.^[3]

The preparation of these kinds of functionalized resins involves the immobilization of a modified chiral auxiliary in a polymeric matrix by grafting or copolymerization.^[1–4] The role of the polymeric backbone is sometimes underestimated, but it is known that the chemical and textural properties of the polymer affect the efficiency of the supported species.^[2] Therefore, important changes in the catalytic activity of a compound can be expected upon its immobilization. Although much less is known about the role played by the

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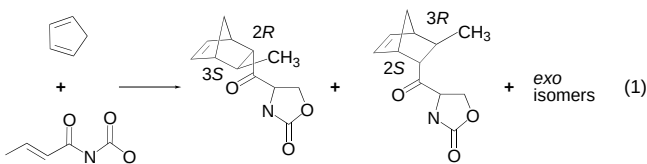
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polymeric backbone in the stereochemical outcome of the reaction, the effects of immobilization can be important. A decrease in stereoselectivity, in particular enantioselectivity, is often obtained for polymeric reagents or catalysts. However, we have observed how the changes in activity associated with structural variations in the chiral auxiliary do not always follow the trends expected from solution studies.^[5] Here we report on the preparation of monolithic columns containing enantioselective Ti-TADDOLate catalysts that show a very high stability, and on the first example, to our knowledge, of an even more drastic effect as seen by the reversal of topicity observed for a Ti-TADDOLate upon immobilization on two different polystyrene matrices.

Since the seminal work of Seebach and other researchers Ti-TADDOLates have become a very important and versatile class of chiral catalysts with application for a broad range of enantioselective organic transformations.^[6] Recently, several groups, including us, have been involved in the preparation of polymeric Ti-TADDOLate analogues so that the advantages associated with the heterogeneous systems might be utilized.^[7]

Initially, Ti-TADDOLates **6** derived from polymers **4** prepared by grafting of a modified TADDOL **1** (Scheme 1) onto a polystyrene–divinylbenzene (PS-DVB) matrix were used as catalysts in the Diels–Alder reaction of cyclopentadiene and 3-crotonoyl-1,3-oxazolidin-2-one [Eq. (1)]. In general, the reactions were nonenantioselective, except for those TADDOL derivatives bearing bulky aryl groups at the α positions (Table 1), which may be a consequence of the conformational restrictions imposed by these groups. The 2*R*,3*S* isomer was obtained as the major product using catalysts containing the 3,5-dimethylphenyl moiety at the α positions (entries 1–3), while Ti-TADDOLates containing other groups gave the 2*S*,3*R* isomer as the major product (entries 5–7) using catalysts containing the naphthyl group. This observation seems to be related to the presence of 3,5-dimethylphenyl groups at the α positions and an aromatic group in the 2-position of the acetal ring.^[8]

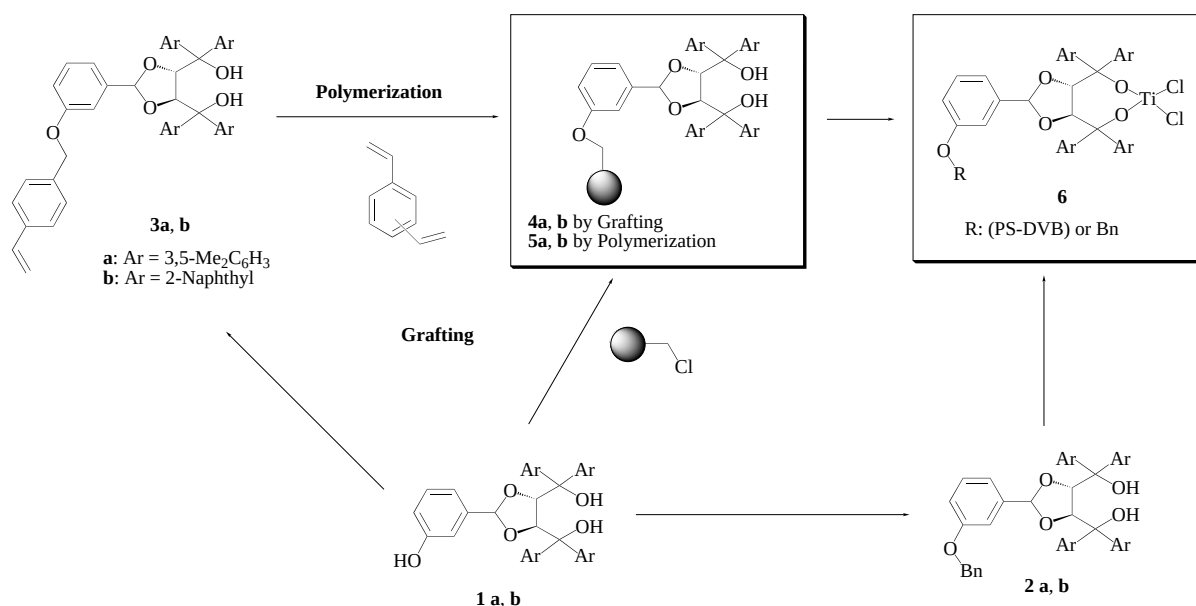
Table 1. Results obtained for the Diels–Alder reaction (1) of Ti-TADDOLates considered in this work.



Entry	Starting TADDOL	Ar	Conversion [%]	endo:exo	ee [%]
1	2a solution	3,5-(CH ₃) ₂ C ₆ H ₃	100	71:29	38 (2 <i>R</i> ,3 <i>S</i>)
2	3a solution	3,5-(CH ₃) ₂ C ₆ H ₃	99	82:18	3 (2 <i>R</i> ,3 <i>S</i>)
3	4a grafting	3,5-(CH ₃) ₂ C ₆ H ₃	98	71:29	17 (2 <i>R</i> ,3 <i>S</i>)
4	5a monolith	3,5-(CH ₃) ₂ C ₆ H ₃	100	80:20	18 (2 <i>S</i> ,3 <i>R</i>)
5	1b solution	2-naphthyl	99	87:13	25 (2 <i>S</i> ,3 <i>R</i>)
6	2b solution	2-naphthyl	96	74:26	61 (2 <i>S</i> ,3 <i>R</i>)
7	4b grafting	2-naphthyl	50 ^[a]	83:17	40 (2 <i>S</i> ,3 <i>R</i>)
8	5b monolith	2-naphthyl	96	79:21	40 (2 <i>S</i> ,3 <i>R</i>)

[a] Low conversion of the dienophile as a result of the total consumption of cyclopentadiene after 24 h.

In some cases chiral-supported catalysts prepared by the polymerization of chiral auxiliaries have been reported to give better asymmetric inductions than those prepared through grafting, particularly those catalysts with high degrees of cross-linking.^[3,5] We assayed this strategy using the vinylic derivatives **3** as the chiral monomers in order to improve the enantioselectivity obtained with our catalysts (Scheme 1). We carried out bulk polymerizations to obtain monolithic columns of **5** with appropriate porosity so as to avoid diffusion problems in the polymeric matrix.^[9] These could act as stable, easily recoverable microreactors, that were even useful under continuous flow conditions. Different monomeric compositions (DVB/3), porogenic agents (1-dodecanol/toluene), and polymerization conditions were assayed. Other studies have described that the addition of toluene to 1-dodecanol in the



Scheme 1. Synthesis of homogeneous and heterogeneous TADDOL derivatives.

porogenic mixture generally results in the formation of smaller pores.^[9] This effect was also observed by us.

Monoliths with the desired morphology and properties were obtained using a mixture containing 40 % of monomers (DVB/3 60/40, no styrene was used) and 60 % of the toluene/1-dodecanol porogenic mixture (9 wt % of toluene). The column prepared in this way using azobisisobutyronitrile (AIBN) as the initiator showed an average pore size of 1100 nm, which gave a back pressure of 47 psi for a 1 mL min⁻¹ flow rate. The corresponding Ti-TADDOLate **6** was prepared from this supported TADDOL by reaction with TiCl₂(*i*PrO)₂. A titration of the excess of TiCl₂(*i*PrO)₂ used in this step, showed a quantitative loading of Ti in the monolithic column (0.4 mmol g⁻¹).

This polymeric Ti-TADDOLate showed an activity comparable to that found for related homogeneous and heterogeneous catalysts in the Diels–Alder reaction of cyclopentadiene and 3-crotonyl-1,3-oxazolidin-2-one. The activity of such catalysts can be maintained almost unaffected for several months, simply by keeping the monolithic column closed (under an argon atmosphere; Figure 1). This result clearly

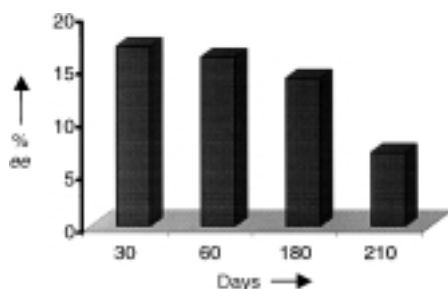


Figure 1. Time-dependent activity of the monolithic column derived from TADDOL **5a** as a catalyst in the Diels–Alder reaction [Eq. (1)].

highlights the great potential of those materials for use in catalytic systems, especially if we consider that they allow reactions to be carried out in a column, and, accordingly, to proceed in a continuous flow system.

One of the most remarkable observations was, however, that the major isomer obtained with the monolithic column was the 2*S*,3*R* isomer, instead of the 2*R*,3*S* isomer that was obtained with the grafted polymer **4a** as well as with the homogeneous analogues (namely, **2a** and **3a**).^[10] Therefore, this reversal of topicity can be attributed to the polymeric matrix. This is the first example of a resin-supported enantioselective catalyst for which the morphology of the polymeric backbone determines the topicity of the resulting products. A simple explanation could be related to the introduction of some kind of main-chain chirality arising from the presence of the chiral monomer. Different approaches to the preparation of polymeric chiral reagents and catalysts using imprinted polymers or resins with main-chain chirality have been described.^[11] However, this change in topicity is only observed for TADDOLates containing 3,5-dimethylphenyl groups at the α -positions. The use of TADDOLates **2b**, **4b**, and **5b** containing 2-naphthyl groups at the α positions gave much better enantioselectivities, but no change in topicity was observed (Table 1). Thus, what can be

the reason for this specific behavior of polymer **5a**? The change in the TADDOL substitution could modify the level of chirality in the chiral main chain. On the other hand, the reversal in topicity is observed in homogeneous catalysis for TADDOLs containing the 3,5-dimethylphenyl moiety as a result of the presence or absence of a phenyl group in the 2-position of the acetal ring. This effect seems to be attributed to the existence of π -stacking interactions between this phenyl group and one of the 3,5-dimethylphenyl substituents.^[8] Accordingly, polymerization of **3a** to form part of a very rigid, cross-linked matrix may increase the steric crowding in the close proximity of the acetal and make these π -stacking interactions more difficult, favoring the obtention of the 2*S*,3*R* cycloadduct. The situation will be different for polymers obtained through grafting procedures as more flexible networks are used and functionalization takes usually place at the more accessible lightly cross-linked regions.

Additional work is being carried out to better understand the reasons underlying this behavior and to obtain more examples of such a change in topicity. However, the present results clearly show the high potential of monoliths for the preparation of heterogeneous chiral catalysts and highlight the important role of the polymeric network in the course of the reactions. In our experiments, the presence of the polymeric matrix provided a way to drastically increase the stability of the Ti catalyst and, in one example, to induce a reversal of the topicity.

Experimental Section

Preparation of the monolithic polymer rods: TADDOL **3** (0.400 g) was dissolved in toluene (0.487 g). Then DVB (0.600 g) and 1-dodecanol (1.012 g) together with AIBN (1 wt % with respect to the monomers) were added to obtain a homogeneous solution. The polymerization mixture was purged with nitrogen for 3 min and poured into a mold. The stainless steel tubular molds were sealed at the two ends, and placed in a vertical position into a water bath. The polymerization was allowed to proceed for 23 h at 70 °C. The seals were removed and fittings attached to the tube before it was connected to a high-pressure pump. THF was pumped through the column at a flow rate of 1 mL min⁻¹ to remove the porogenic solvents and any other soluble compounds.

General procedure for the Diels–Alder reaction (1) with polymeric catalysts obtained by polymerization: A solution of TiCl₂(*i*PrO)₂ was inserted in a syringe pump and passed in a continuous flow (0.6 mL h⁻¹, *V* = 9 mL) through the monolithic column (previously washed with dry toluene for 1 h at 20 mL h⁻¹), then the column was washed with dry toluene (3 h, 20 mL h⁻¹) to remove the excess of titanium. A solution of 3-crotonyl-1,3-oxazolidin-2-one and cyclopentadiene in dry toluene was loaded onto the monolithic column and the reaction mixture was maintained within the column for 24 h. The column was then washed with dry toluene to remove the products. The solvent was eliminated under reduced pressure, and the conversion, the *endo/exo* ratio, and the enantioselectivities were determined by ¹H NMR spectroscopy and chiral HPLC (Chiralcel OD).

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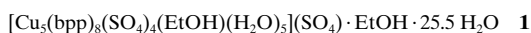
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Polymeric Layers Catenated by Ribbons of Rings in a Three-Dimensional Self-Assembled Architecture: A Nanoporous Network with Sponglike Behavior

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The current interest in the crystal engineering of polymeric coordination networks^[1] stems from their potential applications as zeolite-like materials^[2] for molecular selection, ion exchange, and catalysis, as well as in the intriguing variety of architectures and topologies. Particularly attractive are the novel types of supramolecular intertwinings observed in these species, that still need a rational classification. According to Batten and Robson^[3] an “interpenetrating framework” is comprised of motifs that are infinite and inextricably entangled, that is, they cannot be separated without breaking links. On this basis, we must exclude some interesting polymeric entanglements recently described, including polymeric catenanes,^[4] infinite double helices,^[5] two-dimensional clothlike warp-and-weft sheets,^[6] and other noteworthy supramolecular architectures.^[7] For “true” interpenetrating networks, however, different classes can be envisaged. The dominant type (“class A”) is represented by 2D or 3D species that are comprised of a limited number of individual frames of equal topology that interpenetrate into an array with the same original dimensionality as in, for example, n -fold parallel interpenetrating hexagonal layers ($n \leq 6$) or diamondoid nets ($n \leq 9$).^[3] Other types of interpenetration have been observed in coordination polymers that are reminiscent of molecular catenanes and rotaxanes. Some examples of polymeric catenated species are illustrated in Figure 1. In contrast to the class A interpenetrated nets, these examples all show the following features: 1) the constituent motifs have a lower dimensionality than that of the resulting architectures; 2) each individual motif is intertwined only with the surrounding ones and not with all the others, as “a ring in a chain”; and 3) the concept of “ n -foldicity” cannot be used in the same sense as for class A.^[13] We report here on a new member of this class of catenated motifs, **1**, obtained from the self-assembly of copper(II) sulfate and 1,3-bis(4-pyridyl)propane (bpp).



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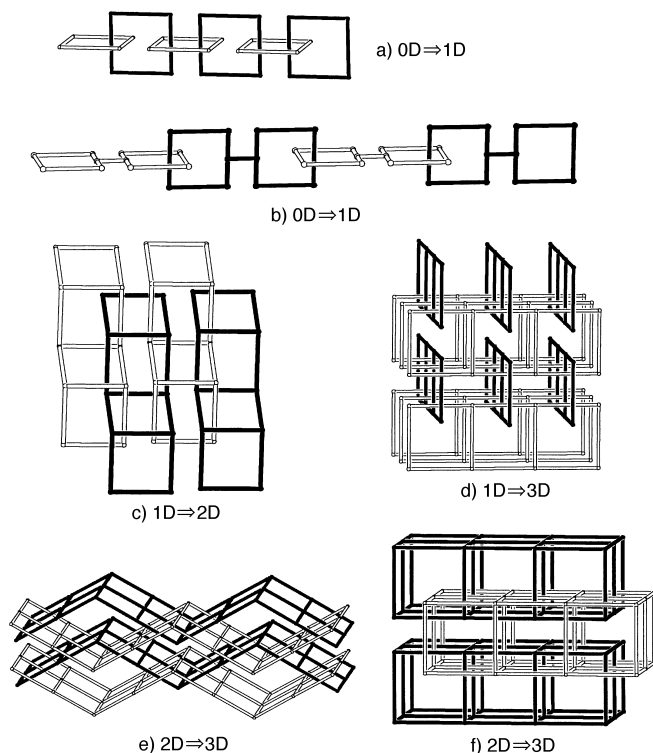


Figure 1. Schematic examples of polymeric catenated structures. Motifs b)–f) are simplified versions of entanglements found in real species: b) a poly[2]catenane;^[4, 8] c) parallel interpenetration of ladders;^[9] d) inclined interpenetration of ladders;^[10] e) catenation of simple undulating layers;^[11] f) catenation of multiple layers.^[12] No real example of an infinite polycatenane of type (a) has yet been reported.

This species presents a remarkable and unprecedented three-dimensional architecture sustained by the polycatenation of two different types of coordination polymers, that is, one-dimensional ribbons of rings and two-dimensional (4,4) layers. It shows, moreover, an interesting nanoporous behavior due to the presence of large cavities full of guest solvent molecules. These solvent species can be completely removed by thermal treatment and regained in a reversible process, to imply some degree of flexibility in the network.

Compound **1** is obtained in high yields as beautiful blue crystals by the slow diffusion of bpp as an ethanol solution into copper(II) sulfate as an aqueous solution, with metal: ligand molar ratios ranging from 1:1 to 1:4. Similar crystalline species are also obtained using other solvents for the ligand (acetone, ethyl acetate, tetrahydrofuran), as shown by X-ray diffraction measurements on the powders. Although crystals start to lose solvated water and ethanol molecules when removed from their mother liquor, they reach an equilibrium at room temperature and display the same X-ray powder diffraction (XRPD) pattern even after two months in the air. Crystals taken from the solution for the XRPD experiments (at 223 K) were manipulated in an ice bath.^[14]

The crystal structure of **1** shows the presence of two different and crystallographically independent polymeric motifs packed together (Figure 2). One motif, the ribbons of rings, consists of 48-membered cycles, in which each ring includes four copper atoms and four bpp ligands. The ribbons

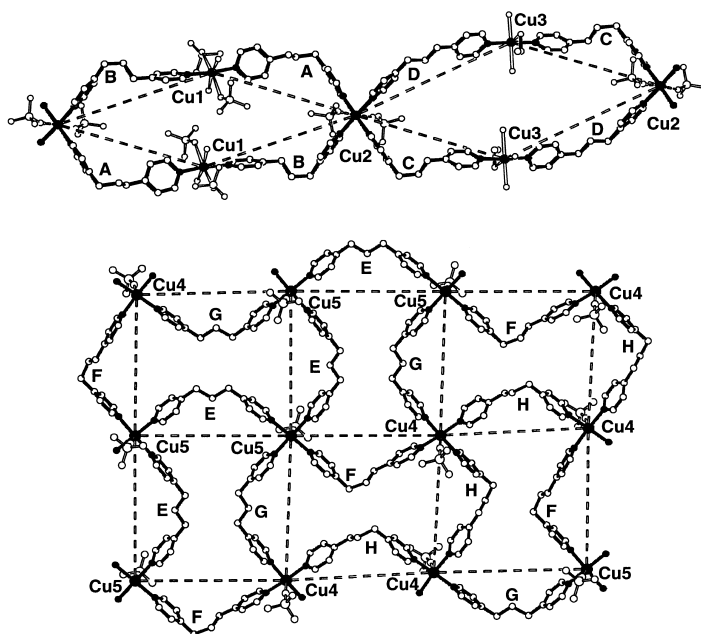


Figure 2. The two polymeric motifs present in **1** are a ribbon of rings (top) and a (4,4) layer (bottom). The eight independent bpp ligands are labelled A–H and show conformations *TG*, *TG*, *TG*, *TT*, *TT*, *TG*, *TT*, and *TG*, respectively (*T*=trans, *G*=gauche). Bond distances [Å] involving the copper atoms are: in the rings: Cu2–N (four bonds) 2.050(5)–2.068(4); Cu2–O_{sulfate} (two bonds) 2.418(4), 2.523(4); Cu1–N (two bonds) 2.020(5), 2.027(5); Cu1–O_{sulfate} (two bonds) 2.435(4), 2.508(4); Cu1–O_{water} (two bonds) 2.001(4), 2.034(4); Cu3–N (two bonds) 2.015(5), 2.032(5); Cu3–O_{water} (three bonds) 2.167(6)–2.333(5); Cu3–O_{ethanol} 2.137(7); in the layer: Cu4–N, Cu5–N (four bonds each) 2.034(5)–2.066(5); Cu4–O_{sulfate} 2.385(4); Cu5–O_{sulfate} 2.305(4).

undulate slightly, with the metal atoms disposed at the vertices of rhombuses (Cu...Cu 11.80–13.53 Å). All these polymers run parallel to the [10 $\bar{1}$] direction with a 47.24 Å period corresponding to two successive rings. Adjacent ribbons show a relative displacement of ¼ of this period. The copper atoms shared by adjacent rings (Cu2) are connected to four bpp ligands, whereas the lateral Cu1 and Cu3 atoms are connected to two such ligands. The octahedral coordination geometries of these metals are completed by sulfate anions and solvent molecules.

The other polymeric motif of **1** is a two-dimensional tessellated sheet of (4,4) topology (Figure 2 bottom) which contains two types of copper atoms, Cu4 and Cu5, and four types of bpp ligands. Within these layers, the copper atoms are located at the nodes of a square grid with edges 11.93–12.49 Å long. Both copper atoms are connected to four equatorial pyridyl rings and are bonded to an oxygen atom of a sulfate group in an axial direction, to form a square-pyramidal coordination. These sulfate anions are the same involved in axial interactions with the Cu2 atoms of the ribbons and represent the only bridge between the two types of polymers. The layers stack in the [10 $\bar{1}$] direction with an *ABCD* sequence.

The most interesting structural feature of **1**, however, is that the ribbons and the layers are entangled (Figure 3) in a unique three-dimensional array. Each ring of the ribbons locks two adjacent layers and each “square” mesh of the layers is



Figure 3. The entanglement of one ribbon with two adjacent layers. Only the metal atoms and the bpp ligands (without hydrogen atoms) are shown.

catenated by two rings belonging to different ribbons. The overall architecture is schematically represented in Figure 4. Few examples of entangled polymeric species with a differing nature, with either identical or different topologies,^[3] are presently known, but this is, to our knowledge, the first example of intertwining involving two polymeric motifs of different (1D and 2D) dimensionality. The coordination network of **1** contains large voids in the interlayer regions (interlayer separation approximately 11.8 Å), which are filled by solvated molecules of water and ethanol (102 and 4 solvent molecules per unit cell, respectively). An analysis of these regions, by neglecting all the solvent molecules but those coordinated to the copper atoms, shows that there are two type of large, isolated chambers of volumes around 790 and 670 Å³ and smaller holes of 140 Å³ (two, two, and four per unit cell, respectively; Figure 5).^[15] The total void space in a unit cell corresponds to 3626 Å³, equivalently, 25.8% of the cell volume. The uncoordinated solvent molecules display a variety of environments and form an intricate, extended net of hydrogen bonds. According to the structural data they can be roughly assigned as: a) tightly bonded molecules, anchored to the network by two or more hydrogen-bond bridges involving the coordinated sulfate or water molecules; b) molecules with “intermediate” bonding, with only one such hydrogen bond described under (a); and c) loosely bonded molecules showing only contacts with other solvated molecules. Group a)

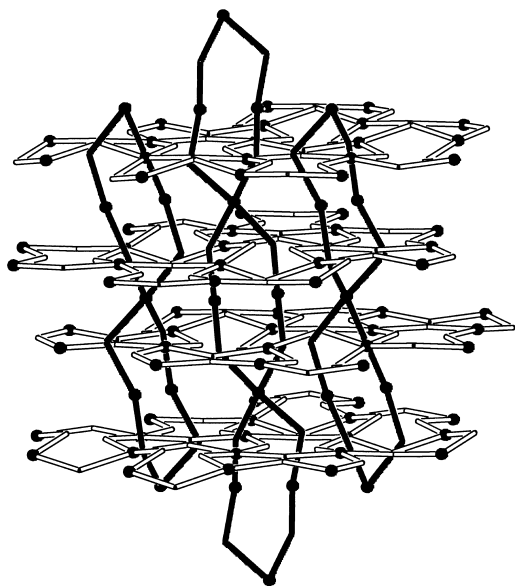


Figure 4. Schematic view of the overall entanglement of **1**. The representation of the bpp ligands is simplified by showing only the central methylene atoms.

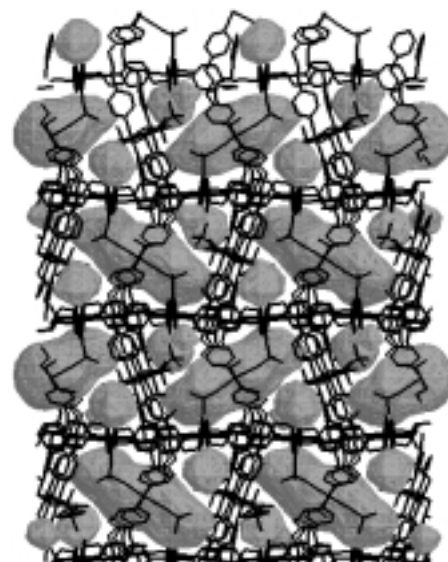


Figure 5. View down the [101] axis of the three-dimensional array of **1** showing the distribution of the empty cavities. The cavities are represented by their limiting surfaces. The layers run horizontally and the ribbons vertically.

includes the free ethanol and about 27% of the solvated water, group b) accounts for about 24% of the solvated water, while the majority (49%) of the water falls into group c). Such distribution is reflected in the nanoporous behavior of this material. When the crystals are removed from the solution they begin to weep solvent. Thermogravimetric analysis (TGA) at room temperature under a N₂ flux shows that an equilibrium situation is achieved after about 100 min, with a 13.5% mass loss (approximately corresponding to the loss of the free ethanol and the solvated H₂O of groups b) and c)). Equilibration in the air at room temperature occurs after an initial mass loss, estimated of 2–4% but this value is very sensitive to temperature and humidity. At this point most of the crystals under the microscope appear almost unchanged in morphology and color but they do not remain monocrystalline. These polycrystalline samples exhibit XRPD spectra quite similar to that simulated from the single crystal structure.^[16] Desolvation can be completed by thermal activation and TGA in the range 40–180 °C shows an almost continuous weight loss. On heating to about 120 °C, all of the guest molecules are eliminated,^[17] while the coordinated solvents are lost in the range 120–180 °C (mass loss 3–4%); the decomposition of the network starts above 200 °C. Monitoring the samples heated to different temperatures (50, 95, 120, 150 °C) reveals a progressive loss of crystallinity—with a significant change of the pattern above 90 °C—resulting in an almost completely amorphous phase. However, these samples left in the presence of water vapors at room temperature for some hours regain solvent (specifically, solvent groups a), b), and about half of c) to correspond to the equilibrium situation described above) and, unexpectedly, crystallinity, showing XRPD patterns identical to the original one. The cycle of desolvation–solvation can be repeated many times as controlled by TGA and monitored by XRPD.^[18] Only after elimination of the coordinated solvent molecules does the array become unstable.

The desolvation of **1** is accompanied by a (reversible) loss of order, probably due to the local structural modifications following the spongelike shrinking of the chambers.^[19] This is possible due to the variable ligand conformations and to the flexibility of the catenated architecture. For more information

on this behavior, we examined **1** by atomic force microscopy (AFM). A sample of **1** was left in the air for several hours (at approximately 25 °C and 50% relative humidity) to observe the initial stages of desolvation on the [10 $\bar{1}$] surface. About 45 min after removal of **1** from its mother liquor, cracks start to appear roughly running orthogonal to [010]. As time elapses, these existing cracks enlarge to 1.5 μm wide (Figure 6a) and accompany the random formation of new ones (Figure 6b). The net of cracks produces a mosaiclike surface with a significant misalignment of the crystal blocks. Cracks parallel to [010] also develop but they shift to the (apparently favored) perpendicular direction. After about 7 h, the cracks are about 4 μm wide (Figure 6c). The shrinking of the crystal is also demonstrated by the height of the macrosteps on the crystal surface decreasing by 10–15% during the first 8 h of the experiment. Interestingly, on leaving the partially desolvated crystal overnight in a sealed AFM fluid cell connected to a water vapor reservoir, spontaneous water uptake from the air produces a partial healing of the cracks (Figure 6d). An attempt to follow the rehydration by AFM of a crystal heated up to 120 °C was hampered by rapid water uptake causing large surface movement that was beyond the imaging capability of the AFM. Though the evolution of cracks in relation to the network structure remains difficult to explain, it is

clearly a consequence of mechanical strain following the depletion of the cavities.

In conclusion, the fascinating three-dimensional catenated structure of **1**, with more than $\frac{1}{4}$ of its volume available for guest molecules, contains a mobility not present in the common rigid zeolite-like networks.^[20] It can be considered prototypical of a new family of “nonrigid”, nanoporous, spongelike coordination frames assembled with long, flexible, polydentate ligands.

Experimental Section

Synthesis of 1: A solution of 1,3-bis(4-pyridyl)propane (bpp) (0.097 g, 0.488 mmol) in EtOH (8 mL) was added to a stirred solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.061 g, 0.244 mmol) in water (8 mL) at room temperature. A blue precipitate formed immediately. The reaction mixture was stirred for 1 h. The precipitate was filtered and dried in the air (yield > 90%). The purity of these powdered samples was confirmed by XRPD. Compound **1** is sparingly soluble in polar organic solvents. Variable elemental analyses were obtained due to the loss of solvent molecules to the air (3–4%). For example, elemental analysis for $\text{C}_{108}\text{H}_{185}\text{Cu}_5\text{N}_{16}\text{O}_{52.5}\text{S}_5$; calcd: C 42.87, H 6.16, N 7.41; found: C 42.96, H 6.11, N 7.67. Single crystals suitable for structural analysis were obtained by slow diffusion of an ethanolic solution of bpp into an aqueous solution of the copper salt at a molar ratio 2:1. The presence of ethanol in **1** has been confirmed by ^1H NMR on solutions obtained by suspending some crystals in $[\text{D}_6]\text{acetone}$. Thermal analyses were performed on Perkin-Elmer DSC7 and TGA7 instruments at a heating rate of 10 °C min $^{-1}$ under a nitrogen flux. X-ray powder diffraction spectra were collected on a Rigaku D/Max horizontal-scan diffractometer. A Digital Instruments “Nanoscope III” AFM, equipped with a J-type piezo scanner, operated in contact mode in the air or using a standard fluid cell for water uptake experiments. Silicon nitride cantilevers with integrated tips and nominal spring constants of 0.06–0.12 N m $^{-1}$ were used. The tip-sample contact force was reduced to the order of a few nN to minimize artifacts and surface erosion phenomena. The scan frequency was 3–4 Hz. All images shown represent unfiltered height data.

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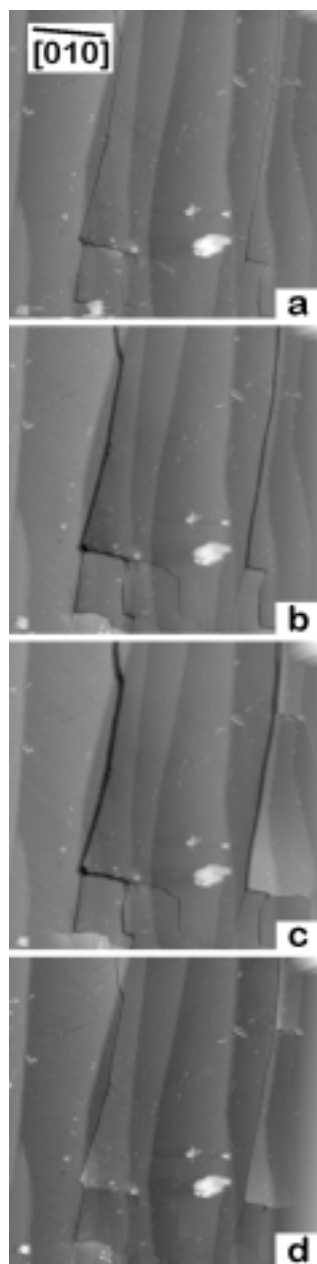


Figure 6. AFM snapshots of the desolvation sequence. Scan area 100 $\times$ 100 μm^2 . Several macrosteps 100–300 nm high running perpendicular to [010] are evident. a) 110 min: the first cracks 1.5 μm wide orthogonal to [010] appear. b) 170 min: cracks continue to enlarge and small, misaligned blocks appear. c) 460 min: main cracks are now 4 μm wide and intercalated with smaller blocks. d) 26 h: a partial healing of the crystalline surface by exposure to water vapor for a few hours is evident.

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Asymmetric Synthesis of an Organic Compound with High Enantiomeric Excess Induced by Inorganic Ionic Sodium Chlorate**

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Recent progress in asymmetric synthesis has been made by the developments of both organic asymmetric catalysts and stoichiometric organic chiral auxiliaries.^[1] The origin of significant enantiomeric enrichments in organic compounds such as L-amino acids on the earth has been an intriguing puzzle.^[2] One of the proposed mechanisms for the enantiomeric enrichments of organic compounds is through asymmetric synthesis and/or subsequent asymmetric adsorption^[3] on the surface of inorganic enantiomorphic crystals. We recently reported an enantioselective synthesis of an organic compound promoted by chiral quartz,^[4] which is an enantiomorphic inorganic molecule with covalent bonds between the silicon and oxygen atoms.

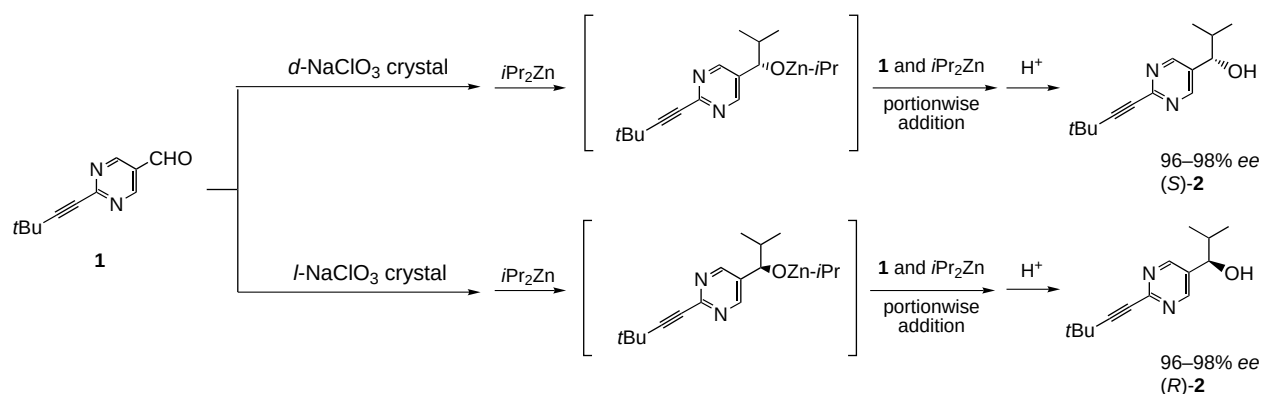
On the other hand, sodium chlorate (NaClO₃) is an enantiomorphic inorganic ionic crystal.^[5] Kondepudi et al. reported that almost all of the NaClO₃ crystals precipitated from a stirred particular solution have the same chirality.^[6, 7] However, the relevance of the chirality of NaClO₃ to that of an organic compound was not established. An earlier report^[8] on the enantioselective adsorption of racemic compounds by NaClO₃ was disproved by the later examination of Gillard and da Luz de Jesus.^[9] Thus, the question has remained as to whether significantly enantiomerically enriched organic compound can be formed using chiral NaClO₃, an inorganic ionic crystal.

Herein we report an unprecedented highly enantioselective synthesis of an organic compound which is induced by *d*- or *l*-NaClO₃ crystals. The enantioselective addition of diisopropylzinc (*i*Pr₂Zn) to 2-(*tert*-butylethynyl)pyrimidine-5-carbaldehyde (**1**) in the presence of *d*- or *l*-NaClO₃ powder gave pyrimidylalkanol **2** with high *ee* values (96–98 % *ee*) in high yields (90–99 %; Scheme 1, Table 1).

The (*S*)-pyrimidylalkanol (*S*)-**2** was obtained with 98 % *ee* in 93 % yield when *i*Pr₂Zn was added to the mixture of *d*-NaClO₃ and aldehyde **1** (Entry 1). The reaction is reproducible (Entries 2 and 3). On the other hand, reactions between aldehyde **1** and *i*Pr₂Zn in the presence of *l*-NaClO₃, instead of *d*-NaClO₃, always gave (*R*)-**2** with 98 % *ee* in yields of 91–98 % (Entries 4–6). When the reactions were run sequentially in the presence of *d*-, *l*-, *d*-, and *l*-NaClO₃, using exactly the same reaction equipments, (*S*)-, (*R*)-, (*S*)-, and (*R*)-**2** with

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Scheme 1. Enantioselective synthesis of **2** in the presence of NaClO_3 .

Table 1. Enantioselective synthesis of pyrimidylalkanol **2** in the presence of *d*- and *l*- NaClO_3 .

Entry ^[a]	NaClO_3	Pyrimidylalkanol 2	
		yield [%]	ee [%] (config.) ^[b]
1	<i>d</i>	93	98 (<i>S</i>)
2	<i>d</i>	99	98 (<i>S</i>)
3	<i>d</i>	90	97 (<i>S</i>)
4	<i>l</i>	91	98 (<i>R</i>)
5	<i>l</i>	95	98 (<i>R</i>)
6	<i>l</i>	98	98 (<i>R</i>)
7 ^[c]	<i>d</i>	93	96 (<i>S</i>)
8 ^[c]	<i>l</i>	94	96 (<i>R</i>)
9 ^[c]	<i>d</i>	93	96 (<i>S</i>)
10 ^[c]	<i>l</i>	94	96 (<i>R</i>)
11	<i>d/l</i> (3/1)	92	97 (<i>S</i>)
12	<i>l/d</i> (3/1)	90	97 (<i>R</i>)

[a] $\text{NaClO}_3/\mathbf{1}/i\text{Pr}_2\text{Zn} = 1.9/1.0/2.0$. See also Experimental Section. [b] The *ee* value was determined by HPLC analysis on a column fitted with a chiral stationary phase (Chiralcel OD). [c] Reactions were carried out sequentially in the order of the entry numbers using the same equipment.

96% *ee* were obtained, respectively, in 93–94% yields (Entries 7–10). These results clearly show that the chirality of NaClO_3 controls the absolute configuration of the newly formed alkanol **2**.

The corresponding reactions in the presence of the mixture of *d*- and *l*- NaClO_3 were also examined. When the 3/1 mixture of *d*- and *l*- NaClO_3 was used, (*S*)-**2** was obtained in 92% yield with 97% *ee* (Entry 11). The reaction using a 1/3 mixture of *d*- and *l*- NaClO_3 , afforded (*R*)-**2** with 97% *ee* (Entry 12). Thus, the final configuration of **2** formed is dependent on the major enantiomorphs of NaClO_3 in the mixture.

The very high enantioselectivity observed in the present asymmetric reaction may be explained as follows: Chiral NaClO_3 ^[5b] induces a very small enantiomeric enrichment in the alkanol **2** that is initially formed from aldehyde **1** and $i\text{Pr}_2\text{Zn}$.^[10] The subsequent asymmetric autocatalysis^[11] of **2** with amplification of *ee* then automultiplies **2** to afford the alkanol **2** possessing the corresponding absolute configurations with high *ee* values in high yields. Further mechanistic details are now under investigation.

In summary, we have demonstrated for the first time that a chiral inorganic ionic crystal, namely *d*- or *l*- NaClO_3 , induces asymmetry in the highly enantioselective synthesis of an

organic compound. Thus, the present reaction correlates the chirality of NaClO_3 with the absolute configuration of an organic compound.

Experimental Section

Preparation of crystals and powders of *d*- or *l*- NaClO_3 : Recrystallization of NaClO_3 from water gave small crystals. A small crystal was put in an aqueous solution of NaClO_3 at room temperature, and the mixture was left until the size of the crystal reached over 5 mm. The chirality of the crystal was determined by polarimetry.^[12] Crystals of *d*- NaClO_3 were ground into a powder using a pestle and mortar (particle size: 5–12 μm), washed with diethyl ether, and dried in vacuo before use.

Typical experimental procedure (Table 1, Entry 2): A 1 M solution of $i\text{Pr}_2\text{Zn}$ in toluene (0.15 mL) was added dropwise with stirring (60–70 rpm) over 30 min to a suspension of aldehyde **1**^[13] (9.4 mg, 0.05 mmol) and *d*- NaClO_3 (222 mg, 2.09 mmol) in toluene (0.2 mL) at 0°C. After the mixture had stirred for 12 h, toluene (4.8 mL), a 1 M solution of $i\text{Pr}_2\text{Zn}$ in toluene (0.4 mL), and a solution of **1** (37.6 mg, 0.2 mmol) in toluene (1.5 mL) were added successively. After 3 h, toluene (14 mL), a 1 M solution of $i\text{Pr}_2\text{Zn}$ in toluene (1.6 mL), and a solution of **1** (151 mg, 0.8 mmol) in toluene (4 mL) were added and the mixture was stirred for a further 3 h. The reaction was quenched by adding 1 M hydrochloric acid (4 mL) and then made alkaline with saturated aqueous sodium bicarbonate (12 mL). The mixture was filtered through celite, and the separated aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated. Purification of the residue by thin layer chromatography on silica gel (hexane/ethyl acetate 2/1) gave **2** (242 mg, 1.04 mmol, 99%). $[\alpha]_D^{25} = -33.1$ ($c = 2.21$, CHCl_3). The *ee* value was determined as 98% by HPLC analysis on a column with a chiral stationary phase (Daicel Chiralcel OD, eluent 3% 2-propanol in hexane, flow rate 1.0 mL min⁻¹, UV detector at 254 nm, retention time: 18 min for (*S*)-**2**, 27 min for (*R*)-**2**).

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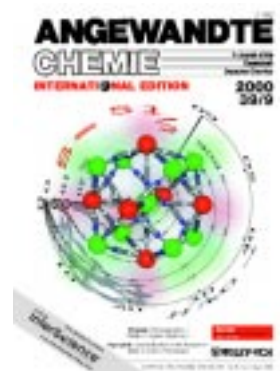
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Cover Picture

**Joulia Larionova, Mathias Gross, Melanie Pilkington,
Hanspeter Andres, Helen Stoeckli-Evans, Hans U. Güdel,
Silvio Decurtins**

The cover picture shows the idealized $[\text{Mn}^{\text{II}}(\mu\text{-CN})_{30}\text{Mo}^{\text{V}}]$ core of a novel cyanide bridged molecular cluster. Six Mo^{V} ions (red spheres) form an octahedron around the central Mn^{II} ion (green sphere in the center). The faces of this octahedron are capped by eight additional Mn^{II} ions (green spheres) and the total geometry is close to a rhombododecahedron. This cluster contains 15 paramagnetic ions and as a consequence has an extraordinarily high number of unpaired electrons, namely 51. The ferromagnetic interaction between the metal ions within a cluster leads to an $S = 51/2$ ground state. Due to additional ferromagnetic intercluster coupling, a complex magnetic behavior is observed below 44 K. More details are given by S. Decurtins et al. on p. 1605ff.



Dead Ends and Detours En Route to Total Syntheses of the 1990s**

Miguel A. Sierra* and Maria C. de la Torre

From the very beginning organic chemistry and total synthesis have been intimately joined. In fact, one of the first things that freshmen in organic chemistry learn is how to join two molecules together to obtain a more complex one. Of course they still have a long way to go to become fully mature synthetic chemists, but they must have the primary instinct to build molecules, as synthesis is the essence of organic chemistry. With the different points of view that actually coexist in the chemical community about the maturity of the science (art, or both) of organic synthesis, it is clear that nowadays we know how to make almost all of the most complex molecules ever isolated. The primary question is how easy is it to accomplish? For the

readers of papers describing the total synthesis of either simple or complex molecules, it appears that the routes followed are, most of the time, smooth and free of troubles. The synthetic scheme written on paper is, apparently, done in the laboratory with few, if any, modifications and these, essentially, seem to be based on finding the optimal experimental conditions to effect the desired reaction. Failures in the planned synthetic scheme to achieve the goal, detours imposed by unexpected reactivity, or the absence of reactivity are almost never discussed, since they may diminish the value of the work reported. This review attempts to look at total synthesis from a different side; it will focus on troubles found during the synthetic work

that cause detours from the original synthetic plan, or on the dead ends that eventually may force redesign. From there, the evolution from the original route to the final successful one that achieves the synthetic target will be presented. The syntheses discussed in this paper have been selected because they contain explicit information about the failures of the original synthetic plan, together with the evolution of the final route to the target molecule. Therefore, they contain a lot of useful negative information that may otherwise be lost.

Keywords: natural products • protecting groups • synthesis design • synthetic methods • total synthesis

1. Introduction

Much of the current chemical literature deals with the synthesis of organic molecules or describes the development of methodology for organic synthesis. The achievements in synthetic methodology are impressive and the most complex molecules are, in principle, accessible.^[1] From the beginning of the 1990s a feeling has spread throughout the chemical community about the maturity of this branch of chemistry,^[2] and today terms such as atom economy,^[3] highly efficient

homogeneous^[4] and heterogeneous catalytic transformations,^[5] combinatorial chemistry,^[6] and so on, are frequently used when talking about organic synthesis.

Great optimism transpires from the chemical literature when describing how the molecules are synthesized. It seems that our ability to devise synthetic routes has become infallible, and that even the most complex target molecules are prepared without apparent effort. Is this always true? Or is a lot of effort still necessary to make every step in a multi-step synthesis possible? The readers of papers that describe the preparation of organic molecules are very familiar with sentences such as “after extensive experimentation it was found, to our delight the reaction worked nicely”, and other synonyms thereof. Apparently, to go into details about the failures or to discuss all the unfruitful approaches decreases the beauty of the synthetic route reported.^[7] Therefore, it is not often easy to recognize when the synthesis developed as planned. In the meantime a lot of useful information may be lost.^[8] The aim of this work is to look at total synthesis from a different point of view. We will focus on the detours from the original synthetic plan, the dead ends that may have arisen at

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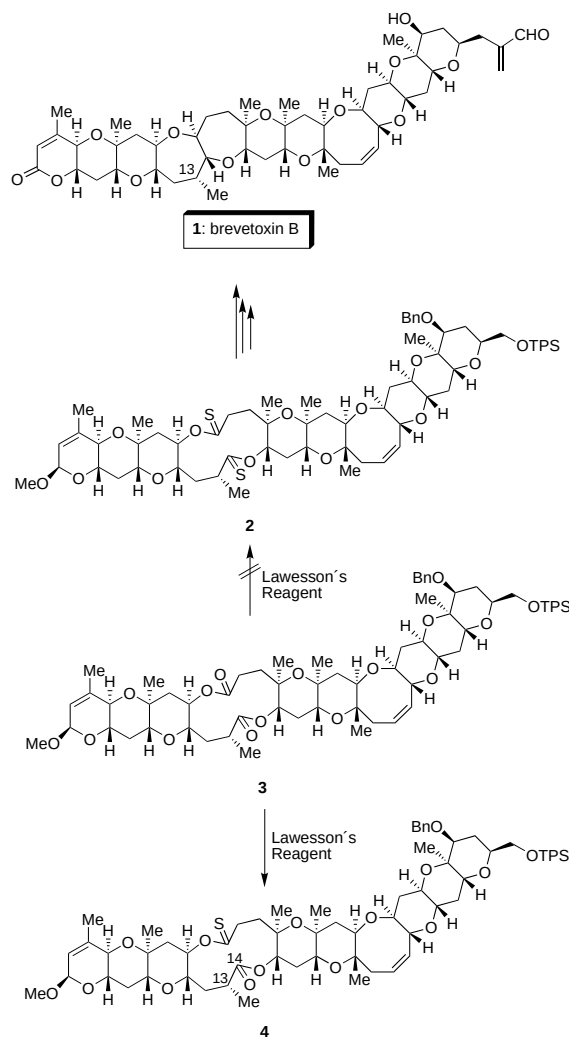
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[**] A list of abbreviations can be found at the end of the article.

specific steps of a total synthesis, as well as the thinking involved to solve the problems en route to the synthetic goal. The final route is often at least of equal beauty to that originally planned. The selection of problems discussed below has been extracted from papers that explicitly expressed the failure of the original planning, and the evolution of the final—mainly—successful solution to the problem.

The following example displaying how the failure of a well-tested transformation can truncate a total synthesis in an advanced step, may serve to focus the aim of this review. The transannular bridging of the 12-membered bis(thiolactone) **2** was designed by Nicolaou et al. to build the remaining two rings of brevetoxin B (**1**, Scheme 1).^[9] The process had been thoroughly tested^[10] in model systems such as **6** (Scheme 2) and seemed to be a very attractive strategy to prepare the desired final product. However, all attempts to prepare compound **2** by reaction of the macrodilactone precursor **3** with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,2,3,4-dithiadiphosphetan-2,4-dithione)^[11] produced very low yields of the desired di(thiolactone) **2**.^[9] The lactone carbonyl group at C(14) remained unaltered, and the reaction product was monothiolactone **4**. Other Lawesson-like reagents were also unable to effect the transformation, and this route was eventually abandoned.^[12] In spite of this apparent failure a full body of methodology to build fused seven-membered rings was developed in the process.^[10] The successful synthesis of brevetoxin B by Nicolaou and co-workers is now a landmark in organic synthesis.^[13]

This example shows how the failure of a single transformation can thwart a beautiful idea. In most of the cases, the nature of the trouble found in a specific synthesis may be attributable to more than one cause. The selected syntheses that follow are classified into seven different groups pertaining to the nature of the main problem found in each case.



Scheme 1. The steric hindrance of the C(13) methyl group provokes the failure of the transformation of dilactone **3** to di(thiolactone) **2**, and, hence, truncates the synthesis of brevetoxin B at an advanced stage.

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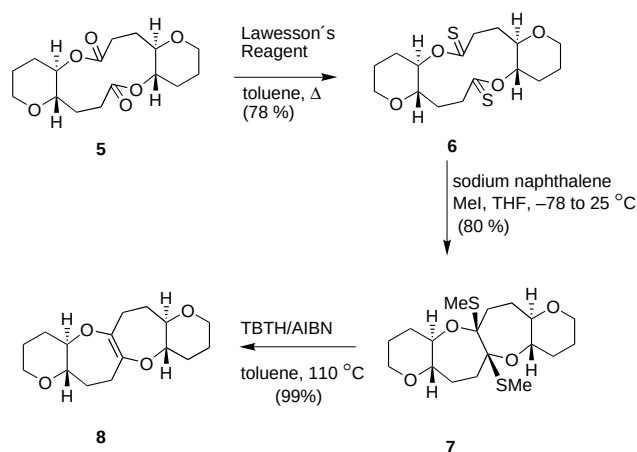


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Maria C. de la Torre studied chemistry at the UCM and received her doctorate in 1986. After postdoctoral stays at Imperial College with Prof. Steven V. Ley (1987–1988) and Colorado State University with Prof. Albert I. Meyers (1988–1989), she returned to Madrid where she was appointed Colaborador Científico (Consejo Superior de Investigaciones Científicas) in 1989. Her current research interest focuses on the chemistry of densely functionalized natural products, development of insect antifeedants, and in the preparation of natural product hybrids with mixed and/or complementary biological properties.



Scheme 2. Models for brevetoxin B synthesis: the efficient bridging of macro di(thiolactones) to obtain fused seven membered rings.

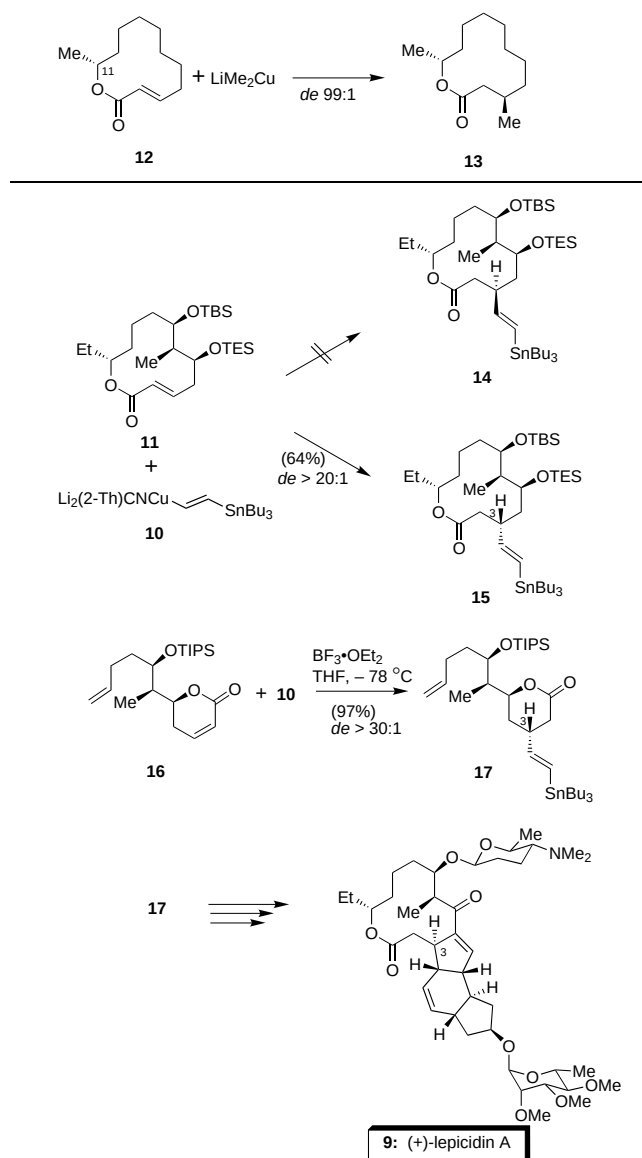
2. Working Models that do not Work

Let's consider first the use of model reactions. Their usefulness in synthetic chemistry is undoubted as demonstrated by the huge amount of work published detailing the construction of model compounds of specific molecules. Nevertheless, how applicable to the real targets are the results obtained when working with models? Thankfully for us, most of the time they are, but sometimes they are not. The synthetic plan resting on reactions that have been developed for the model compound then needs to be changed, or at least thoroughly modified, to achieve the desired result.

One troublesome situation arises when the configuration of a newly formed stereogenic center obtained in a synthetic reaction is opposite to that predicted by the results obtained previously in a suitable model system. One of these cases arose in Evans' synthesis of (+)-lepicidin A (**9**, Scheme 3).^[14] An early planned route to obtain lepicidin A rested on the conjugate addition of cuprate **10** to the α,β -unsaturated lactone **11**. Previous studies carried out on macrolactone **12** as a model (which formed the Michael adduct **13** by reaction with Me_2CuLi)^[15, 16] as well as computer calculations,^[17] pointed to the nearly exclusive production of the desired Michael adduct **14**. However, the addition of cuprate **10** to compound **11** yielded lactone **15** with the wrong stereochemistry at C(3). Therefore, the original idea of delaying the introduction of the labile vinylstannane moiety until the later stages of the synthesis was abandoned.

In the successful approach to lepicidin A, the vinylstannane moiety was placed in the precursor **16**. Michael addition of cuprate **10** to **16** gave this time compound **17** with the desired α stereochemistry. The sensitive tin moiety had to be carried through the whole synthetic route and finally intermediate **17** was successfully converted into **9** (Scheme 3).

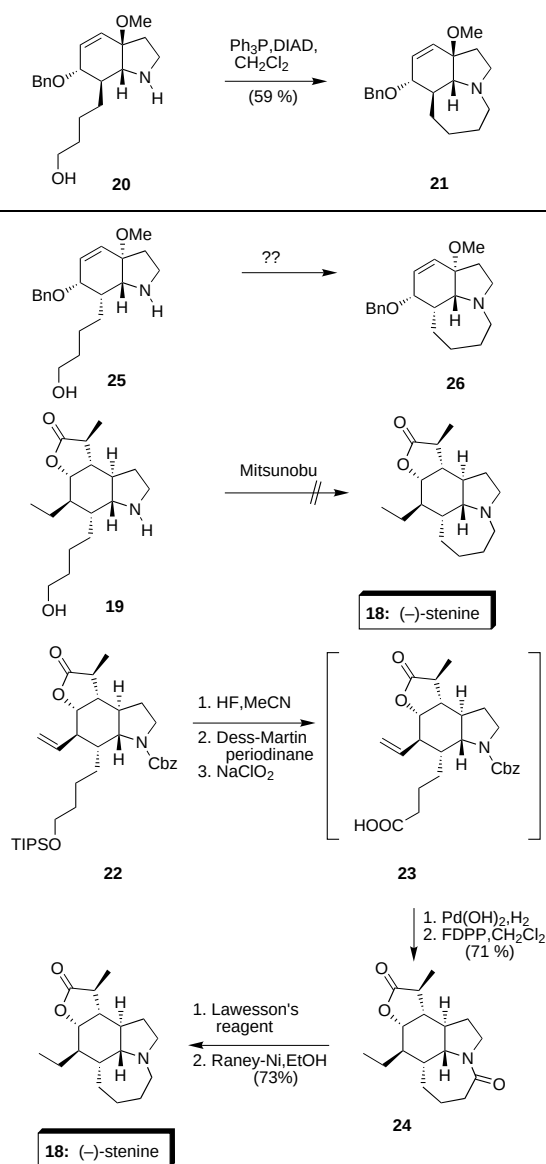
Sometimes a cyclization step works well on a compound having a structure that is reminiscent of the compound being used to access the target molecule. However, sometimes the same reaction stubbornly refuses to occur with the desired intermediate. One of these cases is found in Wipf's synthesis of (–)-stenine (**18**, Scheme 4).^[18] The key step to complete the



Scheme 3. Obtaining the wrong stereochemistry with respect to the model reaction necessitates carrying a labile group from the early stages of the synthesis.

synthesis of (–)-stenine was the Mitsunobu cyclization of **19** to **18**.^[19] The cyclization step worked nicely on the related model **20**. In fact, bicycle **20** yielded the tricycle **21** when submitted to the Mitsunobu reaction conditions. However, when intermediate **19** was subjected to these reaction conditions the cyclization failed. This failure was claimed to be due to the fact that formation of a medium ring by a Mitsunobu reaction strongly depends on the rate of cyclization versus side reactions of the activated alcohol. According to the authors, compound **20** is more preorganized towards the formation of the seven-membered ring than **19**. Therefore access to (–)-stenine (**18**) through a Mitsunobu cyclization was abandoned.

The desired target was reached from the doubly protected intermediate **22**. Removal of the silyl protecting group followed by sequential oxidation of the free alcohol to carboxylic acid **23**, hydrogenation of the double bond, and



Scheme 4. Unsuccessful and successful synthesis of (-)-stenine.

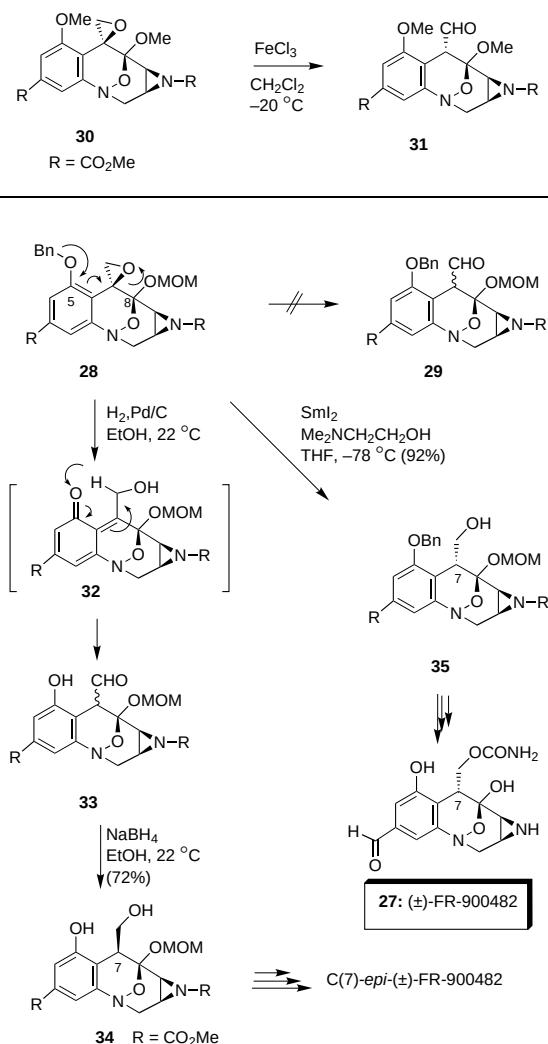
ring closure formed **24**. Finally, the two-step reduction of the amide group of **24** furnished (-)-stenine.

What have **19** and **20** in common, since they are significantly different compounds? The failure of intermediate **19** to cyclize may be attributable to reasons other than the absence of a hypothetical preorganization present in **20**. In fact, molecular mechanics analysis showed no appreciable differences between the two compounds regarding a preorganization towards cyclization.^[20] The *cis-anti*-tricyclic system **21** is 7.8 kcal mol⁻¹ more stable than **26**, which harbors the ring stereochemistry present in compound **18**. Perhaps the energetically more-demanding cyclization to yield the *trans-syn*-fused system present in stenine is responsible for the failure of compound **19** to cyclize under Mitsunobu conditions.

Other troublesome situations may arise when protecting groups that work well in a model can not be applied to an intermediate used in the synthesis. For example, Danishefsky's approach to (±)-FR-900482 (**27**) was designed to include

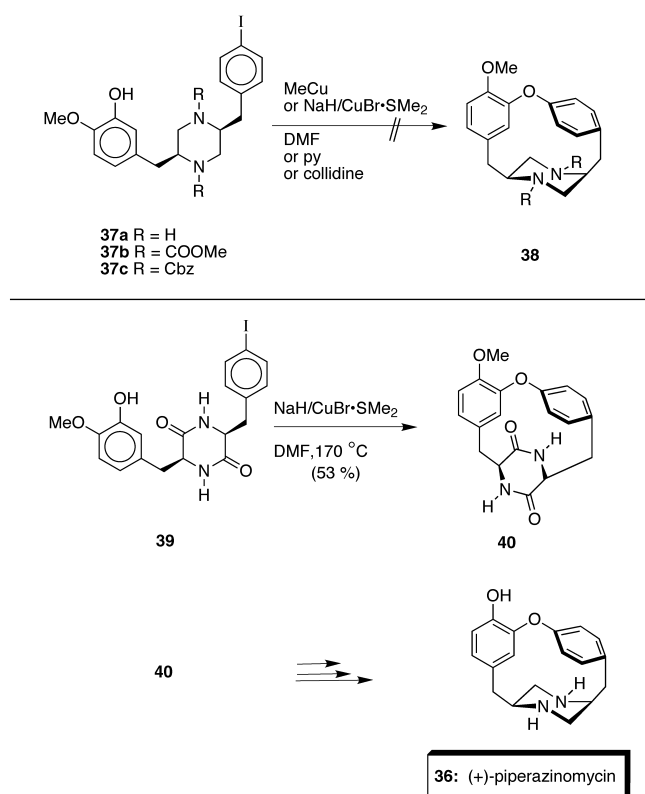
the rearrangement of epoxide **28** to aldehyde **29** as a key step (Scheme 5).^[21] This reaction worked efficiently in the model epoxide **30**, which smoothly rearranged to **31** in the presence of FeCl₃.^[22] Unfortunately, all attempts to realize the analogous reaction with **28** failed to yield aldehyde **29**, and only highly complex mixtures resulted from the use of FeCl₃ or other mild Lewis acid catalysts. These results were explained by considering the lability of the ether functions at C(5) and C(8) on intermediate **28**. In the words of the authors "the seemingly innocuous alterations of two protecting groups resulted in a breakdown of some of the model system chemistry".

Interestingly, the lability of the benzyl ether group on **28** was actually exploited in the synthesis of (±)-FR-900482 (**27**). Hydrogenolysis of the benzyl ether group of compound **28** formed aldehyde **33** via **32**. Reduction of **33** with NaBH₄ afforded product **34** with a configuration of C(7)-*epi*(±)-FR-900482. Formation of compound **34** was explained by the initial formation of aldehyde **33** in the natural α -configuration


 Scheme 5. The seemingly innocuous alteration of two protecting groups resulted in a breakdown of some of the chemistry used successfully in the model system. However, the chemistry learned was successfully applied to the synthesis of (±)-FR-900482 (**27**).

and its rapid epimerization to the more stable C(7)- β -series. Hence, reaction conditions were fine-tuned to effect protonation at C(7), after the opening of the epoxide from the less-hindered β -face, which led to a nonepimerizable product with the correct configuration at C(7). Treatment of compound **28** with SmI_2 afforded compound **35** in excellent yield, which fulfilled all of these stereochemical requirements, and was then transformed to **27**. This example shows how the chemistry learned from a failure can be successfully applied to a new approach to the desired target. Could the reader have known if that happened if only the final route would have been reported?

Other times the structurally closest compound to the planned intermediate does not produce satisfactory results with the desired transformation, but the desired results are obtained with a structurally distant, yet synthetically equivalent product. This situation arises quite often and may be exemplified by Boger's synthesis of (+)-piperazinomycin (**36**, Scheme 6).^[23]



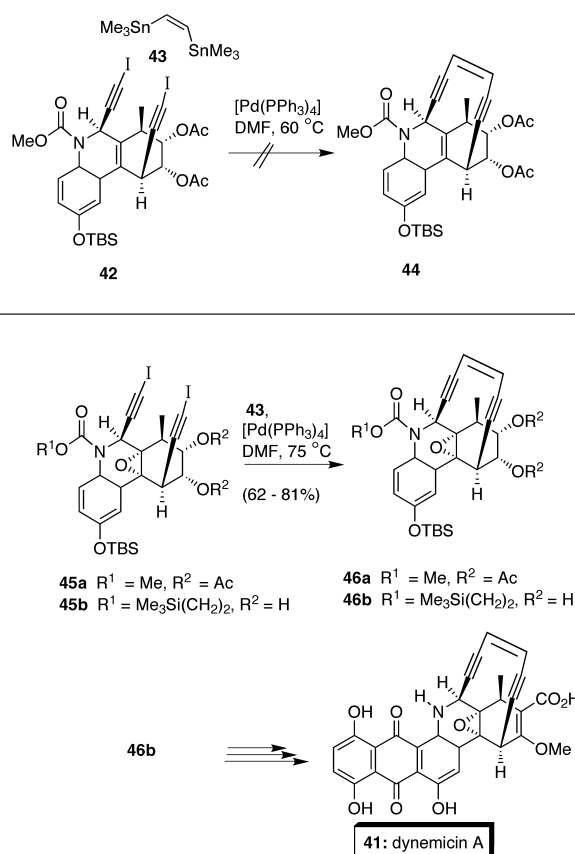
Scheme 6. How close should the model molecule be to the intermediate? For the total synthesis of (+)-piperazinomycin **36** not so close. The flattening of the six membered ring of **39** may be the key for a successful Ullmann cyclization.

Prior to the implementation of the successful cyclization reaction that ultimately leads to (+)-piperazinomycin (**36**), the cyclization of a number of compounds **37**, closely related to the natural product, were studied. The common feature of these models was the piperazine nucleus that is present in the natural product. While other molecules related to **37** but lacking the six-membered ring were cyclized with different degrees of success, compounds **37** systematically failed to produce the desired macrocycles **38**. Nevertheless, com-

pounds **37** were potentially excellent substrates for the cyclization, as there exists no possibility for their racemization during the conditions employed to close the ring. Access to (+)-piperazinomycin (**36**) was finally gained by utilizing the diketopiperazine **39** to effect the Ullmann ring closure to give macrocycle **40**.^[24] These reaction conditions were carefully optimized to minimize the racemization of substrate **39**. Reduction of the amide carbonyl groups of **39** and deprotection of the phenolic group finally afforded (+)-piperazinomycin (**36**).

The observed differences found during the cyclization step could clearly be explained by modeling compounds **37** and **39**. Both compounds must adopt a boat conformation to cyclize. This conformational switch is energetically more demanding for piperazines **37** ($E_{\text{boat}} - E_{\text{chair}} = 6.6 \text{ kcal mol}^{-1}$) than for the flatter diketopiperazine **39**, for which the preferred conformation is already boatlike ($E_{\text{boat}} - E_{\text{chair}} = -0.4 \text{ kcal mol}^{-1}$).

An interesting situation emerges when a reaction tested in a model system (or in an earlier precursor in a synthetic route) does not work at all, but is thereafter successfully applied to the final synthetic route. Unfortunately, it is not easy to ascertain how often this situation arises because of the lack of reported instances. Nevertheless, even against the odds and coupled with negative results from models in hand, to try a nice idea on a few milligrams of an advanced intermediate may be appealing. One of these examples is found in Danishefsky's synthesis of dynemicin A (**41**, Scheme 7).^[25]



Scheme 7. When a sensitive transformation fails in an early intermediate, it may be worthwhile to try it in a more elaborate compound. The chemistry learned from the failure of the building of dynemicin A was applied to reach the target molecule.

One of the most sensitive steps in the building of dynemicin A was the incorporation of the enediyne moiety characteristic of this class of compounds. This transformation was first tested on the intermediate **42**. Reaction of tricycle **42** with distannane **43** in the presence of $[\text{Pd}(\text{PPh}_3)_4]$ resulted in a detrimental and rapid cross-coupling, to give the product of two intermolecular couplings without any of the desired enediyne **44**. The reaction was tested next on compound **45a**, which had the epoxide ring of the final product in place. Reaction of **45a** with **43** in the presence of $[\text{Pd}(\text{PPh}_3)_4]$ under medium dilution conditions yielded 62 % of the enediyne **46a**. The explanation for this success was that the presence of the epoxide shortens the approach of the two ethynyl groups, while providing some relief from the projected strain in the cyclization product. The introduction of this strain may be what forces the Bergman cyclization upon epoxide opening.^[26] Success of the bis-Stille cyclization step ultimately led to the total synthesis of dynemicin A from **46b**.

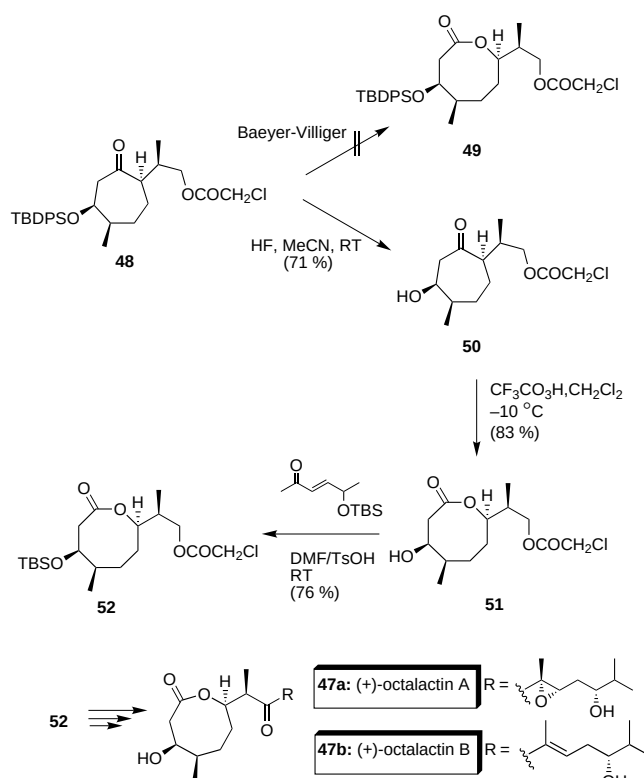
Evidently, the extensive use of model compounds to predict the reactivity of a complex synthetic intermediate, or the outcome of a reaction to be carried out on a densely functionalized molecule, has many other drawbacks. The few examples we have presented so far are also a brief introduction to the specific troublesome situations discussed below. The overbearing question pertaining to the huge amount of work done to synthesize models of a plethora of different kinds of molecules, often barely resembling the real target, could be: is the effort really worth it? We have selected four examples of the many possible. From the lepicidin A (**9**) and stenine (**18**) cases, it may be learned that the model and the real system have to be as similar as possible in the region of the reactive center. However, this is not the case for piperazinomycin (**36**) where the closest models (or precursors) to the target refuse to cyclize. For dynemicin A (**41**), the reaction carried out on an early intermediate in the synthetic route fails, while stepping ahead and introducing a new element of structural constraint results in success. The final conclusion is that models are useful training grounds that provide critical information before entering the real battlefield, and even when a model fails there is a lot of chemistry already done that will help to smooth the rough road ahead that leads to the target. Nevertheless, the answer to the question: What makes a model good? is, probably, to sculpt the model as similar to the real system as possible. From here the conclusion is clear, after exploring all facets of the upcoming chemistry on a model substrate, why not do the real thing?

3. Troublesome Protecting Groups

A primary necessity when planning the synthesis of any molecule is the use of protecting groups. Every freshman of organic chemistry learns that the selectivity of an organic transformation can be controlled in a molecule harboring a multitude of functional groups by selecting an appropriate protecting group. There exists a huge arsenal of protecting groups available to the synthetic chemist for almost every situation and necessity imaginable.^[27] Sometimes, however, a

protecting group can serve dual roles, not only does it have a protective role but it becomes a nuisance to the synthesis by either inhibiting a crucial step or refusing to be displaced when its protecting role has finished. The presence of troublesome protecting groups, even with the multitude of known alternatives, is much more habitual than would be desired.

Let us consider first the inhibition of a crucial step by the presence of a protecting group. This problem is solved by removing the protecting group and effecting the desired transformation, either with a new protecting group or with the free functional group, without significant deviations from the original planning but with additional deprotection–protection steps. Clardy's synthesis of (+)-octalactins A and B **47a–b** illustrates this point succinctly (Scheme 8).^[28] The Baeyer–Villiger reaction carried on the seven-membered ring ketone **48** to form the eight-membered ring lactone **49** characteristic of octalactins A and B, resulted in low conversions and substantial decomposition of the substrate.



Scheme 8. During the synthesis of octalactins A (**47a**) and B (**47b**) the TBDPS group protected not only the alcohol but the carbonyl group, thus inhibiting the Baeyer–Villiger oxidation needed to access the eight-membered ring of octalactins.

After removal of the TBDPS protecting group and treatment of the free hydroxyketone **50** with $\text{CF}_3\text{CO}_3\text{H}$ the desired lactone **51** was obtained in 83 % yield. The free alcohol **51** was reprotected and the intermediate **52** was used to prepare octalactins A and B. Examination of the molecular models of ketone **48** clearly shows that the bulky silicon protecting group is not only protecting the hydroxyl group, but also shielding the carbonyl group by its immense steric bulk. In

fact, both faces of the carbonyl group are blocked, one by the ring and the other by both the TBDPS and the methyl groups on the side chain.

The troublesome transformation in the previous example resulted in only a minor deviation from the original planning, since it was resolved by removing the source of the problem. Nevertheless, such failed reactions consume precious material that could be further allocated to complete the synthesis. Other times it is not so simple to pass through the bottleneck caused by the presence of a stubborn protecting group that either inhibits a crucial step or switches the reaction to a different and undesired end. Now a new protecting group must be carefully selected and placed in an early intermediate and the synthesis has to be repeated in order to avoid the problematic step. Overman's synthesis of (±)-akuammicine (**53**, Scheme 9) serves as an example for both situations.^[29]

The aza-Cope-Mannich rearrangement^[30] of compound **54** worked splendidly to form **55**, which was transformed to (±)-dehydrotubifoline (**56**) by base-mediated hydrolysis of the amide pivaloyl group. The transformation of **56** into (±)-akuammicine by direct acylation at C(3) was then attempted. After the diverse reaction conditions employed met with no success, the carbomethoxy group was introduced at C(3) of

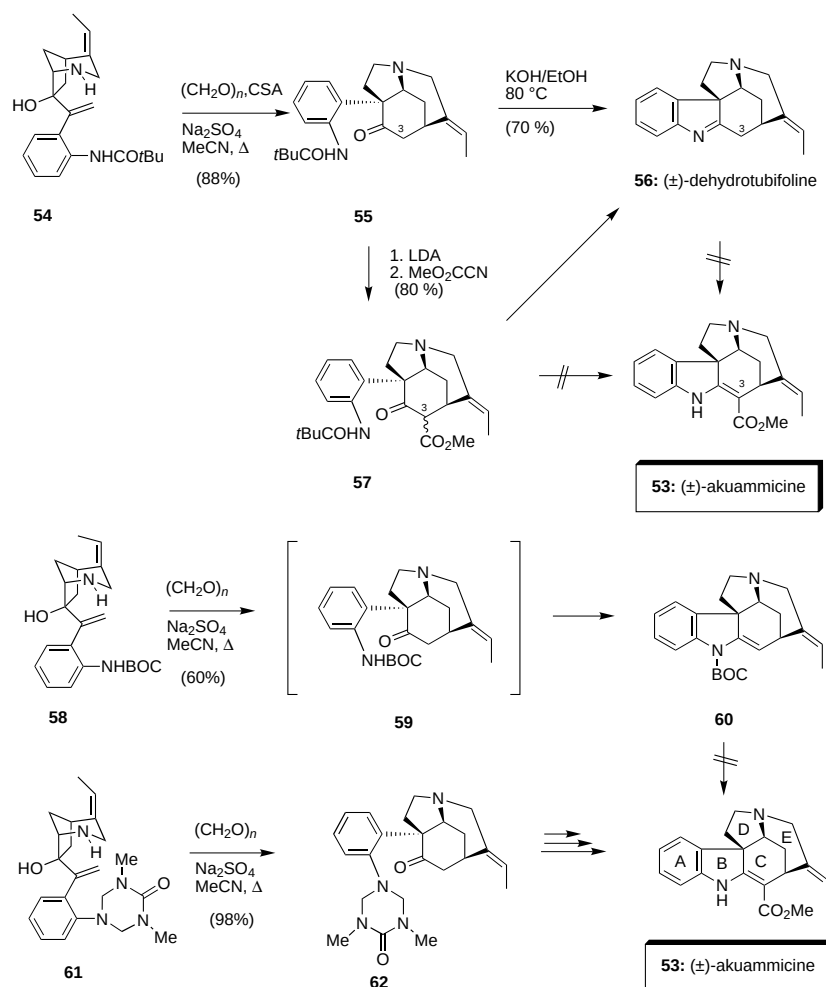
ketone **55** prior to ring closure. Thus, ketone **55** was acylated to yield β-keto-ester **57**. All attempts to remove the pivaloyl group from **57**, either returned **57** or led to the formation of dehydrotubifoline (**56**).

The robustness of the pivaloyl group was certainly responsible for the inability to convert **57** into akuammicine (strikingly the hydrolysis of the same group in compound **55** gave dehydrotubifoline (**56**) in 70 % yield). Hence, the BOC group was chosen to protect the aromatic amine nitrogen atom, as it could be removed by mild acid treatment. Compound **58** was procured after a good number of difficulties caused by the seemingly innocuous change of a protecting group were encountered. The reaction of **58** under standard aza-Cope-Mannich conditions led not to the expected ketone **59** but instead gave the tetracyclic compound **60**. All attempts to isolate the intermediate ketone **59** were fruitless. Presumably, the formation of **60** arises from the greater nucleophilicity of the carbamate nitrogen atom on **59**, relative to the pivaloyl-protected nitrogen atom of **54** that successfully rearranged to ketone **55**.

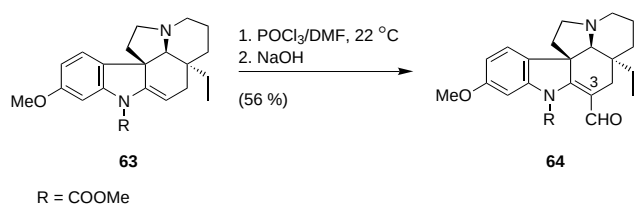
Tetracycle **60** could not be transformed to (±)-akuammicine either. In the author's words the striking difference in reactivity of BOC- and pivaloyl-protected anilines in these series "underscores the profound effects on reaction outcome that can arise from small changes in electron density". The solution (once all the chemistry above was learned) was to use a protecting group that was able to shield both amine protons. The selected group should have the considerable stability required to survive the aza-Cope-Mannich rearrangement but should also be easily removed at the end of the synthesis. The chosen group was a triazone (1,3-dimethylhexahydro-2-oxo-1,3,5-triazine), which was incorporated at the very beginning of the synthesis and carried through the complete synthetic route to the aza-Cope-Mannich precursor **61**. Intermediate **61** rearranged uneventfully to ketone **62**, which was further converted into (±)-akuammicine **53**.

The reactions shown in Scheme 9 illicit one additional intriguing question: Why couldn't enamine **56** be transformed to (±)-akuammicine? Apparently, the C(3) position is fully shielded by the adjacent bridged E ring, thus precluding any transformation at this carbon atom. In agreement with this is the fact that acylation of compound **63** to yield **64** occurred in the *Aspidosperma* alkaloid series which lacks the bridged E ring (Scheme 10).^[31]

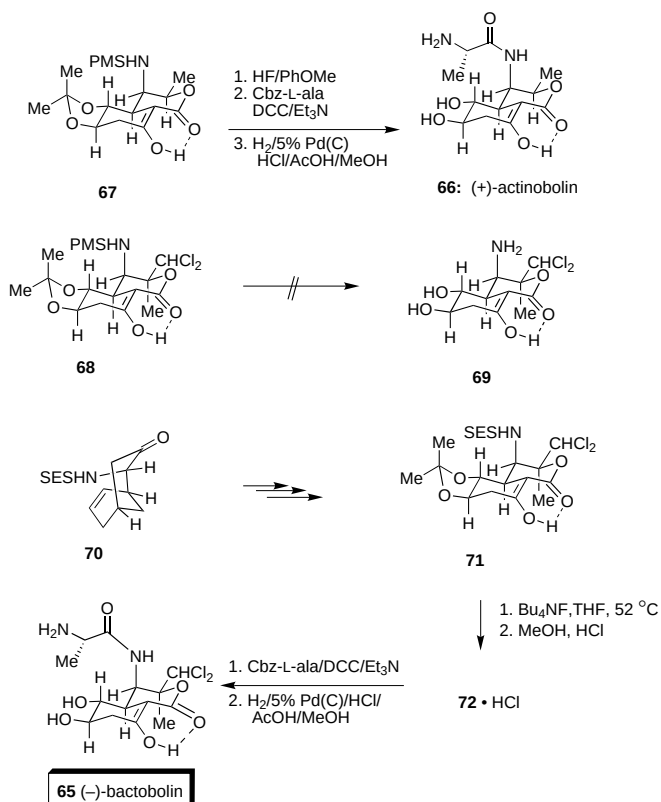
The occurrence of an overprotective protecting group is more frequent than one could imagine. Once the protecting group has fulfilled its role in the synthesis it has to be removed. Usually, before choosing a blocking group to protect a certain functional group, the reaction conditions to remove it



Scheme 9. The profound effects on reaction outcome that can arise from small changes in electron density, in this case changing an amide for a carbamate group, thwarted the synthesis of (±)-akuammicine in its final stages. Placing a new protecting group at the aniline nitrogen atom obliged the authors to repeat the synthetic scheme almost from the beginning.

Scheme 10. Successful formylation of **63**.

are carefully evaluated. Nevertheless, sometimes the removal of a protecting group becomes the problem step of a synthesis, which if not totally frustrating the original plan, at least forces the synthesis to be restarted from the very beginning with a new protecting strategy. Weinreb's synthesis of (–)-bactobolin (**65**) is one of such cases (Scheme 11).^[32]



Scheme 11. The presence of an overprotective protecting group truncated the synthesis of (–)-bactobolin in its final stages. Once again, a new protecting group has to be placed at the very beginning of the synthesis.

The late stages of the synthesis of the closely related actinobolin **66** involved the deprotection of amide **67**. The removal of the PMS group from **67** was effected by treatment with liquid HF, which concomitantly removed the acetonide group. An analogous treatment on **68**, the immediate precursor of (–)-bactobolin, resulted in the exclusive removal of the acetonide moiety and failed to remove the PMS group. Decomposition was noted under forcing conditions. Other reaction conditions, including a variety of reductive (H_2 , Pd/C, HF) or oxidative methods (LHDMS/ O_2 or MoOPH) did not afford any of the desired amine. It was therefore necessary to mask the nitrogen atom in a different way and at the very

beginning of the synthetic route, in this case in precursor **70**. The [β -(trimethylsilyl)ethyl]sulfonyl (SES) group was chosen this time and it was carried through the complete synthetic scheme to be finally removed from intermediate **71** by treatment with fluoride. The amino derivative **72** thus obtained was transformed into (–)-bactobolin in two steps.

The steric hindrance caused by the bulky substituents at the carbon atom contiguous to the reactive nitrogen atom, coupled with the stability of the sulfonyl protecting group may be responsible for this failure. The over-stability of the sulfonyl-protecting group was eventually overcome by the use of a β -silylethyl group.

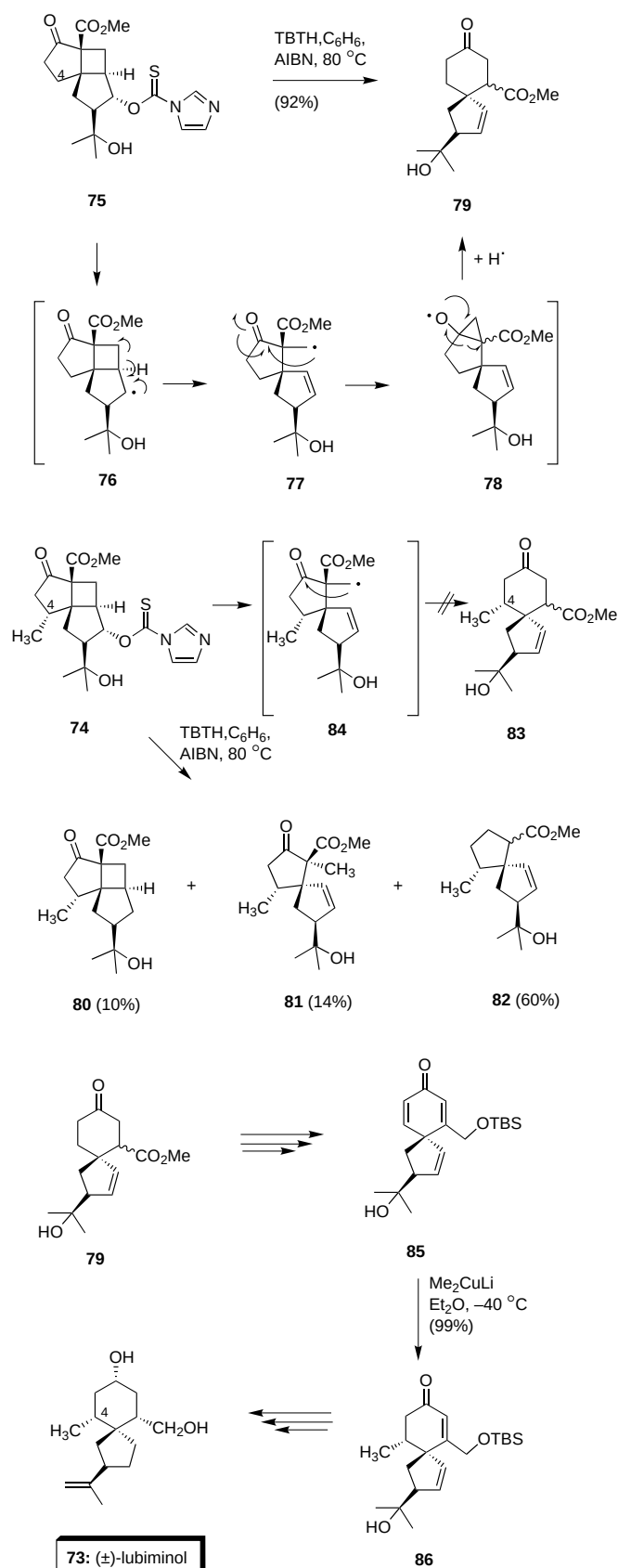
These few examples show that, even with an impressive array of very specific protecting groups in hand, things can go wrong just because a troublesome protecting group appears. Most of the time the source of the problem is easily explained, but the explanation is generally found after the trouble has truncated the designed route. Unless we understand why structurally similar compounds such as **55** and **57**, or **67** and **68** behave so differently, it will be extremely difficult to foresee troubles such as those found in the examples presented.

4. The Unexpected Influence of Remote Substituents

During the designing stages of the synthesis of a target molecule (not necessarily a complex one) the chemist studies the transformations needed to reach the desired target. Retrosynthetic analysis often gives more than one alternative to achieve a specific transformation.^[33] The individual steps are studied and a sketch of the work to be done is produced. The crucial steps are carefully and critically evaluated, in many cases thoroughly tested in models and, except for those syntheses done to probe the efficiency of a new synthetic procedure, well established synthetic transformations are generally chosen. Sometimes, however, an extensively tested transformation fails in an advanced intermediate because of the presence of an offending remote substituent. Crimmins' synthesis of ($\pm$)-lubiminol (**73**) is one of these cases (Scheme 12).^[34]

Compound **74** has all the carbon atoms required for the target molecule and the synthesis of lubiminol seemed to be in hand. The projected radical rearrangement to access lubiminol (**73**) worked very efficiently on compound **75**, which lacked the C(4) methyl group. Thus, heating **75** in the presence of TBTH/AIBN induces the formation of radical **76**, which evolves by regioselective fragmentation of the cyclobutane ring to give the new radical **77**. Intermediate **77** undergoes a Dowd–Beckwith-type ring expansion^[35] to produce the spirofused intermediate **78**. Compound **79** is obtained by fragmentation of the cyclopropyl ring and hydrogen abstraction. However, heating alcohol **74** resulted in the isolation of a mixture of three products **80–82**, none of them being the desired rearranged product **83**.

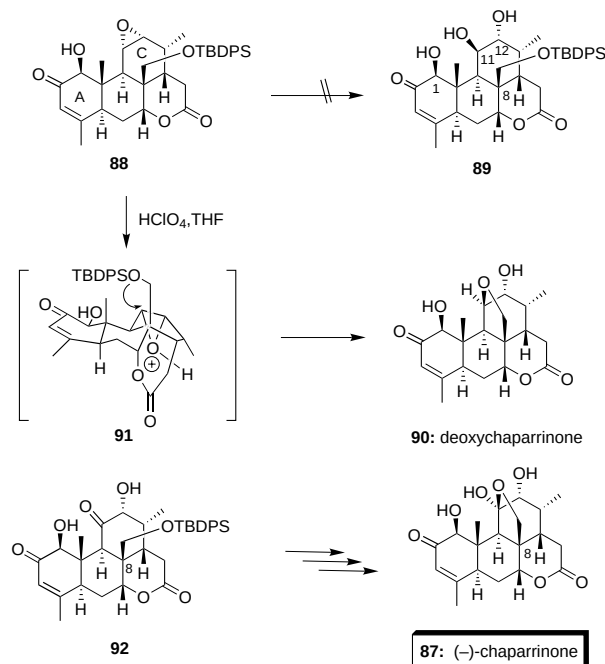
The failure of radical intermediate **84** to undergo the rearrangement to **83** is apparently because of the highly congested transition state necessary for the addition of the



Scheme 12. The dramatic effect of a remote, and in principle innocuous, methyl group inhibits the key Dowd–Beckwith rearrangement designed to access the spirocyclic structure of (±)-lubiminol (**73**). A longer route to introduce the problematic methyl group once the key rearrangement had occurred was used.

primary radical in intermediate **84** to the adjacent carbonyl group in the Dowd–Beckwith rearrangement.^[35] The 1,3-relationship of the primary radical with the α -C(4) methyl group on intermediate **84** may either sterically prohibit the addition to the carbonyl group or promote a hydrogen-atom transfer from the α -methyl group. Compound **80** would be formed by hydrogen capture by the radical derived from **74** prior to fragmentation of the cyclobutane ring, while radical **84** would lead to **81** by hydrogen capture and to **82** by decarbonylation. This failure forced the incorporation of a methyl group on trienone **85** once the rearrangement had occurred, and resulted in a considerable lengthening of the synthesis.

The syntheses of (±)-lubiminol (**73**) is an example in which a group inhibits the desired transformation by imposing several restrictions to the transition states involved, mainly by steric means which may or may not be predicted a priori. A different situation is encountered when the desired transformation is inhibited by the presence of a chemically active group. This problem is found in Grieco's synthesis of (–)-chaparrinone (**87**, Scheme 13).^[36]



Scheme 13. The straightforward transformation of epoxide **88** to triol **89** was truncated because the protected hydroxymethyl group and the oxirane ring are nicely set up to react intramolecularly and yield deoxychaparrinone (**90**). Changes in the alcohol protecting group were useless. A completely different strategy was needed to reach (–)-chaparrinone (**87**).

The transformation of epoxide **88** to (–)-chaparrinone by replacing the ring C hemiketal array appeared to be a straightforward exercise. It was anticipated that an acid-catalyzed opening of the epoxide ring would generate triol **89**. The functionality present in ring A was expected to withstand the strongly acidic conditions required to effect an opening of the epoxide ring, because of the results obtained during the synthesis of the related compound klaineane.^[37] Selective protection of the C(1) and C(12) hydroxyl groups in **89**,

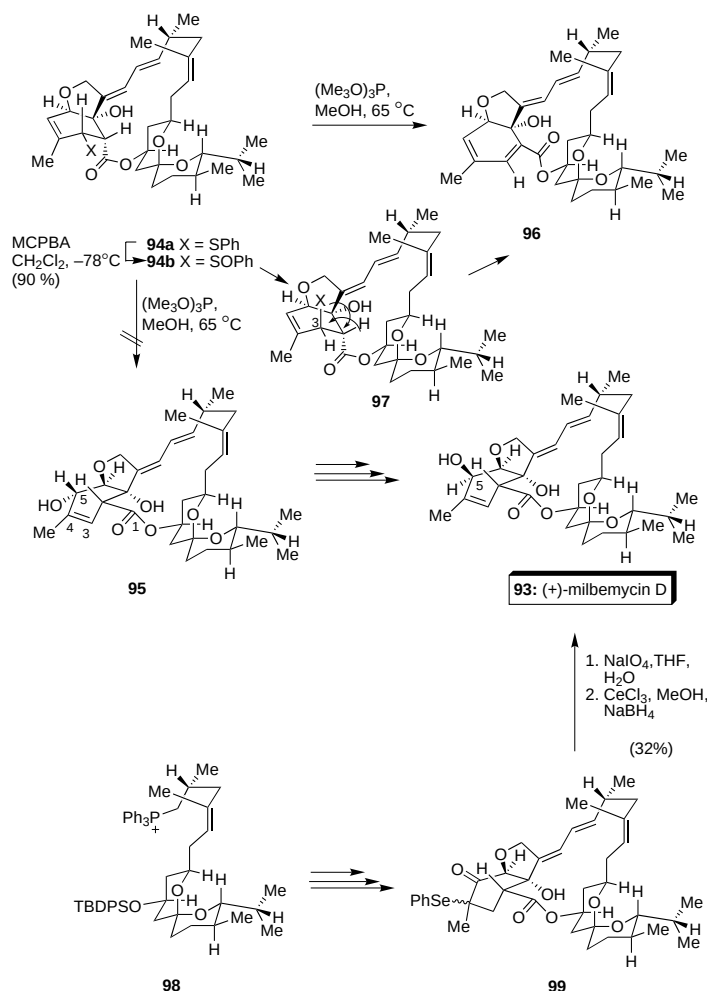
followed by oxidation of the remaining C(11) hydroxyl and subsequent global deprotection would provide access to (–)-chaparrinone. However, treatment of **88** with HClO_4 yielded exclusively deoxychaparrinone **90**. This compound arose from the acid-catalyzed intramolecular epoxide opening by the alcohol group on C(8), since the structure of the plausible intermediate **91** is nicely set up for this transformation. Neither changing the protecting group on the hydroxymethyl group at C(8), nor the preparation of the β -epoxide analogous to **88** proved to be successful. An alternative access to (–)-chaparrinone was developed by attaching the ring A 1β -hydroxy-2-oxo- Δ^3 olefin unit onto a substrate having a fully functionalized, protected ring C. This task was achieved from tetracycle **92**, obtained through a sequence of steps conceptually different from those first attempted.

One final example for this chapter is found in Crimmins' synthesis of (+)-milbemycin D (**93**).^[38] This time the problem appeared at the very final stages of the synthesis with the full carbon skeleton of the target molecule prepared, and resulted in a regrouping to an early precursor. The completion of the synthesis from intermediate **94** to **93** seemed imminent (Scheme 14). Only rearrangement of the allylic sulfide **94a**

via the sulfoxide **94b** and inversion of the resultant C(5) hydroxyl group in **95** remained to be done. Selective oxidation of sulfide **94a** to sulfoxide **94b** was uneventful. However, treatment of **94b** by heating with $(\text{MeO})_3\text{P}$ produced elimination leading to diene **96** rather than the desired [2,3] sigmatropic rearrangement product **95**. The explanation for this behavior was that the equatorial disposition of the phenylsulfinyl group in **94b** and the fact that the macrolactone ring was closed, apparently slowed down the allylic rearrangement to the point where competitive epimerization of either the C(2) or C(3) stereocenters was faster than the [2,3] sigmatropic rearrangement. Epimerization of C(2) or C(3) results in an intermediate having a *syn* relationship between the phenylsulfinyl group and the C(2) hydrogen atom, thereby allowing thermal elimination to occur.

The alternative, and finally successful route to (+)-milbemycin D (**93**) involved the removal of the alkene present in the six-membered ring of **94** to avoid the elimination problems. The C(3)-C(4) olefin was then introduced at the end of the synthesis through selenylation and elimination on the α -position of ketone **99**. The early intermediate **98** was sequentially converted into product **99**, which lacked the troublesome double bond. The olefin functionality and the hydroxyl-bearing stereocenter at C(5) were appended onto **99** to accomplish the total synthesis of **93**.

Evidently a larger number of examples focusing on different drawbacks of the synthetic plans caused by remote substituents may be recorded. The point is that the problems associated with the interference of a remote substituent on a desired transformation still occur. As the complexity of intermediates increases, the number of variables involved in a simple transformation grows exponentially making predictions complicated. The fact that such variables can be minimized demonstrates how predictable modern organic synthesis can be nowadays. It is clear that the ability to devise alternative routes to circumvent the failed transformation and to resolve the specific problem found in the synthetic plan are symptomatic of the maturity of the synthetic science. On the other hand, the lack of predictability in so many cases and the very empirical nature of synthetic chemistry implies that the science is not fully developed.

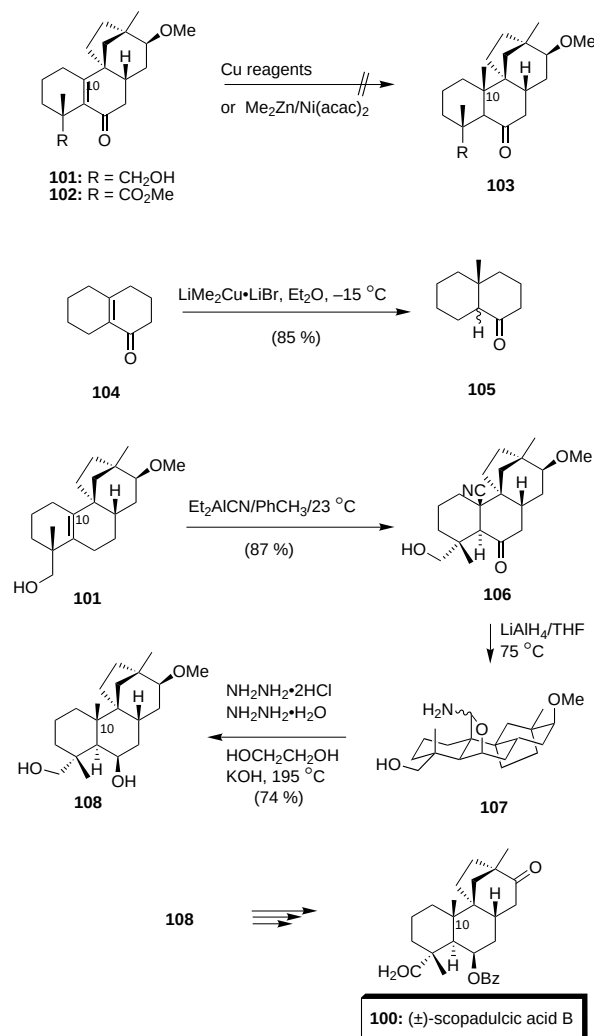


Scheme 14. The approach to (+)-milbemycin D was in hand. However, sulfoxide **94b** undergoes elimination to yield **96** rather than the desired [2,3] sigmatropic rearrangement to **95**. This causes a dead end and the synthesis was redesigned to avoid the formation of the cyclic diene moieties as in compound **96**.

5. The Elusive Side Chain

Many synthetic routes are designed to build the fully functionalized, fully protected main carbon skeleton of a target product. To complete the synthesis a side chain of a few carbon atoms (as few as one) may remain to be included at a late stage. How easy it is to join these “harmless” side chains to the main body of the target molecule? Apparently it should be pretty easy, as very few comments about this question are found in the papers that deal with total synthesis. However, when the matter is considered in depth, it seems that this is not always the case. The three following examples are cases in which the formidable task of building the more complicated features of the target molecule have already been achieved, but gaining access to the final product is lengthened by the incorporation of a side chain.

The preparation of (±)-scopadulcic acid **100** by Overman is a good example of how difficult the joining of a methyl group to a preformed skeleton can be.^[39] The intermediate **101** required just the development of the remaining quaternary center at C(10), to access to the full carbon skeleton of scopadulcic acid **100** (Scheme 15). This functionalization was

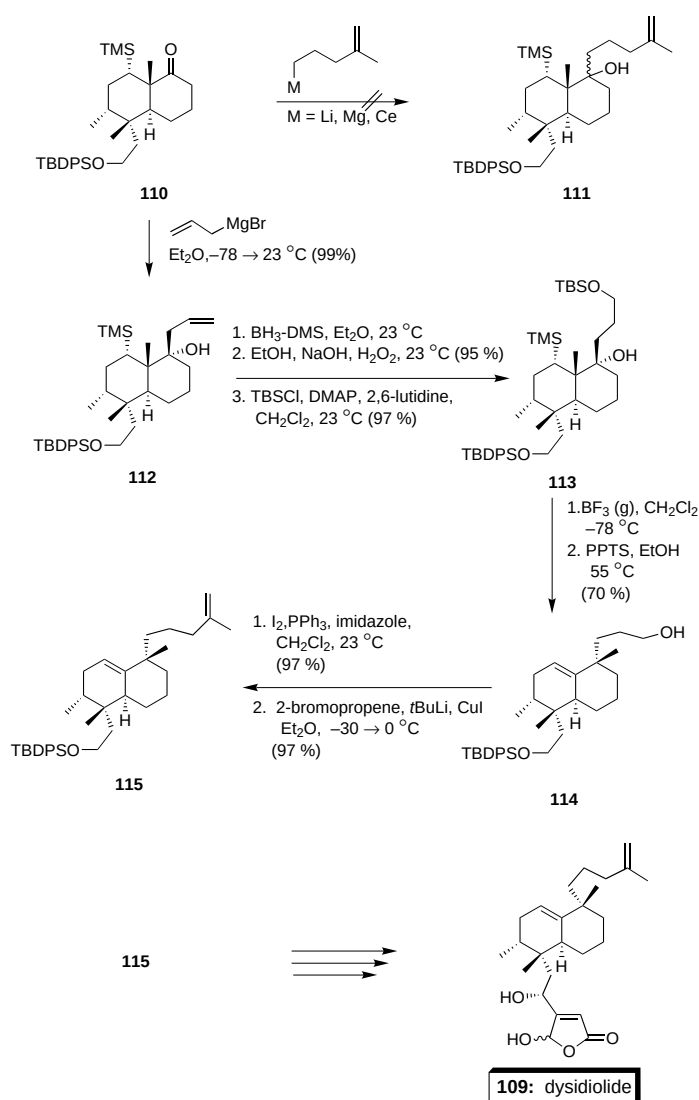


Scheme 15. The joining of the last carbon atom at C(10) to obtain the full carbon skeleton of scopadulcic acid **100** required a number of steps, as the straight introduction of the methyl group on **101** or **102** was not achieved.

anticipated to be difficult, since C(10) was flanked by a quaternary center of the bicyclo[3.2.1]octane unit. All attempts to introduce the angular methyl group on intermediates **101** or **102** directly were met with failure. These included $\text{Me}_2\text{CuLi}/\text{TMSCl}$; $\text{MeCu} \cdot n\text{Bu}_3\text{P}$; “higher order” cyanocuprates, $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed cuprate addition, and the $[\text{Ni}(\text{acac})_2]$ -catalyzed addition of Me_2Zn . The starting enone and/or the 1,2 adduct were obtained in these reactions. As a matter of fact, $\beta\beta$ -disubstituted enones are known to be poor Michael acceptors.^[40] However, the authors found that 1,4 adduct **105** could be obtained in good yields (86%) when model enone **104** was treated with five equivalents of Me_2CuLi in diethyl ether.

According to the authors, this last obstacle (the introduction of the methyl group at C(10)) was “finally surmounted in an efficient, albeit classical, fashion”. The problem of the quaternary center was solved by hydrocyanating **101** to **106**. An attractive transformation of **106** to the immediate precursor of scopadulcic acid **100**, was discovered when **106** was reduced with LiAlH_4 in THF. These reaction conditions formed pentacycle **107** in essentially quantitative yield. Reduction of this stable cyclic acetal was accomplished in 74% yield under forced Wolff–Kishner conditions, to afford the tetracyclic diol **108**. Compound **108** was thereafter transformed to **100**.

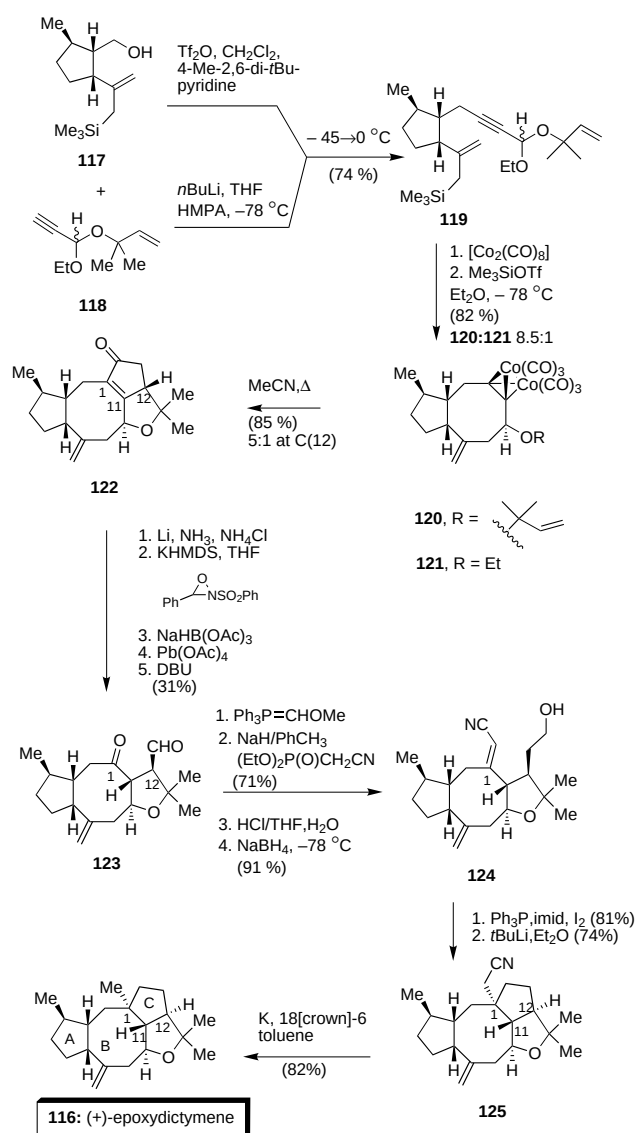
Corey’s synthesis of dysidiolide (**109**) exemplifies a detour caused by the refusal of a side chain to join the preformed bicyclic skeleton of the starting material (Scheme 16).^[41] Compound **110** was treated with 4-methyl-4-pentenyl-lithium, magnesium, and cerium reagents, but only recovered starting material instead of the desired bicycle **111** was obtained. The required side chain was built by the addition of allylmagne-



Scheme 16. The refusal of the carbon side chain present in dysidiolide to join ketone **110**, forced the authors to build this chain sequentially, considerably lengthening the synthesis.

sium bromide to **110** to obtain **112**, which was further elaborated to yield **113**. The 4-methyl-4-pentenyl moiety characteristic of **109** was formed on the three carbon side chain of **114** by sequential halogenation and cuprate nucleophilic substitution. Evidently, things would have been easier if the full side chain had been joined to the bicyclic skeleton of **110**.

A final example for this section is Schreiber's synthesis of (+)-epoxydictymene (**116**, Scheme 17).^[42] The building of the fully functionalized tetracyclic skeleton of the target molecule from cyclopentane **117** and acyclic enyne **118**, through a sequential Pauson-Khand-Nicholas reaction, is a superb example of how to increase molecular complexity in only a few synthetic steps.^[43, 44] With enone **122** in hand, completion of the synthesis required elaboration of the enone ring to the ring C of **116**, with incorporation of the last carbon atom at C(1). This example is more complex than the two precedents



Scheme 17. Epoxydictymene is a superb example of increasing molecular complexity in a few synthetic steps. After the formidable task of building the tetracyclic skeleton of the natural product in a few steps, the synthesis became more complicated because of problems found during the incorporation of the last methyl group.

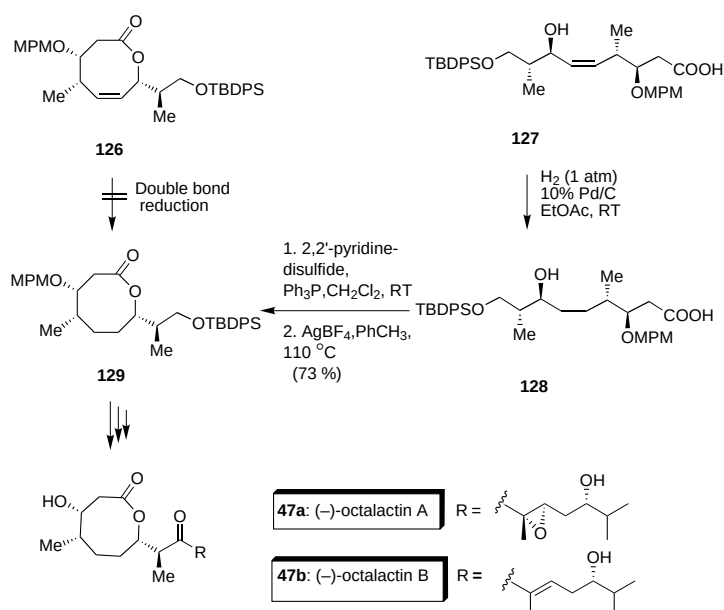
in the sense that there are problems other than attaching the methyl group at C(1), for example, epimerization at C(12) has to be achieved. Neither reductive nor deconjugative alkylation procedures proved successful in effecting the incorporation of the last methyl group at C(1). Complex reaction mixtures or products with the incorrect stereochemistry at the quaternary C(1) center were consistently obtained. Extensive experimentation suggested that alkylation at C(1) with the desired stereochemistry could be achieved only after inversion of the C(12) stereocenter in **122**. This hypothesis was also supported by molecular modeling calculations, which revealed that a two-atom bridge between C(1) and C(12) is more easily accommodated in a *syn* rather than in an *anti* fashion. Thus, the stereochemistry at C(12) was corrected in a five-step sequence from **122**, with ring C being opened. Ring C was reclosed after the methyl group precursor had been incorporated on **123** as a C2 fragment, and the resulting product was refunctionalized to form **124**. The anionic cyclization of **124** yielded **125** with the complete skeletal and stereochemical arrangement of the natural product. Reductive decyanation of **125** completed the synthesis of (+)-epoxydictymene (**116**).

These few examples demonstrate how unexpected hurdles can arise and complicate matters when an advanced intermediate only lacks a few carbon atoms. Perhaps the incorporation of a side chain is not a dead end that forces the researchers to quit the synthetic route, but clearly causes a nearly intractable problem that lengthens the number of steps and, in some cases, causes significant detours before reaching the final target.

6. The Trivial Functional Group Transformation

At this point it may be convenient to ask: How predictable is the reactivity of a certain functional group in a densely functionalized molecule? Taken at face value, this seems to be a silly question since, for instance, a carbonyl group is still a carbonyl group even in the more complex molecular environment. Nevertheless, even the simplest transformation of a functional group can be a nightmare when the reaction outcome is different to the expected, or when the functional group does not react at all. In the introduction of this article we showed one example in which some critical functional group transformations forced abandonment of a synthetic sequence at the final events of the synthesis (Schemes 1 and 2). The additional examples discussed below demonstrate the necessity of gathering more information concerning the reactivity of densely functionalized molecules, and of learning more about the behavior of commonly used reagents in these systems.

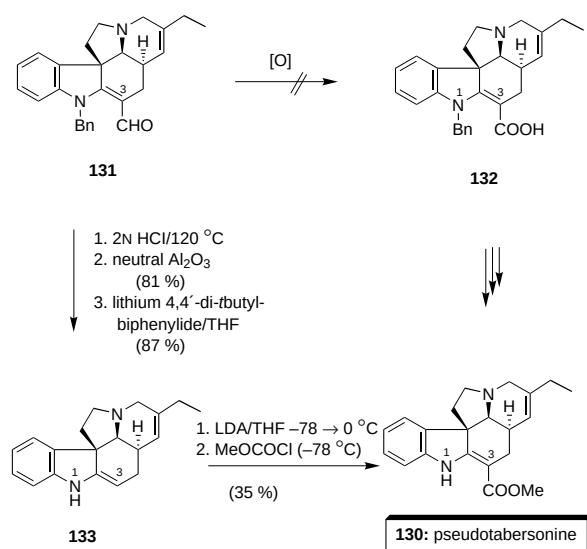
Let's start with one of the first reactions learned at the introductory level of organic chemistry: the standard olefin hydrogenation. Buszek's synthesis of octalactin A (**47a**) and B (**47b**) illustrates this point (Scheme 18).^[45] Unsaturated eight-membered lactone **126** has the cyclic core of octalactin and it is properly functionalized to be transformed to the desired target. Unfortunately, in the words of the authors, "the seemingly prosaic task of reducing the double bond could



Scheme 18. The refusal of the double bond present in **126** to be hydrogenated forced the authors to face up to the risky ring closure of saturated intermediate **128**.

not be carried out under the many conditions tried, including heterogeneous and homogeneous catalytic hydrogenation, diimide reduction...". Thus, the olefinic bond had to be hydrogenated in the open-chain precursor of **127** prior to lactonization, although the literature offered little encouragement for the lactonization of a saturated intermediate such as **128**. In the event, the open-chain hydroxy acid **128** lactonized in high yield to the desired compound **129**.

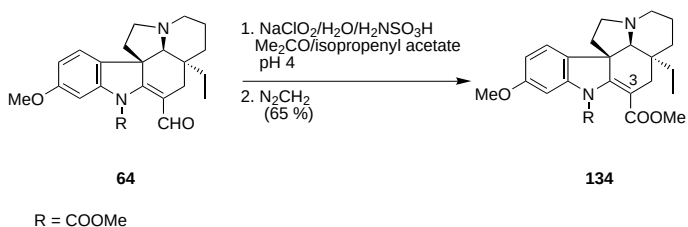
Another standard reaction (this time the oxidation of an aldehyde to a carboxylic acid) that did not occur at the final stages of the synthesis and led to a significant detour of the original plan, is found in Grieco's synthesis of pseudotaber-sonine (**130**, Scheme 19).^[46] Transformation of the formyl



Scheme 19. The oxidation of aldehyde **131** to acid **132** could not be achieved. Hence, a low yielding, long detour had to be undertaken to reach pseudotabersonine.

group at C(3) into a carbomethoxy unit and removal of the N(1) benzyl group were the sole transformations needed to arrive at pseudotabersonine from intermediate **131**. All attempts to oxidize **131** to **132** met with no success. Hydrolytic deformylation of **131**, followed by debenzoylation yielded **133**, which lacked the carbon atom that was to become the carbomethoxy group. Installation of the C(3) carbomethoxy group was realized—albeit in low yield—by lithiation of **133** followed by treatment with methyl chloroformate. This series of reactions finally produced pseudotabersonine (**130**).

It is intriguing that the formyl group of **131** could not be oxidized while the related compound **64** was oxidized uneventfully to **134** in the final stages of Magnus's synthesis of (+)-16-methoxytabersonine (Scheme 20).^[31] The vinylogous amide nature of the formyl group in **131** may be responsible for the failure, while the carbamate group used to block the aniline nitrogen atom of **64** may attenuate this amide-like character, thus allowing its oxidation. This explanation goes back to similar observations made by Overman in his synthesis of (±)-akuammicine (see Scheme 9).^[29]

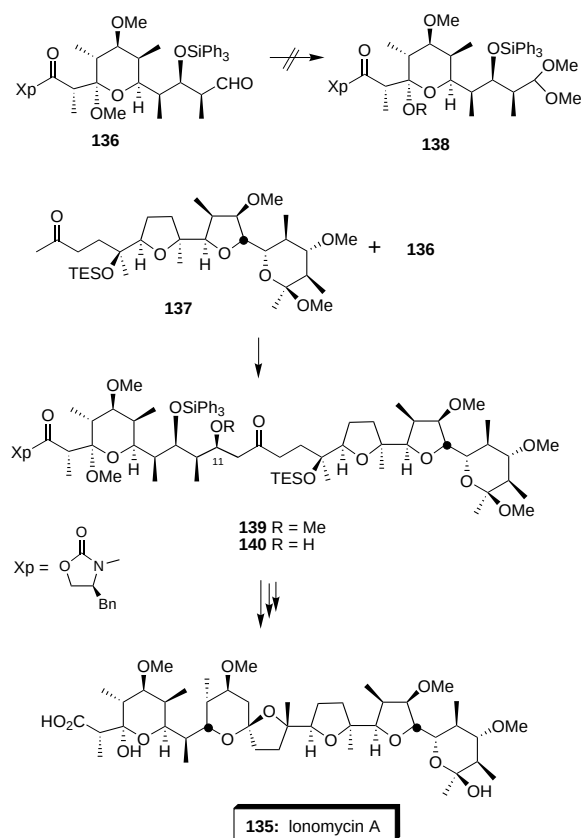


Scheme 20. The conversion of **64** into **134** was achieved by oxidation of the formyl group.

The last example of this section does not cause a deviation in the planned synthesis but it forced the researchers to confront an additional problematic transformation. Evans's synthesis of polyether antibiotic lonomycin A (**135**) involved the joining of fragments **136** and **137** in an advanced stage of the synthesis (Scheme 21).^[47] Two different plans were evaluated for this transformation. The acid-catalyzed reaction of the dimethylacetal **138** and the enol silane derived from ketone **137** was considered more attractive than a conventional aldol union between **136** and **137**. Among the reasons for this, the possibility of obtaining the methylated aldol adduct **139** directly was especially appealing. The second option would involve an obligatory post-aldol methylation to convert aldol **140** into **139**, a step that the authors viewed as highly speculative because of the large number of oxygen-bearing functional groups present in intermediate **140**.

However, all attempts to transform aldehyde **136** into its dimethyl acetal **138** were condemned by the intrinsic acid lability of this intermediate. This failure forced the authors to use the second alternative. The preparation of Ionomycin A was pursued and completed by condensation of the lithium enolate of ketone **137** and aldehyde **136**. The methoxy group at C(11) was incorporated at a latter stage in the synthesis as the aldol **140** could not be methylated, as expected.

The examples shown in this section are just a pale reflection of how matters can complicate when, at first glance, simple



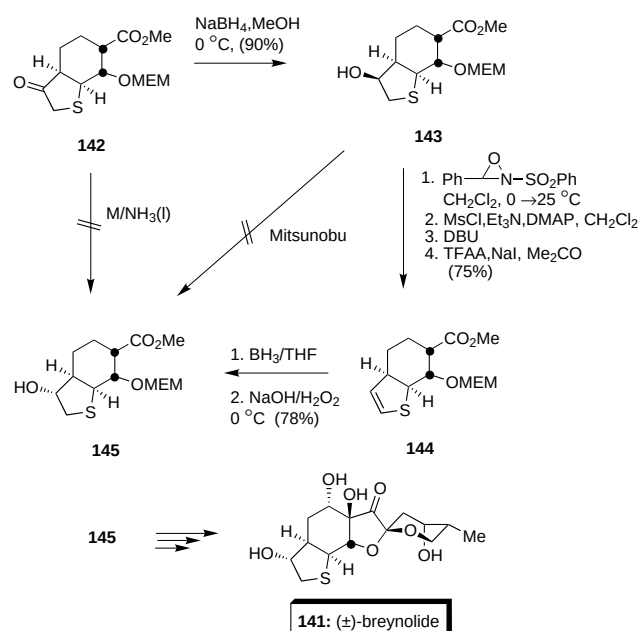
Scheme 21. To avoid the risky methylation of an alcohol in an advanced intermediate, the synthesis of Ionomycin A was designed to include the joining of acetal **138** and the enol silane derived from **137**. The impossibility of transforming aldehyde **136** into acetal **138** forced the authors to use the alternative aldol condensation between **136** and **137**, and to face up to the risky methylation after the aldol reaction.

transformations are done in complex molecules. Evidently, this does not mean that chemical reactions always have unpredictable outcomes. Perhaps this section header should be changed to “how trivial is a trivial synthetic transformation in real life?”

7. The Unpredictable Stereochemistry Problem

Talking about unpredictable stereochemistry in this time of highly stereoselective methods, exquisite stereocontrol, enantio-differentiating reactions, chiral discrimination, etc. may be quite dangerous. Superb achievements have been obtained in the development of methodologies to control the stereochemistry of many fundamental processes and today, asymmetric synthesis^[48] is practically synonymous with organic synthesis. For people like us, who were at high school when modern asymmetric synthesis began and who willingly followed (and still follow) the amazing developments in the field, asymmetric synthesis has become almost a doctrine. But in agreement with the aim of this work, we present some examples in which stereocontrol led to the wrong outcome, again forcing undesirable detours or causing a lengthening of the synthetic path.

One of the simplest cases happens when the main carbon skeleton is in hand, the configuration of the stereocenters is correct, and a new stereocenter is to be placed by the reduction of a ketone to an alcohol. One of such cases is found in Smith's synthesis of ($\pm$)-breynolide (**141**, Scheme 22).^[49] The key intermediate **142** was submitted to NaBH_4 reduction



Scheme 22. The intrinsic facial selectivity of ketone **142** thwarted all the efforts to obtain alcohol **145** by direct reduction of the carbonyl group. This facial selectivity was used to prepare **145** from **142** using a seven-step sequence.

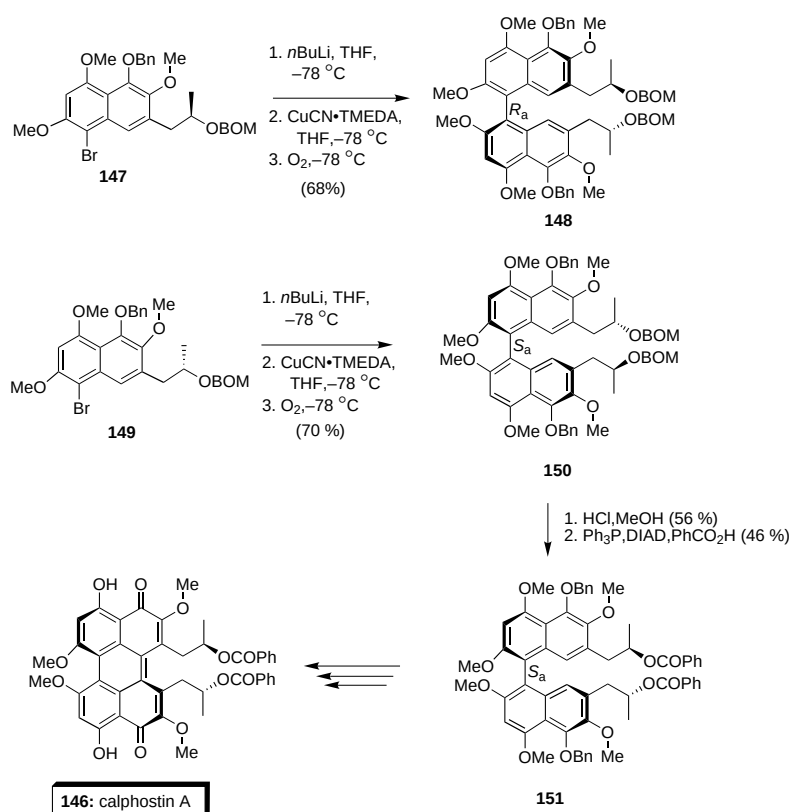
to give the *endo* alcohol **143** as the exclusive product (> 99:1). Since alcohol **143** has the wrong stereochemistry, standard tactics to invert the configuration were enlisted. Unfortunately, a variety of methods including the Mitsunobu inversion of **143**, or reduction of **142** by dissolving metal in liquid ammonia, gave only trace amounts of the desired *exo* isomer **145**. Therefore, a detour was taken to prepare the desired stereoisomer. Alcohol **143** was transformed into the dihydrothiophene derivative **144** in a four-step sequence, and the alcohol group was then reintroduced with the right configuration through hydroboration, by exploiting the convex bias of the bicyclic skeleton to set the *exo* configuration. This bias was, in fact, responsible for the detour as the fully shielded concave face of the molecule forced the hydride attack on **142** to furnish only **143**. The overall yield for this five-step transformation of **143** to **145** was 19%.

Another situation encountered is the coupling of two different enantiomerically pure intermediates, a step present in many convergent syntheses and, in regard to the stereochemical outcome of the process, still in need of refinement.^[50] In the absence of external elements of stereocontrol, the resident chirality determines the stereochemical outcome, which may or may not be the desired one. That question has been nicely addressed in many articles and will not be dealt with here.^[51] We will illustrate the problem using the coupling of two identical chiral compounds in a dimerization reaction

to form a new stereogenic element as in Coleman's synthesis of calphostin A (**146**, Scheme 23).^[52]

The preparation of calphostin A (**146**) was first attempted by the Cu^I-catalyzed coupling of the naphthalene derivative **147**. The reaction produced an 8:1 mixture of diastereomers about the axis of chirality, with the undesired *R_a* diastereomer **148** predominating. Once again this result contrasted with the sense of atropdiastereoselection previously observed for substrates related to **147** and having a protected (*R*)-2-hydroxypropyl side chain that induced *S_a* chirality about the binaphthalene axis.^[53] Access to the desired diastereomer was gained from the enantiomer of **147**, naphthalene **149**, that formed the desired *S_a* atropisomer **150** as the major isomer. Introduction of the 2*R* stereogenic center required for the natural product was accomplished by using a double Mitsunobu inversion on **150** with concomitant introduction of the acyl groups present in the natural product. The double acylated intermediate **151** was hence converted into calphostin A in three steps.

Efforts to control the troublesome intrinsic selectivity of the substrates in reactions depicted in Schemes 22 and 23 were not made and instead were exploited to achieve the designed transformation. One different case is the use of enantiomerically pure reagents to overwhelm the presumed modest diastereofacial preferences of the chiral substrate and to control the stereochemical outcome. In these cases the configuration of the products are highly predictable and a lot of beautiful synthetic work on reagent-based control of stereochemistry has been made during the last twenty years.^[54]



Scheme 23. In the absence of stereocontrol, the formation of a new chiral element with the desired configuration by joining together two fragments having pre-existent stereogenic centers is, in many cases, a matter of luck.

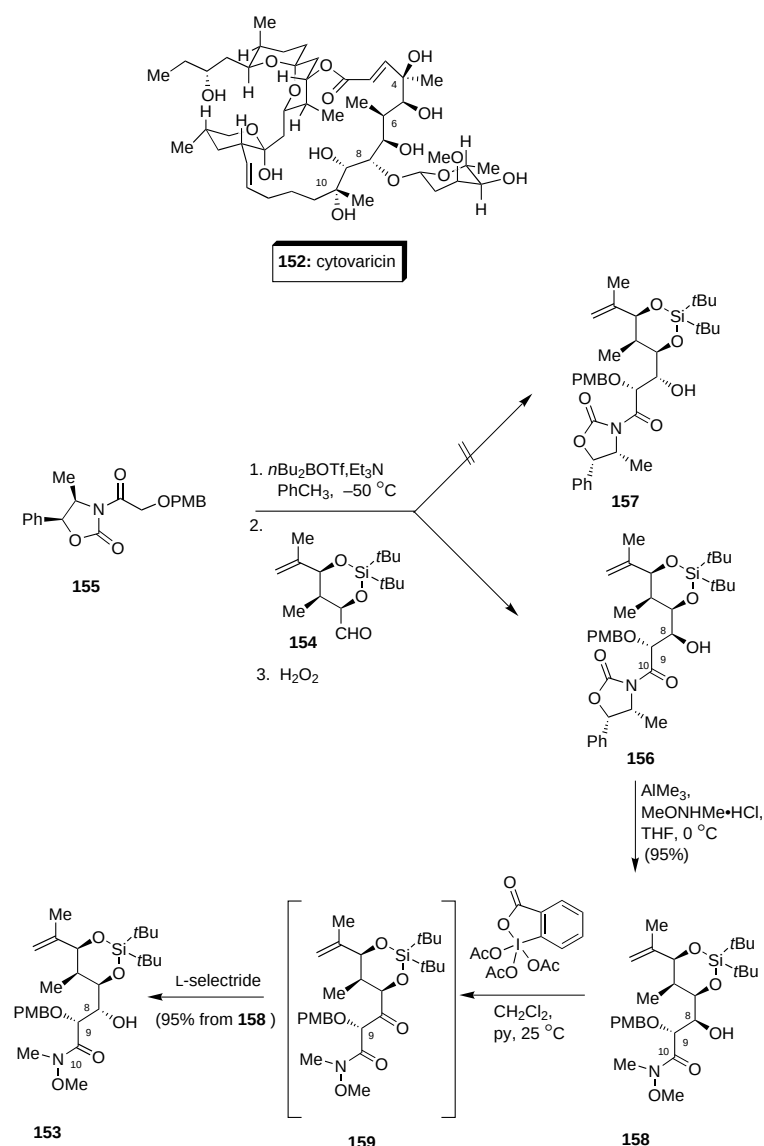
However, surprises are still found sometimes. One such example is met in Evans's total synthesis of cytovaricin (**152**, Scheme 24).^[55]

The synthesis of fragment **153** having the C(3)–C(10) carbon atoms of cytovaricin was made by the asymmetric aldol condensation between aldehyde **154** and the boron enolate derived from **155**. The extensive body of knowledge for this kind of reaction predicted complete control of the stereochemical outcome by the facial bias of the chiral enolate, its geometry, and the cyclic transition states for the aldol condensation, regardless of the configuration of the aldehyde.^[56] Surprisingly, the *anti* aldol adduct **156** was obtained as a single diastereomer (the expected result was a single *syn*-aldol adduct **157**). The reversal of the stereochemistry was unprecedented in this condensation using this chiral enolate reagent. Apparently the configuration of C(9) is defined by the chiral enolate, while the inherent bias (predicted by the Felkin–Anh model)^[57] of the chiral aldehyde determines the formation of the C(8) stereocenter. Other organometallic reagents such as MeLi and MeMgBr add to the same carbonyl diastereoface with selectivity greater than 20:1. All efforts to override the diastereofacial preference of aldehyde **154** were fruitless. In the words of the authors: “ironically all three of the undesired aldol diastereomers could be obtained as major products by variation of reaction conditions. A variety of metal enolates (B, Li, Ti, Zr, Mg) were surveyed. Stoichiometry, solvent, and auxiliary were also varied to no avail.” Inversion of the stereochemistry of the C(8) center was undertaken on transaminated inter-

mediate **158** by using the diastereofacial bias of a trigonal carbon atom at C(8). Oxidation of the alcohol at C(8) followed by immediate reduction of the β -ketoamide **159** with L-selectride gave a single diastereomer of the desired *syn*-alcohol **153**. In spite of the fact that β -ketoamide **159** is the intermediate in the transformation of **158** to **153**, no epimerization at C(9) was observed (an explanation of this fact is that allylic 1,3-strain forces the molecule into a conformation that sufficiently reduces the acidity of the C(9) methine hydrogen atom, to avoid the epimerization at this center).

A final example is found when, to prove its efficiency, the application of a new synthetic reaction at the key step of a synthesis leads to the wrong stereochemistry, either producing a diastereomeric mixture, the desired product being a very minor component or simply the wrong stereoisomer. For example McMurry's synthesis of ($\pm$)-crassin (**160**) was undertaken by using the intramolecular McMurry coupling of the *cis*-keto aldehyde **161** (Scheme 25).^[58, 59]

Treatment of **161** in DME with a slurry of low-valent titanium reagent resulted in a mixture of cyclic diols **162**–**165** having all the possible configurations on the newly created stereocenters. The diol **165** with the configuration present in ($\pm$)-crassin (**160**) was the minor product (1%). To accomplish the synthesis of **160** a double



Scheme 24. In spite of all the powerful methodologies existing to achieve acyclic stereocontrol, and against the background existing for the stereocontrol in the aldol reaction, the unexpected configuration for aldol **156** was obtained this time. Steps to introduce the needed configuration had to be included in the synthetic scheme.

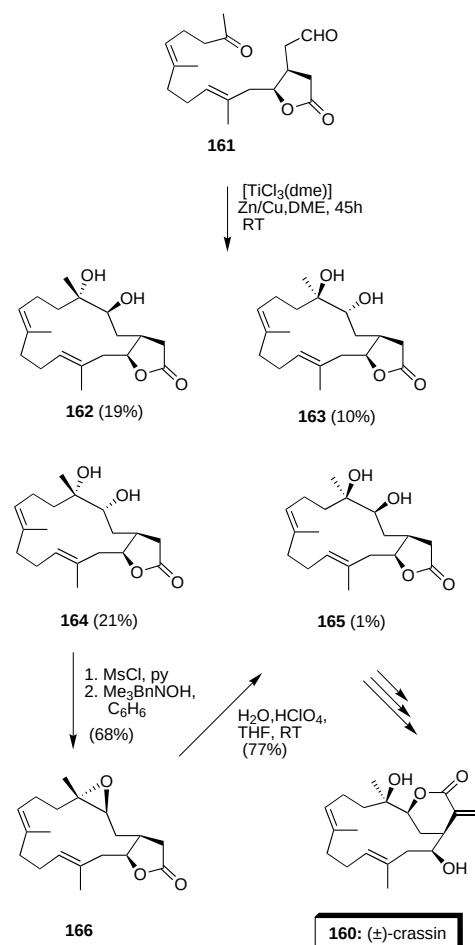
inversion of the hydroxyl groups in the major product (**164**) of this mixture was needed. This transformation was made possible by treatment of **164** with an excess of mesyl chloride, followed by reaction of the monomesylate with benzyltrimethylammonium hydroxide to give epoxide **166**. Rupture of epoxide **166** was accomplished by the action of 10% aqueous HClO_4 to form diol **165** with the correct stereochemistry.

The few examples presented in this section are simple cases of how obtaining the wrong stereochemistry for a given transformation may interfere with a successful synthesis. Much has been learned about the elements involved in the control of the stereochemistry of synthetically relevant procedures, and the efficiency in terms of the stereocontrol obtained with many catalytic and stoichiometric reagents is breathtaking. The new catalytic asymmetric reactions, and the highly efficient chiral auxiliaries developed during the last twenty years are amazing, but there is still much more to be done to

control the generality and selectivity of these transformations. Among others, problems such as the stereocontrol in the joining of two chiral moieties having multiple (or just one as in calphostin A) pre-existent stereocenters, and how to overcome the intrinsic facial selectivity of a cyclic substrate when this does not lead to the desired result (cyclic stereocontrol?) are issues yet to be completely resolved.^[60]

8. Reluctant Ring Closures

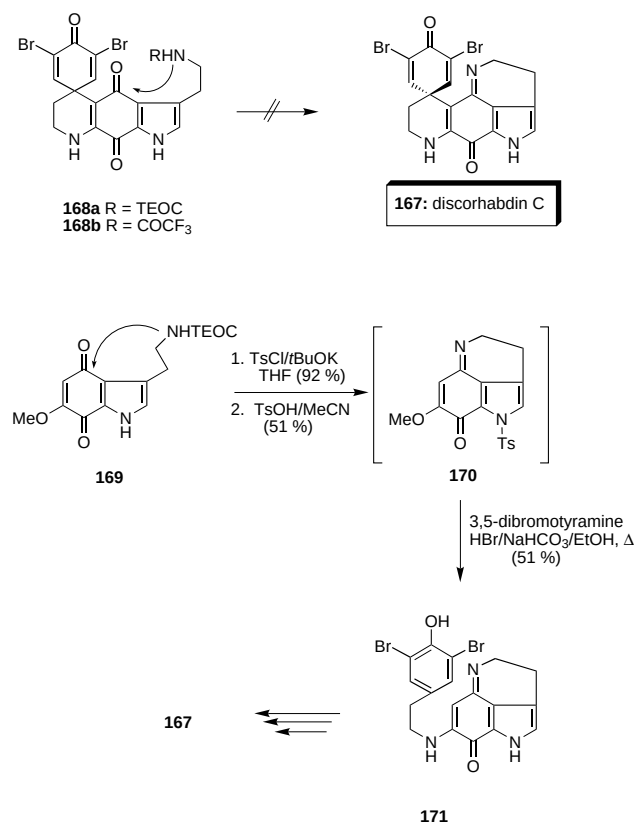
To complete this work we are going to discuss one of the most exciting topics in total synthesis: ring formation. Many synthetic routes devise a ring-closure reaction at some stage, since many synthetic targets bear at least one cycle in their core structure. Not surprisingly, the development of methodologies for ring formation has been (and still is) a priority in chemistry. It is beyond the scope of this article to review the many ways to access ring systems, or to evaluate their efficiency, but we have selected a few examples that show how cyclization processes are



Scheme 25. The building of the macrocyclic ring of crassin through a McMurry coupling produced a mixture of four possible diastereomers. The desired diastereomer was formed in less than 1 % yield.

not always totally under our control. On the other hand, it is also worth noting that failures in closing the desired ring may cause greater changes to the planned synthesis than any of the troubles discussed previously.

The final step of the original route to discorhabdin C (**167**) in Kita's synthesis (Scheme 26)^[61] involved formation of an imine between the tryptamine nitrogen atom and the quinone carbonyl group in compounds **168a** or **168b**. All attempts to effect the imine formation in these intermediates were

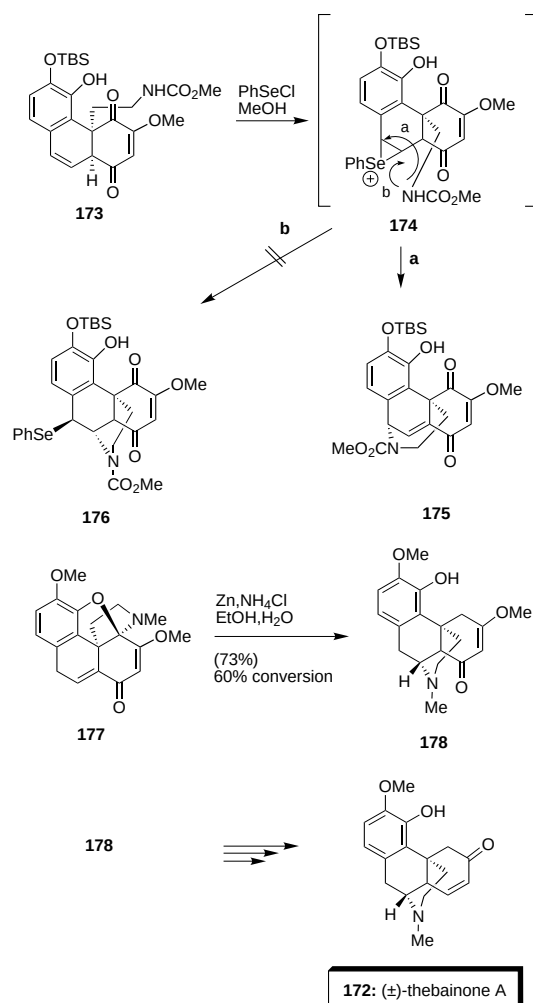


Scheme 26. Failures during a key ring closure involve greater changes in the synthetic scheme than any other event in synthesis. The order of the ring building during the synthesis of discorhabdin had to be changed because of the refusal of the last ring to close.

unsuccessful. The failure of this ring closure was attributed to the weakly electrophilic nature of the carbonyl group of the quinone nucleus on **168**, which may be considered as a vinilous urea and it is also very sterically hindered. The introduction of an electron-withdrawing group at the nitrogen atom also failed, because of the instability of **168b** under the basic conditions used. In the end, the alternative successful route to discorhabdin C used a phenolic coupling on the previously built aminoindoloquinone imine **171** as the final key step. This compound was obtained starting from the early intermediate **169**, which was previously used in the failed approach. This time the formation of imine **170** was ensured by the protection of the quinone nitrogen atom with the electron-withdrawing tosyl group, and by placing a 6-methoxy group on the quinone moiety.

Sometimes the size of the ring to be formed is presumed to be the right one on the basis of the kinetic preference of the

reaction to be used, but the presumption turns out to be wrong. An example is found in the preparation of (±)-thebainone A (**172**, Scheme 27) by Tius.^[62] Initially, access to the tetracyclic core of thebainone A was attempted by the closure of the piperidine ring through activation of the C-C double bond in intermediate **173**, followed by intramolecular



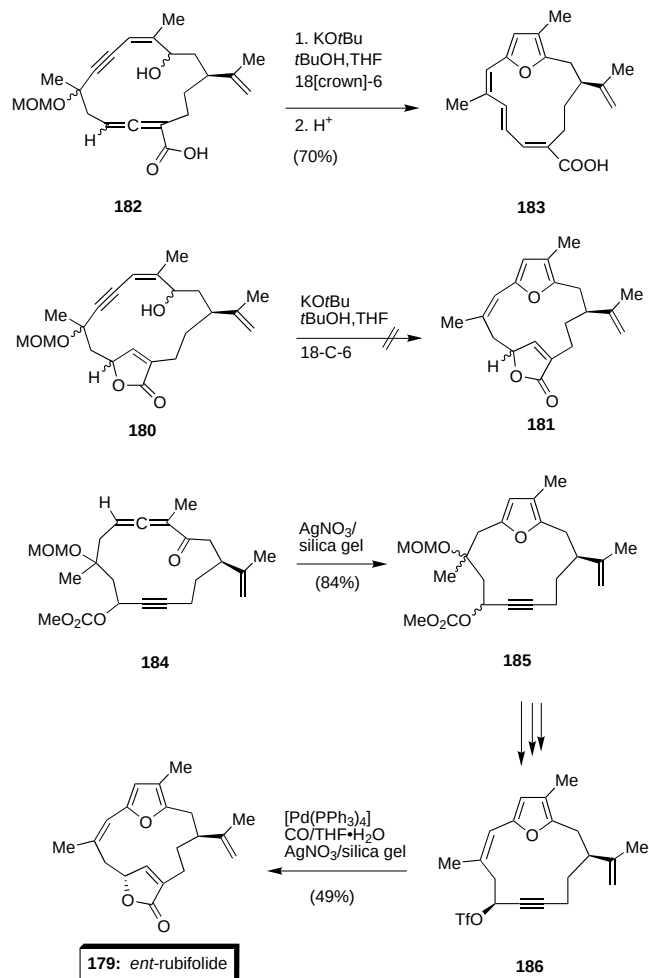
Scheme 27. The hope that a kinetic preference would be observed for the formation of the six-membered rather than the seven-membered ring unfortunately failed.

attack by the nitrogen atom. In the words of the authors “the hope that a kinetic preference would be observed for formation of the six-membered rather than the seven-membered ring from **19** [here **173**] was unfounded.”

Exposure of **173** to PhSeCl in methanol produced the seven-membered nitrogen heterocycle **175** instead of the desired **176**. It was necessary to design a different sequence of steps relying on a conceptually different strategy. This time access to the tetracyclic core of thebainone A was gained from compound **177** by reductive cleavage of both the amine and the cyclic ether oxygen linkages by Zn dust and NH₄Cl. The subsequently released amino group underwent an intramolecular conjugate addition to furnish **178**, which was successfully converted into thebainone A. The origin of the failure of **173** to give the desired compound **176** may reside in the

benzylic nature of the carbon atom attacked by the nitrogen center, which yields the observed product **175**. Selenacyclopropane **174** should be closest to an α -selenocarbocation with the majority of the positive charge centered on the benzylic position. Therefore, the attack of the carbamate nitrogen atom occurs exclusively at this position.

Another interesting situation is found in Marshall's synthesis of the furanocembrane *ent*-rubifolide (**179**, Scheme 28).^[63] The macrocyclic skeleton of **179** was built in compound **180**, to leave just the introduction of the furan ring

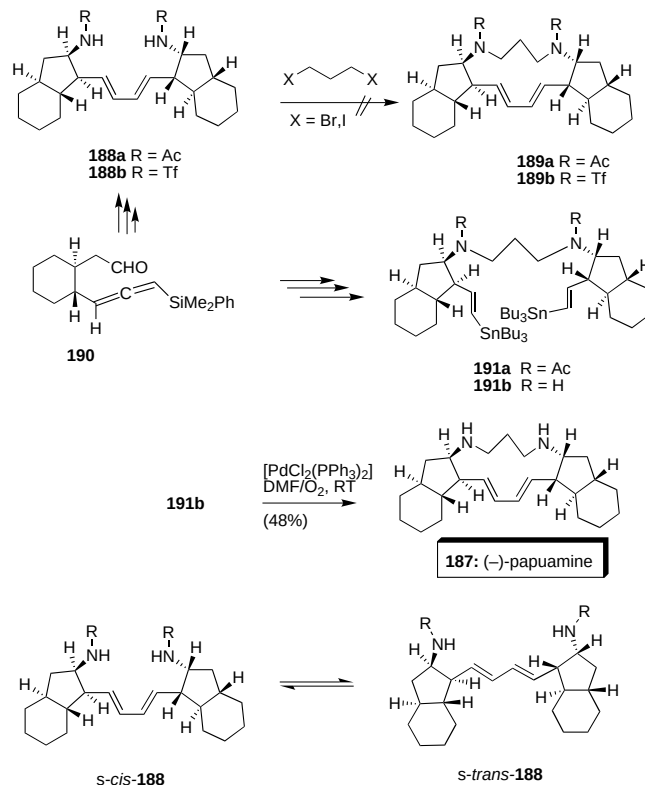


Scheme 28. The building of *ent*-rubifolide by closing sequentially the furan and the butenolide rings failed. However, the inverse situation was successful.

to secure the final product. However, treatment of **180** with KOtBu led to no identifiable products. The desired transformation actually occurred with a 70% yield with the model system **182**. An alternative entry to *ent*-rubifolide (**179**) involved first building the furan ring on the macrocyclic allenone **184** to form **185**. Sequential manipulation of **185** led to **186** on which the butenolide moiety was constructed to finally yield **179**.

Orchestration of the sequence, in which fragments are joined to effect a macrocyclization may become the cornerstone of the synthesis. A striking example is Weinreb's

synthesis of (–)-papuamine (**187**, Scheme 29).^[64] The first route to papuamine used intermediate **188** with the unsaturated chain of the molecule already closed. The 13-membered ring remained to be formed to access *N,N*-diacetylpapuamine (**189**). A number of attempts were made to close the ring by double N-alkylation of **188a** with 1,3-diiodo- and 1,3-dibromopropane. However, **187** was elusive in all attempted cases, even when the bistriflamide **188b** was used.



Scheme 29. There are no evident reasons to explain why the ring closure of diene **188** to give papuamine failed. Nevertheless, the successful approach to this marine natural product **187** had to use the closure of the olefin with the aliphatic chain already in place.

The synthetic route was reevaluated to close first the aliphatic chain of the molecule and then realize the final ring closure on the unsaturated bridge. Starting from the aldehyde **190**, the common intermediate for both approaches, the *bis*-stannane **191a** was prepared, initially with the two secondary amino groups protected as nonbasic acetate groups. All attempts of intramolecular coupling gave no trace of *N,N*-diacetylpapuamine (**189**). This result was explained by the difficulty of **191a** to adopt the conformation required for cyclization because of unfavorable amide rotamers. Finally, the cyclization was effected on **191b** with free amino nitrogen atoms by the action of [PdCl₂(PPh₃)₂]/DMF in the presence of oxygen. (–)-Papuamine was obtained in 48% yield.

It is not easy to rationalize the causes of the failure to access (–)-papuamine by closure of the aliphatic bridge of intermediate **189**. Compound **189** exists as its *s*-trans conformer. One can rationalize that a conformational change to the *s*-cis conformer has to occur prior to closing the ring. The energy associated with this change is 6.5 kcal mol^{–1}. However, the

N-N distance on *s-trans*-**189** at 5.1 Å is shorter than the 6.3 Å in *s-cis*-**189**. Moreover, *s-trans*-papuamine is 1.6 kcal mol⁻¹ more stable than *s-cis*-papuamine. The perplexing conclusion which is drawn is that cyclization should occur in theory, but it does not.

9. Conclusions (and Outlook?)

Many other examples dealing with problems found during the building of molecules are compiled in the literature.^[65] The few discussed above represent particular cases of a general problem. Molecular complexity, additional electronic, steric, and conformational effects are often claimed as the ultimate cause for failures. The source of the trouble may rest in the still scarce knowledge of the behavior of densely functionalized, conformationally flexible molecules. The levels of predictability of computational calculations reach the edge in these cases, and much more has to be learned on how slight changes at the molecular level affect the final outcome of a given reaction. Highly selective reagents are often tested in simple transformations, yet they may be rendered useless when functional groups are present (the “methyl, ethyl, propyl, futile syndrome”).^[66] Without a doubt even the most complex molecules can be prepared by the present synthetic technologies, but the amount of effort devoted to simple transformations is still quite enormous. The simple conclusion is yes, we know how to do it but without doubt we will know how to do it simpler, better, and more efficient in the future.

Throughout this work we have tried not to be too enthusiastic about the beautiful examples presented; we have outlined the superb achievements and the impressive work contained in the syntheses. It is now the time to mention it. The overwhelming beauty of a total synthesis is only comparable with the feeling when looking at a work of art. And as with artworks, the modern techniques can make the work easier but still a veritable artistic heart is needed to construct a complex molecule. Moreover, although nobody cares if some parts of a painting or a symphony had to be erased or rewritten many times for the sake of the final work, in organic synthesis the detailed knowledge of the fruitless routes, the negative results, and those extensive and relentless efforts made during the total synthesis should also be written and discussed. In this way the value of the work performed will be heightened and the path for future developments in organic synthesis will be smoothed.

Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Bn	benzyl
BOC	<i>tert</i> -butoxycarbonyl
BOM	benzyloxymethyl
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N</i> -dicyclohexylcarbodiimide

DIAD	diisopropylazodicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMS	dimethyl sulfide
FDPP	pentafluorophenyldiphenyl phosphinate
HMPA	hexamethylphosphoramide
imid	imidazole
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
MCPBA	<i>m</i> -chloroperbenzoic acid
MEM	(2-methoxyethoxy)methyl
MOM	methoxymethyl
MPM	methoxyphenylmethyl
Ms	methanesulfonyl (Mesyl)
PMB	<i>p</i> -methoxybenzyl
PMS	<i>p</i> -methylbenzylsulfonyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
py	pyridine
SES	[β-(trimethylsilyl)ethyl]sulfonyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TBTH	tri- <i>n</i> -butyltin hydride
TEOC	trimethylsilylethylcarbonyl
TES	triethylsilyl
Tf	trifluormethanesulfonyl
TFAA	trifluoroacetic anhydride
Th	thienyl
TIPS	triisopropylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TPS	triphenylsilyl
Ts	toluene-4-sulfonyl

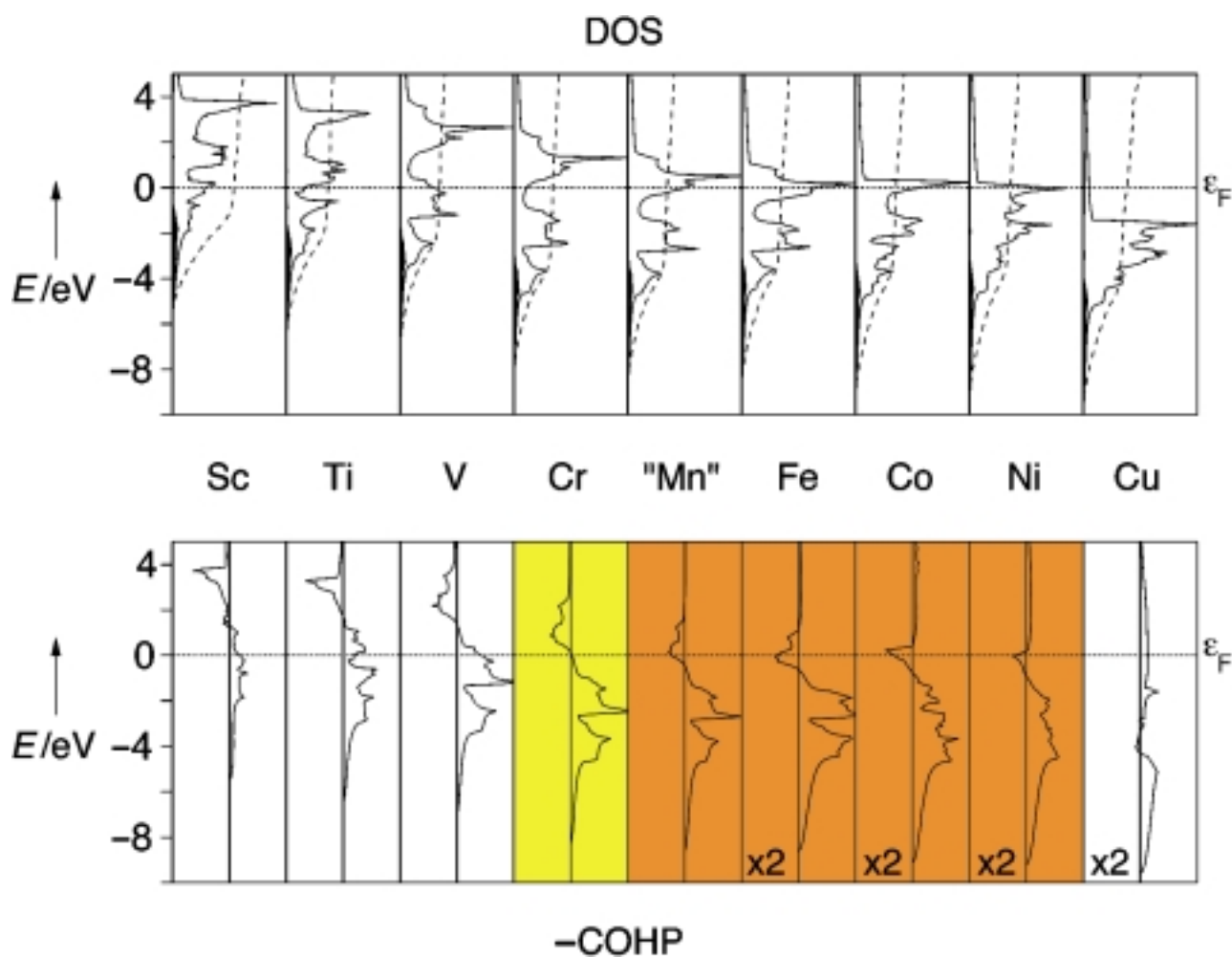
As with organic synthesis from the original idea to the final manuscript significant detours and some dead ends had to be overcome. We are indebted to Prof. Mar Gómez-Gallego and Dr. María J. Mancheño (UCM) for their valuable suggestions and their patience in correcting the manuscript. The assistance by Dr. Bernardo Herradon (CSIC) and his encyclopaedic knowledge of organic synthesis is gratefully acknowledged. We thank to Dr. Jesus Jiménez-Barbero (CSIC) for his invaluable help with molecular mechanics calculations. Finally, we thank the reviewers for their valuable comments, suggestions, criticisms, and different points of view that have contributed to considerably enrich this work. Support for this work under grants PB97-0323, 2FD97-0314-CO2-02 (MAS) and AGF98-0805-CO2-02 (MCT) from the Dirección General de Enseñanza Superior Investigaci3n Científica y Técnica (MEC-Spain), and the European Commission is acknowledged.

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- [7] One reviewer of this review pointed out two additional reasons not to go into details about failures: first: “failed” reactions often lead to results that are not clean. These are usually described in papers as giving “decomposition of starting materials” or “complex mixtures of products”. For those involved in Organic Synthesis such reactions seem to occur far too often! From such experiments conclusive and/or publishable information is difficult to glean. Reporting of results in this fashion, while being honest, does not provide much information from which the reader can learn and is often avoided. Second: often Organic Synthesis relies on luck! It doesn't matter how well planned a synthesis is, the route is nearly always going to have stages which are risky and predictably so in advance. Such risks are assessed in the planning stages before undertaking synthetic work. It may sometimes be judged that a very high-risk strategy may offer significant potential benefits which warrant investigation. Failures of high-risk work may go unreported as with the benefit of hindsight they may look to have strayed across the border between courageous and foolish!
- [8] There are, of course, other points of view for not reporting excessive details about failures. The words written by Danishefsky two years ago are fully illustrative: *Before relating a few of these episodes* [referring to the synthesis of some of the many molecules synthesized in his group], *some important cautionary notes and attributions are in order. For those schooled in the art (of Organic Synthesis), there will be little need for either. The experienced practitioner is well aware that the pathways of synthesis are circuitous, bumpy, and even treacherous. Seldom do straight lines suffice to connect points in a synthesis of real consequence. Hence, the seasoned chemist will appreciate that along with these “magic moments” of success, one could have reported a litany of setbacks and reversals. However, for younger and more optimistic enthusiasts, it is appropriate to underscore the uncertainties, the detours and, yes, the frustrations associated with Organic Synthesis. Success is often a prize reserved for those who temper noble ideas with appropriate measures of realism and skepticism. Given the episodic nature of our science, wisdom may well be more valuable than cleverness. The ability to plumb the implications of each experiment, positive and negative, is central to the process of learning as we go along. Our quest to reach the promised land should not render us insensitive to opportunities for discovery, even as we find our way through the desert.* See: S. J. Danishefsky, *Tetrahedron* **1997**, *53*, 8689–8730.
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The picture shows the non-spin-polarized density of states (DOS; above) and M-M crystal-orbital Hamilton population (COHP; below) curves for the first transition metal series. For the early transition metals like Ti, the Fermi level ϵ_F lies low in the COHP curve and thereby falls in the M-M bonding region. As a result, there

exists no drive towards ferromagnetism for the early transition metals. For Cr, ϵ_F lies in the COHP curve between the bonding and antibonding regions, whereas for the metals from "Mn" (the body-centered cubic form of Mn) to Ni, ϵ_F lies in the region that is clearly responsible for M-M antibonding: Fe, Co, and Ni are all ferromagnetic.

The Orbital Origins of Magnetism: From Atoms to Molecules to Ferromagnetic Alloys

Gregory A. Landrum and Richard Dronskowski*

Dedicated to Professor Arndt Simon on the occasion of his 60th birthday

A chemical view of spin magnetic phenomena in finite (atoms and molecules) and infinite (transition metals and their alloys) systems using the concepts of bonding and electronic shielding is presented. The concept is intended to serve as a semiquantitative signpost for the synthesis of new ferromagnets. After a concise overview of the historic development of related theories developed within the physics community, the consequences of spin–spin coupling (made manifest in the exchange or Fermi hole) in atoms and molecules are explored. Upon moving to a paramagnetic state, the majority/minority spin species become more/less tightly bound to the nucleus, resulting in differences in the energies and spatial extents of the two sets of spin orbitals. By extrapolating well-known arguments from ligand-field theory, the paucity of ferromagnetic transition metals arises from quenching the paramagnetism of the free atoms due to strong interatomic interactions in the solid state. Critical

valence electron concentrations in Fe, Co, and Ni, however, result in local electronic instabilities due to the population of antibonding states at the Fermi level ε_F . Removal of these antibonding states from the vicinity of ε_F is the origin of ferromagnetism; in the pure metals this results in strengthening the chemical bonds. In the 4d and 5d transition metals, the valence d orbitals are too well shielded from the nucleus, so a transition to a ferromagnetic state does not result in sufficiently large changes to occur. Thus, the exceptional occurrence of ferromagnetism only in the first transition series appears to parallel the special main-group chemistry of the first long period. A connection between ferromagnetism in the transition metals and Pearson's absolute hardness η is easily established and shows that ferromagnetism appears only when $\eta < 0.2$ eV in the nonmagnetic calculation. As expected from the principle of maximum hardness, Fe, Co, and Ni all become harder upon moving to the more stable

ferromagnetic state. Magnetism in intermetallic alloys follows the same path. Whether or not an alloy contains ferromagnetic elements, the presence of antibonding states at ε_F serves as a "fingerprint" to indicate a ferromagnetic instability. The differences in the sizes of the local magnetic moments on the constituent atoms of a ferromagnetic alloy can be understood in terms of the relative contributions to the density of states at ε_F in the nonmagnetic calculations. Appropriately parameterized, nonmagnetic, semi-empirical calculations can also be used to expose the ferromagnetic instability in elements and alloys. These techniques, which have become relatively commonplace, can be used to guide the synthetic chemist in search of new ferromagnetic materials.

Keywords: alloys • density-functional calculations • electronic structure • magnetic properties • intermetallic phases

1. Introduction

"The magnetic and associated properties of substances which behave magnetically like iron have long provided a happy hunting ground if not for the "smoother pebble than ordinary" at least for the more curiously shaped one. The rich diversity of

ferromagnetic phenomena, the perennial challenge to skill in experiment and to physical insight in coordinating the results, the vast range of actual and possible applications of ferromagnetic materials, and the fundamental character of the essential theoretical problems raised have all combined to give ferromagnetism a width of interest which contrasts strongly with the apparent narrowness of its subject matter, namely certain particular properties of a very limited number of substances."^[1]

"To understand an observable means being able to predict, albeit qualitatively, the result that a perfectly reliable calculation would yield for that observable."^[2]

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The first of the preceding quotations, describing the state of research into ferromagnetism in 1946, seems almost prescient. Despite active investigation for more than a century, ferromagnetism remains fascinating and somewhat mysterious, at least to most chemists. An incredible amount of effort is still being directed at both characterizing ferromagnetic compounds by experiment and understanding their properties by theory. For example, the condensed-matter physics journal *Physical Review B* in 1998 alone published more than 100 papers devoted to ferromagnetism.^[3] Despite its age, the field is still intensely active and contentious, particularly in the physics and materials-science communities. Given the importance of magnetic materials (what would our modern “information society” look like without the potential to magnetically store and retrieve data?), this fascination with magnetism is completely understandable.^[4]

Our first aim in this contribution is to briefly summarize the history of attempts to understand ferromagnetism. Although the existence of ferromagnetism can now be numerically reproduced by high-level quantum mechanical computations, many find it surprising that it remains difficult to understand why some materials are ferromagnetic and others are not. We then present a new style of thinking, extracted from the results of first-principles calculations, which explains the occurrence (or absence) of ferromagnetism in the transition metals and their alloys in terms of chemical bonding. We do not presume to promote this model as the quintessential description of ferromagnetism (to do so would be presumptuous). Instead, our hope is that it will provide a clearer understanding, in the spirit of the second quotation, of the phenomenon. More importantly, our intention is to derive a semiquantitative

signpost for the skillful experimental chemist to use in the synthesis of new ferromagnetic materials.

2. The Development of a Battlefield: Localized Versus Delocalized Ferromagnetism

To lay the groundwork for what follows, we provide here a concise historical overview of the development of the theory of magnetism and ferromagnetism in particular. This treatment of more than a century’s worth of research is, necessarily, incomplete. The interested reader can find a far more complete account of the early history of the science of magnetism in ref. [5].

2.1. Curie and Langevin: Early Experiments and Theories

Drawing upon the results of an extensive series of careful experiments carried out at the end of the 19th century, Pierre Curie divided materials into three distinct types based upon their magnetic behavior: diamagnets (with small, negative, temperature-independent susceptibilities), paramagnets (with small, positive susceptibilities, which typically vary inversely with temperature), and ferromagnets (substances which exhibit magnetism without an applied field below a critical temperature and behave as strong paramagnets at higher temperatures).^[6] While Curie’s definitions of the types of magnetism are of indisputable importance, they are based upon an empirical approach—observing and describing the observed behavior rather than explaining it.

Richard Dronskowski was born in Brilon (Germany) in 1961. He studied chemistry and physics from 1981 until 1989 and received his Diplomas from the University of Münster. In 1990, he completed his doctorate, on the topic of compounds with condensed clusters, at the Max Planck Institute for Solid-State Research (Stuttgart) under the supervision of Prof. Arndt Simon. After a year as a visiting scientist with Roald Hoffmann at Cornell University in 1991 and completing his habilitation in Inorganic Chemistry at Dortmund University in 1995, he accepted in 1996 the offer of the Rheinisch-Westfälische Technische Hochschule in Aachen to become the successor of Welf Bronger. His research interests lie in the region of solid-state chemistry, in particular the synthesis and structural characterization of low-valent as well as magnetic and intermetallic compounds. In the theoretical realm, acid-base properties and the reactivity of solid compounds lie close to his heart, as do questions of chemical bonding and crystal-chemical simulations. The music of Alban Berg and Béla Bartók hold just as much interest for him.



R. Dronskowski



G. A. Landrum

Greg Landrum, born in Baltimore (USA) in 1970, completed his B. S. in chemistry and computer science at Carnegie Mellon University in 1992. In 1997 he received his Ph. D. from Cornell University, where he worked with Roald Hoffmann and studied the electronic structure and bonding of organometallic, intermetallic, and main-group compounds. During his post-doctoral stay at the Rheinisch-Westfälische Technische Hochschule in Aachen he has applied density-functional calculations to the study of nitrides, intermetallic phases, and magnetism. His research interests lie in the use of high-level theoretical methods to construct chemical explanations for the reactivity and properties of molecules and solids. Though his musical tastes are not as refined as those of his co-author, they are just as strongly held.

Paul Langevin, one of Curie's students, introduced in 1905 the idea of the *magnetic moment* in order to explain the experimental data for diamagnetic and paramagnetic materials.^[7] Within Langevin's theory, the magnetization M of a paramagnetic substance made up of N molecules or atoms can be expressed by [Eq. (1)], where a is given in [Eq. (2)].

$$\frac{M}{M_0} = \coth a - \frac{1}{a} \quad (1)$$

$$a = \frac{\mu H}{kT} \quad (2)$$

In Equation (2), μ is the magnetic moment of an individual molecule or atom, H is the strength of the applied field, T is the temperature, k is Boltzmann's constant, and $M_0 = N\mu$ is the magnetization of the sample if all magnetic moments are aligned. Langevin explained ferromagnetism by invoking the presence of intermolecular or interatomic interactions which cause individual magnetic moments to align parallel. While the classical theory of paramagnetism was fundamentally flawed—falsely predicting diamagnetic and paramagnetic susceptibilities to be of equal magnitude—it provided a framework for the work of Pierre Weiss.

2.2. Weiss's Molecular Field: a Local View

Only two years later, Weiss developed a radical idea still found in many textbooks. According to Weiss, ferromagnetism depends on the existence of a "molecular field", an enormously large, internal magnetic field in the crystal which acts to align neighboring magnetic moments.^[8] This approach adds an extra term h to Equation (2) [Eq. (3)].

$$a = \frac{\mu(H + h)}{kT} \quad (3)$$

This term, where $h = qM$ (q is the molecular field constant), reflects the response of the molecular field to the magnetization of the sample. Weiss demonstrated that the molecular field can give rise to a magnetization in the sample *even when the applied field H is zero*. This "spontaneous magnetization", M_s , can be graphically determined by plotting the Langevin equation [Eq. (1)] using the form of the variable a from [Eq. (3)]. At a given temperature T the spontaneous magnetization is determined by the intersection of the Langevin equation with the line given by [Eq. 4] (Figure 1)

$$M = \left(\frac{k}{q\mu}\right)a = (cT)a \quad (4)$$

When the temperature T is smaller than the Curie-Weiss temperature T_{CW} (the ferromagnetic ordering temperature; see the dashed line in Figure 1), M_s is determined by the intersection of the curve of the Langevin equation and the line $(cT)a$. When T is larger than T_{CW} (dotted line in Figure 1), there is no such intersection and the spontaneous magnetization is zero.

The physical origin of the molecular field central to Weiss's theory remained mysterious for years. In fact, Weiss himself was never able to provide any meaningful explanation of the

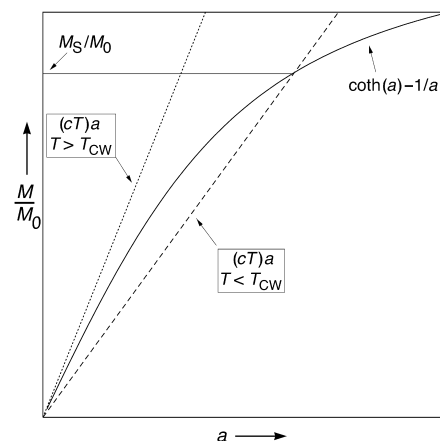


Figure 1. Graphical solution for the spontaneous magnetization M_s of a material within Weiss's theory of ferromagnetism. Refer to the text for details.

huge strength of the molecular field. However, by this hypothesis Weiss showed that the intermolecular or interatomic forces in crystals do not extend beyond a certain "active region." A number of ingenious intermetallic dilution experiments led Weiss to realize that the molecular field in ferromagnetic iron decays with the sixth power of the interatomic distance.^[9]

2.3. Quantum Mechanics: Heisenberg and Stoner

The puzzle of the molecular field was solved by Heisenberg in 1928^[10] and, almost simultaneously, by Dirac.^[11] Only four years later, most theoretical expressions had been brought into a self-consistent form by van Vleck in his widely acclaimed textbook on magnetism.^[12] The theory shows that ferromagnetism may be understood to arise from quantum-mechanical exchange interactions which lead to the parallel alignment of spins $\vec{S}_i$ and $\vec{S}_j$ [Eq. (5)].

$$V_{ij} = -2J_{ij}\vec{S}_i\vec{S}_j \quad (5)$$

Here, J_{ij} , the exchange integral between atoms i and j , is *positive*. It is important to realize that this view is a *local* one, and it treats the system as if the electrons responsible for ferromagnetism are fixed on the atoms. Thus, Heisenberg's approach bears a strong resemblance to the Heitler–London treatment of the hydrogen molecule. In chemical terminology, the model is similar to valence-bond (VB) theory.

Most chemists will immediately sense the problems inherent in applying Heisenberg's model to the archetypical ferromagnets iron, cobalt, and nickel. In these metals, the experimentally determined magnetic moments (the number of unpaired electrons) are all nonintegral: 2.21, 1.60, and 0.62 for Fe, Co, and Ni, respectively. Clearly, the unpaired spins cannot be fully localized since atom-centered magnetic moments should adopt integer values.^[13] It also seems somewhat ill-advised, at best, to assume the presence of localized spins in a metal where the conduction electrons are strongly *delocalized* (itinerant).

The itinerant nature of the conduction electrons in metals had been recognized long prior to Heisenberg's theory of ferromagnetism. An early theory of the electronic structure of metals, developed by Drude and Lorentz, treated the electrons as an ideal gas fully delocalized throughout the crystal. While this theory was quite successful in explaining the conductivity of metals, problems arose with respect to their electronic heat capacities; these were predicted to be much too large. Sommerfeld replaced the classical Boltzmann statistics (appropriate for gas molecules) of the Drude model with Fermi–Dirac statistics (appropriate for electrons), thereby implicitly taking the Pauli exclusion principle into account. The success of Sommerfeld's theory in describing the experimentally observed properties of metals provided solid support for the idea that the conduction electrons are *itinerant*: delocalized throughout the crystal. In what is probably one of the first applications of the rigid-band model to the electronic structure of solids, Slater used the first calculated electronic structure of elemental copper^[14] to argue that the ferromagnetism of nickel must be due to these itinerant electrons. Slater went so far as to say that Heisenberg's model of ferromagnetism “is considered to be unsuitable for application to ferromagnetism, except in its general principle of explaining the energy of orientation of elementary magnets in terms of exchange energy.”^[15]

Based upon this theoretical framework, an alternative treatment of ferromagnetism was proposed by Stoner in 1938–1939.^[16, 17] By assuming an average spin field interacting with a single spin (equivalent to a mean-field treatment of electronic correlation) and parabolic energy bands, Stoner presented a predictive model of itinerant-electron ferromagnetism. It is clear that such a delocalized treatment is closely related to the Hund–Mulliken molecular orbital (MO) approach for the hydrogen molecule. Stoner's theory of ferromagnetism is quite detailed. In addition to predicting whether or not a given metal is ferromagnetic, it included methods for calculating the temperature dependence of both the magnetic susceptibility and the electronic specific heat. Here we limit ourselves to discussing the “Stoner criterion” for the presence of ferromagnetism.

The Stoner criterion can be concisely expressed as Equation (6), where I is a measure of the strength of the exchange interaction in the metal and $\text{DOS}(\varepsilon_F)$ is the density of states at the Fermi level, ε_F .

$$I\text{DOS}(\varepsilon_F) > 1 \quad (6)$$

In the original formulation of the model, I and $\text{DOS}(\varepsilon_F)$ were approximated for the transition metals. Once accurate electronic-structure calculations became possible, $\text{DOS}(\varepsilon_F)$ was also immediately accessible. A number of authors (see, for example, refs. [18, 19], and references therein) proposed various ways to extract I from their results. The first comprehensive tabulation of I and $\text{DOS}(\varepsilon_F)$ pairs was presented by Janak in 1977.^[19] His results, along with the product $I\text{DOS}(\varepsilon_F)$, are plotted in Figure 2. Using Janak's parameters, iron and nickel are predicted to be ferromagnetic and palladium is predicted to be almost ferromagnetic; palladium is, in fact, known as an “incipient ferromagnet”.

The one failure within this model is for cobalt ($I\text{DOS}(\varepsilon_F) = 0.972$), predicted to be nonmagnetic. It is also somewhat strange that nickel, the *weakest* ferromagnet, has the *largest* $I\text{DOS}(\varepsilon_F)$ value.

In the years after their introduction, either the Heisenberg or Stoner approach came into or went out of favor, depending upon the subject and the school of interacting disciplines. This back-and-forth battle is probably all too familiar to many chemists if one recalls the long-time struggle between the VB and MO approaches for the study of bonding in molecules. In 1966, Herring finally demonstrated that the descriptions are not mutually exclusive.^[20] In our view, however, the delocalized theory is certainly much better suited to transition metals.

Nowadays, most solid-state physicists accept the Stoner criterion to decide whether or not a metal or alloy should be ferromagnetic. While (with the exception of cobalt) this model is predictive, it doesn't provide much helpful information to use in truly understanding the nature of ferromagnetism; certainly none at all to help in developing a chemical understanding. The original model, derived from an assumed parabolic band shape, does not take into account either the shape of the DOS curves or the position of ε_F within those curves. These are two of the places where the chemistry hides.

3. Magnetism in Atoms and Molecules

The study of spin-spin coupling supplies the key to understanding magnetism, the macroscopic quantum effect. The underlying antisymmetry of the wave functions of a system has a deep impact upon the magnetism and chemistry of atoms and molecules.

3.1. The Exchange Hole and its Consequences

Since the exchange hole, which goes by a number of other names (such as “Fermi hole”), is central to our analysis of ferromagnetism, we briefly discuss it here. Although our discussion relies on results derived for an idealized system (the free-electron gas), we will demonstrate that the general conclusions are applicable to real systems such as atoms, molecules, and crystals.

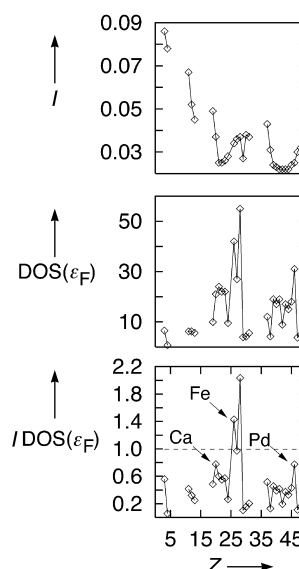


Figure 2. Plots of the Stoner exchange parameter I , $\text{DOS}(\varepsilon_F)$, and $I\text{DOS}(\varepsilon_F)$ versus atomic number Z for selected metallic elements. Metals lying above the dashed line at $I\text{DOS}(\varepsilon_F) = 1$ are predicted to be ferromagnetic. Data are taken from ref. [19].

When two electrons are brought into proximity to each other, they experience a Coulombic repulsion due to their negative charges. Since, by Pauli's principle, two electrons with the same magnetic spin quantum number are forbidden from occupying the same position, there is an extra repulsion between like-spin electrons known as the exchange repulsion. One of the major consequences of this repulsion is the appearance of the exchange hole in the free-electron gas. For a given α (spin-up) electron, it experiences an effective electron density arising from all of the other electrons in the electron gas. The effective density close to the electron is relatively low because the Coulomb repulsion keeps all of the other electrons away. The exchange repulsion results in a

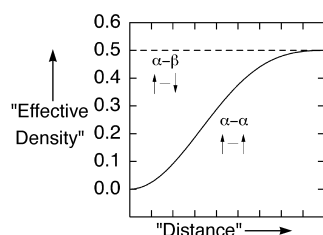


Figure 3. A schematic illustration of the exchange hole.

further depletion of the α -electron density, but does not affect the β spins. This "hole" in the effective α -electron density (α - α curve in Figure 3) is known as the exchange hole. No such hole exists in the α - β curve. Although the perturbations to the electron density arising from the exchange term are quite small compared to those from the Coulombic interactions, their effects can be extraordinarily important. Because of the exchange hole, like-spin electrons do not shield each other from the nucleus as well as electrons with different spins, that is, α - α shielding is less effective than α - β shielding. Thus there is a differential shielding of α and β electrons in systems with unpaired spins. If we assume, for simplicity, that the α electrons are the majority spin species, then they will be, on average, less shielded from the nucleus than the β electrons. Consequently the α electrons experience a higher effective nuclear charge than the β electrons. The differences in effective nuclear charge for the two spin species lead immediately to energy differences in the orbitals associated with each spin.

3.2. Light Atoms

Figure 4 shows the changes in energy levels of atomic oxygen upon moving from a singlet to a triplet state. When the spins are allowed to unpair (a process we will refer to as spin-polarization), the α electrons, which are now less shielded due to the smaller number of β electrons, drop in energy. At the same time, the β spins experience greater shielding and the associated spin orbitals increase in energy. The resulting splittings between equivalent α and β spin orbitals (the exchange splittings) in triplet atomic oxygen are

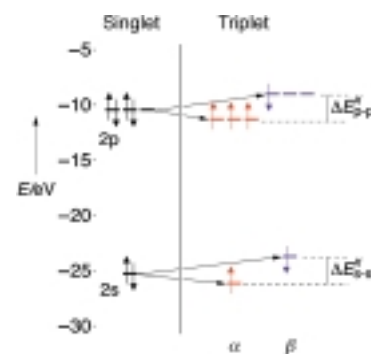


Figure 4. Energy level diagrams for atomic oxygen in a singlet excited state (left) and the triplet ground state (right). On the right side lie *spin orbitals*, each of which has a maximum occupation of one electron.

$\Delta E_{s-s}^x = 2.43$ eV und $\Delta E_{p-p}^x = 2.29$ eV, according to our spin-density-functional calculation (Appendix A).

The differential shielding of α and β electrons, due to the exchange hole, has consequences beyond the exchange splitting, since the spin orbitals associated with the different types of electrons have differing spatial extents (Figure 5). The low-lying α spin orbitals are more spatially contracted than the β spin orbitals. This graphical analysis can be made somewhat more quantitative by examining the compositions of the oxygen 2p atomic orbitals (AOs) and the positions of the maxima in their radial wavefunctions. Within the triple- ζ Slater-type orbital (STO) basis used in our calculations, the radial part of each AO ψ is expressed as a linear combination of three STOs (ϕ)^[21] [Eq. (7)], where the individual STOs are defined by [Eq. (8)]

$$\psi^{2p} = \sum_{i=1}^3 c_i^{2p} \phi_i^{2p} \quad (7)$$

$$\phi_i^{2p} = r e^{-\zeta_i^{2p} r} \quad (8)$$

For a numerical illustration, the expansion coefficients (c_i^{2p}) for the 2p AOs of both singlet and triplet oxygen are given in Table 1. The triplet $\psi^{2p}(\alpha)$ orbital has significantly larger contributions from the two more contracted basis functions (ϕ_2^{2p} and ϕ_3^{2p}) than triplet $\psi^{2p}(\beta)$. Conversely, $\psi^{2p}(\beta)$ has a larger contribution from the more diffuse ϕ_1^{2p} . The non-spin-

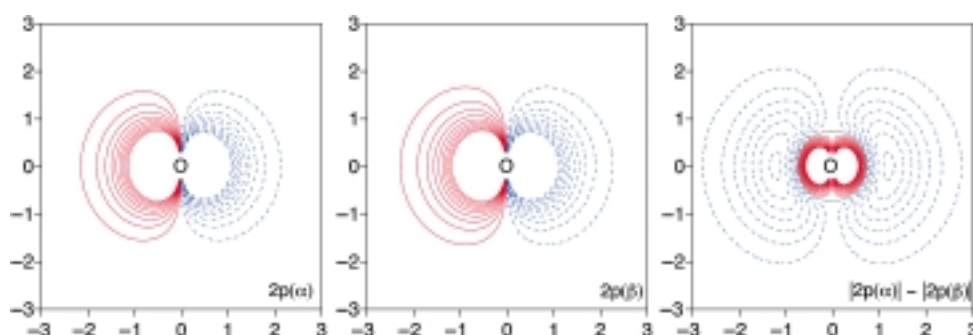


Figure 5. Contour plots of the 2p spin orbitals of triplet atomic oxygen: The left picture shows an α and the middle a β orbital. Since it is almost impossible to distinguish these from each other with the naked eye, the right pane shows an AO difference plot, the result of $|2p(\alpha)| - |2p(\beta)|$. In the AO plots the contours run from -0.1 to 0.1 in steps of 0.01 ; negative values are drawn with dashed lines. The contours in the difference plot run from -0.01 to 0.01 in steps of 0.001 ; negative values are drawn with dashed lines and the dotted line indicates the zero contour. All distances are in Å.

Table 1. Expansion coefficients (c) and locations of the maxima in the radial functions ($r_{\max}$) for the 2p AOs of atomic oxygen. The orbital exponents of the STO basis functions (defined in [Eq. (8)]) are: $\zeta_1^{2p} = 1.12$, $\zeta_2^{2p} = 2.08$, $\zeta_3^{2p} = 4.08$.

	c_1^{2p}	c_2^{2p}	c_3^{2p}	$r_{\max}$ [Å]
Singlet $\psi^{2p}(\alpha, \beta)$	0.289	0.574	0.243	0.292
Triplet $\psi^{2p}(\alpha)$	0.255	0.602	0.245	0.284
Triplet $\psi^{2p}(\beta)$	0.348	0.528	0.239	0.307

polarized (singlet) AOs come somewhere in between the α and β values. Accompanying these changes is a shift in the positions of the radial maxima of the atomic orbitals: $r_{\max}(\text{triplet } \psi^{2p}(\alpha)) < r_{\max}(\text{singlet } \psi^{2p}(\alpha, \beta)) < r_{\max}(\text{triplet } \psi^{2p}(\beta))$. Other light atoms behave in an analogous way.

To summarize, the exchange hole gives rise to a differential shielding of the α and β electrons of a spin-polarized system such that 1) the α/β electrons experience a higher/lower effective nuclear charge; 2) the α/β spin orbitals decrease/increase in energy; 3) they become less/more spatially diffuse relative to the non-spin-polarized system.

The above findings allow an easy interpretation of the work of Boyd, who concluded that the preference for a high-spin state in atoms (Hund's first rule) can be attributed to an increase in electron–nuclear attraction upon moving to the spin-polarized state.^[22] Boyd's arguments run counter to the questionable textbook reasoning, stating that Hund's rule is due to a decrease in electron–electron repulsion in the high-spin state; rather, Hund's rule can be understood in terms of the foregoing differential shielding argument. In the triplet state, the electron–nuclear attraction in oxygen is stronger because the α electrons experience a higher effective nuclear charge; the β electrons experience a lower effective charge, but they are the minority. The electron–electron repulsion, on the other hand, *increases* since the α electrons are more spatially contracted and, on average, closer to each other.

3.3. Heavier Atoms

Upon moving down in the periodic table, the situation changes dramatically. For example, although both sulfur and selenium still exhibit a preference for the triplet state, their exchange splittings are considerably smaller: Moving down the group (O, S, Se), ΔE_{s-s}^x falls from 2.43 to 1.19 and finally to 0.91 eV and ΔE_{p-p}^x changes from 2.29 to 1.00 and then to 0.78 eV. In addition, the changes in the spatial extents of the orbitals are now much smaller (Figure 6). There is a significant decrease in the magnitudes of both the exchange splittings and the differences in spatial extent of the spin orbitals on moving from the first long row of the periodic table to the second and an additional, much smaller, decrease on moving from the second to the third.

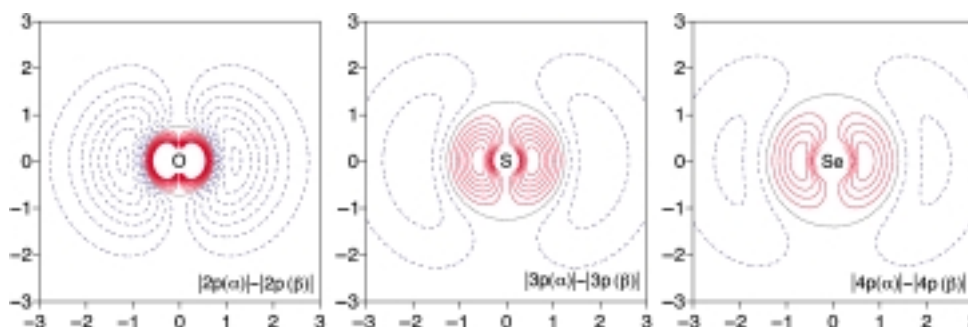


Figure 6. AO difference plots for the p orbitals of triplet-state atoms O (left), S (center), and Se (right). The contours and line patterns are the same as those in the right pane of Figure 5.

We believe that the differences between the first and second long rows and the similarities between the second and third long rows can be understood in terms of the presence or absence of p orbitals in the nonvalence (core electron) region of the atom. Before presenting this explanation, which is very similar to that proposed by Kutzelnigg,^[23] it is useful to briefly review the determination of the exponents of STOs.

Within Slater's original scheme^[24] for determining the shielding of valence electrons by core electrons, the types of the core and valence orbitals^[25] concerned were not taken explicitly into account. In fact, the 2s and 2p orbitals of oxygen have the same orbital exponent. In later work from Clementi and Raimondi, a series of fits of STOs in order to reproduce total atomic energies from numerical SCF calculations led to a modified version of Slater's rules.^[26] In a less well-known publication, Burns presented yet another alternate formulation of Slater's rules.^[27] Burns directly fitted STOs to atomic wavefunctions instead of trying to match the energies of these orbitals. Burns developed a different set of orbital exponents from those of Clementi and Raimondi, a set which is perhaps more reasonable for studying molecules since it treats the inner and outer parts of the wavefunction on more equal footing.^[28] More importantly, Burns realized that a more effective set of rules for calculating STO shielding parameters could be produced by including the type of orbitals involved in the shielding expression. For example, using Burns's rules, a valence p electron is more effectively shielded by a core p electron than by a core s electron. The net result is that the 2p orbitals of oxygen are considerably more contracted (reduced shielding produces a larger exponent) than the 2s orbital since there is no 1p orbital within the core. This result is, of course, very well known within pseudopotential theory: The first instance of a particular type of orbital (such as 2p, 3d, 4f) is always quite contracted.

Since the 2p orbitals of oxygen atoms are more contracted than either the 3p orbitals of sulfur or the 4p orbitals of selenium, the p electrons of oxygen spend considerably more time close to the nucleus than those of either sulfur or selenium. Consequently, small changes in the shielding of the oxygen 2p electrons, such as those caused by spin polarization, must have a larger impact than they do for the 3p or 4p electrons. The net result is that the perturbations caused by the transition to the triplet state in sulfur are smaller than those in oxygen. The perturbations for selenium, which has two p shells in the core, are even smaller.

3.4. Diatomic Molecules

The same arguments about the exchange hole and shielding used above for atoms also apply to molecules with unpaired electrons. For example, the energy levels of O₂ change in an exactly analogous way to those of atomic oxygen when the molecule changes from a singlet to a triplet state (Figure 7). Focusing only on the HOMO—the antibonding 2π(π*) orbital—the exchange splitting in O₂ ($\Delta E_{2\pi-2\pi}^x$) is 1.85 eV. Moving down to S₂ and Se₂, $\Delta E_{2\pi-2\pi}^x$ falls to 0.81 and 0.63 eV, respectively. The exchange splitting decreases upon moving down the group.

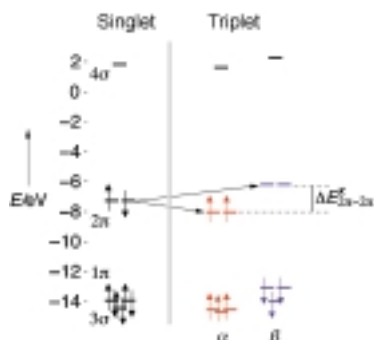


Figure 7. Energy level diagrams for molecular oxygen in the singlet excited state $^1\Delta_g$ (left) and in the triplet ground state $^3\Sigma_g^-$ (right).

The α and β spin orbitals of triplet O₂ (Q = O, S, Se) show the same behavior and trends as those in triplet Q (Figure 8). The 2π spin orbital of the majority spin species (α) is more contracted than that of the minority species (β). The differences in both exchange splittings and spatial extents of the 2π(α) and 2π(β) spin orbitals are again larger upon moving from first to second row (O₂ → S₂) than from second to third (S₂ → Se₂).

One final word about the molecular results before considering the solid state. In all three diatomic molecules discussed above, the process of spin polarization increases the splitting between the highest-occupied molecular orbital (HOMO) and the lowest-unoccupied molecular orbital (LUMO).^[29] This energy difference may be interpreted in the context of the theory of chemical hardness,^[30] which is intimately connected with questions of chemical reactivity. In fact,

density-functional theory reveals that the chemical hardness η of a molecule may be defined by Equation (9)^[31]

$$\eta = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \quad (9)$$

It is noteworthy that O₂, S₂, and Se₂ all become chemically *harder* (less reactive) by a few percent upon changing from the singlet excited state to the triplet ground state. The decrease of their total energies is parallel to an increase in their chemical hardness upon a distortion; in this case an electronic distortion. This effect fits nicely into the principle of maximum hardness: In general, more stable species are chemically harder.^[30]

4. Ferromagnetism in the Elemental Transition Metals

“Es geht auch anders, doch so geht es auch.”^{[*][32]}

4.1. The Phenomenon

Though transition metal atoms are paramagnetic in the gas phase, only a few exhibit cooperative magnetism, such as ferromagnetism, in the solid state (Figure 9). The only “magnetic” transition metals occur close to the end of the first transition series. Metals Fe, Co, and Ni are all ferromagnetic, whereas Cr and Mn have antiferromagnetic ground states. Let us initially limit our attention to the ferromagnetic metals as the antiferromagnetic structures of Cr (incommensurate spin-density waves) and Mn (with 58 atoms in the magnetic unit cell) pose computational difficulties. It is obvious from Figure 9 that ferromag-

Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu
hcp	hcp	bcc	bcc	X	bcc	fcc	fcc	fcc
Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag
hcp	hcp	bcc	bcc	hcp	hcp	fcc	fcc	fcc
La	Hf	Ta	W	Re	Os	Ir	Pt	Au
hcp	hcp	bcc	bcc	hcp	hcp	fcc	fcc	fcc

Figure 9. A section of the periodic table showing the structures and magnetic properties of the transition metals. Elements with yellow backgrounds are antiferromagnetic, while those with orange-red backgrounds are ferromagnetic. The abbreviations for the structures are: hcp: hexagonal close packed; bcc: body-centered cubic; fcc: face-centered cubic; X: the α -Mn structure type.

[*] “There are other ways, but this one’s fine, too.”

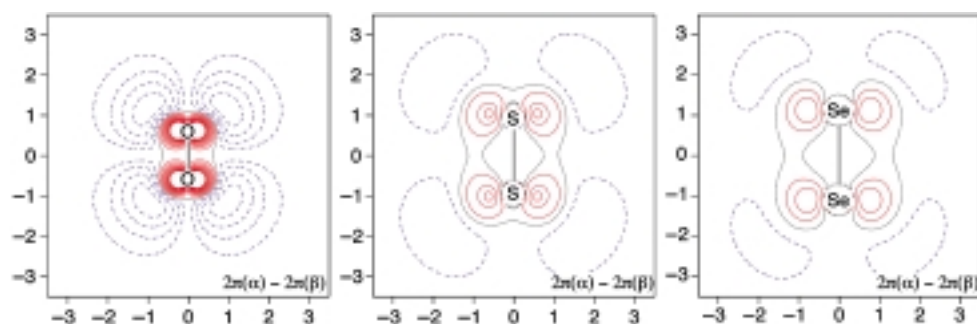


Figure 8. Molecular orbital difference plots for the 2π(π*) orbitals of triplet O₂ (left), S₂ (center), and Se₂ (right). The contours and line patterns are the same as those in the right pane of Figure 5.

netism is not solely a consequence of structure or electron count. For example, Pt and Pd both adopt the same face-centered cubic (fcc) structure and have the same number of valence electrons as Ni, yet neither is ferromagnetic. Ferromagnetism clearly arises from a set of special electronic circumstances.^[4]

In order to understand these circumstances, we adopt the view that the nonmagnetic state is “normal” in the solid and ferromagnetism is an unusual phenomenon. Using this approach, we will come to ferromagnetism by first understanding why most elemental metals are not ferromagnetic. This can be most directly achieved by drawing an analogy with molecular complexes of the transition metals and their ions.

Hund’s first rule states that the most stable form of free atoms or ions is the high-spin state; a d^6 transition metal ion has preferentially four unpaired electrons (Figure 10a). When we introduce a perturbation by a set of ligands with an octahedral coordination, the degeneracy of the d orbitals is

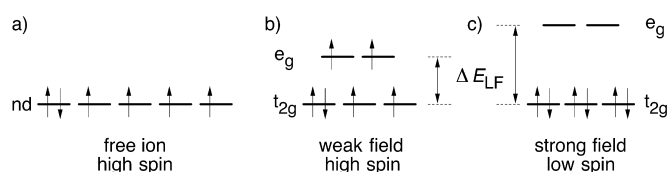


Figure 10. Energy-level diagrams and electronic configurations for the d orbitals of: a) a free d^6 transition metal ion; b) a d^6 transition metal ion with an octahedral environment of weak-field ligands; c) a d^6 transition metal ion with an octahedral environment of strong-field ligands. For simplicity, we limit ourselves to the one-electron picture, neglect spin–orbit coupling, and ignore the spherical energetic part of the ligand field.

broken and they split into t_{2g} and e_g sets. If the metal–ligand interactions are weak and the perturbation is small (Figure 10b), then the splitting between e_g and t_{2g} (ΔE_{LF}) is also small; the six electrons fill the energy levels in a high-spin arrangement just as in the free ion. If the metal–ligand interactions are strong and the perturbation is larger (Figure 10c), then ΔE_{LF} is also large enough so the electrons form pairs in the t_{2g} orbitals and the complex is nonmagnetic. One could say that the strong ligand field has totally quenched the magnetism of the free ion.

The situation is similar in the elemental structures of the transition metals: The magnetism of the free atoms is quenched when those atoms are condensed into a crystal. Like many other concepts in the band theory of solids, this is most easily illustrated using a simple model: a one-dimensional chain of hydrogen atoms (Figure 11). A free hydrogen atom is, of course, Curie paramagnetic, with one electron sitting unpaired in an s orbital. When we form a one-dimensional chain, the energy levels of the atoms spread out to form a band. If the interactions between the atoms in the chain are weak (a small perturbation), then the resulting band, ΔE_{BW} , is narrow and each crystal orbital is half-filled (Figure 11a). This is the crystalline equivalent of the weak ligand-field case (Figure 10b). A large perturbation (strong interactions between the atoms in the chain) results in all the electrons pairing (Figure 11b). The magnetism of the free atoms is quenched in the crystal when the interatomic interactions, and thus bandwidths, are large.

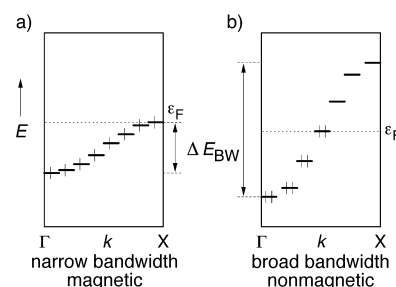


Figure 11. Qualitative band structures and electron fillings for a one-dimensional chain of hydrogen atoms with: a) narrow bandwidth (weak H–H interactions) and b) broad bandwidth (strong H–H interactions).

The rare-earth elements typically display the narrow-bandwidth magnetism sketched in Figure 11a. The majority of the interatomic bonding in these metals is mediated through the 5d and 6s electrons. The 4f orbitals, which are strongly spatially contracted, are only slightly perturbed by the neighboring atoms and give rise to very narrow bands. The localized-electron magnetism of the rare-earth metals is characterized by magnetic moments which approach those in the free atoms and by complicated magnetic structures.^[33] The origin of this localized-electron magnetism is reasonably easy to understand: The f bands are so narrow that the energetic cost associated with populating the entire band with electrons is small compared to the cost associated with pairing the electrons.^[34] Consequently, the band is filled, in a manner analogous to the configuration of atomic energy levels following Hund’s rule, and results in unpaired spins and magnetic moments. What is considerably more difficult to understand is what determines the structure adopted by those unpaired f electrons. The magnetic structures of the rare earths run the gamut from the simple ferromagnetism observed in gadolinium to the sinusoidal spin structures of erbium and terbium.^[33]

As localized-electron magnetism is not our focus here, we leave this complicated story and return to itinerant-electron ferromagnetism in the transition metals. In these metals, the d orbitals contain the electrons responsible for magnetism. However, in contrast to the f orbitals of the rare-earth elements, transition metal d orbitals are involved in strong interatomic interactions. This gives rise to fairly broad bands in the elemental transition metals. Figure 11b is a more appropriate model of their bands than Figure 11a. Consequently, most elemental transition metals are non-magnetic.

4.2. Itinerant (Delocalized) Electron Ferromagnetism

The changes to the electronic structure of a system with broad bands which allow ferromagnetism are best introduced using qualitative density of states (DOS) plots.^[35] In Figure 12a, the DOS of a nonmagnetic metal is sketched as a rectangular block, divided into boxes to allow states to be counted. The same DOS is shown in a spin-resolved way (where the α and β states are plotted separately) in Figure 12b. The occupations of the α and β spin sublattices, determined by counting the number of boxes lying below the

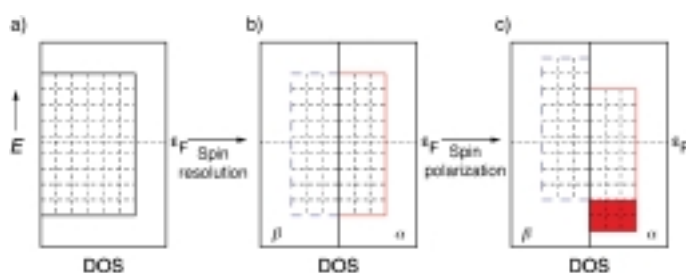


Figure 12. Qualitative DOS curves for a transition metal. a) The DOS of a nonmagnetic metal. b) Spin-resolved form of the same DOS (DOS for α and β electrons are drawn separately). c) Shifts in the α and β spin sublattices upon the onset of magnetism (spin polarization). The red-shaded region indicates the “excess” α spins. In all three panes, the horizontal dotted line indicates the position of the Fermi level (ϵ_F). The grid superimposed on the DOS curves facilitates the counting of states.

Fermi level (ϵ_F), are identical. When this system becomes magnetic, the α and β DOS curves change in energy: The α/β spin sublattice moves down/up (Figure 12c). Since the two sublattices must share a common Fermi level, the net result of this spin polarization is a higher occupation of the α states. The number of “excess” α states, and thus the permanent magnetic moment of the system, can be determined by counting the number of boxes in the red-shaded region of Figure 12c.

Notice the strong similarities, on moving from the low- to the high-spin configuration, between the DOS of a solid becoming magnetic and the changes in the energy-level diagrams of atoms (Figure 4) and molecules (Figure 7). In each case the states (energy levels) associated with the α electrons (the majority spin species) decrease in energy relative to the nonmagnetic case while the β energy levels increase. In this respect, itinerant-electron ferromagnetism is not so different from atomic and molecular magnetism. As we shall demonstrate later, the similarities run even deeper than the shifts in energy levels.

4.3. The Archetype: Iron

We begin our examination of ferromagnetism in the transition metals with a detailed analysis of the archetypical ferromagnet: body-centered cubic (bcc) iron (α -Fe). In α -Fe each iron atom is surrounded by eight nearest neighbors, in a cubic arrangement, at a distance of 2.485 Å and six next-nearest neighbors, in an octahedral arrangement, at a distance of 2.870 Å (Figure 13). Below its Curie temperature ($T_c = 1044$ K) α -Fe is ferromagnetic, with a saturation magnetic moment of $2.21 \mu_B$.^[33]

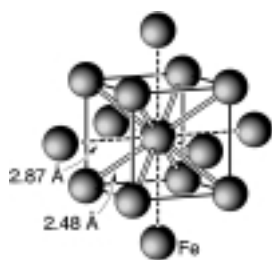


Figure 13. The coordination environment of iron in the bcc α -Fe structure.

We start with the electronic structure of an Fe phase which does not exist: *nonmagnetic* bcc Fe. This is not a model of Fe above T_c , which has a different lattice constant and significant (albeit short-range) magnetic order.^[36] The calculated band structure, the DOS and Fe-Fe

crystal-orbital Hamilton population (COHP) curves for this phase, are presented in Figure 14. The computational methodology is explained in Appendix A. At most high-symmetry points in the first Brillouin zone (BZ), which is shown in

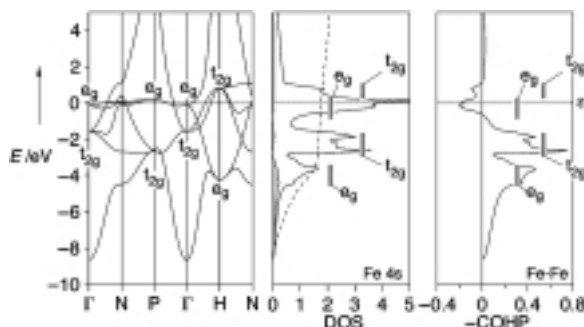


Figure 14. Band structure (left), DOS, and Fe-Fe COHP curves for nonmagnetic α -Fe. The shaded region and dashed line in the DOS curve corresponds to the projected DOS of the Fe 4s orbital and its integration, respectively. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

Figure 15, the crystal orbitals which arise from the Fe 3d block split into two sets: triply degenerate t_{2g} and doubly degenerate e_g ; the point-group irreducible representation labels used here are those appropriate for the cubic point symmetry of the Fe atoms. Labeling the bands in this manner allows us to roughly characterize the peaks in the DOS and COHP curves to their orbital composition. The primarily e_g crystal orbitals are mostly flat (exceptions of $\Gamma \rightarrow H$ and $H \rightarrow N$) whereas the t_{2g} orbitals show reasonable dispersion along every symmetry direction. We can understand this disparity by considering the shapes of the crystal orbitals, sketched at the symmetry points Γ and N in Figure 16. The t_{2g} orbitals are pointed more directly at the nearest-neighbor atoms (which lie on the corners of the cube in this Figure). These orbitals have π symmetry with respect to the more distant next-nearest neighbors at the ends of the dashed lines. The e_g orbitals, involved in σ interactions with the next-nearest neighbors, are not oriented particularly well for nearest-neighbor interactions. The symmetry line from $\Gamma \rightarrow H$ lies along one of the Cartesian reciprocal axes (Figure 15), therefore motion along this line strongly affects next-nearest-neighbor interactions and gives rise to a large e_g bandwidth from Γ to H . The nearest-neighbor interactions are affected along all directions, therefore the t_{2g} orbitals show a significant bandwidth along every symmetry line.

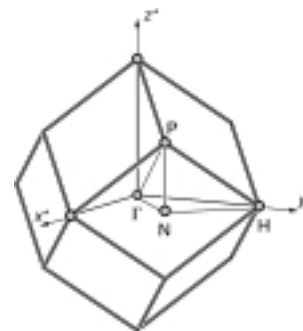


Figure 15. The first Brillouin zone for a bcc lattice with high-symmetry points labeled. The vectors x^* , y^* , and z^* are Cartesian reciprocal axes.

Continuing our analysis of Figure 14, we observe the three-peaked DOS typical of bcc metals. As is true for all transition metals, the s band penetrates the d block to yield s-dominated

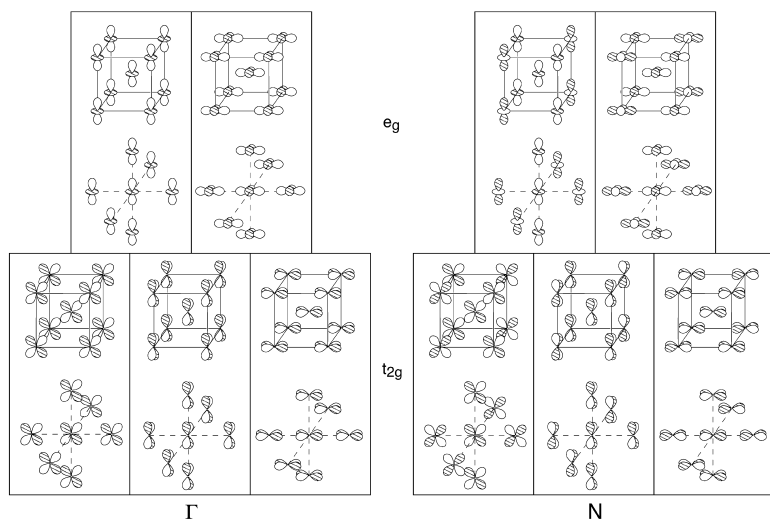


Figure 16. Iconic representations of the crystal orbitals of α -Fe at the high-symmetry points Γ and N. Each orbital is drawn in two parts: one showing nearest-neighbor contacts, the other next-nearest-neighbor contacts. The t_{2g} and e_g labels, strictly valid in Γ , are used only to qualitatively group orbitals in N.

states at the base of the DOS. Up to this point, we have encountered nothing unusual in the electronic structure of hypothetical nonmagnetic α -Fe. The first indication that something is wrong appears in the Fe-Fe COHP curve.

As we would expect, the low-energy end of the DOS, that is primarily composed of s states, is Fe-Fe bonding. This is followed by two Fe-Fe bonding peaks. The first, between -3 and -5 eV, mostly arises from the e_g orbitals. The second, between -3 and -1 eV, mainly has a t_{2g} character. Of these two peaks, the one from the t_{2g} set is more strongly bonding between nearest neighbors, as we anticipate based upon the discussion above. In the next-nearest-neighbor COHP curve (not shown here), the e_g states are significantly more strongly bonding between next-nearest neighbors; again, fitting our expectations. The integrated Fe-Fe COHPs (ICOHPs) are -1.448 and -0.683 eV per bond for the nearest-neighbor and next-nearest-neighbor interactions, respectively. The curious thing about the electronic structure of nonmagnetic α -Fe is that ϵ_F falls in a strong Fe-Fe *antibonding* region. Normally, the appearance of ϵ_F in strongly antibonding states is an alarm that indicates a system is unstable with respect to some sort of structural change. However, we know that Fe does not undergo any such distortion and that the bcc structure is stable. How are we to understand this? The answer is that α -Fe *does undergo a distortion* but instead of the atoms of the structure rearranging themselves, the *electrons* do. Nonmagnetic α -Fe is unstable with respect to an electronic structure distortion, which makes the α and β spin sublattices inequivalent (thereby reducing the electronic symmetry), lowers the energy, and gives rise to ferromagnetism.

When a spin-polarized calculation is performed for bcc Fe, the two spin sublattices become inequivalent and shift in energy (Figure 12c). This results in different populations of the α and β sublattices and a calculated spin magnetic moment of $2.27 \mu_B$, very close to the experimental value of $2.21 \mu_B$. The total energy decreases by 0.43 eV upon spin polarization. The spin-polarized DOS and Fe-Fe COHP curves of ferromagnetic α -Fe are shown in Figure 17. The α and β DOS curves in

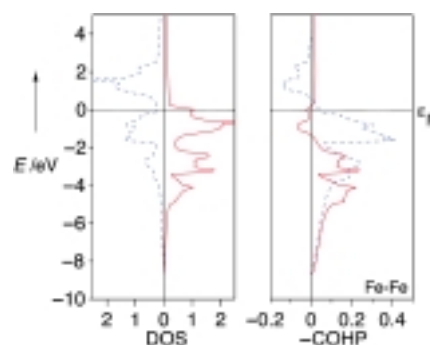


Figure 17. DOS and Fe-Fe COHP curves for ferromagnetic α -Fe. In each plot, the solid red/dashed blue line corresponds to the α/β spins. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

Figure 17 are very similar to each other and to the nonmagnetic DOS in Figure 14: Spin-polarization has *not* significantly affected the shape of the DOSs; merely shifted them in energy. While

the α spin sublattice has decreased in energy enough to almost completely fill the d block, the β spins have increased to maintain a constant number of electrons in the system as a whole. The shift of the primarily s states (at the base of each DOS curve) is quite small—the s orbitals are not significantly affected by the onset of ferromagnetism. Moving our focus to the chemical bonding in magnetic Fe, the α and β COHP curves are similar in shape but differ in size. Firstly, the α COHP curve is quite a bit smaller in magnitude than its β counterpart. Secondly (and equally important), the shifts in the two curves have removed the Fe-Fe antibonding states from the vicinity of ϵ_F . The integrated Fe-Fe COHPs for the α and β electrons are -0.552 and -0.975 eV per bond and a total ICOHP of -1.527 eV per bond. The onset of ferromagnetism has *strengthened* the Fe-Fe nearest-neighbor bonds by more than 5%, parallel to the decrease in the total energy.

As expected, spin-polarization results in a rearrangement of the electron density in α -Fe. The nature of the electron density shifts are shown in Figure 18 by plotting the quantity $\Delta\rho = \rho(\text{magnetic}) - \rho(\text{nonmagnetic})$ evaluated in a plane

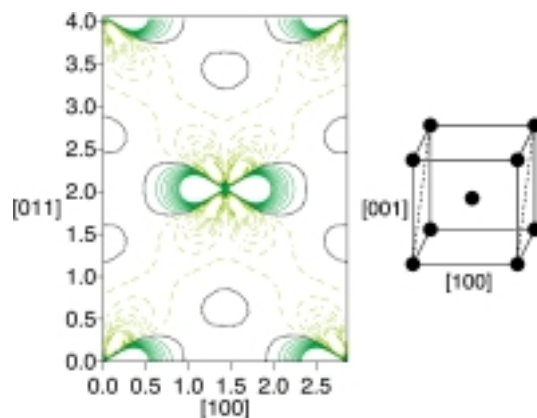


Figure 18. Changes in the electron density of α -Fe upon spin polarization. Solid green curves indicate positive values (higher electron density in the magnetic state) and dashed yellow curves negative (lower electron density in the magnetic state); the dotted black lines are the zero contours. The location of the plane in the unit cell is sketched on the right.

containing both nearest-neighbor and next-nearest-neighbor contacts. In nonmagnetic bcc Fe, the states at and just below ε_F are antibonding between nearest neighbors; these regions lie along the diagonal of the plot in Figure 18. These states are depleted in the magnetic form, to result in a shift of electron density out of the spatial regions between nearest neighbors. The “lost” electron density accumulates in the areas between next-nearest neighbors.

As mentioned above, the energy shifts of the α and β spin sublattices in ferromagnetic Fe mirror those of the atomic/molecular orbitals of O/O₂ (Figures 4 and 7). These shifts are once again a consequence of the exchange hole. The majority spin species (α) is not as effectively shielded from the nucleus as in the nonmagnetic “phase”, so the α states decrease in energy. The β states, on the other hand, experience better shielding and increase in energy. We would expect that these changes give rise to differences in the spatial extents of the two sets of states as well. This effect is indeed present and responsible for the different sizes of the α - and β -COHP curves. The more spatially contracted α states are not as strongly Fe-Fe bonding as the β states, which have become more diffuse. The differing spatial extents of the spin-sublattices is one of the major factors contributing to the fact that the nearest-neighbor β ICOHP is almost twice as large as the α ICOHP (see above). The fact that almost the entire d block is occupied, including the Fe-Fe antibonding states at the top, also plays a large role. The α ICOHP, which was smaller than β to start with due to the spatial contraction of the α spin orbitals, is weakened further by the population of antibonding states, in contrast to those of the β spin sublattice which lie above ε_F . Despite the weaker α interactions, the strengthening of the nearest-neighbor interactions in the β sublattice is sufficient to result in an ICOHP value for ferromagnetic Fe larger than that for the nonmagnetic structure.

We can also demonstrate the differential spatial extents of the α and β spin sublattices by a plot similar to those of Figures 6 and 8. Within the linear muffin-tin orbital (LMTO) calculations, the electron density is the only physically meaningful quantity accessible. However, since the α and β sublattices contain different numbers of electrons, a straightforward plot of $\rho(\alpha) - \rho(\beta)$ does not contain the sought information; rather, this result gives the spin density and shows where in real space the electrons responsible for magnetism are located. In order to see the differences in the spatial extents of the α and β electron densities, we must scale either one or both of them in order to equalize the effective numbers of electrons they contain. Figure 19 shows such a plot, namely the scaled quantity of Equation (10), where n_α and n_β are the total number of electrons in the α and β spin sublattices (5.135 and 2.865, respectively).

$$\frac{n_\beta}{n_\alpha} \rho(\alpha) - \rho(\beta) \quad (10)$$

Just as the α AOs/MOs of O/O₂ were more spatially contracted than the corresponding β AOs/MOs, the α electron density of ferromagnetic Fe is greater near the nucleus, whereas the β electron density is greater in the regions further away from the nuclei, particularly around the nearest-neighbor contacts.

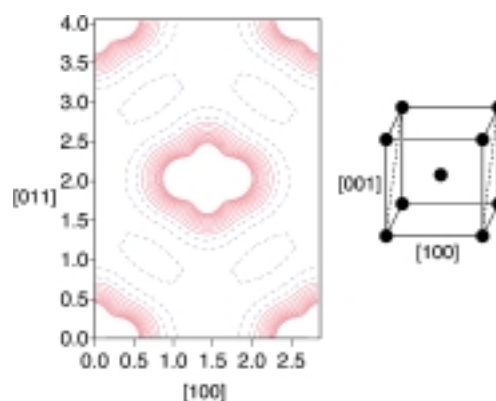


Figure 19. Scaled electron-density difference (defined in [Eq. (10)]) in α -Fe evaluated in the (011) plane of the cubic unit cell. Solid red curves indicate positive values (regions where α spins are dominant), dashed blue curves negative (β spins dominant). The location of the plane in the unit cell is sketched on the right.

Though the similarities in the electronic structural changes on the transition from low- to high-spin states in atoms and molecules were not unexpected, it is rather surprising how analogous the situation is for itinerant-electron ferromagnetism. Spin polarization causes differential shielding of the majority and minority spin species. Majority (α) electrons see a larger nuclear charge, decrease in energy, and become more spatially contracted. The β electrons, better shielded from the nuclear charge by the α electrons, increase in energy and become more diffuse.

Before closing the iron section, we would like to comment on the localized/delocalized antagonism in the understanding of transition-metal ferromagnetism. The alert reader might have noticed that we have started by using a fairly localized basis set—the short-ranged, tight-binding, linear muffin-tin orbitals (TB-LMTO)—in order to generate totally delocalized crystal orbitals (Bloch functions) that spread over the entire crystal. In the spirit of Stoner’s ideas, the valence electrons responsible for ferromagnetism in iron are also completely delocalized.

Our interpretation of itinerant-electron ferromagnetism as an essentially chemical phenomenon retrieves the localized picture from the delocalized wave functions. The driving force for ferromagnetism lies in the *local* antibonding character of the states around ε_F . It comes as no surprise to realize that the strength of the covalent bonding interactions between Fe atoms decays rapidly with interatomic distance. For example, the nearest-neighbor bonds (2.485 Å, ICOHP = −1.527 eV) in α -Fe are significantly stronger than the next-nearest-neighbor bonds (2.870 Å, ICOHP = −0.658 eV). When these two energies are related using a simple distance power law—as done for the molecular field by Weiss—an exponent of 5.8 arises, almost coincident with Weiss’s experimental exponent of 6.0. In our view, there is a *local* source for the delocalized ferromagnetism.

4.4. Cobalt and Nickel

α -Fe is, of course, only one of the three ferromagnetic transition metals. When we go from Fe to Co or Ni, in addition

to increasing the number of valence electrons, the structure itself changes from bcc to fcc. This structural change alters the shapes of the DOS and COHP curves and the presence of additional d electrons moves ϵ_F up in both curves. Although the crossover point from bonding to antibonding in the M-M COHP curve of the fcc structure comes somewhat later than that in the bcc structure (discussed in greater detail below), the presence of the extra d electrons raises ϵ_F enough such that it lies in strongly antibonding states. Once again there is a driving force for the onset of magnetism, and the spin polarization process results in a net stabilization.

The spin-polarized DOS and COHP curves of ferromagnetic Ni (calculated $\mu = 0.62 \mu_B$, precisely matching the experimental value), shown in Figure 20, displays features similar to those of Fe (Figure 17). Whereas the α states

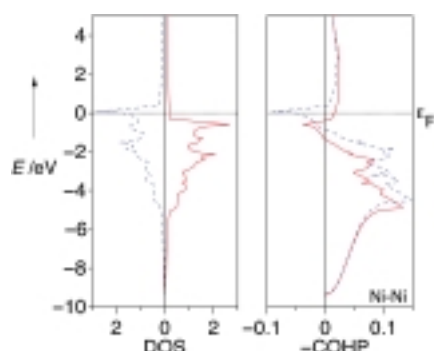


Figure 20. DOS and Ni-Ni COHP curves for ferromagnetic Ni. In each plot, the solid red/dashed blue line corresponds to the α/β spins. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

decrease in energy and are filled to just above the top of the d block, the β states increase in energy and the d block is partially empty. The contracted α states are involved in weaker interactions between nearest neighbors than the more diffuse β states. The difference in energies between the two spin sublattices (the exchange splitting) is smaller for Ni than for Fe, as is the size difference between the two COHP curves. The reason the α and β spin sublattices are so similar is the magnetic moment of Ni ($0.62 \mu_B$) is quite small when compared to that of α -Fe ($2.27 \mu_B$). The similarly small resulting differential-shielding effects are reflected in small exchange splittings and little difference in the spatial extents of the α and β spin sublattices. The magnetic moment in Ni is so small because the 3d block is almost full—there is insufficient room to accommodate a significant excess of α states. In keeping with the small magnetic moment and little difference between the α and β sublattices, the increase in the Ni–Ni bond strength with the onset of magnetism is only about half a percent: the Ni–Ni ICOHP increases from -0.991 to -0.996 eV per bond.

As we expect, Co, with its calculated magnetic moment of $1.60 \mu_B$ (experimental value: $1.74 \mu_B$ ^[33]), lies somewhere in between Fe and Ni. The differences between the α and β DOS and COHP curves (not shown) are smaller than those in Fe but larger than in Ni. The Co–Co ICOHP increases from -1.177 to -1.224 eV per bond upon spin-polarization, or about 4%.

To recap, Co and Ni show behavior similar to that of α -Fe, but to a lesser degree:

1. In the nonmagnetic calculations, ϵ_F falls in a region of significant M-M antibonding.
2. Spin polarization results in the α/β levels decreasing/increasing in energy.
3. Spin polarization leads to differing spatial extents of the α and β spin sublattices: α becomes more contracted while β becomes more diffuse.
4. Spin polarization removes M-M antibonding levels from the vicinity of ϵ_F .

4.5. Other 3d Transition Metals

The discussion has led us to a point where we can comfortably assert that ferromagnetism is associated with the presence of M-M antibonding states at ϵ_F . This assertion is easily tested by examining the M-M COHP curves for the entire first transition series. These are presented, along with the corresponding DOS curves, in Figure 21. All calculations

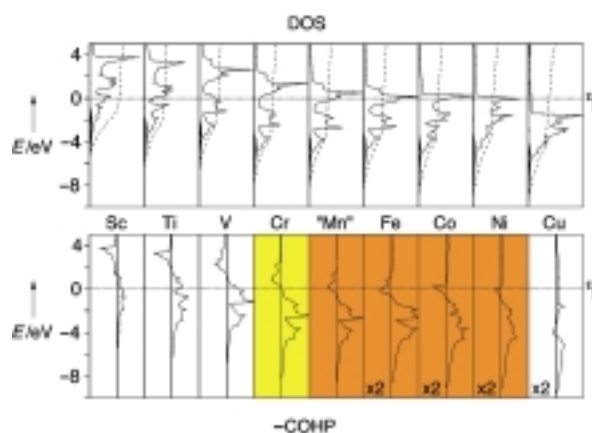


Figure 21. Non-spin-polarized DOS (top) and M-M COHP curves (bottom) for the first-row transition metals. The electronic structure of Mn was calculated in a bcc structure with a lattice constant of $2.88 \text{ \AA}$. The shaded area in each DOS curve indicates the contribution of the M 4s states. All curves are on the same horizontal and vertical scales except for the M-M COHPs in Fe, Co, Ni, and Cu, which have been multiplied by a factor of two. The curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

were carried out using the experimental structures of the metals (taken from ref. [37]) with the exception of manganese. The 29 atom crystallographic unit cell of α -Mn does not lend itself to high-level electronic structure calculations well, so we need a simplifying model. Since both the neighbors of Mn in the periodic table (Cr and Fe) adopt bcc structures, we use here a bcc structure with a lattice constant halfway in between those of Cr and Fe ($2.88 \text{ \AA}$). The density of the structure by this model is only 2% lower than that of α -Mn itself. We will refer to this pseudo-manganese structure as “Mn”. All calculations in Figure 21 were carried out in a non-spin-polarized mode.

In the early transition metals, such as Ti, ϵ_F is low enough in the COHP curve that it falls in a region of M-M bonding. In

the early transition metals there is thus no driving force for ferromagnetism! By Cr, ε_F has moved up far enough in the COHP curve that it occurs at the crossover point between bonding and antibonding. The nonbonding nature of the states at ε_F in Cr may well be responsible for the observed spin-density-wave antiferromagnetism, but we will not examine that in detail here. From “Mn” to Ni, ε_F lies in states which are clearly M-M antibonding. As we know, Fe, Co and Ni are all ferromagnetic, and our calculations predict that “Mn”, if it existed at low temperatures, would also be ferromagnetic; the calculated moment is $0.99 \mu_B$.^[38]

These results seem quite straightforward and clear: the presence of M-M antibonding states at ε_F in the nonmagnetic electronic structure of a transition metal is a sign that indicates this metal would “prefer” to be ferromagnetic. We believe that these M-M antibonding states are not only indicative of an instability with respect to spin polarization, but also that they are *causative*. That is, the antibonding interactions are actually responsible for the instability and drive the system to ferromagnetism.

4.6. Iron Revisited: the Face-centered Cubic Phase

Before examining the second- and third-row transition metals, there is a legitimate question on the first-row metals to answer: Why is the face-centered cubic phase of iron not ferromagnetic?

In order to facilitate comparison with the α -Fe results, we have chosen to calculate the electronic structure of fcc Fe with a lattice constant of 3.51 Å. This gives Fe-Fe nearest-neighbor distances identical to those in α -Fe. While this is admittedly an underestimation of the lattice constant (the bond lengths for the twelve coordinate fcc structure should be larger than those in the eight-plus-six coordinate bcc structure), it does allow direct comparison of the relative Fe-Fe bond strengths in the two structures. The DOS and Fe-Fe COHP curves for fcc Fe with this lattice constant are shown in Figure 22. Clearly, the shape of the DOS of fcc Fe is considerably different from that of α -Fe (Figure 14). The characteristic three-peaked bcc DOS has been replaced with the considerably more uniform DOS typical for fcc metals (compare too with the DOS curves for

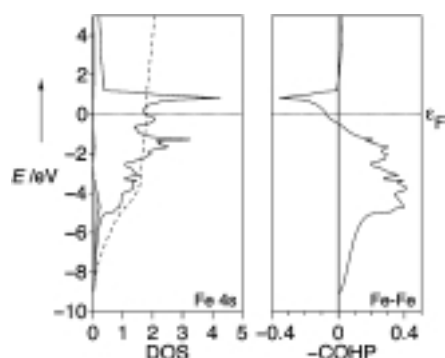


Figure 22. DOS and Fe-Fe COHP curves for nonmagnetic fcc Fe. The shaded region and dashed line in the DOS curve corresponds to the projected DOS of the Fe 4s orbital and its integration, respectively. All curves have been shifted in energy so that ε_F , indicated with a horizontal dotted line, lies at 0.0 eV.

Ni and Cu in Figure 21). In addition, ε_F no longer lies in a strongly antibonding peak in the COHP curves! In this fcc structure ε_F lies on the weakly antibonding shoulder of the Fe-Fe antibonding states. The Fe-Fe ICOHP is -1.519 eV per bond, intermediate between those of nonmagnetic and magnetic α -Fe. Since the number of electrons is the same in the bcc and fcc structures, the antibonding COHP peak lying above ε_F implies that the crossover point from bonding to antibonding in the fcc structure has been shifted to higher electron filling. Face-centered cubic iron is not ferromagnetic because the states around ε_F are only weakly antibonding—the driving force for ferromagnetism is just not strong enough. In fact, the almost nonbonding character of the states around ε_F reminds us strongly of the bonding situation in Cr, which is antiferromagnetic. Further: when embedded in a Cu matrix, fcc Fe is known to be antiferromagnetic at low temperatures,^[39, 40] leading us to expect that bulk fcc Fe would also be antiferromagnetic if it were stable at low temperatures. The presence of ε_F in a region of nonbonding states may well be a sign for antiferromagnetism.

In order to make fcc Fe ferromagnetic, ε_F must be moved into the strongly M-M antibonding states by adding more electrons to the system. This is precisely what happens in iron-rich fcc alloys, such as Fe₃Pd, to be discussed later.

4.7. The 4d and 5d Transition Metals

There is another question about ferromagnetism in the transition metals: Why does it only appear in the first row? For example, why are palladium and platinum, which have the same structure and same number of valence electrons as nickel, not ferromagnetic?

It is reasonable to assume that the second- and third-row transition metals have COHP curves similar in shape to those of the corresponding first-row elements. This assumption was confirmed by a series of calculations (not shown here). The early transition metals of the second and third rows are very similar to those of the first row: ε_F lies in M-M bonding states low in the COHP curve and there is no driving force for magnetism. However, at the end of a series, we would expect ε_F to lie in the antibonding levels at the top of the d block. For example, given that Pd and Pt are both isostructural and isoelectronic (referring only to the number of valence electrons) to Ni, this qualitative analysis leads to the tentative prediction that Pd and Pt should be ferromagnetic. This is, evidently, not the case. To explain this puzzle, we shall focus our attention on Pd; similar arguments apply to all other late second- and third-row metals.

The DOS and Pd-Pd nearest-neighbor COHP curve for elemental Pd is shown in Figure 23. As we predicted above, ε_F falls in a region of Pd-Pd antibonding, just as it did in Ni. In fact, aside from the somewhat broader and more uniform d block, the electronic structure of Pd is very similar to that of Ni (Figure 21). It seems like Pd should be ferromagnetic.

In order to understand why Pd is more stable in a nonmagnetic state, it is most convenient to computationally force it into a ferromagnetic state and see why that state is unstable. However, any reliable, self-consistent, spin-polar-

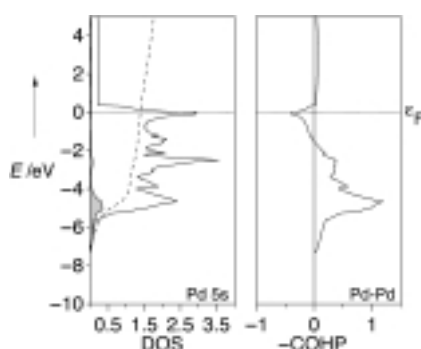


Figure 23. DOS and Pd-Pd COHP curves for Pd. The shaded region and dashed line in the DOS curve corresponds to the projected DOS of the Pd 5s orbital and its integration respectively. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

ized calculation of the electronic structure of Pd which starts from a magnetic state will eventually shed the magnetic moment and become nonmagnetic. A straightforward trick to overcome this problem is to start from the self-consistent potential for nonmagnetic Pd, set the magnetic moment of Pd to some small number, and carry out a single iteration of the self-consistency cycle. This is not an optimal solution, simply because the frozen potential here does not correspond to the magnetic state. We solve this problem by carrying out what we call *spin-locked* calculations. Starting from the potential of the nonmagnetic state, we introduce a magnetic moment and carry out two normal self-consistency iterations. This allows the potential to adjust to match the magnetic moment, but it will lower the (unstable) moment itself. The moment is then reset back to the starting value and another two cycles are run. This process is repeated until the potential stops changing. What we are left with in the end is a *fully self-consistent electronic structure with a locked magnetic moment*.

Recall that the driving force for ferromagnetism was the removal of M-M antibonding states from the vicinity of ϵ_F as a result of the exchange splitting. The exchange splitting itself—as well as the differing spatial extents of the two spin sublattices—arises because of differential shielding of the α and β electrons. In other words, the exchange splitting provides a measure of the extent of differential shielding. Plots of the calculated exchange splitting versus the spin-locked magnetic moment for Ni, Pd, and Pt in the range $0.0 \mu_B \leq \mu \leq 0.5 \mu_B$ (not shown here) are essentially linear. Least-squares fits to the data give slopes of 0.66, 0.47, and $0.45 \text{ eV} \mu_B^{-1}$ for Ni, Pd, and Pt, respectively; the exchange splitting in Ni increases much more quickly with increasing magnetic moment than that in Pd. Clearly, Pt is very similar to Pd and, at least in terms of the exchange splittings, Ni responds more dramatically to the presence of a magnetic moment.

Another difference between Ni and Pd can be seen by examining the spin-polarized M-M COHP curves from the spin-locked calculation with $\mu \equiv 0.5 \mu_B$, shown in Figure 24. The difference in magnitude of the Ni α and β COHP curves, as well as the exchange splitting between the two spin sublattices, is clearly visible. For Pd, on the other hand, the α and β COHP curves are very similar in size and the exchange splitting is quite small. The spin-locked magnetic moment

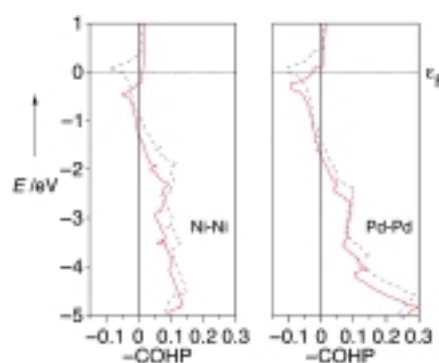


Figure 24. The M-M COHP curves of spin-locked ($\mu \equiv 0.5 \mu_B$) Ni (left) and Pd (right) within a small energy window around ϵ_F . In each pane the solid red/dashed blue line corresponds to the α/β spins. All curves have been shifted so that $\epsilon_F = 0.0 \text{ eV}$.

does force the α and β sublattices apart in energy. However, this shift is small and there is little or no change in the spatial extents of the spins.

In Figure 25 is another difference between transition series: the changes in the M-M ICOHP values as the spin-locked moment increases. Here we see that the Ni-Ni ICOHP decreases considerably faster (and the bond strength goes up more quickly) than those in Pd or Pt, which are again similar to each other. Although the M-M bonds strengthen in all three metals with increasing magnetic moment, the ICOHP for Ni increases more rapidly. Once again, Ni seems to be perturbed more by the presence of a magnetic moment than either Pd or Pt.

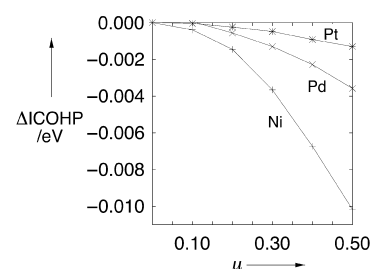


Figure 25. Changes in M-M ICOHP values with increasing spin-locked magnetic moment for Ni, Pd, and Pt.

For the second and third row transition metals, the presence of a magnetic moment does not alter the bonding significantly. Thus, although the antibonding states at ϵ_F may “push” towards a ferromagnetic structure, its formation does not result in a large enough exchange splitting to remove those states and the metals remain nonmagnetic.

The differences between Ni and Pd or Pt may be understood in the same way as we explained the differences between O_2 and S_2 or Se_2 . The first-row transition metals have a special set of orbitals: the 3d orbitals. These are not shielded by any symmetry-similar orbitals in the core and are thus fairly contracted. Small changes to the shielding of the 3d orbitals, caused by spin polarization, give rise to comparably large changes in their energies and spatial extents. On the other hand, Pd and Pt have d functions in the core which help to screen their valence d orbitals. The small perturbations

from spin polarization do not have such a dramatic effect upon these well shielded orbitals. Consequently, the higher transition metals will not become ferromagnetic.

Here is a chemical analogy: We have seen that the special behavior of the light main-group elements, such as carbon, nitrogen, and oxygen, with respect to both magnetism and their “chemistry” can be traced back to the “missing” 1p orbital. Because of that, the susceptibility of these atoms to spin polarization is significantly enhanced. In these elements the 2s and 2p orbitals have similar spatial requirements. This has well known consequences for element–element multiple bonding, organic chemistry, and all the rest.

The situation for iron (and cobalt and nickel) is somewhat similar. Because of the “missing” 2d orbital, spin polarization does lead to large exchange splittings and a strengthening of metal–metal bonding (easily seen in the COHP curves). In this respect, the exceptional finding of ferromagnetism within the transition metals may be looked upon as analogue of the special situation of carbon chemistry within chemistry as a whole.

4.8. Ferromagnetism and Chemical Hardness

Using the standard definition of the term [Eq. (9)], the chemical hardness η of a metal is always zero because it has no gap between occupied and unoccupied levels.^[30] However, hardness can be determined more rigorously from the first derivative of the chemical potential with respect to the number of electrons N . Since the chemical potential in metals is identical with the Fermi energy, we can express the chemical hardness of a conductor as Equation (11), where N_0 is the number of valence electrons in the neutral system and the subscript V indicates that the derivative is being taken with a frozen potential.

$$\eta = \frac{1}{2} \left(\frac{\partial \varepsilon_F}{\partial N} \right)_{V, N_0} \quad (11)$$

Equation (11) allows us to simply determine the chemical hardness of a transition metal from the slope of a plot of $\varepsilon_F(N)$ versus N at $N=N_0$.^[41] Such a plot is shown for both the nonmagnetic and magnetic “forms” of α -Fe in Figure 26. It is clear that ε_F depends more or less linearly on N in the region around N_0 ($N_0=8$ for α -Fe) and that the slope of the curve increases with the onset of magnetism. A linear least-squares

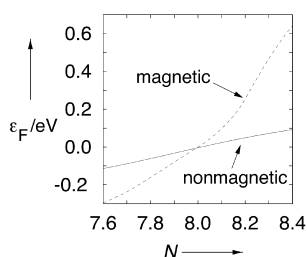


Figure 26. Calculated ε_F versus N curves for nonmagnetic (solid line) and magnetic (dashed line) α -Fe in the vicinity of N_0 (N_0 , the number of valence electrons, is 8.0 in Fe). Both curves have been shifted so that $\varepsilon_F(N_0)=0.0$ eV.

fit of the points between 7.9 and 8.1 valence electrons gives η values (half the calculated slope) of 0.132 eV and 0.428 eV for nonmagnetic and magnetic α -Fe, respectively. The chemical hardness of iron more than triples upon spin-polarization! Analogous increases in η are observed for Co (0.198 $\rightarrow$ 0.384 eV) and Ni (0.115 $\rightarrow$ 0.235 eV). In contrast to these drastic results, the η values of Pd in its nonmag-

netic (0.202 eV) and spin-locked ($\mu \equiv 0.5 \mu_B$; 0.256 eV) “forms” are not too different. Compared with the 0.115 $\rightarrow$ 0.220 eV hardness change for spin-locked Ni ($\mu \equiv 0.5 \mu_B$), the value of η changes very little when Pd is forced to be magnetic.

To further explore the connection between chemical hardness and magnetism, the hardnesses of all of the transition metals were calculated (Table 2). These hardnesses, based upon nonmagnetic calculations, reveal a curious fact: The

Table 2. Calculated chemical hardness values [eV] for the elemental metals of all three transition series. The results were derived from least-square fits of $\varepsilon_F(N)$ plots calculated for the nonmagnetic “forms”. Mn was calculated in the hypothetical bcc structure, discussed above.

M	η	M	η	M	η	M	η
Sc	0.280	Ti	0.528	V	0.282	Cr	0.723
“Mn”	0.165	Fe	0.132	Co	0.198	Ni	0.115
Y	0.481	Zr	0.509	Nb	0.368	Mo	0.862
Tc	0.544	Ru	0.611	Rh	0.402	Pd	0.202
La	–	Hf	0.718	Ta	0.422	W	1.077
Re	0.698	Os	0.820	Ir	0.552	Pt	0.252

only metals with hardness values below 0.2 eV are those that are ferromagnetic! In addition to this, *all* of the ferromagnetic metals have $\eta < 0.2$ eV! In other words, for all transition metals a necessary and sufficient condition for ferromagnetism is Equation (12)

$$\eta < 0.2 \text{ eV} \quad (12)$$

The same relation holds for all of the ferromagnetic alloys we will discuss below (FeNi₃, Fe₃Pd, FePd₃, and MnSb) with the single exception of FePd. Though we are certain that there are other exceptions to this rule that lurk in the myriad of ferromagnetic (and nonmagnetic) alloys known, it is quite remarkable and surprising that such a simple rule is able to accurately describe and predict ferromagnetism in all of the transition metals (including borderline cases such as Co and Pd) and many ferromagnetic alloys.

At a qualitative level, we feel that it is fairly straightforward to understand this connection between chemical hardness and ferromagnetism by, again, falling back on the chemistry of atoms and molecules. An atom or molecule with a low chemical hardness tends to have a high polarizability, that is, it is easy to rearrange its electronic charge distribution. As we have shown in detail for α -Fe, a redistribution of charge density is required for the transition from the nonmagnetic to the magnetic state. These electron shifts are easier to realize in soft rather than in hard metals. The origin of the mysterious 0.2 eV quantity in Equation 12 is not yet clear and is still under investigation.

Within the definition of Equation 11, the chemical hardness of a metal is very sensitive to the value of the density of states at ε_F . At large values of DOS(ε_F), small changes to the number of electrons do not significantly affect the position of ε_F ; the metal will be chemically soft. A plot (not shown) of η versus DOS(ε_F) can be fit very satisfactorily with the function $\eta = 6.53/\text{DOS}(\varepsilon_F)$. However, since the DOS at ε_F alone cannot account for ferromagnetism (see the earlier discussion about

the Stoner criterion in Section 2.3), there must be some other essential physical quantity carried within the chemical hardness concept. What that is remains unclear at this point.

5. Interlude: Modern Developments in the Physics Community

Although Stoner's arguments have dominated the reasoning of many physicists within the last five decades, there have been other, more modern ideas. Here we give a short overview of two of the more prominent directions of research.

5.1. The Hubbard Model and Its Relatives

The Hubbard model^[42] for the electronic structure of solids with strong electron–electron interactions has been quite successful at explaining the anomalous behavior of Mott insulators.^[43] In this simple, powerful, but mathematically awkward model, there is a one-electron (hopping) energy term H_{ij} competing, as a function of the band-width parameter W (ΔE_{BW} in Figure 11), with an electron–electron repulsion parameter U .

The Hubbard model has been widely applied to ferromagnetic systems with flat bands.^[44, 45] Simply speaking, our qualitative treatment of rare-earth ferromagnetism in Figure 11a was intuitively based on the assumption of a repulsion parameter U which is much larger than the small bandwidth W . The scenario in Figure 11b corresponds to the opposite limit, producing an ordinary, half-filled metallic band. In order to understand itinerant-electron ferromagnetism (as observed in the transition metals) in more detail, extensions of Hubbard's model are required. A number of these extensions have also been pursued with varying degrees of success.^[46, 47] In an exhaustive series of publications, the impact of adding various additional interactions to the Hubbard model has been studied by Hirsch and coworkers.^[48–54] Applications of the Hubbard model to metallic ferromagnetism have been recently reviewed.^[55]

The problem with applying many of these Hubbard or Hubbard-like models to the understanding of ferromagnetism in transition metals and their alloys is that they presume systems have either a single band or a set of degenerate bands. While these simplifications are made in order to make the models exactly solvable (or as close as possible), much of the fundamental physics is lost. The elemental transition metals do *not* have bands which are either flat or purely degenerate. We feel that it is preferable to use a model which, although not exact, contains at least the correct behavior of the metallic bands.

5.2. First-Principles Calculations

Building upon the foundations of the Thomas–Fermi model for the electronic structure of atoms,^[56–59] Hohenberg and Kohn developed the fundamental underpinnings of density-functional theory (DFT) in 1964.^[60] In the following

year, Kohn and Sham provided a set of equations which allowed this new theory to actually be applied to determine the electronic structure of real systems; in addition they introduced the local density approximation (LDA).^[61] Kohn and Sham also realized the intimate connection between their new theory and the $X\alpha$ method developed earlier by Slater.^[62] In 1972, von Barth and Hedin generalized both the density-functional theory itself and the local density approximation to systems with unpaired spins.^[63]

Just as it did for the body of solid-state theory, DFT (particularly in its spin-polarized form) revolutionized the study of ferromagnetism. Given the enormous quantity of literature in the area, we here provide only an overview and a few highlights. For a comprehensive overview of recent first-principles studies of ferromagnetism and antiferromagnetism, see ref. [64] and references therein.

In 1975, Vosko and Perdew proposed a Stoner-like model to be used to approximate the magnetic susceptibilities of metals based upon their ground-state properties.^[65] This model was extended to transition metals by Gunnarsson by using a set of approximate wave functions.^[66] In 1977, Andersen et al. presented a systematic study of the electronic structure of iron and a number of other transition metals, as well as an approximation that allowed the parameters of the Stoner model to be extracted from their results.^[18] That same year a paper, arguably among the most influential in the field, was published by Janak.^[19] Janak, working from the model presented by Vosko and Perdew,^[65] extracted the Stoner parameters for all of the first- and second-row transition metals, as well as many simple metals (see Figure 2) from their electronic structures as calculated within spin-density functional theory. In 1978, Moruzzi, Janak, and Williams coauthored a book which compiled the electronic structures of the metals.^[67]

Problems with the local spin-density approximation (LSDA) were discovered in 1981 by Kübler, who realized that, at least within the augmented spherical-wave (ASW) method, the calculated energy of antiferromagnetic face-centered cubic iron was lower than that of the ferromagnetic body-centered cubic phase.^[68] Wang et al., using the linear-augmented plane-wave (LAPW) method, generalized this result and concluded that the LSDA did not predict the correct ground state for iron.^[69] Four years later, Bagno et al. demonstrated that the introduction of gradient corrections to the LSDA removed these problems.^[70]

In a series of papers published in the late 1980s and early 1990s, Moruzzi, Marcus, and co-workers produced a comprehensive study of the structural and magnetic properties of the 3d and 4d transition metals using a fixed spin-moment procedure within the ASW method. By holding the magnetic moment fixed and iterating until self-consistency was reached, Moruzzi et al. were able to study the potential-energy surfaces for both the onset of ferromagnetism in the first-row^[71, 72] and some second-row^[73] transition metals. The energetic circumstances of antiferromagnetism in both the 3d^[74] and 4d^[75] metals were also studied and discussed.

In this Review, we have essentially followed the density-functional theory route. Indeed, our findings are all based

upon the results of spin-density-functional calculations (see Appendix A). While density-functional theory does provide quantitative answers in many—but not all—cases, its advantage is, however, mostly due to it being an orbital theory, making a chemical interpretation easy. This is the goal of our approach, extending a theoretical track which originated within theoretical physics and making it compatible with related ideas of theoretical chemistry (see Appendices A.2 and B).

6. Ferromagnetism in Alloys

With reference to Section 4, we will now demonstrate that the same ideas developed to explain ferromagnetism in metallic elements can be applied also to metallic alloys.^[76] Due to restrictions imposed by our computational methodology and resources, we limit our attention to ordered binary alloys; we are confident that this discussion applies to both disordered structures and alloys containing more than two elements.

6.1. A Model for Spin Polarization in Binary Systems

While Figure 12 provided the qualitative underpinnings necessary to interpret the densities of states of magnetic transition metals, it requires some modifications in order to understand those of alloys. The following model is intended to serve for a better understanding in more complicated systems; the impatient reader may go directly to the next Section, which offers realistic calculations without assumptions.

Consider the alloy $M_xM'_y$. Since M and M' are different types of atoms, their projected densities of states will certainly have different sizes and bandwidths. These differences and their effects upon the spin-polarization process are sketched qualitatively in Figure 27. A number of assumptions and simplifications went into this. Listed in order of increasing severity they are:

- We are using a rigid-band model: The forms and compositions of the crystal orbitals do not change upon spin polarization (that is, the α - and β -DOS curves have exactly the same shape and size but occur just at different energies).
- The shifts in the energies of the α and β sublattices upon spin polarization (exchange splittings) are assumed to be the same in panes b) and d).
- The exchange splittings in the DOS of M and M' are the same.

Despite this massive oversimplification of a truly complicated problem, the DOS curves in Figure 27b and 27d reveal several important findings about magnetism in alloys. Unlike the simple elemental transition metals, where each atom is identical, the different atom types in alloys do not necessarily carry the same local magnetic moments. For example, in Figure 27b, the difference between the occupations of the α and β sublattices of M—which determines the number of unpaired electrons on M—is four boxes, while that between

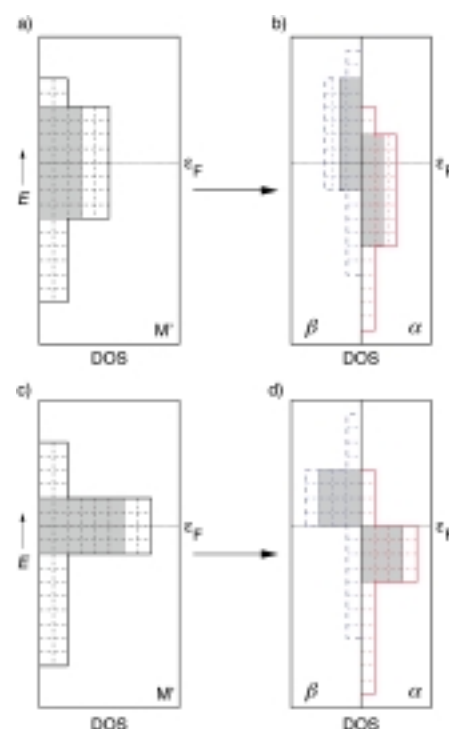


Figure 27. Qualitative DOS curves for a binary transition-metal alloy $M_xM'_y$. In a) and b) are the DOS and spin-polarized DOS of an alloy where the bandwidth of M' is one-half that of M. In c) and d) are the DOS and spin-polarized DOS of an alloy where the bandwidth of M' is one-quarter that of M. In all four panes, the horizontal dotted line indicates the position of the Fermi level (ϵ_F) and the shaded region corresponds to the M' projected DOS. The dashed grid superimposed on the DOSs is included to facilitate the counting of states.

the α and β sublattices of M' is six boxes. Thus M' has a higher local magnetic moment than M.

In the second case, where the distribution of M' states is half as broad and their contribution to the DOS around ϵ_F is larger (Figure 27d), the local moment on M is still determined by the four box difference, but all of the M' α states are occupied while all of the M' β states are empty. The local magnetic moment of M', calculated from a differential occupation of twelve boxes, is thus twice as large as it was before. This observation may be generalized to give a rule of thumb for transition metal alloys: Those atoms with the largest contributions to the nonmagnetic DOS around ϵ_F will also have the largest local moments upon spin-polarization.

6.2. Alloys Between Ferromagnetic Metals: Realistic Calculations

Our archetype for a binary alloy between two ferromagnetic transition metals is FeNi_3 . This alloy crystallizes in the AuCu_3 structure,^[77] an fcc arrangement of nickel atoms in which every fourth Ni has been replaced by Fe in an ordered fashion (Figure 28). The lattice constant (3.552 Å) is only

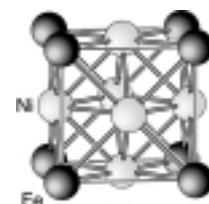


Figure 28. The unit cell of FeNi_3 with the AuCu_3 structure.

slightly larger than that of elemental Ni (3.524 Å). The experimental magnetic moment of FeNi₃ is 1.18 μ_B .^[78] Neglecting the fact that FeNi₃ is a structurally ordered alloy, its valence-electron concentration (9.5 electrons per atom) allows us to think of it as either a heavily electron-enriched fcc Fe or a slightly electron-poor fcc Ni.

As we did with α -Fe, we start by examining the results of a nonmagnetic calculation of FeNi₃ (Figure 29). One might expect that FeNi₃ is electronically similar to elemental Ni and, indeed, its DOS is almost superimposable on that of Ni (Figure 21). The major difference is that ε_F is located in a sharp, narrow DOS peak at the top of the d block. The Fe

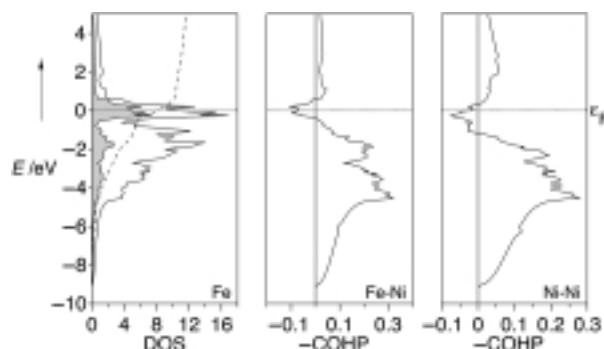


Figure 29. Calculated DOS, Fe-Ni, and Ni-Ni COHP curves for nonmagnetic FeNi₃. The shaded region and dashed line in the DOS curve corresponds to the projected DOS of the Fe atom and its integration, respectively. All curves have been shifted in energy so that ε_F , indicated with a horizontal dotted line, lies at 0.0 eV.

states (projected DOS in Figure 29) are spread almost evenly throughout the DOS except for the sharp peak at ε_F , which is almost half derived from Fe. Since only one quarter of the atoms are Fe, this is a quite large contribution. Given that Ni is more electronegative than Fe (the Pearson absolute electronegativities are 4.40 eV and 4.06 eV respectively),^[30] we would have expected the upper regions of the d block to be mostly Fe. The chemical hardness of FeNi₃, corrected for the presence of four atoms in the unit cell, is 0.182 eV and lies comfortably below the proposed cutoff value for the appearance of ferromagnetism (0.2 eV).

We now turn to the COHP curves of Figure 29. The Fe-Ni and Ni-Ni COHP curves are very similarly shaped and have ICOHP values of -1.130 and -0.961 eV per bond, respectively. The sharp peak at the top of the d block is, as expected, strongly antibonding for both Fe-Ni and Ni-Ni bonds. As in the elements, these strongly antibonding states at ε_F give rise to an instability with respect to a ferromagnetic distortion in FeNi₃.

A spin-polarized calculation of its electronic structure results in an average spin moment of 1.182 μ_B , in quantitative agreement with the experimental data. The DOS and COHP curves for magnetic FeNi₃ are presented in Figure 30. In addition to being shifted in energy, the α and β DOS curves are also quite differently shaped. The α DOS is almost uniform in shape—very similar to that in magnetic Ni (Figure 20)—while the β DOS retains a sharp peak at the top of the d block. Although the Fe states are spread

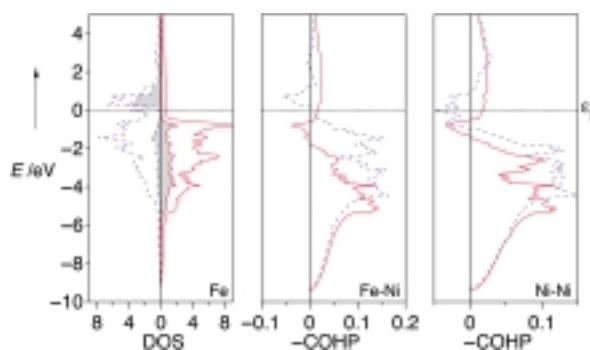


Figure 30. Calculated DOS, Fe-Ni, and Ni-Ni COHP curves for magnetic FeNi₃. The shaded region in the DOS curve corresponds to the projected DOS of the Fe atom. In each plot, the solid red/dashed blue line corresponds to the α/β spins. All curves have been shifted in energy so that ε_F , indicated with a horizontal dotted line, lies at 0.0 eV.

essentially evenly throughout the d block in the α DOS, they remain a major contributor to the sharp peak above ε_F in the β spin sublattice.

Based upon the qualitative picture for the magnetic moments in alloys presented above, we would expect Fe (which makes a large contribution to a set of narrow states at ε_F in the nonmagnetic electronic structure) to have a high local magnetic moment in FeNi₃. This is shown in the calculated local magnetic moments: 2.878 μ_B for Fe and 0.617 μ_B for Ni. As we shall see, the high moment for Fe (as compared to that in metallic iron) is typical in alloys between Fe and other late transition metals. The Ni moment is very similar to that calculated for elemental Ni. The chemical hardness of magnetic FeNi₃ is 0.546 eV, three times larger than in the nonmagnetic calculation.

Based upon the differences in the calculated net charges in the magnetic and nonmagnetic systems,^[79] each Fe transfers approximately 0.09 electrons to the Ni atoms upon spin polarization. This charge transfer, which is not included in the simple model of Figure 27, is in large part due to the fact that the exchange splitting of the Fe states in FeNi₃ is larger than that of the Ni states.

The Fe-Ni and Ni-Ni COHP curves of Figure 30 are analogous to those in the preceding sections: In both sets of COHP curves, the β spin sublattice has stronger interactions than α and the antibonding character of the states at ε_F has been either reduced or removed completely (see Fe-Ni COHP curves). In magnetic FeNi₃, the Fe-Ni and Ni-Ni ICOHPs are -1.114 and -1.105 eV per bond, respectively; spin polarization has weakened the covalent part of the Fe-Ni bonds by 1.4% and strengthened the Ni-Ni bonds by more than 15%. Interestingly enough, the Ni-Ni bonds in magnetic FeNi₃ are even stronger than those in magnetic Ni (ICOHP = -0.996 eV per bond), which may hint towards the driving force to adopt an ordered atomic arrangement. Since there are more Ni-Ni than Fe-Ni bonds, the net result of these changes is an increase in bonding.

Despite the extra complications arising from the presence of two different sorts of atoms in the unit cell, the qualitative features of ferromagnetism in FeNi₃ are similar to those seen in the elemental transition metals; refer to points 1–4 in the discussion of Co and Ni in Section 4.4.

6.3. Alloys Containing a Single Ferromagnetic Metal

Let us now replace one of the ferromagnetic elements with a nonferromagnetic one but remain with a ferromagnetic alloy. One “natural” choice is the iron/palladium system, where alloys are known with average valence electron concentrations of 8.5 (Fe_3Pd), 9.0 (FePd), and 9.5 (FePd_3) electrons per metal atom. Fortunately, all of these phases adopt fcc-like structures, with Fe_3Pd ^[80] and FePd_3 ^[81] crystal-

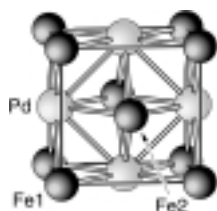


Figure 31. The structural motif of FePd with the AuCu structure.

lizing in the AuCu_3 structure type (Figure 28) and FePd ^[82] in the AuCu structure type (Figure 31). Conflicting claims of substitutional disorder further complicate the structural chemistry of these alloys.

For the sake of brevity, we will discuss the electronic structures of the alloys together. The DOS and COHP curves for both the nonmagnetic and magnetic calculations of Fe_3Pd , FePd , and FePd_3 are presented in Figures 32–37. Numerical details of the interatomic bond strengths (as measured by ICOHP values), calculated magnetic moments and chemical hardnesses are presented in Table 3.

To start with, all three alloys have antibonding Fe-Pd as well as Fe-Fe and/or Pd-Pd interactions at ϵ_F in their unstable

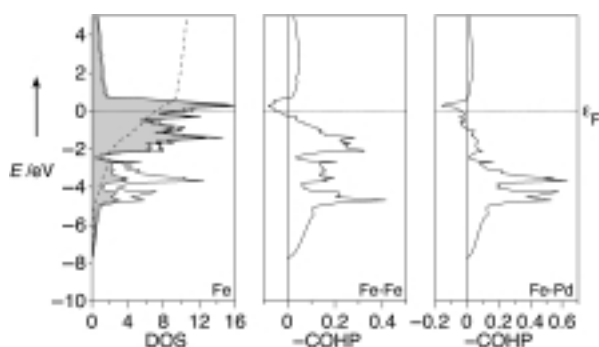


Figure 32. Calculated DOS, Fe-Fe, and Fe-Pd COHP curves for non-magnetic Fe_3Pd . The shaded region and dashed line in the DOS curve corresponds to the projected DOS of the Fe atom and its integration respectively. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

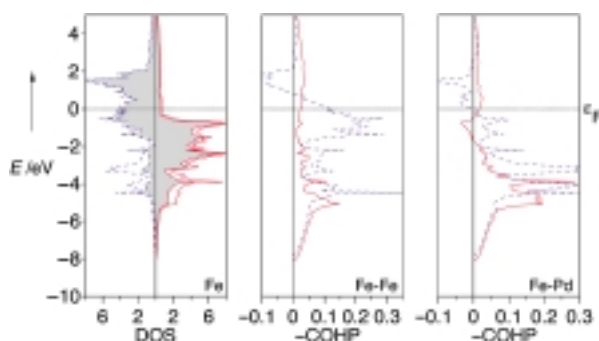


Figure 33. Calculated DOS, Fe-Fe, and Fe-Pd COHP curves for magnetic Fe_3Pd . The shaded region in the DOS curve corresponds to the projected DOS of the Fe atom. In each plot, the solid red/dashed blue line corresponds to the α/β spins. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

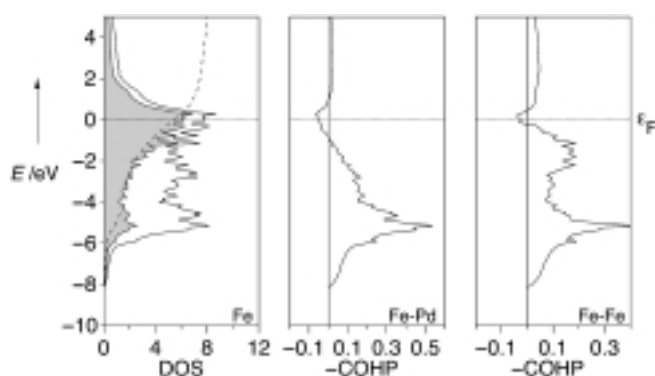


Figure 34. Calculated DOS, Fe-Pd, and Fe-Fe COHP curves for non-magnetic FePd . The shaded region and dashed line in the DOS curve corresponds to the projected DOS of the Fe atom and its integration respectively. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

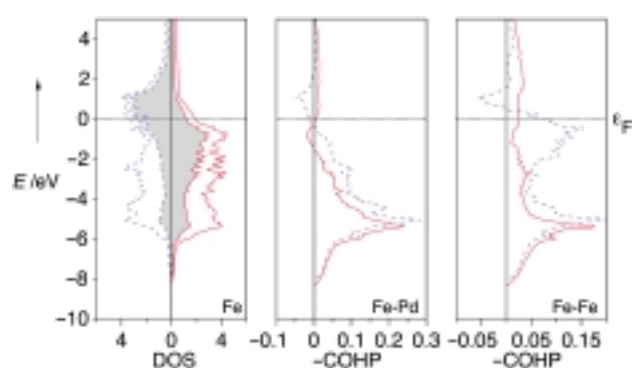


Figure 35. Calculated DOS, Fe-Pd, and Fe-Fe COHP curves for magnetic FePd . The shaded region in the DOS curve corresponds to the projected DOS of the Fe atom. In each plot, the solid red/dashed blue line corresponds to the α/β spins. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

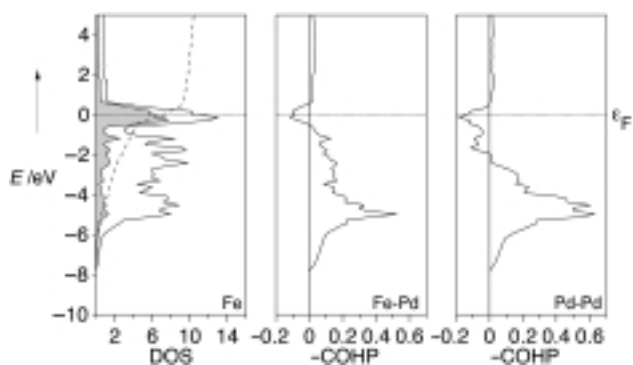


Figure 36. Calculated DOS, Fe-Pd, and Pd-Pd COHP curves for non-magnetic FePd_3 . The shaded region and dashed line in the DOS curve corresponds to the projected DOS of the Fe atom and its integration respectively. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

nonmagnetic “forms” (Figures 32, 34, 36). This is most easily seen for the more electron-rich alloys (FePd and FePd_3) but is seen also for Fe_3Pd . A prediction of ferromagnetism would thus be justified for all three. This prediction is borne out by the results of the spin-polarized calculations (Table 3), which, for Fe_3Pd and FePd_3 , match satisfactorily with the few pieces

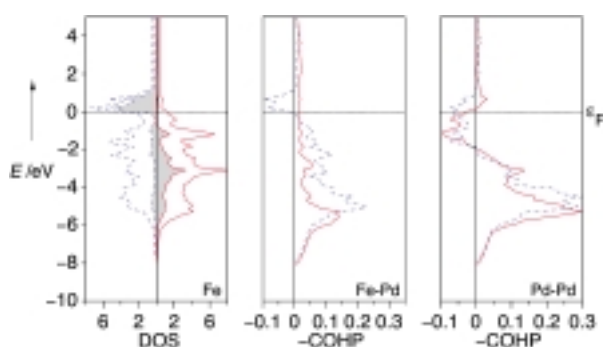


Figure 37. Calculated DOS, Fe-Pd, and Pd-Pd COHP curves for magnetic FePd_3 . The shaded region in the DOS curve corresponds to the projected DOS of the Fe atom. In each plot, the solid red/dashed blue line corresponds to the α/β spins. All curves have been shifted in energy so that ϵ_F , indicated with a horizontal dotted line, lies at 0.0 eV.

of experimental data available^[33, 83] and independent first-principles calculations.^[84, 85] For FePd , our calculations seem to somewhat underestimate the sizes of the individual moments. Nevertheless, there is general agreement that all three alloys are ferromagnetic with approximate moments of $0.3 \mu_B$ for Pd and $2.6 \mu_B$ for Fe; the latter moment is known to rise beyond $3 \mu_B$ with increasing Pd concentration, in good agreement with neutron diffraction data.^[86] We believe more experimental studies, with respect to structure, composition, and order, might be needed for this binary system.

Upon spin polarization, the total energies of Fe_3Pd , FePd , and FePd_3 lower by 1.35, 0.32, and 1.21 eV, respectively. This is paralleled by increases in the overall bonding strengths of 6.3, 1.1, and 1.7 % (calculated by summation of all ICOHP values in the unit cell). With the exception of a single set of interactions (the Fe-Pd bonds in FePd_3), all bonds in these alloys are strengthened by the shifting of antibonding states away from ϵ_F . The loss of Fe-Pd bonding energy in FePd_3 is more than counterbalanced by the increase in Pd-Pd bonding. As expected from the calculations on the pure elements discussed above, the exchange splitting for the Fe states is much larger than that for the Pd states. This large difference in exchange splitting, along with the Fe domination of the states at ϵ_F in all three alloys, leads to the considerably higher (roughly an order of magnitude) magnetic moments of Fe.

It is interesting to note that some spin-polarized COHP curves no longer exhibit antibonding contributions in the α spin sublattice (majority); this can be seen for the Fe-Fe bonds of Fe_3Pd (Figure 33) and FePd (Figure 35) as well as the Fe-Pd bonds of FePd_3 (Figure 37). This curious phenomenon can be understood by considering the M-M distances in these structures.

In Fe_3Pd and FePd , the Fe-Fe distances (2.70 and 2.73 Å, respectively) are considerably longer than those in $\alpha\text{-Fe}$ (2.48 Å), a result caused by the spatial requirements of the large Pd atoms. For the Fe 3d orbitals in the highly contracted α spin sublattice, these distances are effectively larger still. The Cu-Cu COHP curve in Figure 21 demonstrates that, in systems with highly contracted d orbitals, the bonding arising within the s band (which penetrates the entire d block) outweighs the antibonding contributions from the d states at the top of the d block. The result in Cu is a COHP curve which is, in the energy window we examine, almost completely bonding throughout. The Fe-Fe bonds in Fe_3Pd and FePd show the same effects: the Fe 4s states are not significantly perturbed by the spin polarization, and the 3d contributions to the α DOS are highly contracted. The Fe-Pd bonds in FePd_3 (2.72 Å) are not much longer than those in Fe_3Pd (2.70 Å) or FePd (2.68 Å), yet the same phenomenon is observed because of the very high local magnetic moments on the Fe atom ($3.333 \mu_B$). The α 3d states on Fe here are even more contracted than those in Fe_3Pd and FePd .

With the exception of FePd , the chemical hardness values of these alloys also fit our expectations: The η values, which start from less than 0.2 eV in the nonmagnetic “phases”, increase dramatically with the onset of magnetism. The FePd alloy is an exception (and the only one we have found at this point) to our rule that the calculated η of the nonmagnetic “form” of a ferromagnetic substance should be less than 0.2 eV. Upon spin polarization, the hardness of FePd does increase, as expected. Further exploration of this area is necessary.

With a few exceptions, the qualitative characteristics of ferromagnetism in these ordered Fe-Pd alloys follow the rules developed above for both the pure transition metals and FeNi_3 .

6.4. Alloys without Ferromagnetic Metals

Since the early days of metallurgical research on ferromagnets, experimentalists have produced, mostly by trial-and-error synthetic strategies, an astounding variety of ferromagnetic alloys which do not contain any ferromagnetic metals (that is, alloys without Fe, Co, or Ni). Among these phases the Heusler alloys X_2YZ (for example, Cu_2MnAl , which has a Curie temperature of around 600 K^[87]) are probably the most prominent. In the Heusler alloys, the Y atoms form a face-centered cubic lattice while the X and Z atoms occupy all of the tetrahedral and octahedral voids, respectively.^[88]

Here we will examine an even simpler, possibly more fundamental case: MnSb . This material, which has a Curie

Table 3. Calculated values for the Fe/Pd alloys.

	ICOHP [eV]						η [eV]		Local magnetic moments [μ_B]	
	nonmagnetic			magnetic			nonmagnetic	magnetic	$\mu(\text{Fe})$	$\mu(\text{Pd})$
	Fe-Pd	Fe-Fe	Pd-Pd	Fe-Pd	Fe-Fe	Pd-Pd				
Fe_3Pd	−0.925	−0.980	— ^[a]	−0.981	−1.043	— ^[a]	0.184	0.392	2.760	0.294
FePd	−1.078	−0.949	−0.944	−1.086	−0.949	−0.969	0.258	0.408	2.257	0.170
FePd_3	−0.957	— ^[a]	−0.994	−0.937	— ^[a]	−1.023	0.196	0.416	3.333	0.342

[a] Not calculated.

temperature of 600 K,^[89] adopts the NiAs structure type (Figure 38). In this structure, the Mn atoms are octahedrally coordinated by Sb and the Sb atoms are found in a trigonal prism of Mn. The Mn–Sb distance is 2.805 Å. The Mn atoms

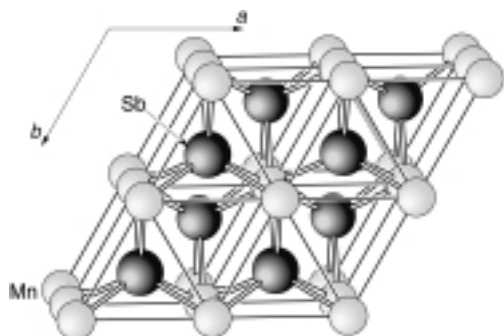


Figure 38. A view along the c axis of the structure of MnSb (NiAs structure type).

form linear chains with Mn–Mn distances of 2.878 Å.^[90] The experimental bulk magnetic moment of $\text{Mn}_{1.09}\text{Sb}$ is $3.25 \mu_{\text{B}}$. Polarized-neutron diffraction experiments reveal a local (Mn-centered) moment of $3.45 \mu_{\text{B}}$.^[91] The difference between these two numbers indicates that each Sb atom carries a moment of about $0.20 \mu_{\text{B}}$ oriented in the *opposite* direction from that on Mn. Strictly speaking, MnSb is thus better described as a *ferrimagnetic* alloy. Our electronic interpretation does not have to be modified in order to cover this additional perturbation though.

The electronic structure of nonmagnetic MnSb is shown in Figure 39. Though the DOS peak, which runs from -5 to 3 eV and contains the Fermi level, is composed of both Mn 3d and Sb 5p states, the region directly around ε_{F} itself is heavily

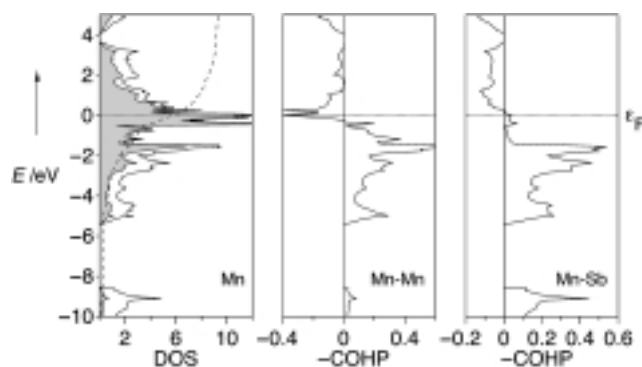


Figure 39. Calculated DOS, Mn-Mn, and Mn-Sb COHP curves for non-magnetic MnSb. The shaded region and dashed line in the DOS curve corresponds to the projected DOS of the Mn atom and its integration respectively. All curves have been shifted in energy so that ε_{F} , indicated with a horizontal dotted line, lies at 0.0 eV.

dominated by Mn. The states arising from the Sb 5s orbitals are partially visible at the bottom of the DOS curve. Because the Mn 3d and Sb 5p orbitals are close to each other in energy and because of the strength of the Mn-Mn interactions, the expected $e_{\text{g}}-t_{2\text{g}}$ splitting of the Mn 3d states is not visible here. All of the occupied states are in the Mn-Sb bonding region, whereas ε_{F} falls in a strongly Mn-Mn antibonding region. The

calculated Mn-Sb and Mn-Mn ICOHP values are -1.349 and -1.081 eV per bond, respectively. The absolute electronegativities of Mn (3.72 eV) and Sb (4.85 eV)^[30] lead us to suspect that Sb should be the “anionic” component in this intermetallic alloy.

The presence of ε_{F} in antibonding states indicates that MnSb would prefer to adopt a ferromagnetic structure. In addition, the large Mn contributions to the DOS near ε_{F} should point to a large local magnetic moment on Mn in the magnetic phase. A spin-polarized calculation of the electronic structure of MnSb gives a magnetic moment of $3.24 \mu_{\text{B}}$. This moment is formed from the $3.37 \mu_{\text{B}}$ (Mn) and $-0.13 \mu_{\text{B}}$ (Sb) local magnetic moments. These results are in satisfying agreement with the experimental values given above, and the small differences easily attributable to the fact that the experimental measurements were carried out on a non-stoichiometric (Mn-rich) compound. We can understand the small size of the local magnetic moment on Sb by realizing that Sb has no magnetically active orbitals; the Sb 4d orbitals are completely occupied and are of low energy and the valence 5s and 5p orbitals are very well shielded from the nucleus and do not have significant exchange splittings. As mentioned above, the large moment on Mn comes about because of the large contribution of Mn to the states near ε_{F} in the nonmagnetic electronic structure (Figure 39).

The DOS and COHP curves of the magnetic “form” of MnSb are shown in Figure 40. The Sb contributions to the total α and β DOS curves (the unshaded regions in Figure 40)

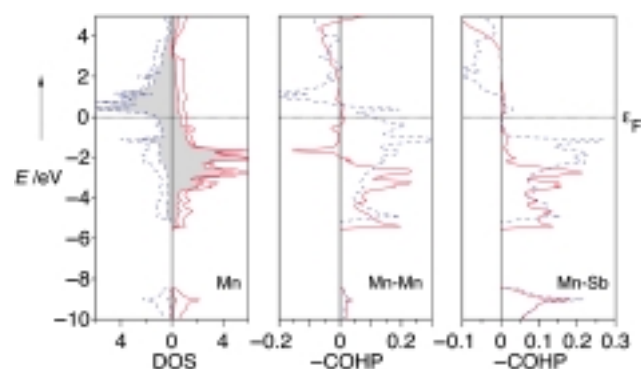


Figure 40. Calculated DOS, Mn-Mn, and Mn-Sb COHP curves for magnetic MnSb. The shaded region in the DOS curve corresponds to the projected DOS of the Mn atom. In each plot, the solid red/dashed blue line corresponds to the α/β spins. All curves have been shifted in energy so that ε_{F} , indicated with a horizontal dotted line, lies at 0.0 eV.

are very similar, as we would expect given that Sb states should not exhibit a large degree of exchange splitting. The spin-polarized DOS of MnSb is qualitatively composed of a nonmagnetic background arising from the Sb states with the magnetic Mn DOS superimposed. This is a useful way of thinking of MnSb itself: ferromagnetic chains of Mn atoms surrounded by an almost nonmagnetic sea of Sb atoms.

The calculated ICOHP values for the Mn–Sb and Mn–Mn bonds in ferromagnetic MnSb are -1.273 and -1.100 eV per bond, respectively. While the Mn–Mn bonds strengthen, as we would expect, the Mn–Sb bonds become considerably *weaker* upon spin polarization. This leads us to a very important

point: Although the presence of antibonding levels at ε_F in a nonmagnetic calculation indicates the presence of a driving force for spin polarization (which removes those levels from around ε_F), this does not necessarily mean that the total bond strength in the system must increase when it becomes magnetic. In other words, the antibonding character of the states around ε_F provides the *motivation* for ferromagnetism, but the “payback” does not necessarily have to come from a strengthening of bonds, as measured by ICOHP values. A closer analysis shows that the stabilization in MnSb results from atom-centered contributions (otherwise known as on-site COHP terms).^[92]

The potential for ferromagnetism in MnSb may also have been predicted by the knowledge of the chemical hardness of its nonmagnetic “phase”: 0.142 eV. With the emergence of ferromagnetism, η increases by more than a factor of 5 (!) to 0.766 eV, the largest increase we have found so far.

7. Epilogue and Future Perspectives

We have already come a long way in our exploration of the orbital origins of magnetism. As we have tried to explain, there are strong similarities in the changes wrought by magnetism as we increase in complexity from atoms to molecules to ferromagnetic alloys. Examination of the nature of the bonding (where appropriate) and the consequences of the exchange hole in all of these systems has led us to an understanding of a fascinating macroscopic quantum effect: ferromagnetism. According to our interpretation, ferromagnetism is a *chemical* phenomenon, arising only in systems with a critical electron concentration—one which causes ε_F to fall in a region of antibonding states. The resulting instability results in the expected lowering in symmetry. However, rather than altering the spatial coordinates of the atoms, the electronic symmetry is lowered by making the α and β spins inequivalent. This break in the electronic symmetry leads to energy level shifts, repopulation of the spin sublattices, and a redistribution of charge density. It is straightforward to extend this new interpretation of the phenomenon of ferromagnetism to complicated species such as alloys. The interpretation itself fits nicely into general useful chemical ideas such as the principle of chemical hardness.

7.1. Theory

The perceptive reader might have noticed that we have refrained from going too deeply into the curiosities of the localized-electron magnetism of the rare-earth metals. As we have tried to suggest, a chemical-bonding interpretation of magnetism arising from 4f orbitals seems to be ill fitting. Some preliminary calculations, however, indicate that similar thinking might be applied even here, at least for mixed d block/f block magnetic materials, such as SmCo_5 or $\text{Nd}_2\text{Fe}_{14}\text{B}$, where the spin–spin interactions are mediated through the conduction electrons (Rudermann-Kittel-Kasuya-Yoshida (RKKY)).^[93–95]

With respect to numerical investigations, one of us (R.D.) is most curious to learn more about the almost coincidental decay of both the molecular field and the bond strength as a function of the interatomic distance. As it stands now, the other of us (G.A.L.) believes that it is purely accidental. The source of the mysterious size of the hardness criterion for ferromagnetism (0.2 eV) also needs to be studied. The latter project, however, would have to be based upon an analytical approach. Given the limited success of various model techniques to date (Hubbard model, and so forth) this goal might be challenging to achieve.

An extension of the interpretative COHP technique presented here to deal with *disordered* alloys is needed. A lot can be learned from the successes of various mean-field approaches, such as the coherent-potential approximation (CPA), a standard approach in theoretical solid-state physics.^[96–99]

Work is also currently underway to understand the connection between antiferromagnetism and COHP curves. In particular, the importance of, and the role played by, the nonbonding states around ε_F for Cr is being studied.^[100]

7.2. Syntheses and Experiments

Here is a recipe for the restless synthetic chemist trying to create new ferromagnetic materials: Try to adjust, by chemical means such as oxidation and reduction, the Fermi energy of the starting material in order to maximize the antibonding interactions between those atoms which have narrow band widths in their elemental forms. We have, in part, demonstrated the impact of such gradual electron fillings for the Fe_xPd_y alloys upon local atomic magnetic moments. One alternative example, of the hundreds or thousands which are also worth investigating, is given by the MnSb phase. Based upon the two nonmagnetic COHP curves, one might now envision the partial replacement of Mn or Sb by other metals, or even the introduction of oxidizing or reducing atomic species. Without our present knowledge about the structure of the COHP curves at ε_F , metallurgists long ago pursued this course by synthesizing ferromagnetic materials such as Cu_2MnSb . It remains to be seen what can be done when one follows a slightly more rational approach.

Due to the fact that the “alarm” signaling a preference for the ferromagnetic state (antibonding $\text{COHP}(\varepsilon_F)$) shows up in *nonmagnetic* band structure calculations, a properly parameterized semi-empirical (extended-Hückel tight-binding,^[101–103] for example) calculation—nowadays so ubiquitous in solid-state chemical laboratories—can provide an equivalent COOP result to guide the experimentalist. This is discussed in somewhat more detail in Appendix B.

As a final synthetic challenge, we would like to suggest an attempt to prepare body-centered cubic manganese under standard conditions, having predicted that it will be a ferromagnet with a moment of about one Bohr magneton. Since the phase cannot be quenched from high temperature, a softer (perhaps organometallic) route may be required.

Appendix A: Computational Methodology

A.1. Solids

Electronic structure calculations on solids were performed using the linear muffin-tin orbital (LMTO) method^[104–107] within the local spin-density approximation (LSDA)^[63]. All calculations were checked for convergence of energies, orbital moments, integrated COHP values, and magnetic moments with respect to the number of k points used in the reciprocal space integrations.^[108] Atomic sphere radii used in the TB-LMTO-ASA calculations were chosen using an automated procedure (TB = tight binding; ASA = atomic sphere approximation). The program used was TB-LMTO 4.7.^[109]

While the LSDA is known to have problems with metallic Fe—predicting an antiferromagnetic fcc structure to be more stable than the magnetic bcc form^[69] (see Section 5.2)—it reproduces the experimental magnetic moments of Fe, Co, and Ni (2.21, 1.74, and $0.62 \mu_B$ per atom, respectively^[33]) quite closely (2.27, 1.62, and $0.62 \mu_B$). The spin-polarized DOS of magnetic bcc Fe, generated using a gradient correction scheme within the framework of a linear augmented plane wave (LAPW) calculation,^[110, 111] is essentially identical to that generated using the LSDA within the LMTO method. Since we are not interested here in energy differences between particular structures (using instead experimental structures and lattice constants), we believe that the LSDA is accurate enough for our purposes.

A.2. Crystal-Orbital Hamilton Population Analysis

Crystal-orbital Hamilton population (COHP) analysis^[92] is a partitioning of the band structure energy (sum of the energies of the Kohn–Sham orbitals) in terms of orbital-pair contributions. The COHP analysis, while in many ways analogous to the familiar crystal-orbital overlap population (COOP) analysis used in extended Hückel calculations,^[112, 113] provides a quantitative measure of bond strengths and is probably more appropriate for a first-principles calculation.

Before proceeding, a word about the connection between COHP and total energy is needed. Within the framework of density-functional theory, the total electronic energy $E_{\text{tot}}[\rho]$ is given in [Eq. (13)], where ρ is the electron density and $E_{\text{kin}}[\rho]$, $E_{\text{Hartree}}[\rho]$, $E_{\text{el-nuc}}[\rho]$, and $E_{\text{xc}}[\rho]$ are the kinetic, electron–electron repulsion, electron–nuclear attraction, and exchange–correlation energies.^[31]

$$E_{\text{tot}}[\rho] = E_{\text{kin}}[\rho] + E_{\text{Hartree}}[\rho] + E_{\text{el-nuc}}[\rho] + E_{\text{xc}}[\rho] \quad (13)$$

By definition, the sum of all the integrated COHP values (the ICOHP value) in a system is equal to the band-structure energy, which is the sum of the Kohn–Sham one-electron eigenvalues,^[92] [Eq. (14)], where the ICOHP sum includes both on-site (diagonal) and off-site (off-diagonal) terms, ϵ_i is the energy of the i -th Kohn–Sham orbital, and the subscripts j and k label atomic orbitals. The sum over eigenvalues in Equation (14) can be expanded to give Equation (15), where $\mu_{\text{xc}}(\vec{r})$ is the exchange–correlation potential.^[31]

$$\sum_j \sum_k \int_{-\infty}^{\epsilon_F} dE \text{COHP}_{jk}(E) = \sum_j \sum_k \text{ICOHP}_{jk} = \sum_i \epsilon_i \quad (14)$$

$$\begin{aligned} \sum_j \sum_k \text{ICOHP}_{jk} &= \sum_i \epsilon_i \\ &= E_{\text{kin}}[\rho] + 2E_{\text{Hartree}}[\rho] + E_{\text{el-nuc}}[\rho] + \int d\vec{r} \mu_{\text{xc}}(\vec{r}) \rho(\vec{r}) \end{aligned} \quad (15)$$

Finally, substituting Equation (13) into Equation (15) gives us the connection between $E_{\text{tot}}[\rho]$ and the ICOHP values [Eq. (16)].

$$E_{\text{tot}}[\rho] = \sum_j \sum_k \text{ICOHP}_{jk} - E_{\text{Hartree}}[\rho] + E_{\text{xc}}[\rho] - \int d\vec{r} \mu_{\text{xc}}(\vec{r}) \rho(\vec{r}) \quad (16)$$

Equations (15) and (16) demonstrate that 1) the ICOHP values contain contributions from all terms of the density-functional electronic energy and 2) there is a direct link between the ICOHP values and the total electronic energy of a system. The success of one-electron theories in quantum chemistry (for example, extended Hückel theory) is due in no small part to the intimate connection between the sum of one-electron eigenvalues (COHP terms) and the total energy. This connection is one of the pillars of qualitative molecular-orbital theory.

All COHP curves are presented here in a format similar to COOP curves: positive values are bonding and the negative antibonding (that is, we plot $-\text{COHP}$ instead of COHP).

A.3. Molecular Orbital Calculations

Molecular-orbital calculations were carried out within the framework of density-functional theory using the Amsterdam Density Functional (ADF) program, version 2.3.^[114–116] Triple- ζ Slater-type orbital (STO) basis sets with either one (Se) or two (O, S) polarization functions (ADF basis set V) were used to represent the valence orbitals; the core orbitals were frozen to 1s (O), 2p (S), and 3p (Se).^[117] The local spin-density approximation (within the Vosko, Wilk, and Nusair parameterization^[118]) was augmented using the Becke–Lee–Yang–Parr (BLYP) gradient correction scheme.^[119, 120] All plots were generated using Viewkel, a part of YAeHMOP.^[121]

Appendix B: The Extended Hückel Method and Magnetism

The extended Hückel theory^[122–124] is known for its flexibility and the ease with which its results lend themselves to chemical interpretation. To those familiar with the method, it will come as little surprise that the qualitative features of the crystal-orbital overlap population (COOP) curves from a well parameterized, extended Hückel, tight-binding calculation^[101–103] are qualitatively similar to the COHP curves from an equivalent calculation from a better method.^[125] To demonstrate this, the extended Hückel band structure, DOS, and COOP curves for α -Fe are shown in Figure 41. Comparing these results with Figure 14, we see both similarities and differences. It is obvious that the parameterization chosen leads to an underestimation of s dispersion and an overestimation of d dispersion; the s-d mixing is probably also too

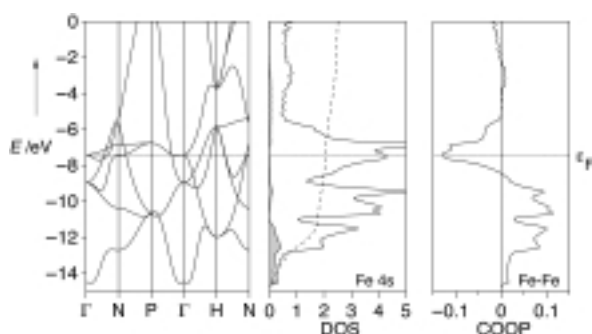


Figure 41. Band structure, DOS, and Fe-Fe COOP curves for nonmagnetic α -Fe calculated using the extended Hückel, tight-binding method.

strong. The chemically (or magnetically) most important finding is fully retained though: ϵ_F appears in a set of strongly Fe-Fe antibonding levels in each calculation, leading us to expect the presence of an instability with respect to ferromagnetism. Although it is impossible to carry out a spin-polarized calculation within this method itself, we believe that it can be used to rapidly screen metallic structures for a tendency to become ferromagnetic.

The parameters used in this extended Hückel, tight-binding calculation on α -Fe ($H_{ii}(4s) = -9.2$ eV, $\zeta(4s) = 1.9$, $H_{ii}(4p) = -3.8$ eV, $\zeta(4p) = 1.9$, $H_{ii}(3d) = -9.2$ eV, $\zeta_1(3d) = 5.35$, $\zeta_2(3d) = 1.80$, expansion coefficients $c_1(3d) = 0.5366$, $c_2(3d) = 0.6678$) were adapted from the standard metallic Fe parameter set^[126] with modifications to the parameters for the 4s orbitals in order to reproduce the degree to which the 4s band penetrates the 3d block. The extended Hückel calculations were carried out using YAEHMOP.^[127]

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Atomic Glimpses on a Billion-Year-Old Molecular Machine

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The ribosome is the universal molecular machine for the synthesis of proteins in biological cells. Each *Escherichia coli* cell contains about 30 000 ribosomes. Eubacterial ribosomes are made up of two main components, each of which is composed of an intricate assembly of proteins and RNAs, totaling about 270 000 atoms. In prokaryotes the small subunit (30S particle) comprises the 16S rRNA and 21 proteins, while the large subunit (50S particle) consists of two RNAs, the 5S rRNA, and the 23S rRNA, together with some 33 proteins.^[1] Functionally, the small subunit is devoted to the recognition of messenger and transfer RNAs, while the large subunit is the center of protein synthesis. A prokaryotic ribosome measures about 200 Å along each direction, which corresponds to the close packing of approximately 16 nucleosomes, the fundamental constituent of chromatin. Recently, crystal structures of each prokaryotic subunit^[2–4] and of the whole prokaryotic ribosome,^[5] the 70S particle, have been published. The resolution of the structures is still rather low (4.5–7.8 Å; Table 1), but the prospects for a rapid increase in resolution are real.

Like all great endeavours in science, the quest for structural information on the ribosome has been eventful and ought to inspire ambitious young scientists, especially in days where science is shunned by students. The structures we can now admire were solved in the laboratories of scientists who have been involved in ribosome research for decades. Ada Yonath, from the Weizmann Institute in Rehovot, Israel, started first in the early 1980s, with the enthusiastic support of H. G.

Wittmann at the Max-Planck-Institute für Molekulare Genetik in Berlin. Over the years, despite some open scepticism, Ada Yonath^[6] persevered, incrementally improving the quality of the crystal structures by choosing to extract ribosomes from extreme halophilic and thermophilic bacteria and applying successive technical advances in X-ray crystallography (like cryocrystallography^[7] to overcome radiation damage and synchrotron radiation to surmount weak diffraction power). Her group has now published the structure of the 30S particle at 4.5 Å resolution.^[2]

However, in the meantime, she had so successfully convinced fellow crystallographers of the feasibility of the project that other groups moved in, no longer content to study the structure of the ribosome piecemeal. Peter Moore, at Yale University, had deduced the relative positions of the proteins in the 30S subunit using neutron diffraction.^[8, 9] This required over a decade of dedicated work since each single protein had to be isolated and purified in deuterated form before being reinserted singly or in pairwise combination with other proteins into reconstituted ribosomes. He teamed up with the well-known structural biologist Tom Steitz, also at Yale University, and their groups solved the structures of the 50S particle, first at 9 Å,^[10] and then at 5 Å.^[4] In parallel, Venki Ramakrishnan (first at the University of Utah in Salt Lake City and then at the Medical Research Council in Cambridge, UK), who had worked with Peter Moore on the relative positions of ribosomal proteins and, since then, solved the structure of several ribosomal proteins in isolated form,^[11] has

Table 1. The different crystal structures which have been solved, together with their characteristics.

Particle	Size [MDa] ^[a]	Contents ^[a]	Unit cell parameters [Å]	Space group	Resolution [Å] (no. of reflections)
30S <i>Thermus thermophilus</i>	0.9	16S rRNA (1542 nt), 21 proteins	$a = b = 407, c = 176$	$P4_2, 2_1, 2$	4.5 (85 991), ^[2] 5.5 ^[3]
50S <i>Haloarcula marismortui</i> ^[4]	1.6	23S rRNA (2900 nt), 5S rRNA (120 nt), 34 proteins	$a = 212, b = 301, c = 576$	$C222_1$	5 (185 190)
70S <i>Thermus thermophilus</i> ^[5]	ca. 2.5		$a = b = 508, c = 803$	$I422$	7.8 (121 730)

[a] For *E. coli* ribosomes, nt = nucleotides.

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managed to produce a remarkable 5.5 Å resolution structure of the 30S particle with his group.^[3] These two teams worked on crystals of isolated particles previously shown by Yonath's group to crystallize.^[12, 13]

Since the mid 1980s, working in the group of the ribosome researcher A. Spirin (at the Protein Research Institute in Puschino, Russia), G. Yusupova and M. Yusopov worked to produce better and better crystals of a whole ribosome of a

thermophile.^[14] They later brought their expertise in biochemistry and crystallogenes to the laboratory of Harry Noller, a pioneer in the sequencing and characterization of ribosomal RNAs,^[15–18] at the University of California in Santa Cruz. Noller's team, which had already been joined by Jamie Cate, who had previously participated in the ground-breaking structure of the P4-P6 domain of group I introns,^[19] cracked the structure of the whole ribosome.^[5]

Once the challenging difficulties of obtaining stable and well-diffracting crystals were overcome, crystallographers faced the tremendous problem of phasing the reflections diffracted by crystals containing such large asymmetric objects. The 30S particles were solved using the multiple isomorphous replacement method, with multimetal clusters^[20] based on tantalum or tungsten, and anomalous scattering in one case^[3] or oligomers modified by metal clusters and targeted to specific targets in the other.^[2] For the 50S particle, the crystallographic problem was compounded by the fact that the crystals were twinned, but, again, multiple isomorphous replacement and multiwavelength anomalous scattering were used to phase at high resolution, once the phases at low resolution were obtained with the help of cryoelectron microscopy (cryo-EM).^[10] The solution of the whole ribosome relied also on a battery of theoretical and experimental techniques: 1) several complexes of the 70S ribosome (with messenger RNA and transfer RNAs or analogues) were crystallized and measured in order to guarantee internal consistency; 2) low-resolution phases were determined using molecular envelopes derived from cryo-EM; and 3) extension of the phases to high resolution was achieved using multiwavelength anomalous dispersion experiments to locate heavy-atom clusters.^[5]

The resolution, while not high enough to resolve and identify individual RNA bases or protein amino acids, is sufficient to distinguish protein α helices from RNA double helices, and thus the images reveal some of the overall arrangements of the proteins with respect to the RNAs. In the 1970s, to obtain the structures of tRNAs, crystallographers developed programs fitting the previously determined structures of RNA building blocks, phosphates, sugars, bases, and mononucleotides to the electron density of the tRNA polynucleotide.^[21] To solve the present structures, whole domains—RNA helices, conserved hairpin stem-loops, recurrent RNA modules,^[22, 23] and available complexes between RNA fragments and proteins^[24, 25]—have to be recognized and fitted into the electron density. All seven 30S proteins that had been previously crystallized and solved to atomic resolution (S4, S5, S6, S7, S8, S15, and S17)^[11]

could be fitted in the electron density of the small subunit. Moreover, with the aid of data from the low-resolution neutron-scattering map^[9] and biochemical experiments, the positions of some of the other 30S proteins could be identified (S2, S3, S11, S16, S18, and S20). In the large subunit, 12 proteins have been located. The atomic coordinates of five previously solved proteins (L1, L2, L6, L11, and L14) and two RNA fragments have been fitted to the electron density. Three of these proteins (L6, L11, and L14) and the two RNA fragments (the sarcin/ricin stem-loop and the L11-binding site of 23S RNA) comprise a major part of the binding site for G-protein factors.

Overall, the structures confirm clearly the beautiful reconstructions obtained by cryo-EM.^[26–30] Thus, most of the features of the small subunit (head and neck connected to the platform and body; Figure 1) are discerned in the overall shapes with some modulations depending on the crystal and, importantly, the functional state of the particle. For the large subunit, some meaningful differences appear on the left- (L1) and right-hand (L7/L12) sides of the central protuberance (Figure 1) between the structures obtained by cryo-EM and crystallography. The cryo-EM images and biochemical data served also to dock the previously solved structures of the G-protein translation factors EF-G and EF-TU (complexed to aminoacyl-tRNA and GTP) to this site.^[29, 30]

The synergism between these two experimental approaches has indeed great potential. This is illustrated by two recent developments.^[31, 32] The insertion of a tRNA sequence within

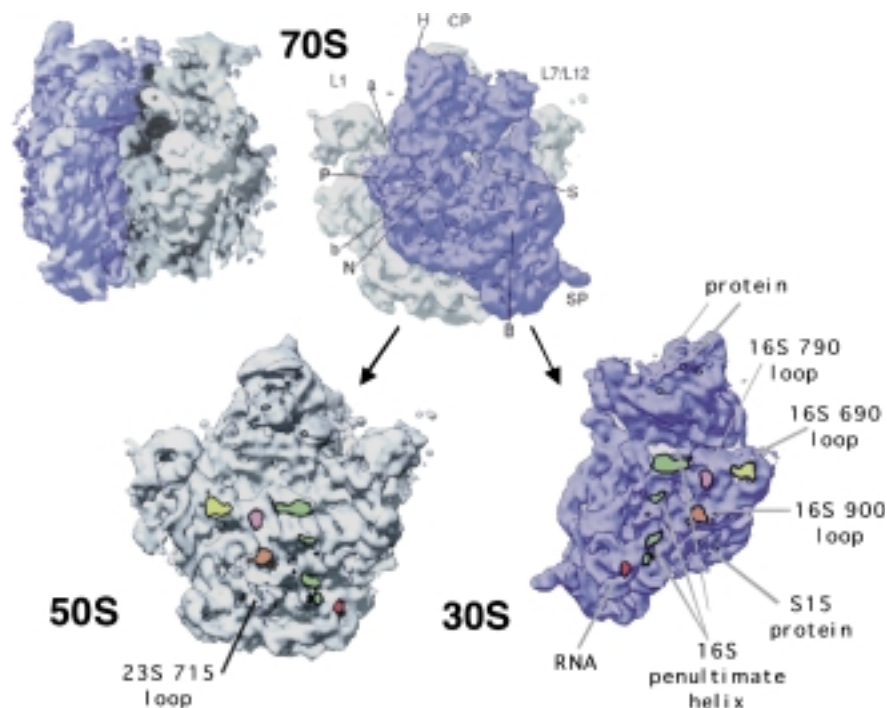


Figure 1. Interactions between the small (30S) and large (50S) ribosomal subunits participating in the formation of the functional 70S ribosome, as seen in the structure at 7.8 Å resolution. Top: Two views of the 70S particle, one edge-on and the other rotated by 90° to show the orientation of the 30S particle on the 50S particle. Bottom: The 70S particle is opened up to reveal the corresponding contact points on the two subunits. The contact points are color-coded and labeled to indicate the corresponding “bridges” first identified by cryoelectron microscopy, and the specific RNA hairpin loops or helices and ribosomal proteins now assignable at the higher resolution^[41] (see also Table 2). The figure is adapted from Figures 2 and 3 of ref. [5] and used with permission from the American Association for the Advancement of Science (copyright (1999).

the bacterial gene for the 23S rRNA allows the isolation of ribosomes with the L-shaped tRNA structure visible, thereby permitting the identification of specific regions within the whole particle.^[31] The cryo-EM structure at 7.5 Å resolution of the *E. coli* 50S particle reveals new details concerning the L7/L12 region and the L8 complex as well as the extensive conformational changes occurring upon binding of the 30S particle.^[32] The functional significance of the differences seen between X-ray and EM structures is now difficult to assess, but one expects large movements and rearrangements to occur within the ribosome during the cycles of protein synthesis (binding and release of tRNAs, progression along the messenger, extrusion of the synthesized peptide, etc.).^[18]

Various examples of known RNA structural motifs are prominent in the areas of electron density (Figure 2). Firstly, most of the canonical double-helical elements can be identified as such, by following the regularly spaced “knobs” of electron density corresponding to phosphate groups. Second-

ly, hairpin loops capped by 5'-GNRA-3' tetraloops can be identified, as these share a characteristic conformation, featuring continuous stacking of three bases (5'-NRA-3').^[33] Thirdly, several internal loops displaying characteristic S-motifs^[34] have been identified, and two of these have been assigned to functionally significant regions in each subunit. One can be assigned to the 900 hairpin stem-loop in the small subunit (nucleotides 890–910 of 16S RNA, which includes the “switch-helix” at its base), and another to the sarcin/ricin hairpin stem-loop in the large subunit (nucleotides 2650–2670 of 23S RNA), which participates in translation-factor binding. Finally, multiple examples of RNA helices interacting side-by-side perhaps through “ribose zippers”^[19] are observed. At the resolution of the present structures, however, single-stranded regions of RNA cannot be traced unambiguously over long distances. Nonetheless, the RNA backbone of 16S rRNA in the small subunit could be traced over most of the central core domain.^[3] In addition, a

conspicuous 100 Å long, slightly distorted RNA helix, seen in the 30S^[2, 3] and 70S particles,^[5] can be identified with the “penultimate” helix (residues 1400–1500) of 16S RNA. This functionally important domain includes the decoding site of 16S rRNA and forms a significant part of the interface to the 50S subunit, including bridges B2a, B3, and B5 (Table 2). Moreover it directly contacts the 900 hairpin stem-loop containing the S-motif and switch helix, which is implicated in modulating translation accuracy and which itself is seen to contact the 50S subunit at its hairpin loop (bridge B2c).

What do the proteins do? An answer to this question is also emerging. The ribosomal proteins are dispersed throughout the structures of both subunits and most appear to cross-link noncovalently two or more RNA helices, a fact consistent with abundant data on chemical protection and cross-linking indicating that the same protein

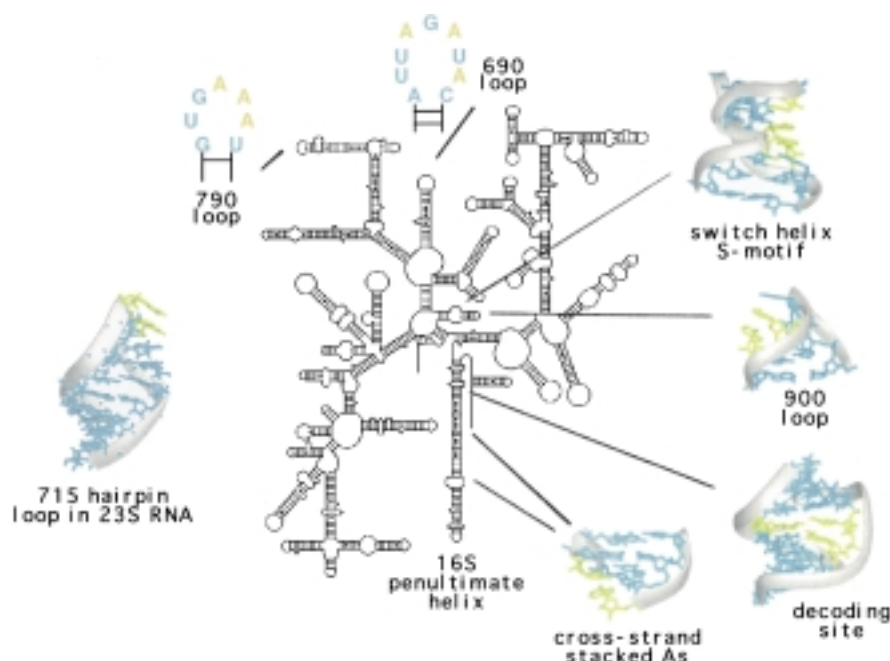


Figure 2. Some RNA elements participating in intersubunit interactions, mapped onto the secondary structure of the 16S ribosomal RNA. Conserved, exposed adenine residues, which are recurrently used in tertiary contacts,^[46] are colored yellow.

Table 2. RNA–protein and RNA–RNA intersubunit contacts identified in the 70S eubacterial ribosome around the core region which bind mRNA and tRNAs.^[5, 41] [a]

Contact	Type	Location	Small subunit	Large subunit
B1a	RNA–protein	peripheral	protein	RNA
B1b	RNA–protein	peripheral	protein	RNA
B4	RNA–protein	peripheral	S15 protein	715 RNA hairpin stem-loop
B6	RNA–protein	peripheral	RNA	protein
B2b	RNA–RNA	central core	790 hairpin stem-loop	RNA
B7	RNA–RNA	central core	690 hairpin stem-loop	RNA
B2c	RNA–RNA	central core	900 hairpin stem-loop	1700 hairpin stem-loop
B2a	RNA–RNA	central core	top PL-Sh.Gr.	1910 hairpin stem-loop
B3	RNA–RNA	central core	PL-Sh.Gr.	RNA
B5	RNA–RNA	central core	PL-D.Gr.	RNA

[a] The contact names were first established and named as “bridges” of electron density by cryoelectron microscopy.^[41] PL corresponds to the penultimate helix in the 16S rRNA which carries the decoding site; the grooves of the RNA helix are denoted Sh.Gr. for the shallow, and broad, groove (corresponding to the minor groove in the B-DNA helix) and D.Gr. for the deep, and narrow, groove (corresponding to the major groove in B-DNA helix).

contacts regions of the RNA distant in the primary or secondary structure. Thus, the general answer to the question is that the ribosomal proteins help to organize and stabilize the tertiary structural elements present in the RNAs. The organization of the RNA itself is built around a scaffold of RNA Watson–Crick helices connecting and positioning structural motifs, often recurrent and assembled from non-Watson–Crick base pairs,^[35] with a diverse set of accessible binding sites. It is still much too early to discuss the relative contribution of RNA–protein and RNA–RNA contacts to the assembly of the subunits and the whole particle (see Table 2 for the present state of knowledge).

However, more direct functional roles for certain ribosomal proteins cannot be dismissed. In fact, the new structures reveal surprises, including the observation that proteins S5 and S4 in the small subunit interact directly, creating an interface that comprises the amino acids, which, when mutated, affect the ability of the ribosome to select the correctly aminoacylated tRNA (*ram* mutations). Furthermore, the structures are sufficiently detailed to reveal cavities and tunnels, some of which are used to bind and channel the substrates and products during the repetitive and highly processive cycle of protein synthesis. The presence of a channel leading from the active site of the peptidyl transferase straight through the body of the large subunit, and ascribed to the path of newly synthesized polypeptide, stands out in the structure of the 50S subunit. This tunnel, first suggested 30 years ago,^[36] has been much discussed since it was seen in reconstruction models of the 50S and 70S particles.^[37] Recently, cryo-EM provided evidence for its existence in yeast ribosomes.^[38] It is 20 Å wide, 100 Å long, and filled by four W₁₁ clusters in the 50S crystals.^[4] Very striking is the almost complete absence of protein at the interface between the 30S and 50S subunits. It is at this interface that substrates are bound and peptide bond formation takes place. This pertains to the question: Is the ribosome a ribozyme or, in other words, is the RNA the chemically active component for catalysis of peptide bond formation? Although experimental evidence points to that possibility, definite proof is still missing.^[39] Bridges representing points of contact between the subunits (Table 2) were first identified in lower resolution images obtained by cryo-EM.^[40] On the basis of the present structure of the 70S subunit,^[5] supplemented by additional biochemical work, an RNA–protein bridge spanning the subunit interface was identified as protein S15 of the 30S particle and the hairpin loop 715 in the 23S rRNA of the 50S particle.^[41]

The new crystal structures crown decades of determined work and open up avenues for fundamental and applied scientific developments. The 16S ribosomal RNA has already played a central role in our classification of living forms. The subdivision of the tree of life into three main forms (archaea, eubacteria, and eukarya) was based on analysis of the sequences of 16S rRNAs.^[42] Structurally, the ribosome is a gold mine of motifs and contacts. Extended comparisons between the three-dimensional structural motifs and the available sequences should yield the rules linking sequence and structure in RNA, as well as those responsible for RNA–protein recognition. The ribosome has been the subject of an

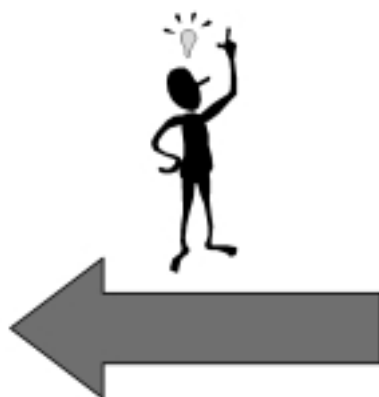
intense modeling activity,^[43] and thus the structures should help delineate the limits and future possibilities. Several antibiotics inhibit protein synthesis—either at the 50S level, like the macrolides, or at the 30S level, like the aminoglycosides—but organisms resistant to virtually any available antibiotic occur.^[44] However, our knowledge at the atomic level of the antibiotic binding sites on the eubacterial ribosome is still scanty,^[45] and we can now hope to see in the future complexes involving antibiotics. These will provide crucial new structural data to guide efforts in drug design necessary to overcome the imminent crisis in antibacterial therapy resulting from the spread of resistance.

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The Synthetic Route to a Target Molecule

The Planning

**Starting
Materials**



**Target
Molecule**

The Reality

**Starting
Materials**



Advanced
Intermediate



Dead End

~~**Target
Molecule**~~

**Starting
Materials**



Advanced
Intermediate



A failed key step



Needful
Knowledge



More and More Steps



**Bulls-Eye!
(Finally...)**

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How Does Tyrosinase Work? Recent Insights from Model Chemistry and Structural Biology**

Heinz Decker,* Renée Dillinger, and Felix Tuczek*

Introduction

The catalysis of oxygenation and oxidation reactions by tyrosinase and catecholoxidase is currently one of the most exciting topics of bioinorganic chemistry. These enzymes belong to the family of type3 copper proteins which is involved in a variety of biological functions. Hemocyanins (Hcs) serve as O₂ carriers in the hemolymph of arthropods and molluscs,^[1] catecholoxidases (COases) oxidize *ortho*-diphenols to *ortho*-quinones (diphenolase activity),^[2] and tyrosinases mediate the hydroxylation of monophenols to *ortho*-diphenols as well as the subsequent oxidation to *ortho*-quinones (monophenolase activity).^[3] Although they have been studied for over 100 years, these reactions and the observed functional differences are far from being understood on a molecular level.

With the notable exception of tyrosinase, X-ray structures are available for all classes of type3 copper proteins: the deoxy form of the Hc from spiny lobster (*Panulirus interruptus*),^[4] the deoxy and oxy forms of the Hc from horseshoe crab (*Limulus polyphemus*),^[5] the oxy form of the Hc from *Octopus dofleini*,^[6] and the deoxy, met, and inhibitor-bound forms of the COase from sweet potato (*Ipomoea batatas*).^[7] As expected, all of these proteins contain virtually the same binuclear copper active site which in its Cu^I–Cu^I deoxy form reversibly binds O₂, leading to a binuclear Cu^{II} unit with O₂ as a side-on bridging (μ - η^2 : η^2) peroxide group. Based on these structural data, a mechanistic understanding of the corresponding biochemical reactions now appears within reach. In this respect, the recent finding of mono- and diphenolase activity in activated Hcs^[8] is of great interest, as it provides information regarding the orientation of monophenolic substrates within the protein pocket containing the binuclear copper active site.

Importantly, the growing structural insight into COase and tyrosinase activity is complemented by a significant amount of chemical and mechanistic information obtained from the study of synthetic low molecular weight analogues.^[9] The current electronic-structural, spectroscopic, and chemical characterisation of the Cu₂O₂ cores present in these inorganic model systems constitutes a fascinating area of bioinorganic research in itself and will most probably be crucial for a further understanding of the oxygenation reactions mediated by tyrosinase. The present highlight first describes key results of these model studies and these are then contrasted with mechanistic proposals derived from structurally characterized proteins.

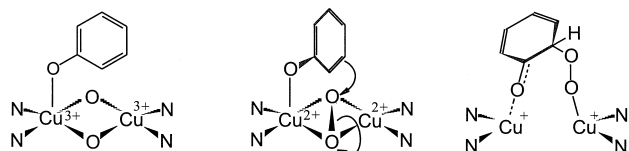
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Cu-O₂ Model Chemistry: What is the Hydroxylating Species?

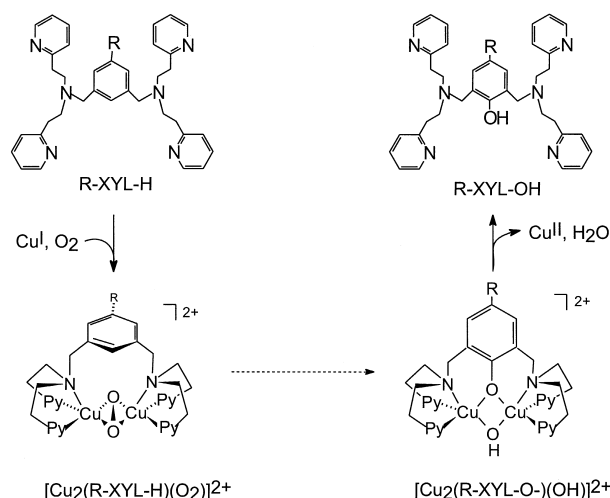
The mechanistically most demanding step of tyrosinase activity involves the introduction of a second OH group in the *ortho* position of the aromatic ring of a monophenol (such as tyrosine), coupled with the two-electron oxidation of the resulting catechol to the corresponding quinone (for example, dopaquinone). The primary question is whether splitting of the O-O bond occurs *prior to*, *along with*, or *after* attack by oxygen on the aromatic ring.^[3a] In the first case, the hydroxylation would be mediated by a bis(μ -oxo) core (Scheme 1, left). The last scenario would lead to an intermediate aryl peroxide species (Scheme 1, right) which then



Scheme 1. Possible reaction mechanisms for the oxygenation of phenols by Cu₂O₂ centers.

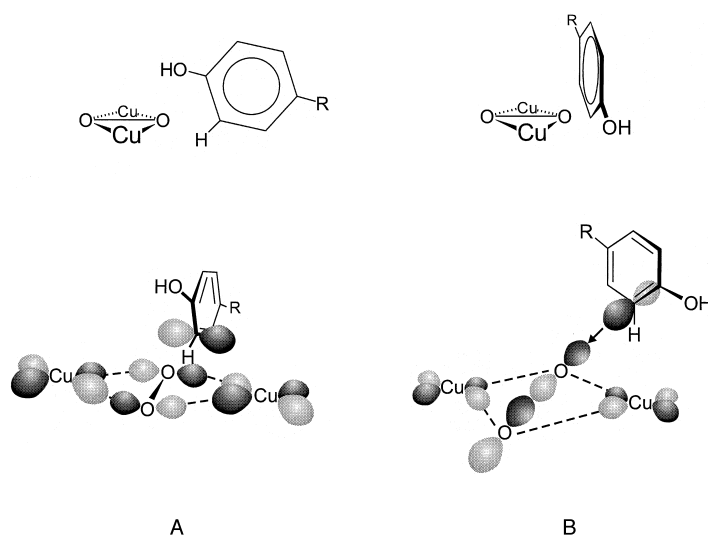
reacts with the diphenol (quinone). In the second case, the hydroxylation step would represent a case of electrophilic aromatic substitution (S_E) by peroxide with the π system being activated for this reaction by the first OH group (Scheme 1, center). The electrophilic character of the side-on bridging peroxide group has been explained by a large amount of charge donation into the Cu^{II} centers, making this the least negative form of peroxide.^[3b, 10]

A prototypical example for this reactivity is provided by the binuclear copper complex [Cu₂(R-XYL)]²⁺ (Scheme 2). In the binucleating ligand R-XYL-H, two bis[2-(2-pyridyl)ethyl]-amino (PY2) tridentate units are linked by a xylyl spacer which is hydroxylated upon reaction of the Cu^I complex with oxygen.^[11] It has recently been proven through resonance Raman spectroscopy that the hydroxylation of the aromatic π system occurs via a side-on bound peroxide intermediate.^[12] Importantly, both spectroscopy and molecular orbital theory



Scheme 2. Reaction pathway for ligand hydroxylation in the model system of Karlin. The hydroxylation proceeds via a μ - η^2 : η^2 peroxide intermediate.

allowed participation of the bis(μ -oxo) structure Cu^{III}-(O²⁻)₂-Cu^{III} (Scheme 1, left) in the reaction to be excluded (see below). The results have been explained based on a S_E mechanism.^[12] Within a frontier orbital approach, the authors consider two distinct orbital pathways for electrophilic attack of the peroxide onto the aromatic ring of the substrate; the HOMO of the arene ring can either interact with the lowest unoccupied molecular orbital (LUMO) of the side-on peroxide bridged structure, which has π^* character, or with the next unoccupied orbital at higher energy, which is σ^* type. Scheme 3 provides a look approximately along the Cu-Cu (top) or the O-O axis (bottom) for the corresponding “ π^* pathway” (A) and the “ σ^* pathway” (B), respectively. In the

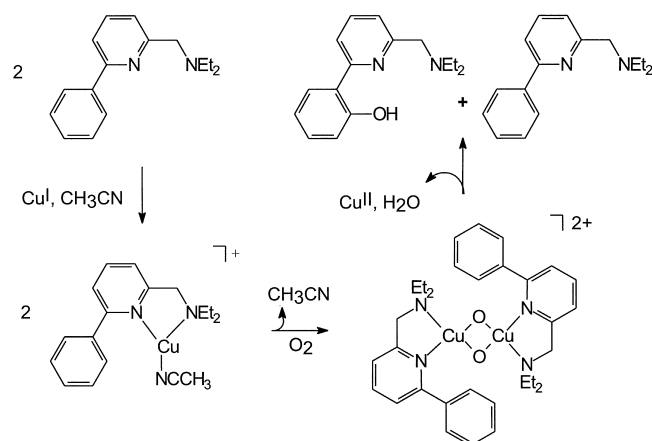


Scheme 3. Substrate orientation and frontier orbital analysis for the hydroxylation of phenols by a μ - η^2 : η^2 peroxide intermediate in the case of an electrophilic substitution. Two possible reaction pathways with corresponding orbital interactions are shown. A: The O-O axis is parallel to the aromatic ring plane of the substrate. B: The O-O axis is perpendicular to the aromatic ring plane of the substrate.

bottom views, the frontier orbital interactions are included schematically (note that only one p orbital of the HOMO of the aromatic ring has been included). The first possibility involves an approach of the substrate with the O-O axis parallel to the aromatic ring plane and a π interaction between the LUMO of the complex and the HOMO of the aromatic system (Scheme 3 A). In the other case, the aromatic ring plane is perpendicular to O-O, and one C atom of the aromatic ring in *ortho* position to the OH group interacts in a σ fashion with peroxide (Scheme 3 B). From geometric and electronic considerations Karlin et al. conclude that the hydroxylation of the xylyl ring in the present system is mediated by the side-on bridged peroxide adduct through the “ π^* pathway”.

In proteins so far only the presence of the μ - η^2 : η^2 peroxide form has been established by crystallography and spectroscopy. However, the recent structural characterisation of the bis(μ -oxo) core in small-molecule model systems^[13, 14] and the observation of its facile interconversion with the side-on bridging peroxide^[15] raise the question: to what extent is this

bis(μ -oxo) form capable of hydroxylating a phenolic substrate, namely does it participate in the enzymatic reaction? As a rule, the side-on peroxide group is more electrophilic than the bis(μ -oxo) form,^[12] and the latter is more prone to H atom abstraction than the side-on coordinated peroxide.^[16, 17] Aliphatic ligand hydroxylation reactions mediated by bis(μ -oxo)dicopper(III) and -dinickel(III) centers also proceed by the latter mechanism.^[18] Experimental evidence for the fact that the bis(μ -oxo)dicopper(III) core is also able to oxygenate an aromatic substrate has recently been provided by Tolman and co-workers;^[19] upon reaction of the ligand 2-diethylamino-methyl-6-phenylpyridine and Cu^I with O₂, an adduct is formed at low temperatures, with spectroscopic properties characteristic for a bis(μ -oxo) core. After warming the reaction solution, hydroxylation of an aromatic ring contained within the ligand system occurs (Scheme 4). This is in contrast



Scheme 4. Reaction pathway for ligand hydroxylation in the model system of Tolman. The hydroxylation proceeds via a bis(μ -oxo)dicopper(III) intermediate.

to earlier systems, where the bis(μ -oxo) core primarily decomposes under N-dealkylation of the respective ligand.^[16] The rate of the hydroxylation reaction and the relative amounts of hydroxylated versus non-hydroxylated ligand strongly depend on the substituents in the phenyl ring in a way that suggests an electrophilic substitution process. The alternative mechanism, H atom abstraction, could be excluded in this case based on the absence of a deuterium effect on the reaction rate.

Enzymatic Systems: The Case of Exogenous Substrates

In both examples considered so far the substrate has been preorganized for hydroxylation as a part of the ligand system. What happens if those substrates forming “endogenous” ligands are replaced by external substrates being coordinated (and possibly converted) as “exogenous” ligands? Possible answers to this question are provided by the study of Cu₂O₂ model systems that react with external phenols. However, in almost all known cases unphysiological radical coupling products are formed in such reactions.^[20] This is explained by the primary formation of phenoxyl radicals through H atom abstraction from the corresponding phenols by the Cu₂O₂ center. Complexes with side-on coordinated perox-

ide,^[20a-e] as well as those having a bis(μ -oxo) core,^[20e,f] show this reactivity. In the meantime however, one small-molecule system is also known that hydroxylates external phenols in a tyrosinase-like fashion.^[21]

Alternatively, the coordination of substrates or corresponding analogues (inhibitors, etc.) to the active sites of structurally characterized type 3 copper proteins can be investigated. A prominent example for this second approach is provided by the recently resolved X-ray structure of a 39 kDa COase of sweet potato which features an open entrance to the active site (Figure 1a).^[7] In the met form, only CuB is free to coordinate a phenolic substrate. Importantly, the structural

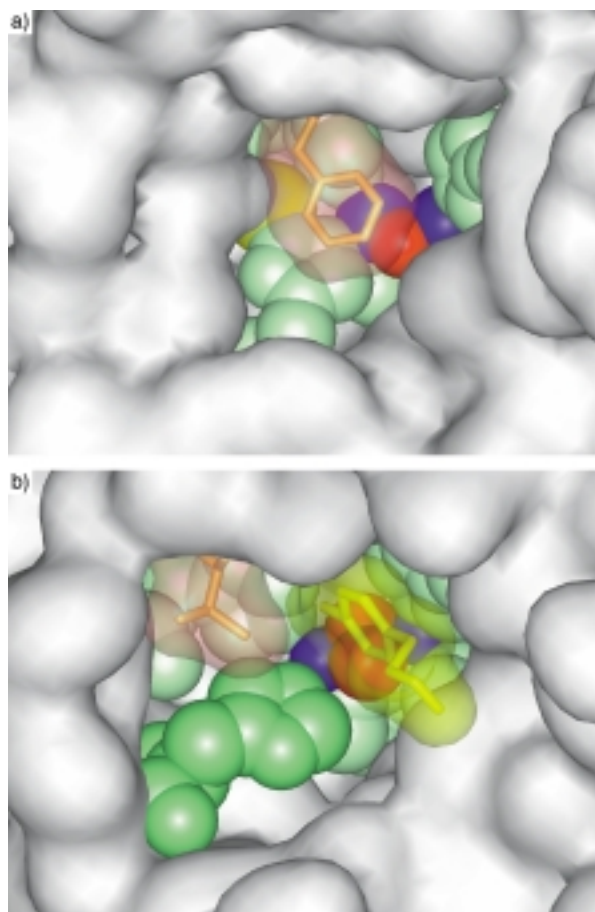


Figure 1. a) View of the active site of catecholoxidase in the met form. The two copper atoms (blue) are coordinated by six histidines (green). A stabilizing cysteine (dark yellow) is shown with van der Waals radius. CuA is shielded by a phenylalanine residue (orange). Bonding of diphenols is assumed to occur to CuB (see text). b) View of the substrate binding pocket and orientation of putative phenolic substrates (tyrosine) in hemocyanins. A putative tyrosine substrate (yellow) in the protein pocket of *Limulus* oxy-hemocyanin replaces Phe49 in the native structure (see text). Space-filling (transparent) atoms demonstrate that the substrate fits perfectly. Dioxygen (red) is bound in a μ - η^2 : η^2 coordination.

characterisation of the inhibitor-bound form of this enzyme allowed a detailed proposal for the coordination of *ortho*-diphenols. Comparable structural insight has been obtained with respect to the bonding of monophenols from the study of “activated” hemocyanins. Most significant in this respect is the finding of mono- and diphenolase activity for spider Hc

after limited proteolysis with trypsin and chymotrypsin.^[8c] This activation mechanism has been explained on the basis of the structurally closely related Hc from *Limulus polyphemus*;^[5] the N-terminal peptide containing Phe49, which is highly conserved among Hcs and phenoloxidases from arthropods, is pulled out of a cavity of the protein leaving a pocket and a free access for dioxygen and potential substrates to the copper active site (Figure 1b). A spacefilling tyrosine (yellow) placed as a phenolic substrate into this pocket exactly like Phe49 demonstrates that not much freedom for other orientations is available. This is due to steric constraints through hydrophobic interactions between the phenyl ring of the substrate and the axial His328 on CuB (green) and a Thr351 residue next to CuA (orange, transparent). The resulting coordination geometry of the substrate shows that the phenyl ring is almost perpendicular to the Cu–O₂–Cu plane with close contacts (under 4 Å) of its hydroxyl group to CuA (blue) and of its ortho position to one of the two oxygen atoms of the peroxide ligand (red, Figure 2).^[8c] This suggests bonding to CuA, in agreement with earlier concepts assuming direct coordination of the phenolic substrates to one Cu center, preferably CuA.^[3a] Furthermore, the vicinity of the ortho position of the aromatic ring to O₂ may be essential for the

hydroxylation reaction (see below). The comparison with the COase active site (Figure 1a) shows that CuA is shielded by a phenylalanine residue (orange) in this case, which may be the reason for the lack of monophenolase activity for this enzyme.

Looking back to the model system of Karlin, it is evident that from the two orbital pathways shown in Scheme 3 only the first reaction mode (A, π donation into the LUMO of the side-on peroxide structure) appears to be compatible with the substrate orientation presented in Figure 2. In contrast, the second possibility (B) is clearly distinct from this picture suggesting that the plane of the aromatic ring would not fit into the active-site pocket in this geometry. The same conclusion has also been reached by Karlin et al.^[12] The proposed substrate bonding geometry raises a question concerning the time sequence of the hydroxylation step (attack of O₂) and possible bonding to CuA; upon primary coordination of the phenol to this center, ligand-to-metal charge transfer would ensue which would act to diminish the activation of the aromatic ring for electrophilic attack. Moreover, upon coordination of the phenolic substrate the charge donation of peroxide to copper would decrease leading to a less electrophilic O₂ ligand. Both factors would be counterproductive with respect to the electrophilic substitution reaction (hydroxylation). In addition to the above-discussed question as to which is the hydroxylating agent (side-on peroxide or μ -oxo), the problem needs to be addressed as to whether a phenolic substrate binds to one Cu center of the Cu₂O₂ unit *at all*, and if it does whether this is *before*, *after*, or *along with* hydroxylation.^[3a, 22] Finally, it should be mentioned that radical reaction paths have also been discussed for tyrosinase, for example in an “early” mechanistic proposal by Kitajima and Moro-oka.^[20c] A recent theoretical study of tyrosinase activity by Lind, Siegbahn, and Crabtree also draws the conclusion that a radical mechanism is a plausible alternative to the electrophilic substitution pathway.^[23] The question of which mechanistic alternative actually applies to tyrosinase (or whether different mechanisms are found to explain the hydroxylation of monophenols) will remain a challenging problem of bioinorganic chemistry in the next few years.

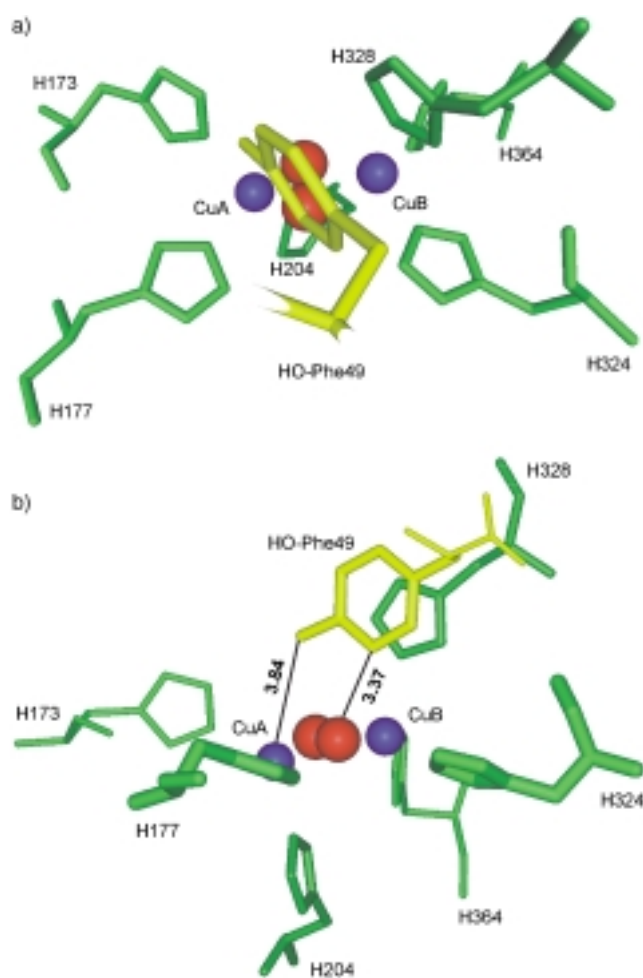
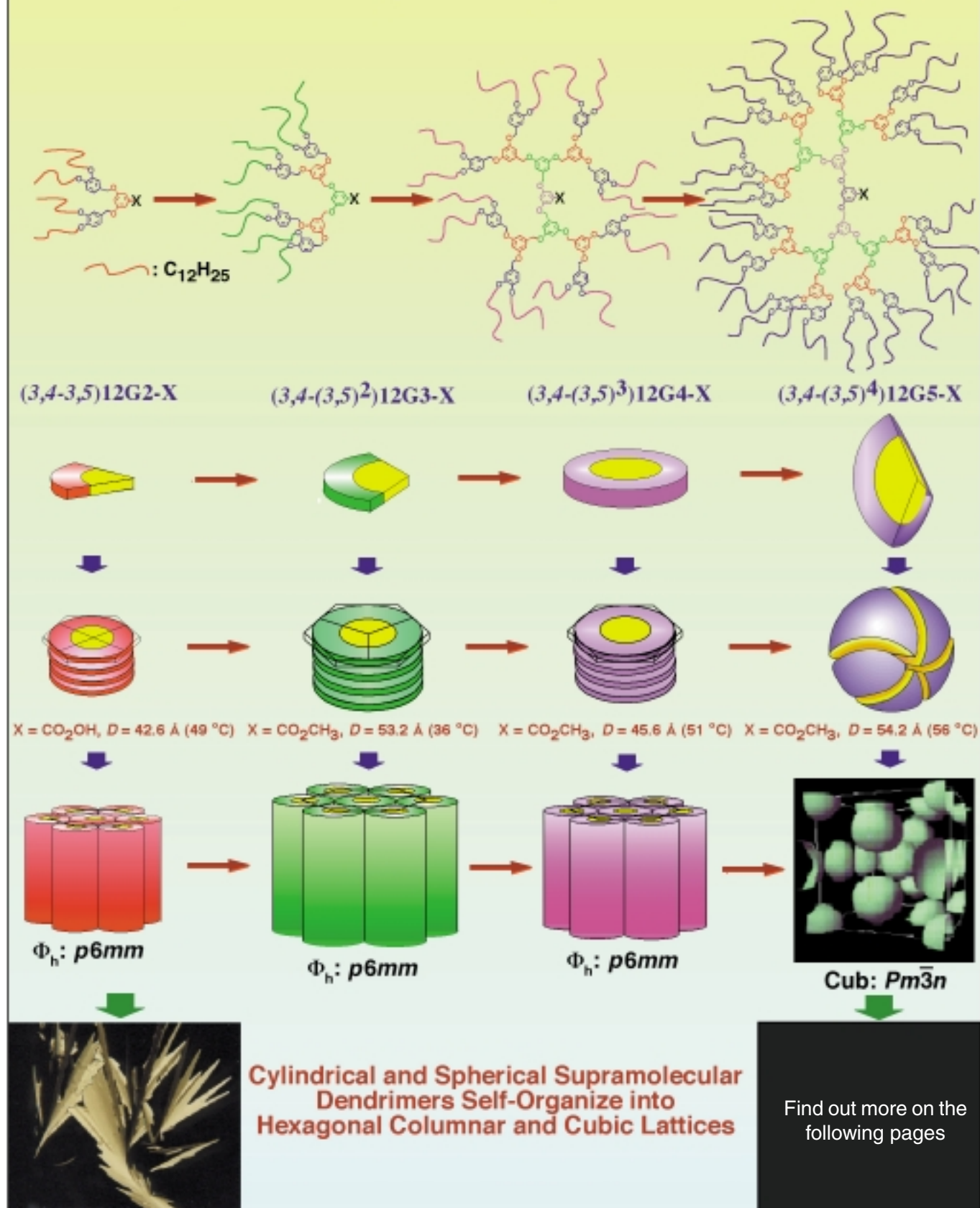


Figure 2. Top (a) and side view (b) of the coordination geometry of the hydroxylated Phe49, a putative substrate according to Decker and Rimke,^[8c] at the active site. Distances from the hydroxyl group and the ortho position of the benzyl ring to dioxygen and CuA are given in Å.

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Flat Tapered, Discotic, and Conical Monodendrons Self-Assemble into Cylindrical and Spherical Supramolecular Dendrimers



From Molecular Flat Tapers, Discs, and Cones to Supramolecular Cylinders and Spheres using Fréchet-Type Monodendrons Modified on their Periphery**

Virgil Percec,* Wook-Dong Cho, Goran Ungar, and Duncan J. P. Yeardley

Dendritic building blocks are one of the most powerful architectural motifs for the construction of complex molecular, macromolecular, and supramolecular functional nano-systems that have the potential to generate many novel technological applications.^[1] We have elaborated a rational approach to the design, synthesis, and structural analysis of dendritic building blocks. These blocks self assemble into cylindrical or spherical supramolecular dendrimers, that in turn semiorganize into a hexagonal columnar $p6mm$ ^[2] or cubic $Pm\bar{3}n$ ^[3a] liquid-crystalline (LC) lattices, respectively (Scheme 1). The analysis of these lattices by X-ray diffraction

(XRD) experiments provides access to the determination of the shape and size of the dendritic building blocks. Subsequently, these blocks are employed in the synthesis of cylindrical or spherical macromolecular objects^[4] with controlled internal structures, that self-organize into similar lattices. More complex objects, able to self-organize into various superlattices,^[5] were also developed from these dendritic building blocks. Cylindrical macromolecules that do not self-organize to hexagonal columnar lattices^[6a-c] or self-organize to a nematic LC phase^[6d] were also reported.

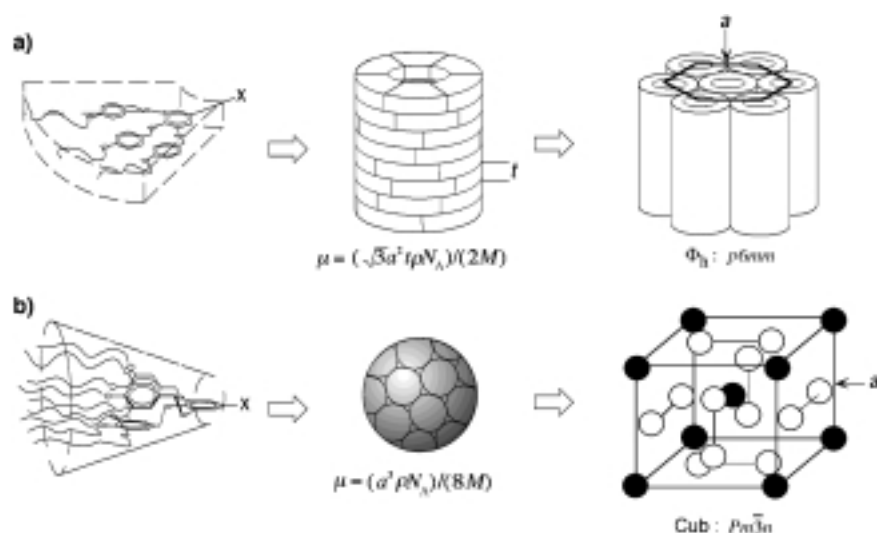
Presently we are elucidating the principles that govern the control of the shape and size of self-assembling monodendrons and, through their architecture, the shape and size of their supramolecular and macromolecular dendritic forms. Toward this end, we are investigating libraries of self-assembling monodendrons which differ in their: minidendron architecture on the periphery;^[2a, 3a, 7] internal repeat unit architectures;^[8] generation number;^[7] core functionalities;^[4a,b] core multiplicities;^[2a, 3a] and so forth.

In this communication, we report the attachment of the first generation 3,4-bis(*n*-dodecan-1-yloxy)benzyl ether monodendron (that is, minidendron^[5]) to the periphery of Fréchet-type dendritic repeat units (3,5-disubstituted benzyl ethers) to produce a class of hybrid self-assembly monodendrons. The first five generations of these monodendrons exhibit the largest diversity of monodendron and supramolecular dendrimer shapes reported to date. Particularly interesting for the design of novel architectural motifs, lattices, and superlattices is that the fourth generation includes the first monodendron that exhibits a dislike shape.

Scheme 2 describes the synthesis of the first five generations of monodendrons (**3,4-(3,5)ⁿ⁻¹12Gn-X** (generation number $n=1-5$) by using our previously reported synthetic procedure.^[3a, 7] Details of their synthesis and characterization, by ¹H and ¹³C NMR, HPLC, GPC, elemental analysis, differential scanning calorimetry

(DSC), XRD and thermal-optical polarized microscopy (TOPM), by our standard procedures^[3a, 7] are available in the Supporting Information and in Tables 1 and 2. The synthesis and characterization of (**3,4**)**12G1-X** ($X=CO_2CH_3$,^[9a,b] CH_2OH ,^[9c,d] CH_2Cl ^[4b]) and of (**3,4-3,5**)**12G2-X** ($X=CO_2CH_3$, $COOH$)^[4b] have been reported. Table 1 summarizes the most representative analytical results and the phase behavior of selected supramolecular dendrimers obtained by a combination of DSC, TOPM (Figure 1), and XRD.

Scheme 3 illustrates the mechanism of self-assembly over four monodendron generations, the lattice dimensions a [Å], the number of monodendrons (μ) forming the cross-section of thickness t ($t=4.7$ Å) of a supramolecular cylinder or of a supramolecular sphere (Scheme 1), and their diameter D [Å]. The temperature at which the XRD analysis was performed is



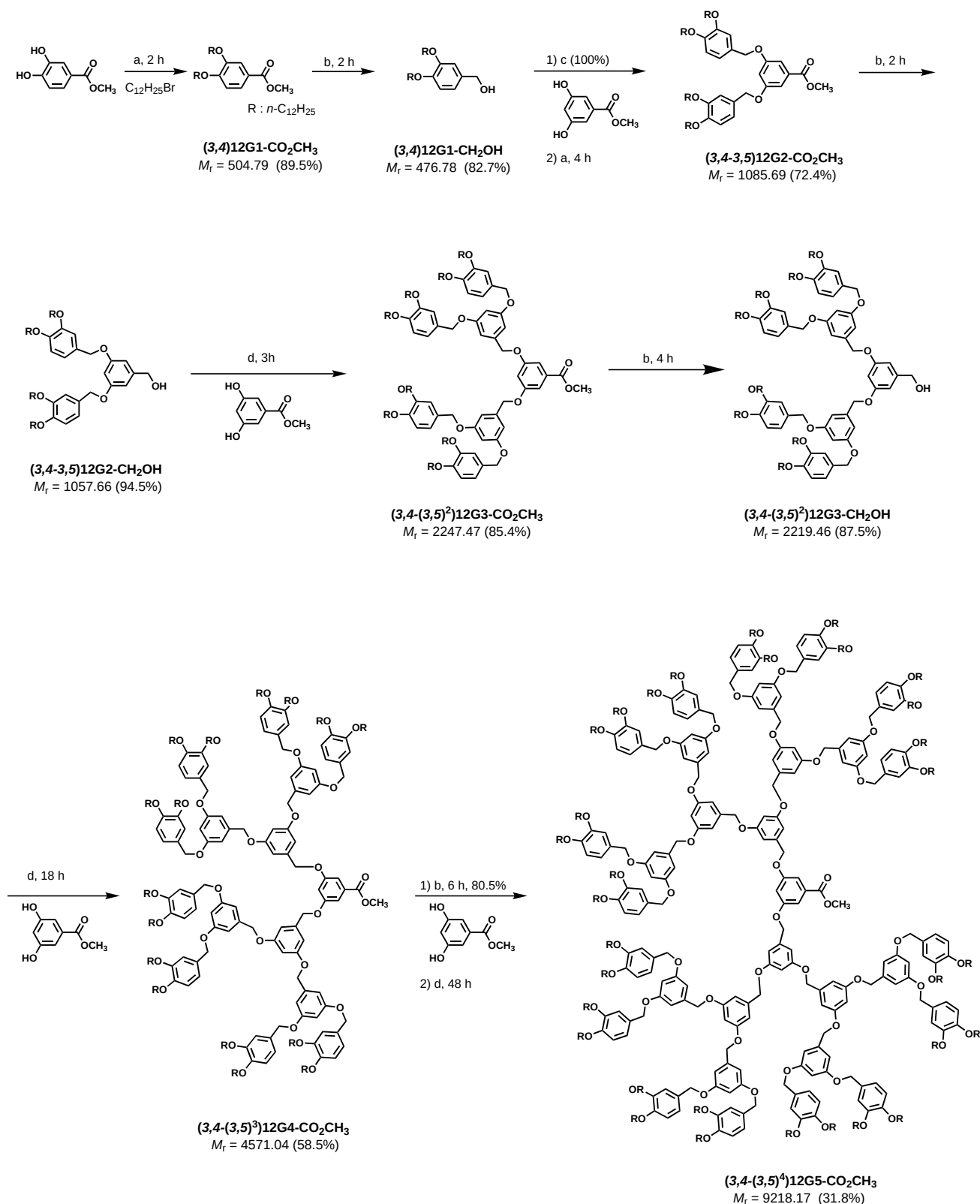
Scheme 1. Schematic representation of a) the self-assembly of flat, tapered monodendrons into a supramolecular cylindrical dendrimer and their subsequent self-organization to a hexagonal columnar $p6mm$ (Φ_h) LC lattice, and b) the self-assembly of conical monodendrons into a supramolecular spherical dendrimer and their subsequent self-organization in the cubic $Pm\bar{3}n$ (Cub) LC lattice. For explanation on the calculation of μ , see Table 2; $t=4.7$ Å. X = endoreceptor or functional group.

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 2. Synthesis of **(3,4-(3,5)ⁿ⁻¹)12Gn-X** (**X** = CO₂CH₃, CH₂OH, and CH₂Cl) monodendrons. a) K₂CO₃, DMF, 70 °C; b) LiAlH₄, THF, 20 °C; c) SOCl₂, CH₂Cl₂, DMF (cat.); d) diethylazodicarboxylate (DEAD), PPh₃, THF, 20 °C.

presented in parentheses in the same Scheme and also in Table 2.

The results from Tables 1, 2, and Scheme 3 can be summarized as follows. The first generation monodendron

(3,4)12G1-X (**X** = CO₂CH₃, CH₂OH) (that is, minidendron), that was used to functionalize the periphery of the later generations of monodendrons, is crystalline (Table 1). The second, third, and fourth generation monodendrons self-

Table 1. Theoretical and experimental (GPC) molecular masses, experimental densities,^[a] and thermal transitions of selected monodendrons **(3,4-(3,5)ⁿ⁻¹12Gn-X** (**X** = CH₂OH, COOH, CO₂CH₃).

Monodendron	M_r	M_n (GPC)	M_w/M_n (GPC)	$\rho_{20}^{[a]}$ [g cm ⁻³]	Thermal transition [°C] and corresponding enthalpy change [kcal mol ⁻¹] heating ^[b] cooling	
(3,4)12G1-CO₂CH₃	504.79	829	1.01	1.01	1) k - 2 (0.92) k 16 (2.93) k 54 (17.13) i 2) k 38 (1.16) - k 41 (3.69) k 54 (16.95) i	i 22 (13.58) k
(3,4)12G1-CH₂OH	476.78	796	1.01	1.01	1) k 12 (4.23) k 53 (16.06) i 2) k 37 (0.53) - k 39 (2.32) k 52 (14.26) i	i 27 (10.91) k
(3,4-3,5)12G2-CH₂OH	1057.68	1663	1.04	0.99	1) k 65 (18.54) - k 69 (0.37) k 76 (5.47) i 2) k 61 (12.91) i	i 49 (1.24) Φ_h 37 (8.72) k
(3,4-3,5)12G2-COOH	1071.66	1673	1.04	1.02	1) k 69 (21.82) i 2) k 14 (3.02) Φ_h ^[c] 68 (3.94) i	i 63 (4.00) Φ_h 5 (2.45) k
(3,4-(3,5)²)12G3-CO₂CH₃	2247.47	3216	1.07	1.01	1) k - 5 (3.55) k 39 (12.56) k 45 (2.33) k 50 (0.86) i 2) k - 4 (4.01) Φ_h 45 (5.22) i	i 39 (2.55) Φ_h 27 (2.06) k
(3,4-(3,5)³)12G4-CO₂CH₃	4571.04	5998	1.11	0.99	1) k 15 (72.96) k 42 (4.38) Φ_h 66 (1.09) i 2) k - 12 (18.92) Φ_h 66 (1.06) i	i 58 (0.86) Φ_h - 18 (14.95) k
(3,4-(3,5)⁴)12G5-CO₂CH₃	9218.17	8638	1.09	0.99	1) k - 6 (41.47) k 46 (11.79) Cub ^[d] 67 (3.79) i 2) k - 5 (34.85) T_g 36 Cub 59 (1.61) Cub 66 (1.40) i	i 57 (0.42) Cub - 11 (36.61) k

[a] Densities were measured at 20 °C. [b] 1) Data from the first heating and cooling scans; 2) data from the second heating scan. [c] Φ_h = Hexagonal-columnar *p6mm* LC phase. [d] Cub = Cubic *Pm3n* LC phase.

Table 2. Structural characterization of supramolecular dendrimers from selected monodendrons **(3,4-(3,5)ⁿ⁻¹12Gn-X**.

Monodendron	T [°C]	Lattice	$\langle d_{100} \rangle^{[a]}$	$\langle d_{210} \rangle^{[b]}$	a [Å]	R [Å]	$\mu'^{[g]}$	μ
(3,4-3,5)12G2-CH₂OH	49	<i>p6mm</i>	36.9		42.6 ^[c]	21.3 ^[e]		4 ^[h]
(3,4-3,5)12G2-COOH	66	<i>p6mm</i>	37.5		43.3 ^[c]	21.6 ^[e]		4 ^[h]
(3,4-(3,5)²)12G3-CO₂CH₃	36	<i>p6mm</i>	46.0		53.1 ^[c]	26.6 ^[e]		3 ^[h]
(3,4-(3,5)³)12G4-CO₂CH₃	51	<i>p6mm</i>	39.5		45.6 ^[c]	22.8 ^[e]		1 ^[h]
(3,4-(3,5)⁴)12G5-CO₂CH₃	56	<i>pm3n</i>		39.0	87.3 ^[d]	27.1 ^[f]	43	5 ^[i]

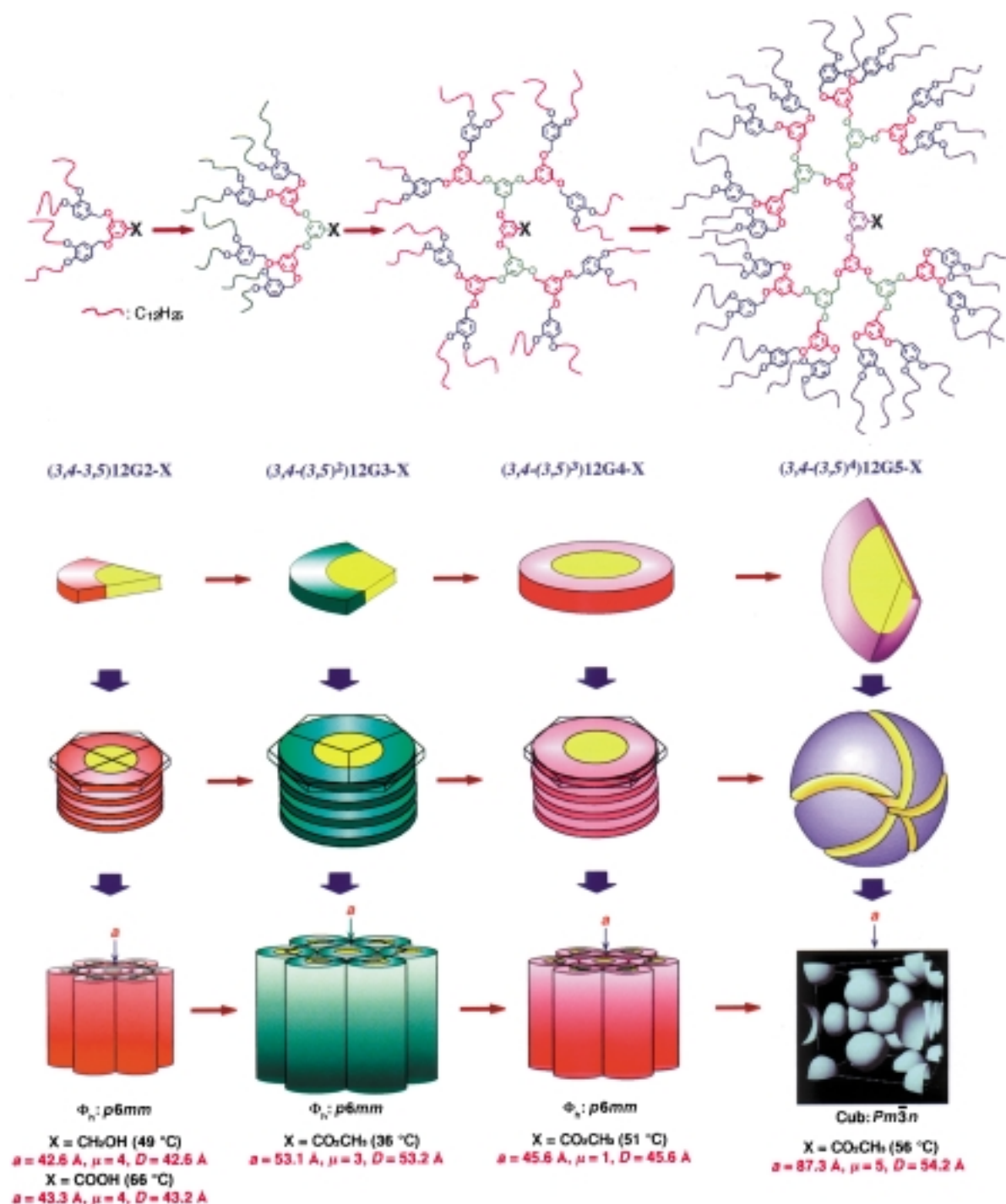
[a] $\langle d_{100} \rangle = (d_{100} + \sqrt{3}d_{110} + 2d_{200})/3$. [b] $\langle d_{210} \rangle = (\sqrt{2}d_{110} + \sqrt{4}d_{200} + \sqrt{5}d_{210} + \sqrt{6}d_{211} + \sqrt{8}d_{220})/5\sqrt{5}$. [c] Hexagonal columnar lattice parameter $a = 2\langle d_{100} \rangle/\sqrt{3}$. [d] Cubic lattice parameter $a = \sqrt{5}d_{210}$. [e] Column radius $R = \langle d_{100} \rangle/\sqrt{3}$. [f] Sphere radius $R = \sqrt[3]{(a^3/32\pi)}$. [g] Number of monodendrons per unit cell $\mu' = (a^3\rho)/M$. [h] Number of monodendrons per cylinder stratum $\mu = (4\sqrt{3}N_A R^2 t \rho)/2M$ (Avogadro's number $N_A = 6.022045 \times 10^{23}$ mol⁻¹, average height of the column stratum $t = 4.7$ Å, M = molecular mass of the monodendron). [i] Number of monodendrons per spherical dendrimer $\mu = \mu'/8$.

assemble into supramolecular cylinders which in turn self-organize in a hexagonal columnar *p6mm* LC lattice. Under the polarized microscope the texture of their LC phase shows a combination of large isotropic domains, characteristic of a homeotropic arrangement of the columns, and a focal conic, fan-shaped anisotropic texture (Figure 1).^[2a, 7] An XRD analysis of these lattices (Scheme 1)^[2a] demonstrates that **(3,4-3,5)12G2-X** (**X** = CH₂OH, COOH) have a flat, tapered shape equivalent to a quarter of a cross section of its supramolecular cylinder ($D = 42.6, 43.2$ Å, respectively; $t = 4.7$ Å). Monodendron **(3,4-(3,5)²)12G3-CO₂CH₃** also has a flat tapered shape. However, its size represents a third of a cross section of its supramolecular cylinder ($D = 53.2$ Å). The shape of **(3,4-(3,5)³)12G4-CO₂CH₃** is equivalent to an entire cross section of its supramolecular cylinder, that is, it is a disclike molecule ($D = 45.6$ Å). This is the first example of a monodendron that has a disclike shape. Monodendron **(3,4-(3,5)⁴)12G5-CO₂CH₃** is equivalent of a fifth of its supramolecular sphere ($D = 54.2$ Å). Under the polarized micro-

scope the texture of the cubic phase, self-organized from the supramolecular spheres, is optically isotropic.

Previously, we reported the first examples of monodendrons and supramolecular dendrimers with a shape controlled by the generation number and quantitative analysis by XRD.^[7a] This experiment demonstrated the validity of the theoretical prediction that the generation number should control the shape of the dendrimer.^[7b] For this previous report, the transition from a supramolecular cylinder to a supramolecular sphere occurred by changing the shape of the monodendron directly, from that of a half disc to a sixth of a sphere without passing through a complete disc shape. The ability to create the disclike molecule **(3,4-(3,5)³)12G4-X** provides a general strategy for the synthesis of supramolecular columns with anisotropic surfaces. This synthesis hinges on the design of surface patterns with **(3,4)12G1-X** minidendrons functionalized with chemically dissimilar, flexible groups.

Finally, the results reported here can contribute in a quantitative way to some of the most interesting applications



Scheme 3. XRD analysis of supramolecular cylindrical and spherical dendrimers self-assembled from $(3,4-(3,5)^{n-1})12Gn-X$ monodendrons. Variables: a [Å] is the lattice parameter; D [Å] is the diameter of the supramolecular columnar or spherical dendrimer; μ is the number of monodendrons forming the 4.7 Å cross-section of a supramolecular cylindrical or spherical supramolecular dendrimer; the temperature [°C] of the XRD experiments is given in parentheses.

that are widely pursued with Fréchet-type monodendrons and dendrimers. For example, several research groups are exploiting these dendritic building blocks to explore concepts based on various site isolation strategies and controlled micro-environments in both the solution and bulk states. Such site isolation is expected to occur during the shape transition to a globular structure.^[10] Elegant experiments by Fréchet et al.^[10] and Aida et al.^[11] have demonstrated that, in solution, this shape transition occurs during the development of the

monodendron from generation three to four, although the extent of site isolation continues to increase from generation four to five.^[11] The fifth generation monodendron adopts a globular shape in the bulk state.^[12] The results from Scheme 3 support all previous reports.^[10, 11, 12] If X in the $(3,4-(3,5)^{n-1})12Gn-X$ monodendron represents the site to be isolated, the site-isolating globular shape begins at generation five in the solid state but at generation four in a dilute solution. This occurs for reasons of conformational flexibility,

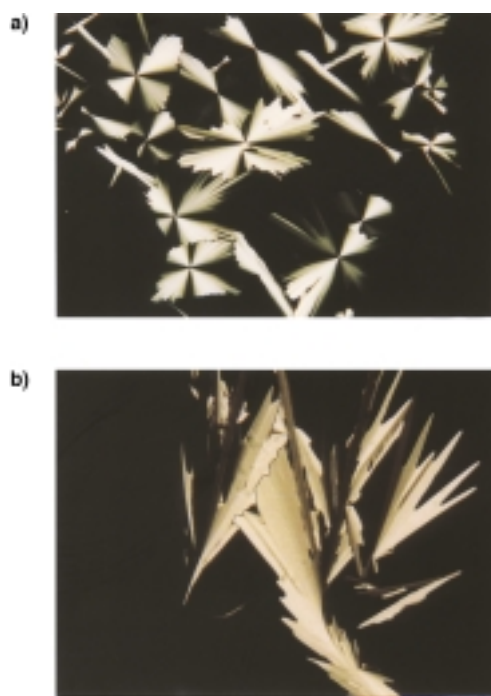


Figure 1. Representative thermal-optical polarized microscopy pictures showing the textures of the hexagonal columnar (Φ_h) mesophases of a) (3,4-(3,5)12G2-CH₂OH upon cooling from 76 °C to 54.9 °C at 1 K min⁻¹; and b) (3,4-(3,5)12G3-CO₂CH₃ obtained upon cooling from 50 °C to 45.1 °C at 1 K min⁻¹.

as the dislike molecule (3,4-(3,5)³12G4-X can adopt a globular shape in solution. The extent of site isolation will increase from the fourth to the fifth and higher generations.

These results suggest synthetic methods that place X in the center of a single spherical monodendron. Such a molecule would generate an ideal site-isolation mechanism both in the bulk and in solution.

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Nickel-Catalyzed Cross-Coupling of Aryl Chlorides with Aryl Grignard Reagents**

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Dedicated to Professor Wilhelm Keim on the occasion of his 65th birthday

The Grignard cross-coupling mediated by nickel and palladium catalysts^[1, 2] represents a useful synthetic approach to biaryls, terphenyls, and oligoaryls which are important

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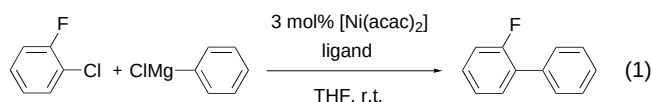
Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

building blocks of natural products, liquid crystals, polymers, and ligands.^[3] Although sterically demanding phosphanes and imidazolin-2-ylidenes assist palladium(0) to activate aryl chlorides in catalytic cross-coupling reactions,^[4] these systems are less effective in the Grignard cross-coupling of aryl chlorides with arylmagnesium halides. Their drawback is the necessity for elevated reaction temperatures, which can lead to problems with regard to selectivity.^[5] The same drawback exists with the use of the heterogeneous catalyst Ni/C.^[6]

Herein, we report on a first economical catalyst system based on nickel for the coupling of aryl chlorides with aromatic Grignard reagents in high yields even at ambient temperature. The air-stable, conveniently available imidazolium salts **1** and **2** as well as tris(*tert*-butyl)phosphane **3** were identified as the most efficient ligands for this general methodology with nickel(II) diacetylacetonate.

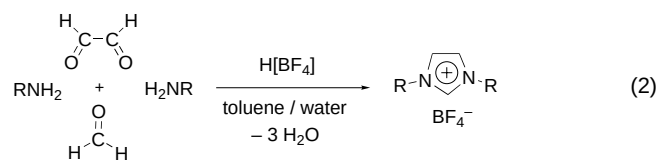


To speed up the optimization process,^[7] we employed a ¹⁹F NMR spectroscopic screening of a large variety of phosphanes, arsanes, and N-heterocyclic carbenes as ligands in combination with various metal precursors^[8] to get a meaningful semiquantitative time/conversion correlation even in the primary screen. ¹⁹F{¹H} NMR spectroscopy was chosen to analyze the reactions for various reasons^[9] including the inertness of C–F bonds under the reaction conditions.^[10] Phenylmagnesium chloride and 1-chloro-2-fluorobenzene proved suitable substrates for this assay [Eq. (1)]. As the



screening results at this stage did not require exact yield determination, we assumed integration faults due to proton decoupling and deviations due to defluorination to be small.^[11]

Generally, imidazolium salts as precursors to N-heterocyclic carbenes^[12] are especially suitable for high-throughput approaches since their synthesis by a multicomponent one-pot reaction under mild conditions in the presence of air and moisture^[13] can be parallelized more easily than, for example, that for phosphanes. Appropriate counterions such as [BF₄][−] or [PF₆][−] allow the isolation of the pure product salt by simple filtration or phase separation [Eq. (2)].^[11, 14]



The primary screen at ambient temperature provided the following findings: 1) [Ni(acac)₂] (acac = acetylacetonate) is much more active than [Pd₂(dba)₃] (dba = dibenzylidene-acetonate) or Pd(OAc)₂, 2) the imidazolium salts **1** and **2** as well as the phosphane **3** are the best ligands and induce highest selectivity, 3) only an equimolar amount of the activating ligands with regard to the metal is necessary, and 4) the anions of the imidazolium salts do not exhibit activity and selectivity effects.

The most active systems were then subjected to preparative-scale experiments with different aryl chlorides and arylmagnesium compounds (Table 1). The electronic properties of the aryl chlorides display the expected consequences,

Table 1. Nickel-catalyzed Grignard cross coupling at ambient temperature.^[a]

Entry	4	5	X	1	2 [%] ^[b]	3
1	H	N	H	Cl	> 99	92
2	4-CF ₃ [c]	C	H	Cl	90	47
3	4-CH ₃	C	H	Cl	72	89
4	4-OCH ₃	C	H	Cl	67	71
5	2-CH ₃	C	H	Cl	70	72
6	2,6-(CH ₃) ₂	C	H	Cl	4	12
7	H	N	4-OCH ₃	Br	> 99	> 99
8	4-CF ₃ [c]	C	4-OCH ₃	Br	> 99	38
9	H	C	4-OCH ₃	Br	95	> 99
10	4-CH ₃	C	4-OCH ₃	Br	85	87
11	2-CH ₃	C	4-OCH ₃	Br	77	77
12	2,6-(CH ₃) ₂	C	4-OCH ₃	Br	8	28
13	H	N	2,4,6-(CH ₃) ₃	Br	> 99	94
14	4-CF ₃ [c]	C	2,4,6-(CH ₃) ₃	Br	78	52
15	H	C	2,4,6-(CH ₃) ₃	Br	99	99
16	4-CH ₃	C	2,4,6-(CH ₃) ₃	Br	96	> 99
17	4-OCH ₃	C	2,4,6-(CH ₃) ₃	Br	98	87
18	2-CH ₃	C	2,4,6-(CH ₃) ₃	Br	78	75
19	2,6-(CH ₃) ₂	C	2,4,6-(CH ₃) ₃	Br	3	5

[a] Aryl chloride (1.0 equiv), Grignard reagent (1.5 equiv), [Ni(acac)₂] (3 mol %), ligand (3 mol %), THF, room temperature, *t* = 18 h. [b] GC yield of desired product **6** using diethyleneglycol-di-*n*-butyl ether as internal standard. For full details on product distribution see the Supporting Information. [c] Reagents were used as received.

that is electron-poor arenes are most reactive. Steric congestion is partially tolerated by the system as demonstrated by 2-chlorotoluene, but two *ortho*-substituents as in 2-chloro-*m*-xylene hamper useful conversions. Generally, the catalysts are less sensitive to steric bulk on the organometallic reagent than on the aryl halide (entries 13–19, Table 1).^[11]

The time/conversion diagram in Figure 1 for the coupling of 2-chlorotoluene with 4-anisylmagnesium bromide [Eq. (3)] reveals that the catalysts with ligands **1**–**3** differ only in their turnover frequencies (TOF) at the beginning of the reaction, but result in roughly the same turnover numbers (TON). The analogous palladium systems do not catalyze the reaction under these mild conditions efficiently. Neither of the nickel

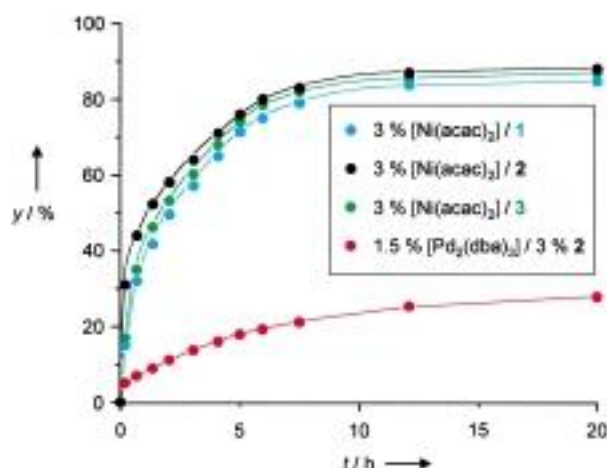


Figure 1. Comparison of the time/conversion characteristics of ligands **1–3** in the nickel-catalyzed Grignard cross-coupling reaction. The most active palladium catalyst is included for comparison. (y = yield of 4-methoxy-2'-methylbiphenyl; 2-chlorotoluene (2.00 mmol), 4-anisylmagnesium bromide (3.00 mmol) in THF (3 mL), $[\text{Ni}(\text{acac})_2]$ (0.06 mmol), ligand (0.06 mmol), diethyleneglycol-di-*n*-butyl ether (50 mg), THF (10 mL)). systems has an induction period. Homocoupling products of the Grignard reagents were observed in all reactions and are formed only at the beginning of the reaction.^[11]

In some reactions minor amounts (<1%) of by-products such as terphenyls occur, suggesting radical side reactions as observed in other nickel-catalyzed cross-coupling reactions.^[15] Nevertheless, the electronic influence of the aryl chloride on the reaction rate and the product distributions indicate that the bulk of the reaction follows a polar pathway. Further by-products derived from activation of $\text{C}_{\text{Ar}}\text{--OCH}_3$ or $\text{C}_{\text{Ar}}\text{--F}$ bonds were formed in amounts of 3% and below, and only after the C–Cl bond had been converted completely as no chlorine containing biphenyls were detectable.

Regarding the coordination mode of the ligand derived from **1** and **2** under the reaction conditions, the formation of an imidazolin-2-ylidene complex of nickel(0) was identified by characteristic ^{13}C NMR signals.^[16]

In summary, highly active catalysts based on nickel as the catalytically active metal were developed for the Grignard cross-coupling reaction of aryl chlorides at ambient temperature and at low catalyst loading. Furthermore, a modified high-yield, facile work-up procedure for the synthesis of imidazolium salts allows the efficient high-throughput screening of N-heterocyclic carbene ligands.

Experimental Section

A Schlenk tube was charged with $[\text{Ni}(\text{acac})_2]$ (7.7 mg, 0.03 mmol), ligand **1**, **2**, or **3** (0.03 mmol), and the aryl chloride (1 mmol) under an atmosphere of dry nitrogen. After addition of THF (1 mL) and the internal standard diethyleneglycol-di-*n*-butyl ether (50 mg), the mixture was stirred for 5 min until the catalytic reaction was initiated by dropwise addition of the Grignard reagent (1.5 mmol, ca. 1M in THF) by syringe at ambient temperature. The reaction was ceased by addition of methanol (1 mL). Yield was determined by GC/MS analysis.

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High-Spin Molecules: A Novel Cyano-Bridged $\text{Mn}^{\text{II}}\text{Mo}^{\text{V}}$ Molecular Cluster with a $S = 51/2$ Ground State and Ferromagnetic Intercluster Ordering at Low Temperatures**

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Dedicated to Professor Andreas Ludi on the occasion of his retirement

The synthesis and investigation of the magnetic properties of novel molecular clusters containing paramagnetic transition metal ions is currently attracting a great deal of interest. This is driven by the ability of selected cluster compounds to function as nanoscale magnets at cryogenic temperatures.^[1–18] These molecular compounds are characterized by a ground state with an unusually large number of unpaired electrons. The existence of a fairly large ground state spin (S) value, together with a large magnetic anisotropy is necessary for molecules to exhibit this new magnetic phenomenon of single-molecule magnetism, and accordingly, such high-spin molecules have been termed “single-molecule magnets” (SMM).^[12]

The importance of a high S value in molecular compounds has stimulated the search for new SMM, but until now molecules with $S > 10$ are very rare.^[1, 9] The highest value reported to date is $S = 33/2^3$ for a cocrystallized Fe_{17} and Fe_{19} species.^[9] The most accurately investigated system so far belongs to the series of manganese carboxylates of general formula $[\text{Mn}_{12}\text{O}_{12}(\text{RCOO})_{16}]$ with a varying number of water molecules.^[1–7] These molecules all contain eight Mn^{III} and four Mn^{IV} ions and the acetate derivative is reported to have a ground $S = 10$ state.^[2] For this cluster, a slow relaxation of the magnetization was detected at low temperature, similar to the blocking temperature of superparamagnets.^[2] Consequently, in the low-temperature regime, this cluster behaves like a single-molecule magnet and shows molecular hysteresis effects. This bistability opens up exciting possibilities for the storage of information at the molecular level.

As research in this field progresses, a question arises, with the realization of cluster compounds with an increasing number of spins, does the S value become so large that we

enter the regime where the cluster magnetic characteristics are interwoven with those of the onset of bulk magnetic behavior?

We report herein the structural and magnetic properties of the novel molecular cluster compound **1**, which exhibits the



largest spin ground state observed to date. Cluster **1** comprises of fifteen cyano-bridged metal ions, namely nine Mn^{II} ions ($S = 5/2$) and six Mo^{V} ions ($S = 1/2$), giving a total of 51 unpaired electrons. For simplification, the molecular configuration of an idealized pentadecanuclear cluster core with O_h symmetry is sketched in Figure 1. The nine Mn^{II} ions define a body-centered cube, and the six Mo^{V} ions constitute an octahedron.

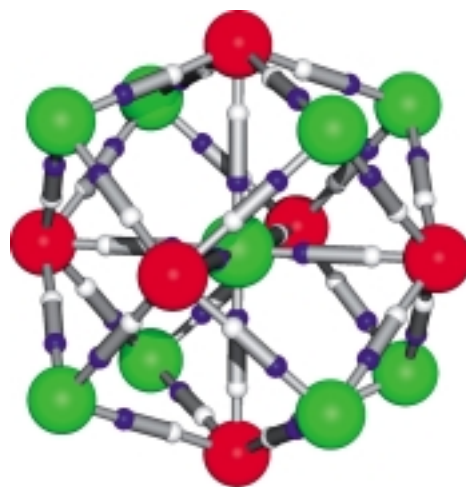


Figure 1. Representation of the $[\text{Mn}_9^{\text{II}}(\mu\text{-CN})_{30}\text{Mo}_6^{\text{V}}]$ cluster core. The figure is drawn for maximal symmetry (O_h) to accentuate the cluster topology. The green spheres represent Mn^{II} ions, the red spheres represent the Mo^{V} ions and the bonds between them represent the μ -cyano ligands.

The central Mn^{II} ion is connected to six Mo^{V} ions by six μ -cyano-ligands. Each of the Mo^{V} ions is linked by four more μ -cyano-ligands to four peripheral Mn^{II} ions. Each of the eight peripheral Mn^{II} ions is connected by μ -cyano-ligands to three Mo^{V} ions, thus the Mn^{II} ions cap the faces of the Mo^{V} octahedron. To summarize, the $\text{Mo}^{\text{V}}\text{-CN-Mn}^{\text{II}}$ geometry is such that the atoms are linked to form an aesthetically pleasing topological pattern in which the polyhedron spanned by the peripheral metal ions is closest in geometry to a rhombic dodecahedron. This topology is reminiscent of the well documented $[\text{Mo}_6\text{X}_8]^{4+}$ unit from molybdenum dichloride/dibromide.^[19]

The exact molecular geometry of the compound has been determined by single-crystal X-ray analysis at 223 K. (Figure 2). In comparison to the idealized sketch of **1** in Figure 1, the actual cluster has a lower symmetry, C_2 , with the central Mn^{II} ion lying on the crystallographic twofold axis. Additional ligands complete the coordination sphere of the peripheral metal ions and complete the charge balance to give a neutral cluster. Three methanol molecules are ligated to the outer Mn^{II} ions, increasing their coordination number to six. Analogously, three additional terminal cyano ligands coor-

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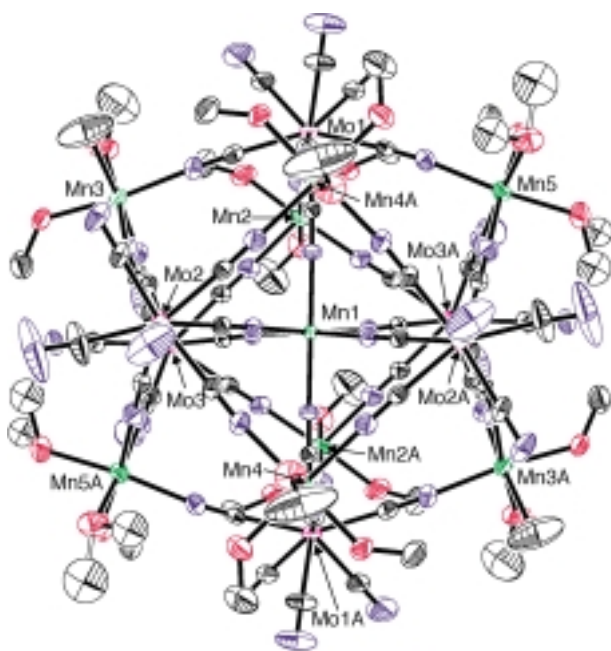


Figure 2. ORTEP representation (ellipsoids at 30% probability) of the molecular structure of **1**; for clarity only the Mn^{II} and Mo^V atoms are labeled and the H atoms are omitted. Ranges for selected distances [Å] and angles [°] are given below (the indices c, p, and t represent an atom linked to the center of the cluster, a peripheral atom, and a terminal atom, respectively). The average bond lengths and angles are given in square brackets after the ranges: Mo–C_c 2.13–2.14 [2.14], Mo–C_p 2.14–2.17 [2.15], Mo–C_t 2.13–2.17 [2.14], Mn1–N_c 2.18–2.19 [2.19], Mn–N_p 2.19–2.23 [2.21], Mn–O 2.16–2.20 [2.19], C_c–N_c 1.14–1.15 [1.15], C_p–N_p 1.13–1.15 [1.15], C_t–N_t 1.12–1.16 [1.14], Mn1–Mo 5.47–5.48 [5.47], Mn–Mo 5.47–5.52 [5.49]; C_c–Mo–C_p 70.9–74.6 [72.9], C_p–Mo–C_p 76.0–99.5 [85.0], N_c–Mn1–N_c 85.8–95.1 [90.1], N_c–Mn1–N_c 173.9–175.6 [174.5], N_p–Mn–N_p 90.5–99.0 [93.5].

dinate to each Mo^V ion establishing an eightfold coordination and giving the overall [Mo^V(CN)₈]^{3–} stoichiometry. Two types of geometry for the Mo–C–N–Mn bridges are found in **1**. Those involving the central Mn^{II} ion are fairly linear (Mn–N–C 175.8–179.2° and Mo–C–N 178.1°–179.0°), whereas the peripheral Mo–C–N–Mn bridges are essentially linear at the cyanide carbon (Mo–C–N 175.9–179.8°), but bent at the cyanide nitrogen (Mn–N–C 169.6–178.8°).

The spin-bearing centers in the cluster (with the exception of the central Mn^{II} ion) are all located at the periphery of the molecule and are essentially free from shielding by bulky organic ligands. This is in contrast to many of the high-nuclearity cluster compounds previously reported,^[1–18] in which the magnetic intercluster interactions are often efficiently suppressed by a layer of organic ligands.

Compound **1** crystallizes in a monoclinic space group (C2/c). An extended intermolecular H-bonded network connects each cluster to eight nearest neighbors; Figure 3 shows the H-bond interactions between three of them. Each peripheral Mn^{II} ion of a cluster has one MeOH ligand which is involved in an intermolecular H-bond to the nitrogen atom of a cyanoligand of a neighboring cluster (terminally attached to a Mo^V). For two of the Mo^V ions, there are two terminal cyano ligands involved in intermolecular H-bonding interactions with neighboring methanol ligands ligated to Mn^{II} ions of different clusters. The remaining four Mo^V ions have one terminal

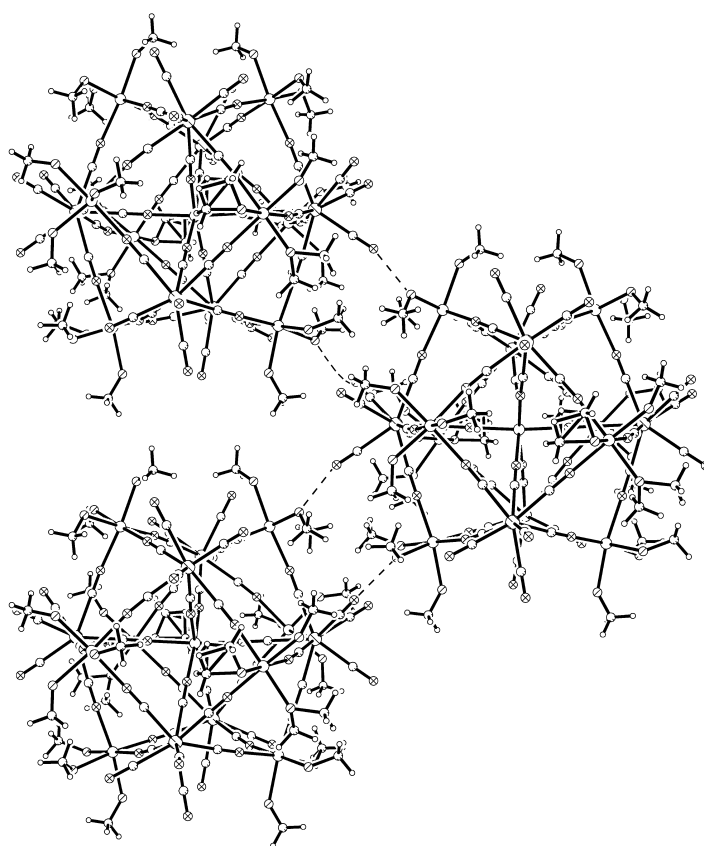


Figure 3. A plot of three nearest neighbor cluster molecules showing the close edge contacts between the Mn^{II} and the Mo^V ions. The dotted lines represent the H-bonding interactions O–H...N.

ciano ligand which takes part in an intermolecular H-bonding interaction with a neighboring methanol ligand. Thus, each cluster is involved in sixteen H-bonding interactions with its nearest neighbors. All of these O–H...N contacts are in the range 2.70–2.76 Å and are well within the sum of the van der Waals radii (2.9 Å), indicative of 'medium strength' hydrogen bonds. This extended intercluster H-bonded network, in which the MeOH donors and CN acceptors are connected in a regular donor-acceptor sequence to give a continuous three dimensional (3D) array, results in close nearest neighbor contacts between metal ions at the edges of the clusters (Mo–Mn 6.97–7.58, Mn–Mn 7.20–7.58 Å). All remaining cyano and methanol ligands not involved in intercluster H-bonding interactions form hydrogen bonds with neighboring solvent molecules. The solvent molecules (MeOH and H₂O) occupy channels between the clusters, filling up the remaining unoccupied space in the crystal lattice.

Cyano-bridged metal assemblies are not new to the field of molecular magnetism, and several examples using cyano-bridged coordination to build up extended networks displaying interesting magnetic and photomagnetic properties have been reported.^[20–22]

Having synthesized and structurally characterized a molecular compound possessing 51 unpaired electrons, we focused our attention on the magnetic behavior of **1**. Variable temperature dc-magnetic susceptibility studies were carried out to determine the spin value for the ground state of **1**. Data

were collected in the temperature range 1.8–300 K for polycrystalline samples, and in preliminary studies on oriented single crystals. In addition, heat capacity measurements were carried out on single crystals in the temperature range 1.8–100 K. First, we discuss the high-temperature regime, namely $50 < T < 300$ K. Figure 4 shows the corresponding plot of $\chi_m T$ versus T , which demonstrates a gradual increase of $\chi_m T$ with the lowering of temperature. This behavior indicates the presence of ferromagnetic intracluster exchange interactions. Even at 300 K, the experimental value of $\chi_m T = 46$ emu K mol⁻¹ is slightly higher than the calculated spin-only value of $\chi_m T = 40.9$ emu K mol⁻¹ for a cluster comprising nine noninteracting Mn^{II} ($g = 2.0$, $S = 5/2$) and six noninteracting Mo^V ($g = 1.98$, $S = 1/2$)^[23] centers, demonstrating the effect of the ferromagnetic intracluster exchange. In conclusion, the magnetic behavior of this compound at $T > 50$ K is dominated by intracluster exchange interactions.

To obtain a rough quantitative estimate of the intracluster exchange interaction parameter J , calculations based on the Hamiltonian $\mathcal{H} = -2J\mathbf{S}_{\text{Mn}}\mathbf{S}_{\text{Mo}}$ were performed. In these calculations we assume only one type of Mn–NC–Mo nearest neighbor interaction and consequently, the temperature dependence of $\chi_m T$ is only a function of one single energy parameter, namely J . Despite this simplicity, the calculation of $\chi_m T$ versus T for the whole pentadecanuclear cluster is still beyond our reach, since the total number of electronic cluster states is simply too large, being of the order of 10^7 . As a consequence of this, we selected three cluster fragments of increasing size, as shown in Figure 4 and calculated $\chi_m T$ for various J values using a reported algorithm.^[24] From a

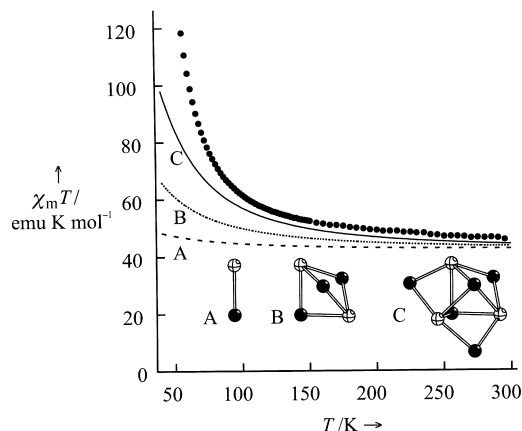


Figure 4. Temperature dependence of $\chi_m T$ above 50 K for the polycrystalline cluster compound **1**. The lines A–C represent calculated results (see text) for the corresponding cluster fractions (Mn^{II}: dark spheres; Mo^V: light spheres) using $J = 7$ cm⁻¹.

comparison with the experimental data and considering an extrapolation to the pentadecanuclear cluster unit, a ferromagnetic exchange interaction parameter J of 7 cm⁻¹ is deduced as an upper limit. For example, for $J = 4$ cm⁻¹, the total energy spread of the exchange-split ground state of the Mn₉Mo₆ cluster is in the order of 500 cm⁻¹. Thus, even at room temperature, there is no complete thermalization within the ground-state multiplet and this is in good agreement with the observed $\chi_m T$ value of 46 emu K mol⁻¹.

Figure 5 shows the plot of $\chi_m T$ versus T for different values of the applied field for the low-temperature regime, $T < 50$ K. Most significantly, the gradual increase of $\chi_m T$ with the lowering of temperature shows a clear break around 44 K, where $\chi_m T$ starts to rise steeply to over 4×10^4 emu K mol⁻¹ for an applied field of 1.5 G. This abrupt increase of $\chi_m T$ indicates the onset of cooperative ferromagnetic intercluster

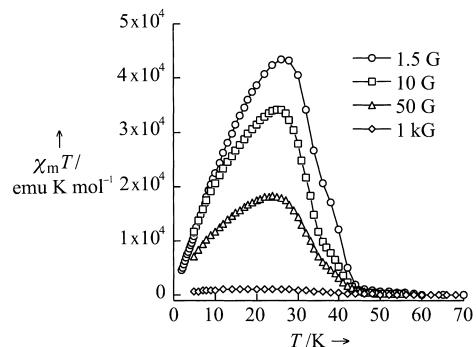


Figure 5. Temperature dependence of $\chi_m T$ below 70 K for the polycrystalline cluster compound **1** at different field values.

interactions. For comparison, the calculated $\chi_m T$ value for magnetically isolated exchange coupled clusters with $S = 51/2$ ground state spin would be only 338 emu K mol⁻¹. The magnetic susceptibility below 44 K is strongly field dependent, indicating the possibility of competing effects between the external field and the intercluster interactions. In addition, preliminary measurements on oriented single crystals show the magnetic susceptibility at $T < 44$ K to be clearly dependent on the crystal orientation relative to the applied field. All these results indicate that on lowering the temperature the magnetic cluster signature is lost and below 44 K a bulk behavior starts to emerge. This relatively high onset of intercluster correlations can be due to both exchange and magnetic dipole–dipole interactions. The former are facilitated by the sixteen hydrogen bonds per cluster between the terminal cyano and MeOH ligands of neighboring cluster molecules. For the latter, the isotropic interaction energy between two magnetic dipoles of $S = 51/2$ separated by 17.5 Å, that is the distance between the centers of nearest neighbor clusters, is of the order of 0.2 cm⁻¹.^[25] The estimate of 0.2 cm⁻¹ is valid at the very lowest temperatures with only the $S = 51/2$ cluster level populated. Around 40 K it is definitely lower because of the population of cluster levels with lower S values. From a calculation on the cluster fragments in Figure 4, a mean spin value of about $S = 12$ can be extrapolated for the whole cluster. This S value results in a magnetic dipolar interaction energy of the order of 0.05 cm⁻¹. Using these values and the molecular-field approximation, we estimate a T_C of about 30 K. This is in reasonably good agreement with the observed onset of cooperative intercluster correlations around 40 K. We conclude that magnetic dipolar interactions account for the major part of intercluster correlations in this temperature range.

A plot of χ_m^{-1} versus T shows linear behavior between 300 and 120 K (Curie constant $C = 41.8$ emu K mol⁻¹) which extrapolates to a positive Curie–Weiss constant Θ of 30.4 K.

This positive value is also related to the presence of ferromagnetic exchange interactions.

To confirm the characteristic behavior of the ferromagnetically correlated phase, the temperature dependences of the magnetization M under a weak magnetic field (1 G) and the remanent magnetization were measured. The field-cooled magnetization (FCM), zero-field-cooled magnetization (ZFCM) and remanent magnetization (RM) curves are shown in Figure 6. The FCM obtained by cooling the sample under

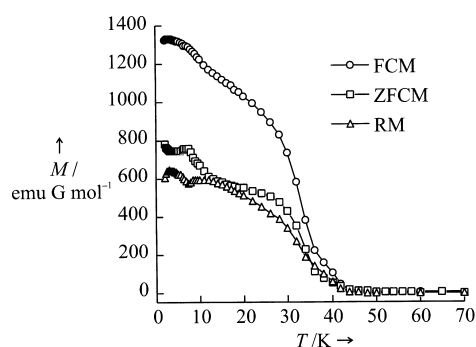


Figure 6. Temperature dependence of the magnetization M for the polycrystalline cluster compound **1** with FCM, ($H = 1$ G), ZFCM, and RM measuring protocols.

1 G shows a rapid increase when the temperature is lowered below 44 K and has inflection points around 35 K and 8 K. When the field was switched off at 1.8 K, a remanent magnetization was observed which vanished as the temperature was increased to 44 K. If the inflection point at 35 K is attributed to a distinct 3D ferromagnetic phase transition, the remanent magnetization should vanish at that temperature. Analogously, the ZFCM (cooling in zero field and warming under 1 G) would be expected to merge with the FCM curve at 35 K. This is not strictly, but approximately observed in Figure 6.

In addition (Figure 7) a sharp λ -peak appears in the heat capacity measurement at 2.9 K. Considering the very high spin value of $S = 51/2$, only a relatively low experimental

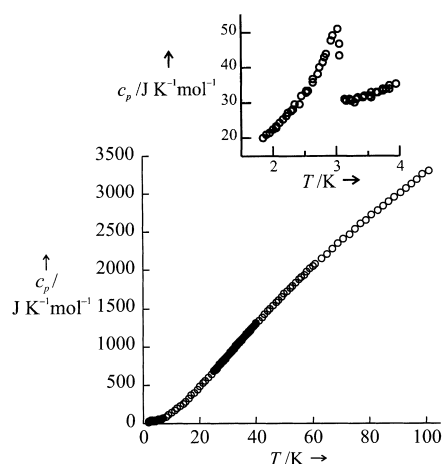


Figure 7. Temperature dependence of the molar heat capacity c_p for the crystalline cluster compound **1**.

magnetic heat capacity contribution C_m of $1.3 R$ is observed, indicating that the substantial part of the magnetic intercluster correlation occurs between 44 and 2.9 K. This low value can be compared with the experimental C_m of $2.8 R$ for another molecular ferromagnetic material ($T_C = 6$ K) where, within an extended 2D network, Mn^{II} ions ($S = 5/2$) and Cr^{III} ions ($S = 3/2$) are bridged by μ -oxalato ligands.^[26] The nature of the transition at 2.9 K is not yet understood.

Finally, the magnetization data collected at several temperatures between 2 K and 60 K with applied fields up to 50 kG are shown in Figure 8. The curve at 2 K exhibits a very high zero-field susceptibility and reaches a saturation value near

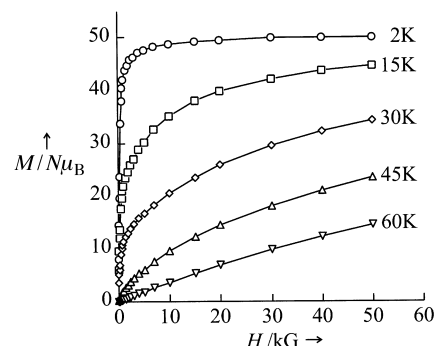


Figure 8. Field dependence of the magnetization M for the polycrystalline cluster compound **1** at different temperatures.

the expected $M_s/N\mu_B$ value of 51 for a $S = 51/2$ ground state, calculated with a value of $g(\text{cluster}) = 2.0$. In addition, a very narrow hysteresis loop was observed at 2 K with a coercive field of 15 G. A clear change in the shape of the magnetization curves taken below and above 44 K is observed; below 44 K, a high zero-field susceptibility value appears, whereas above 44 K this signature of ferromagnetic intercluster interactions is missing.

In summary, we have prepared and magnetically characterized a new compound containing high-spin clusters with a $S = 51/2$ ground state. In contrast to other high-spin clusters, such as Mn_{12} acetate,^[2] compound **1** does not exhibit the typical phenomena of molecular hysteresis and slow quantum tunneling at low temperatures. In **1**, a competitive interplay of intra- and intercluster interactions leads to a very interesting magnetic regime in the temperature range below 44 K. Magnetic dipole–dipole as well as exchange interactions may contribute to the intercluster coupling in **1**. It is clear that dipole–dipole intercluster interactions will become increasingly important with increasing ground state S values of high-spin clusters; it will therefore be increasingly difficult to observe typical nano-magnetic properties of spin clusters, unless specific measures are taken to isolate and insulate them.

In compound **1**, the magnetic properties above 44 K are characterized by ferromagnetic intracluster coupling. Extraction of J values requires approximation techniques, by which we obtain 7 cm^{-1} as an upper limit. A modeling of the magnetic data below 44 K, where magnetic ordering seems to arrive, is not possible at present because this new and interesting situation has not been dealt with theoretically so far.

Experimental Section

Compound **1** was obtained from the reaction of a 3:2 molar ratio of $[\text{Mn}^{\text{II}}(\text{H}_2\text{O})_6](\text{NO}_3)_2 \cdot x\text{H}_2\text{O}$ and $(\text{NBu}_4)_3[\text{Mo}^{\text{V}}(\text{CN})_8]$ in a (1:1) methanol/propanol mixture at room temperature.^[27] After a few days, dark red-brown crystals with an elongated polyhedral shape formed. The compound is fairly air and light sensitive, so all physical measurements were performed in the dark with polycrystalline material or single-crystals embedded in a grease envelope. The composition of the crystalline compound was established by single-crystal X-ray diffraction at 223 K.

Magnetic susceptibility data were collected with a Quantum Design SQUID magnetometer (XL5S) in the temperature range of 300–1.8 K. The output data were corrected for the diamagnetism of the samples and the sample holder as well as for a temperature independent paramagnetism (TIP) contribution (estimated to be $3 \times 10^{-3} \text{ emu mol}^{-1}$ per formula unit). Heat capacity data were taken on single crystals with a Quantum Design Physical Property Measurement System (PPMS) (6000/6500) in the temperature range 100–1.8 K.

X-ray structure analysis for **1**: $M_r = 3284.31$, crystal dimensions $0.7 \times 0.6 \times 0.4 \text{ mm}^3$, monoclinic, space group $C2/c$, $a = 29.3847(18)$, $b = 19.3861(11)$, $c = 32.8841(11) \text{ \AA}$, $\beta = 114.188(6)^\circ$, $V = 17088.0(15) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 1.277 \text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 1.126 \text{ mm}^{-1}$, $2\theta_{\text{max}} = 44.66^\circ$, $T = 223(2) \text{ K}$. Intensity data were collected on a Stoe Image Plate diffraction system equipped with a ϕ circle, using $\text{MoK}\alpha$ graphite-monochromated radiation ($\lambda = 0.71073 \text{ \AA}$) with an image plate distance of 90 mm, ϕ range $0-200^\circ$, increment 1.0° , θ range $1.66-22.33^\circ$, $D_{\text{max}} - D_{\text{min}} = 16.00-0.93 \text{ \AA}$. A total of 36821 reflections were measured, of which 10834 independent ($R_{\text{int}} = 0.0836$), and 9146 independent for $I > 2\sigma(I)$. The structure was solved by direct methods using the program SHELXS-97.^[28] The refinement and all further calculations were carried out using SHELXL-97.^[29] An empirical (DIFABS) correction was applied ($R_{\text{int}} = 0.0488$). Hydrogen atoms were included in calculated positions and treated as riding atoms using SHELXL-97 default parameters. The majority of the non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2 . Certain coordinated methanol ligands are disordered with the C atoms occupying two alternative positions and these atoms were refined isotropically. In the final rounds of refinement the solvent molecules of crystallization (CH_3OH and H_2O) were held fixed; 716 refined parameters, $R1 = 0.0458$, $wR2 = 0.1345$ for $I > 2\sigma(I)$ data (without DIFABS these values were 0.0476 and 0.1425, respectively). In general the light atoms in the structure undergo considerable thermal disorder. This is reflected in a certain deviation from the expected values for the C–N (mean value $1.14(2) \text{ \AA}$) and C–O (mean value $1.39(11) \text{ \AA}$) bond lengths of the groups on the peripheral of the cluster. The cluster molecule possesses crystallographic C_2 symmetry. In the crystal there are two molecules of water and five molecules of methanol per molecule of cluster. The water H-atoms and the methanol hydroxyl H-atoms could not be located. Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-136762. 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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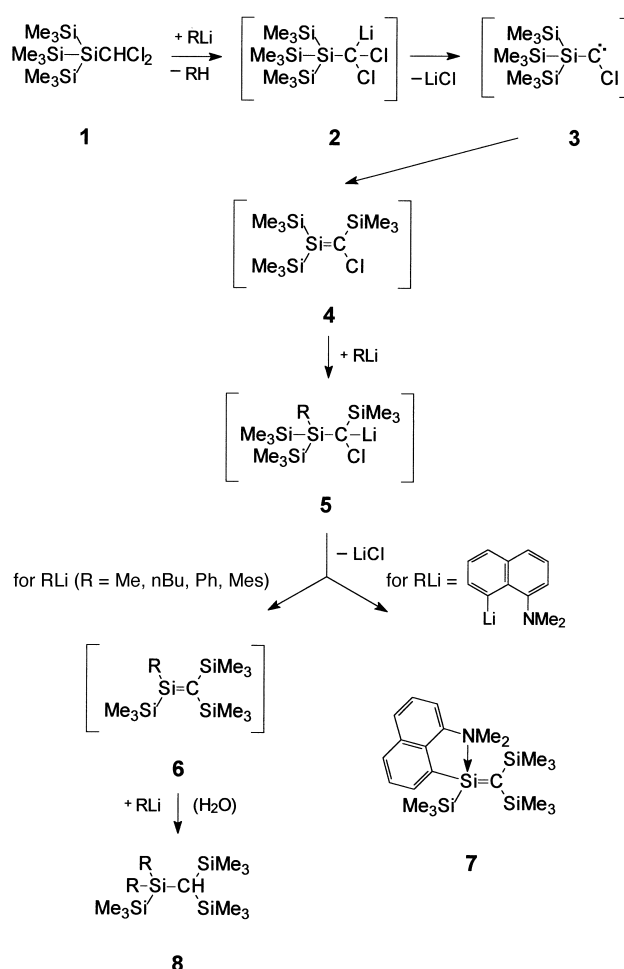
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Reaction of Dichloromethyltris(trimethylsilyl)silane with Organolithium Reagents: Synthesis of an Intramolecularly Donor-Stabilized Silene**

Martin Mickoleit, Kathleen Schmohl, Rhett Kempe and Hartmut Oehme*

Derivatives of three-coordinate silicon, such as $\text{Si}=\text{X}$ systems ($\text{X}=\text{CR}_2$, SiR_2 , NR , PR , S) and silylium salts, are labile compounds that can only be isolated and handled under usual conditions when sufficient stabilization is provided by suitable structural effects.^[1] Recently, besides kinetic stabilization by using space-filling substituents, above all the introduction of ligands with additional donor groups, which permit an intramolecular interaction with the electrophilic silicon center, have contributed decisively to the fact that compounds of this class have been isolated and in some cases structurally characterized.^[2] Herein we report on an intramolecularly donor-stabilized silaethene, 1-(8-dimethylamino-1-naphthyl)-1,2,2-tris(trimethylsilyl)silene (**7**), whose remarkable thermal stability and considerably limited reactivity are attributed to the intramolecular interaction of the 8-dimethylamino group of the naphthyl substituents with the silene-silicon atom. A stable dibenzosilafulvene with an 8-dimethylaminomethyl-1-naphthyl group at the Si atom, which could possibly also be regarded as an intramolecularly donor-stabilized silene, was isolated by Chernyshev and co-workers;^[3] however, there is no X-ray crystal structure analysis of this compound.

In the course of investigations into the synthesis of geminal bis(hypersilyl) compounds,^[4] we had observed that dichloromethyltris(trimethylsilyl)silane (**1**) reacts with an excess of organolithium reagents RLi ($\text{R}=\text{Me}$, $n\text{Bu}$, Ph , Mes) to give silanes of the type $\text{R}_2(\text{Me}_3\text{Si})\text{Si}-\text{CH}(\text{SiMe}_3)_2$ (**8**) (Scheme 1). In this process the transient silenes **4** and **6** occur as intermediates, which are trapped by the organolithium reagent present in the reaction mixture, and the reaction affords **8** as the end product after aqueous workup.^[5] However, if, for the reaction with **1**, an organolithium reagent is chosen with a group R which when introduced at the silene-Si atom of **6** provides sufficient stabilization of the silaethene because of its steric demand or through an intramolecular donor-acceptor interaction, it possible to halt the reaction at this stage and to isolate the silene. This was achieved, for example, in the reaction of **1** with 8-dimethylamino-1-naphthyllithium in the molar ratio 1:2, which led to the isolation of **7**.



Scheme 1. Reaction of dichloromethyltris(trimethylsilyl)silane (**1**) with organolithium reagents and synthesis of **7**.

Our concept regarding the route to the formation of **7** is outlined in Scheme 1. Deprotonation of the dichlorosilane **1** by the organolithium reagent followed by elimination of lithium chloride from the carbenoid **2** resulted in the carbene **3**. In accordance with the known silylcarbene-silene rearrangement,^[6] **3** isomerizes to give the transient silene **4**, which is trapped by excess organolithium reagent. Repeated elimination of LiCl from **5** and renewed 1,2-Si,C-trimethylsilyl migration afford **7**, which is isolated as a yellow crystalline compound in 79% yield.

The structure formulated for **7** was confirmed by NMR and MS studies (see Experimental Section). The X-ray structure analysis (single crystals of **7** from pentane) gave the expected picture of an intramolecularly donor-stabilized silene with a four-coordinate silicon center (Figure 1).^[7] The interaction of the dimethylamino group with the silene-Si atom is the reason for the high stability of **7**. This corresponds to our expectations, since Wiberg et al. have already shown in 1986 that silenes can be stabilized by adduct formation with donors such as amines, THF, or F^- ions.^[8a]

The chelate-like coordination of the dimethylamino group with the silene-silicon atom ($\text{Si1}-\text{N1}$ distance 2.069(2) Å) leads to a pyramidalization at the Si1 atom (sum of angles 345.51°). In contrast, the configuration at the silene-carbon

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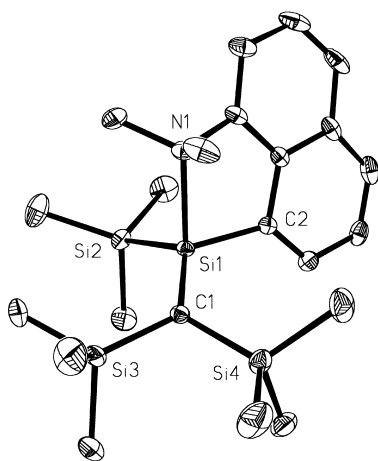
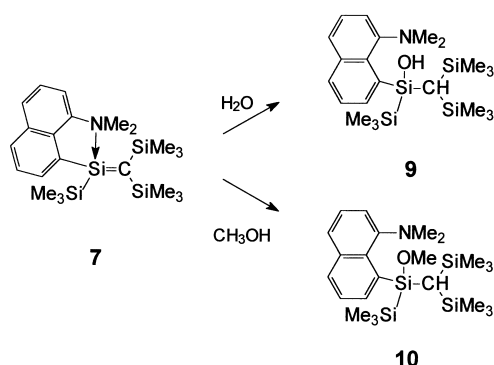


Figure 1. Structure of **7** in the crystal (hydrogen atoms omitted for clarity, thermal ellipsoids with 30% probability). Selected bond lengths [Å] and angles [°]: C1–Si1 1.751(3), C1–Si3 1.830(3), C1–Si4 1.832(3), Si1–C2 1.889(3), Si1–Si2 2.3827(12), Si1–N1 2.069(2), Si1–C1–Si3 123.03(15), Si1–C1–Si4 120.17(15), Si3–C1–Si4 115.66(14), C1–Si1–C2 119.98(12), C1–Si1–Si2 125.63(10), C1–Si1–N1 113.93(11), C2–Si1–Si2 99.90(8), C2–Si1–N1 86.30(10), Si2–Si1–N1 103.28(7).

atom is almost trigonal-planar (sum of angles at C1 358.86°). The Si1–C1 bond length in **7** (1.751(3) Å) is in good agreement with the value reported by Wiberg et al. for the open-chain ethyldimethylamine adduct of the silene $\text{Me}_2\text{Si}=\text{C}(\text{SiMe}_2\text{Ph})_2$ (1.761 Å).^[8b] The Si=C distances in the stable silenes $(\text{Me}_3\text{Si})_2\text{Si}=\text{C}(\text{OSiMe}_3)\text{Ad}$ (1.764 Å; Ad = 1-adamantyl)^[9] and $(\text{Me}_3\text{Si})_2\text{Si}=\text{CAd}'$ (1.741 Å; Ad' = 2-adamantylidene)^[10] are similar to the value obtained for **7**. The Si=C distance in **7** is slightly longer than that reported for the uncomplexed stable silene $\text{Me}_2\text{Si}=\text{C}(\text{SiMe}_3)(\text{SiMe}_t\text{Bu}_2)$ (1.702 Å),^[8c] which we regard as an indication of the ylide character of **7**.

The silene **7**, which is thermally stable up to about 140 °C, is converted with water to the silanol **9**, and methanol adds to the Si=C bond in **7** to give the methoxysilane **10** (Scheme 2). However, **7** behaves indifferently towards 2,3-dimethyl-1,3-butadiene, which reacts with reactive silenes by [2+4] cycloaddition.^[11]



Scheme 2.

Experimental Section

7: Compound **1** (0.60 g, 1.8 mmol) was added at –78 °C to a suspension of 8-dimethylamino-1-naphthyllithium diethyl ether complex (1.00 g, 3.9 mmol) in diethyl ether (30 mL). After the mixture had been allowed to warm slowly to room temperature and then left to stand for about 14 h, the LiCl precipitate was removed by filtration. The remaining yellow

solution was concentrated and the 1-dimethylaminonaphthalene formed was removed by distillation at 100 °C/10^{–2} mbar. The residue was recrystallized from *n*-pentane. Yellow prisms, yield 0.61 g (79%), m.p. 139–140 °C. ¹H NMR (250 MHz, [D₆]benzene): δ = –0.17, 0.28 and 0.60 (3 s, SiCH₃, 3 × 9 H), 2.39 and 2.44 (2 s, NCH₃, 2 × 3 H), 6.55–7.83 (m, Ar-H, 6 H); ¹³C NMR (75.5 MHz, [D₆]benzene): δ = 0.6 (SiSiCH₃), 7.9 and 8.2 (CSiCH₃), 22.4 (Si=C), 46.1 and 52.0 (NCH₃), 115.1, 125.6, 127.1, 127.6, 128.3, and 132.7 (arom. CH), 132.9, 133.3, 139.2, and 148.2 (arom. quat. C); ²⁹Si NMR (79.5 MHz, [D₆]benzene): δ = –18.2 (SiSiMe₃), –8.0 and –7.0 (CSiMe₃), 39.4 (Si=C); MS (70 eV): *m/z* (%): 429 (6) [*M*⁺], 414 (10) [*M*⁺ – CH₃], 356 (100) [*M*⁺ – SiMe₃]; UV/Vis (*n*-heptane): λ_{max}(ε) = 301 nm (4400); elemental analysis (%): calcd for C₂₂H₃₉NSi₄ (429.91): C 61.47, H 9.14, N 3.26; found: C 60.81, H 8.93, N 3.43.

9: Colorless crystals from acetonitrile, m.p. 81–83 °C. IR (cap.): ν̄ = 3300–3450 cm^{–1} (br., O–H_{ass}); ¹H NMR (250 MHz, [D₆]benzene): δ = –0.18, 0.28 and 0.47 (3 s, SiCH₃, 3 × 9 H), the CH signal is covered by a Me₃Si signal (in [D₆]acetone: δ = 0.10 (s, CH, 1 H)), 2.30 and 2.45 (2 s, NCH₃, 2 × 3 H), 6.95–7.64 (m, Ar-H, 6 H), 9.15 (br. s, OH, 1 H); ¹³C NMR (75.5 MHz, [D₆]benzene): δ = 0.6, 3.5, and 4.0 (SiCH₃), 8.1 (CH), 44.1 and 48.6 (NCH₃), 118.8, 124.6, 125.3, 128.1, 130.5, and 136.2 (arom. CH), 134.3, 136.6, 140.2, and 151.4 (arom. quat. C); ²⁹Si NMR (79.5 MHz, [D₆]benzene): δ = –19.7 (SiSiMe₃), –0.1 (CSiMe₃), 1.1 (SiOH); MS (70 eV): *m/z* (%): 447 (7) [*M*⁺], 432 (95) [*M*⁺ – CH₃], 374 (100) [*M*⁺ – SiMe₃], 288 (20) [*M*⁺ – CH(SiMe₃)₂]; elemental analysis (%): calcd for C₂₂H₄₁NOSi₄ (447.96): C 58.99, H 9.23, N 3.13; found: C 59.13, H 9.13, N 3.11.

10: Colorless needles from methanol, m.p. 121 °C, yield 68%. IR (KBr): ν̄ = 1107 cm^{–1} (SiOCH₃); ¹H NMR (250 MHz, [D₆]benzene): δ = –0.21, 0.35, and 0.38 (3 s, SiCH₃, 3 × 9 H), 0.43 (s, CH, 1 H), 2.30 and 2.48 (2 s, NCH₃, 2 × 3 H), 3.46 (OCH₃), 6.90–8.00 (m, Ar-H, 6 H); ¹³C NMR (75.5 MHz, [D₆]benzene): δ = 2.5, 3.7, and 4.2 (SiCH₃), 6.4 (CH), 43.4 (OCH₃), 51.2 and 52.7 (NCH₃), 114.7, 125.3, 125.6, 129.4, 136.0, and 136.1 (arom. CH), 125.6, 134.4, 138.3, and 153.6 (arom. quat. C); ²⁹Si NMR (79.5 MHz, [D₆]benzene): δ = –17.5 (SiSiMe₃), 0.1 and 1.8 (CSiMe₃), 4.2 (SiOMe); MS (70 eV): *m/z* (%): 461 (0.5) [*M*⁺], 446 (14) [*M*⁺ – CH₃], 388 (100) [*M*⁺ – SiMe₃]; elemental analysis (%): calcd for C₂₃H₄₃NOSi₄ (461.95): C 59.80, H 9.38, N 3.03; found: C 59.53, H 9.21, N 3.13.

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- X-ray crystal structure analysis of **7**: STOE-IPDS diffractometer, graphite-monochromated MoK_α radiation, λ = 0.71069 Å, structure solution with direct methods (SHELXS-86: G. M. Sheldrick, *Acta*

Crystallogr. Sect. A **1990**, *46*, 467), refinement with full-matrix least-squares methods against F^2 (SHELXL-93: G. M. Sheldrick, unpublished results), graphical representation of the structure: XP (Siemens), yellow prisms $0.4 \times 0.1 \times 0.1$ mm, space group $P2_1/c$, monoclinic, $a = 8.938(2)$, $b = 14.528(3)$, $c = 20.225(4)$ Å, $\beta = 99.28(3)^\circ$, $V = 2591.9(9)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.102$ g cm⁻³, 6363 measured, 3899 symmetry-independent reflections, of which 2531 observed ($I \leq 2\sigma(I)$), $R = 0.039$, wR^2 (all data) = 0.088, 244 parameters. 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-137407. 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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Linking Icosahedral, Strong Molecular Magnets {Mo₇₂Fe₃₀^{III}} to Layers—A Solid-State Reaction at Room Temperature**

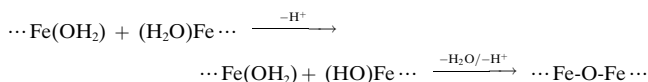
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Dedicated to Professor Heinrich Vahrenkamp on the occasion of his 60th birthday

The controlled generation of nanostructured materials and building units defines one of the contemporary challenges in chemistry. In this context, designed properties such as mesoporosity (in the form of well defined cavities or channels), electron and ion transport capabilities, and (high spin) nanomagnetism (including switching) are of particular interest^[1]. Following the successful synthesis of nanostructured icosahedrally or spherically shaped clusters of the

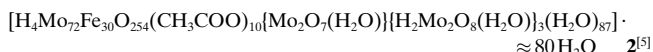
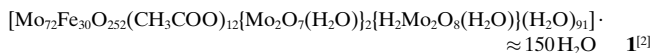
Keplerate type with, for example, the metal frame {(Mo)-Mo₅}₁₂Fe₃₀^{III} **1a**^[2] of 30 high-spin, and in principle, switchable Fe^{III} centers, it is now possible to interconnect the strong molecular magnets of that type. The linking of the icosahedral entities, which is in itself an interesting crystallographic problem (see below), takes place in a solid-state reaction at room temperature.

The aforementioned clusters **1a** in the compound **1a** ≈ 150 H₂O comprise Fe centers, with H₂O ligands which become linked according to the inorganic-condensation reactions known for the formation of polycations with a low activation energies^[3] (Scheme 1). The corresponding reaction product **2** results from several subsequent reaction steps. Product **2**,



Scheme 1.

with a layer structure, was characterized by elemental analysis, thermogravimetry (to determine the number of crystallized water molecules), bond valence sum (BVS) calculations,^[4] spectroscopy (IR, Raman, UV/Vis, and ⁵⁷Fe Mössbauer), magnetochemical measurements, and single-crystal X-ray structure analysis.^[5]



Compound **2** crystallizes in the space group *Cmca*. In this structure, every cluster unit of the **1a** type is covalently linked to four other units through Fe-O-Fe bridges (Fe-Fe = 3.79(4) Å) and thereby forms a two-dimensional layer structure (Figure 1). The geometrical parameters of each single cluster building unit in **2** are, as expected, equal to the corresponding values found in the discrete cluster **1a**.^[2,5] A

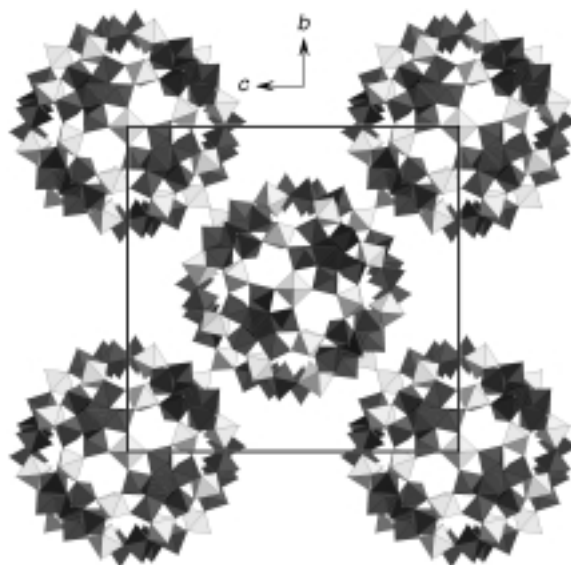


Figure 1. Structure of one layer of **2** as a polyhedral representation.

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remarkable result of this work is, besides the simplicity of the synthesis of **2**, the cross-linking of giant spheres in a solid-state reaction at room temperature as well as the packing of icosahedral units into a two-dimensional layer structure. The absence of C_5 crystallographic axes has led to a number of interesting investigations on the problem of packing icosahedra.^[6] In the present case, the tiling that leads finally to the crystallographic grid is achieved by the covalent binding of the icosahedral units through oxygen atoms; these covalent bonds induce symmetry breaking. The observed electronic structure and the magnetism may be of interest in materials science, since the nanoscale building unit of the layer structure **1a**, which contains 30 high-spin Fe^{III} centers, represents the cluster with the highest number of paramagnetic centers known. The presence of 26 Fe^{III} centers, which are not involved in linking the spherical units, was confirmed not only from the structure analysis but also from the observed magnetism. The measured $\chi_{\text{mol}}T$ value of $112.9 \text{ emu K mol}^{-1}$ at room temperature fits well with the theoretical value of $113.7 \text{ emu K mol}^{-1}$ for 26 uncorrelated $S = 5/2$ centers.^[7] The remaining four Fe^{III} centers (per cluster unit) of the Fe-O-Fe bridges are apparently so strongly coupled that they do not significantly contribute to the paramagnetism, a situation typical for μ -oxo-bridged, linear, dinuclear Fe^{III} complexes.^[8] A suitable model system for the $(\text{H}_2\text{O})(\text{O})_4\text{Fe}(\mu\text{-O})\text{-Fe}(\text{O})_4(\text{OH}_2)$ groups in **2** is the recently described complex $[(\text{H}_2\text{O})_5\text{Fe}(\mu\text{-O})\text{Fe}(\text{OH}_2)_5]^{4+}$, for which (due to the strong coupling) a $\chi_{\text{mol}}T$ value of only about $0.35 \text{ emu K mol}^{-1}$ per Fe^{III} center at room temperature was reported.^[9] Plotting $1/\chi_{\text{mol}}$ versus T yields, on extrapolation due to the antiferromagnetic coupling, a Weiss temperature of $\Theta = -21.1 \text{ K}$. The ^{57}Fe Mössbauer spectrum of **2** shows the anticipated similarity to **1** but a slight asymmetry of the two main peaks and of the quadrupole doublet ($\delta_1 = 0.51$ and $\Delta E_Q = 0.65 \text{ mm s}^{-1}$).

In the context of the cluster units, the following is noteworthy: When the freshly filtered, and thus not yet dry, crystals (type I; space group $P2_1/n$) which will form **2** after dehydration are immediately investigated by X-ray structure analysis at low temperature, their structure shows the discrete, not yet covalently linked clusters of $\{(\text{Mo})\text{Mo}_5\}_{12}\text{Fe}_{30}^{\text{III}}$ (Figure 2).

Interesting aspects of the conversion process of the discrete spherical clusters in the solid state at room temperature, according to Scheme 2 (see also Figure 1 and 2), are 1) the discrete clusters approaching one another then finally covalently bonding during the drying process was observed by single crystal X-ray structure analysis^[10] by means of the decrease in spacing between the spheres, and 2) the change to a space group of higher symmetry in an ordering process due to the covalent bonding of the spheres.

The reaction steps, according to Schemes 1 and 2, show a corresponding volume decrease of the unit cells and the decrease of the number of crystallized water molecules and represent a highly interesting process in solid-state physics and chemistry. For the proton transfers during the condensation process $\text{II} \rightarrow \text{2}$, either the clusters or crystallized water molecules act as acceptors. This remarkable process is driven by the thermodynamically favorable formation and release of water molecules.^[11]

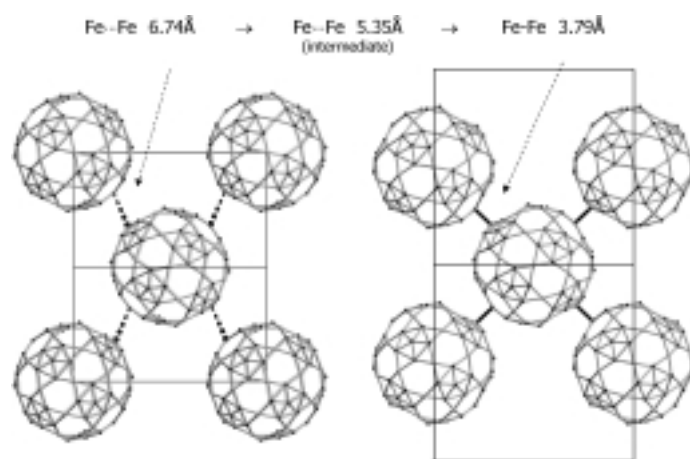
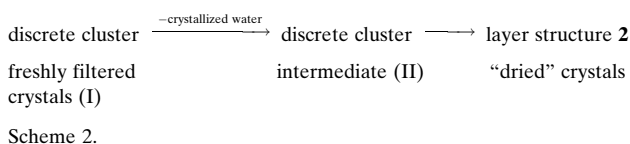


Figure 2. Wireframe representation of the metal frame of the cluster building units in **2** with an indication of covalent linking (right). The solid-state conversion process (see text) leading to **2** takes place according to Schemes 1 and 2.^[10] The reaction proceeds from discrete cluster units present in the wet crystals freshly filtered from the mother liquor (type I; left) via an intermediate (type II; middle) with discrete units positioned at the minimum distance possible without bond formation.



Experimental Section

To a solution of **1**^[2] (1.0 g, 0.05 mmol) in H_2O (100 mL; **1** dissolves slowly), NaCl (0.5 g, 8.6 mmol) was added with stirring. The pH value of the solution was adjusted to approximately 2.0 with 1 M HCl, then the reaction solution kept free of vibration in an open beaker (250 mL, wide necked) for crystallization. Yellow crystals of **2** (thin plates) were collected after 6 days by filtration through a glass frit, then washed with iced water and dried under air. Yield: 0.4 g (43% based on **1**).

2: Characteristic IR bands (KBr; $1800\text{--}500 \text{ cm}^{-1}$): $\tilde{\nu} = 1620 \text{ (m, } \delta(\text{H}_2\text{O}))$, $1535 \text{ (m, } \nu_{\text{as}}(\text{COO}))$, $1425 \text{ (w-m, } \nu_{\text{s}}(\text{COO}))$, 971 (m) , $948 \text{ (m, } \nu(\text{Mo=O}))$, 855 (sh) , 781 (s) , 623 (w-m) , $567 \text{ cm}^{-1} \text{ (s)}$; characteristic Raman bands (solid state; $\lambda_{\text{e}} = 1064 \text{ nm}$, $1000\text{--}200 \text{ cm}^{-1}$): $\tilde{\nu} = 950 \text{ (s)}$, 908 (w) , $\nu(\text{Mo=O})$, 835 (s) , 510 (m) , 370 (m) , $238 \text{ cm}^{-1} \text{ (w-m)}$; UV/Vis (solid-state reflection spectrum, cellulose used as a white standard): $\lambda \approx 285 \text{ (sh)}$, 370 nm .

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- [1] See, for example *Chemistry of Advanced Materials* (Eds.: L. V. Interrante, M. J. Hampden-Smith), Wiley, New York, **1998**, and, in relation to the problem presented here, S. Mengel, *Technologiefrüh-erkennung, Technologieanalyse, Magnetismus, Band 1, Molekulare Magnete*, VDI-Technologiezentrum und bmb + f, Düsseldorf, **1999**.
- [2] a) A. Müller, S. Sarkar, S. Q. N. Shah, H. Bögge, M. Schmidtman, Sh. Sarkar, P. Kögerler, B. Hauptfleisch, A. X. Trautwein, V. Schünemann, *Angew. Chem.* **1999**, *111*, 3435–3439; *Angew. Chem. Int. Ed.* **1999**, *38*, 3238–3241. In the first published giant-sphere compound, the pentagons are linked via $\{\text{Mo}_5\}$ spacers according to: b) A. Müller, E. Krickemeyer, H. Bögge, M. Schmidtman, F. Peters, *Angew. Chem.* **1998**, *110*, 3567–3571; *Angew. Chem. Int. Ed.* **1998**, *37*, 3360–3363; c) A. Müller, P. Kögerler, C. Kuhlmann, *Chem. Commun.* **1999**, 1347–1358.
- [3] a) F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, *Advanced Inorganic Chemistry*, 6th Ed., Wiley, New York, **1999**; b) D. T.

Richens, *The Chemistry of Aqua Ions*, Wiley, New York, 1997, p. 372; c) For condensation processes in which aqua ligands are linked to oxo (or hydroxo) bridges, see: W. Schneider, *Comments Inorg. Chem.* **1984**, 3(4), 205–223. The paper is appropriately entitled “Hydrolysis of Iron(III)—Chaotic Olation versus Nucleation”. In the present case, a chaotic process is not favorable due to the spherical shape of the educt.

- [4] I. D. Brown in *Structure and Bonding in Crystals, Vol. II* (Eds.: M. O’Keeffe, A. Navrotsky), Academic Press, New York, 1981, pp. 1–30.
- [5] Crystal structure analysis of **2**: space group *Cmca*; $H_{382}Fe_{30}C_{20}Mo_{80}O_{476}$; $M = 17591.96 \text{ g mol}^{-1}$; $a = 36.815(2)$, $b = 34.403(2)$, $c = 35.056(2) \text{ \AA}$, $V = 44399(4) \text{ \AA}^3$, $Z = 4$, $\rho = 2.63 \text{ g cm}^{-3}$, $\mu = 3.25 \text{ mm}^{-1}$, $F(000) = 33800$, crystal size $0.28 \times 0.24 \times 0.02 \text{ mm}^3$. Dried crystals of **2** were measured at 183(2) K on a Bruker axis SMART diffractometer (three-circle goniometer with a 1 K CCD detector, $Mo_{K\alpha}$ radiation, graphite monochromator; hemisphere data collection at 0.3° wide ω scans over three runs of 606, 435, and 230 frames ($\phi = 0^\circ$, 88° , and 180°) from a 5.00 cm-distant detector). A total of 111705 reflections ($1.50^\circ < \theta < 24.97^\circ$) were collected, of which 19819 unique reflections ($R(\text{int}) = 0.1308$) were used. An empirical absorption correction using equivalent reflections was performed with the SADABS program. The structure was solved with the program SHELXS-97 program and refined using the SHELXL-93 and SHELXL-97 programs (G. M. Sheldrick, University of Göttingen, 1997 and 1993) to $R = 0.045$ for 9308 reflections with $I > 2\sigma(I)$ and a max./min. residual electron density of $2.06/-1.17 \text{ e \AA}^{-3}$. The problem of locating the disordered molybdate fragments of the type $[Mo_2O_8]_{9/10}$ and the acetate ligands is equivalent to the situation in **1**,^[2] although in the present case the lower symmetry leads to a significantly reduced disorder (the certainty of the number of both of these structural elements is ± 1 in the formula). To confirm the above statements, multiple crystal-structure analyses were carried out for the intermediate structures. Not all positions of noncoordinated H_2O molecules inside the sphere and in the crystal lattice could be refined for the same reason as above. Structure graphics were produced with DIAMOND 2.1 program (K. Brandenburg, Crystal Impact GbR, 1999). 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-138290. 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—cannot be clearly determined because of the disorder problem (see the argument in ref. [5]). The negatively charged dinuclear molybdate fragments $[Mo_2O_8]_{9/10}$ are responsible for the charge balance during the formation of neutral **1a** clusters;^[2a] a spherical cluster of the same type without these fragments but correspondingly more acetate ligands should also exist.

- [11] Note added in proof (March 31, 2000): In the meantime we were also able to obtain the neutral spherical cluster of the type $[Mo_{72}Fe_{30}]$ with only CH_3COO^- ligands. This reduces the problem of determining the exact formula.^[5]

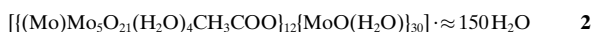
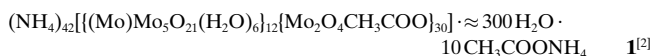
Thirty Electrons “Trapped” in a Spherical Matrix: A Molybdenum Oxide-Based Nanostructured Keplerate Reduced by 36 Electrons

Achim Müller,* Syed Qaiser Nazir Shah, Hartmut Bögge, Marc Schmidtman, Paul Kögerler, Björn Hauptfleisch, Stefan Leiding, and Kai Wittler

Dedicated to Professor Reinhardt Ahlrichs on the occasion of his 60th birthday

Giant molecular spheres of variable size can be generated by linking pentagons with various spacers.^[1,2] Herein, we describe a route which facilitates the generation of unusual electronic structures based on polyoxomolybdate spheres: Each sphere, comprised of 12 pentagonal units, can act as a matrix for trapping 30 electrons on the spacers that correspond to the centers with a predominantly Mo^V character.

When the molecular giant sphere **1a**, consisting of 12 pentagonal units of the type $\{(Mo^VI)Mo_5^{VI}\}$ and 30 $\{Mo_2^V\}$ spacers assembled with the structural characteristics of a Keplerate,^[2] is oxidized, the deep blue, crystalline, molybdenum oxide acetate-type molecules containing **2** is formed. Product **2** was characterized by elemental analysis (including cerimetric titration to determine the (formal) number of Mo^V centers), thermogravimetry (to determine the number of crystal water molecules), spectroscopy (IR, UV/Vis, resonance Raman, ESR), magnetochemical measurements, extended Hückel (EH) MO calculations, and single crystal X-ray diffraction^[3] including bond valence sum (BVS) calculations (to determine the positions of the H_2O ligands and to differentiate between Mo^{VI} and Mo^V centers).



Compound **2** crystallizes in the space group $C2/c$. In contrast to anionic **1a** (space group of **1**: $Fm\bar{3}$), the neutral cluster **2a** (Figure 1) does not form an (exact) closest cubic

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packing. The neutral cluster **2a** is, like the cluster anion **1a**, composed of 12 pentagonal units but, in contrast to **1a**, these are partially reduced. The pentagons are interlinked through 30 O=Mo(H₂O) spacers (Mo=O about 1.67 Å; Mo–H₂O (*trans*) about 2.30 Å) which form themselves, like the midpoints of the {Mo₂^{VI}} units in **1a**, into an Archimedean solid, namely, an icosidodecahedron (12 pentagons and 20 triangular areas). The Mo=O groups point towards the center of the sphere.

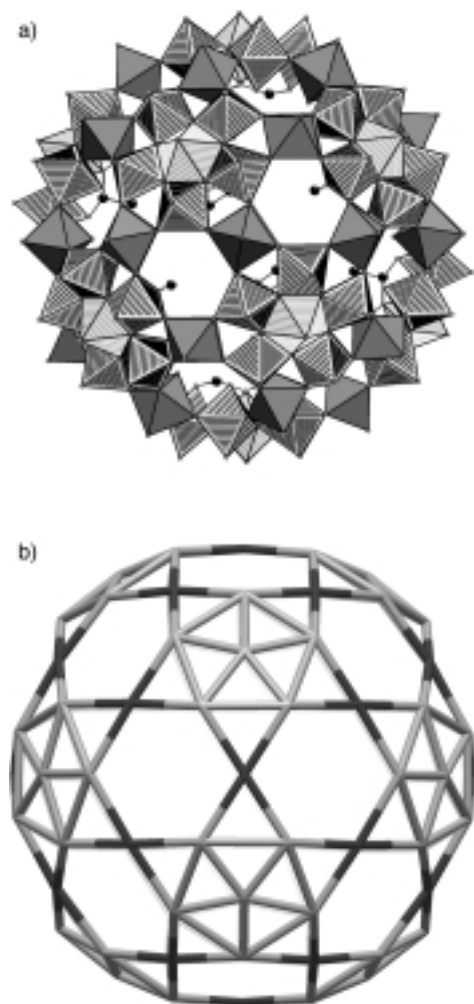


Figure 1. a) Polyhedral representation of the structure of **2a** in the direction of a C₂ axis in crystals of **2** (acetate ligands as a ball-and-stick representation), and b) wireframe representation of the {Mo₁₀₂} metal skeleton. The building units, the {(Mo)Mo₃} pentagons with central pentagonal bipyramids linked by the O=Mo(H₂O) spacers (dark gray), can be readily identified in (a).

In agreement with the intense blue color, **2a** can be assigned as a mixed valence species of type II according to the Robin–Day scheme.^[4] Of the (total) 36 Mo(4d) electrons (formal Mo^V centers, as determined by cerimetric titration of the neutral cluster), 30 electrons are mostly localized on the 30 Mo atoms which act as spacers (conforming to the significant BVS value of 5.3 of these sites), while the remaining 6 electrons are mostly delocalized over the Mo centers of the 12 pentagonal groups.^[5a] The predominant localization of the 4d

electron density on the aforementioned 30 Mo centers can also be shown qualitatively by EHMO calculations. At room temperature, **2** is ESR inactive due to the very strong exchange interactions.^[5b]

In contrast to the classic, highly soluble molybdenum blue species, the isolation of which is based on the destruction of their strong hydration shell (due to the large number of terminal H₂O ligands) in aqueous solution^[6], the generation and isolation of species such as **2** does not require such a process since the hydrophilicity of the surface, and hence the solubility of the cluster, is much lower.

Despite the relatively high number of (formal) Mo^V centers in **2a**, it is remarkable that a structure with Mo^V–Mo^V dumbbells (that is, with localized Mo–Mo bonds) does not result. The partial oxidative local degradation of the former {Mo₂O₄}²⁺ spacers under mild reaction conditions corresponds formally to the scheme {Mo₂^{VI}} → {Mo^V} + Mo^{VI} and subsequent formation of soluble polyoxomolybdates(vi). Here, no restructuring occurs since the 30 Mo^V centers, products of the former {Mo₂^{VI}} groups, are trapped in the spherical matrix of pentagons. It is interesting that this reaction takes place on functional linker groups positioned on the surface of the giant sphere, which inevitably leads to a change in the size of the molecule. Further oxidation does not occur because the neutral cluster **2a**, formed by this slow, partial oxidation, has a low solubility and precipitates after it forms. Precipitation prevents subsequent oxidation reactions of **2a** which would otherwise easily take place in solution.

Apart from being a novelty in the chemistry of clusters, the blue species **2a** ranks as an exceptional molybdenum oxide cluster for the following reasons: **2a** belongs neither to the group that forms Mo^V–Mo^V dumbbells because of a high Mo^V/Mo^{VI} ratio,^[7,8] nor to the group without trapped 4d electrons because of a low Mo^V/Mo^{VI} ratio. The latter group usually shows a delocalization of the 4d electrons, as in the example of the classic soluble molybdenum blue species.^[9] Remarkably, no pronounced electron delocalization in the form of “electron hopping” can be observed.^[8,10] The unusual electronic structure of an icosidodecahedral {Mo^V}₃₀ fragment is the result of the described special reaction type.

Experimental Section

To a red-brown solution of **1** (1.4 g, 0.05 mmol, in 25 mL H₂O), HCl (25 %, 1.5 mL) and NaCl (2.2 g, 37.65 mmol) were added. The reaction solution was stirred for 1 h at room temperature in presence of air, filtered, and stored in a closed 50-mL Erlenmeyer flask at room temperature. Blue rhombohedral crystals of **2** were collected after 3 d by filtration, washed several times with water and dried under air. Yield: about 0.29 g (31 % based on **1**).

Characteristic IR bands for **2** (KBr): $\tilde{\nu}$ = 1620 (m, δ (H₂O)), 983 (m, ν (Mo=O)), 961 (m, ν (Mo=O)), 749 (w), 680 (w), 629 (w), 551 (m), 464 cm⁻¹ (m); characteristic resonance Raman bands (λ_e = 1064 nm; diluted with KBr): $\tilde{\nu}$ = 765 (s, breathing vibration of the bridging oxygen atoms between Mo^V and Mo^{VI} centers), 659 (m), 440 cm⁻¹ (s); UV/Vis (solid-state reflection spectrum, cellulose used as a white standard): λ ≈ 300 (br), 750–800 nm (br) (intervalence charge transfer (IVCT) with Mo^V → Mo^{VI} character); correct elemental analysis; cerimetric titration for 36 electrons.

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- [2] A. Müller, E. Krickemeyer, H. Bögge, M. Schmidtmann, F. Peters, *Angew. Chem.* **1998**, *110*, 3567–3571; *Angew. Chem. Int. Ed.* **1998**, *37*, 3360–3363. Evidence for the ten CH_3COO^- groups, assigned as lattice constituents, was strongly indicated by elemental analysis and IR spectroscopy, but it was not possible to locate these groups crystallographically due to a disorder problem. It cannot be excluded that these groups are (at least partially) coordinated to the $\{(\text{Mo})\text{Mo}_5\}$ pentagons, where many orientations are possible. The denomination “Keplerate”, used in this paper for an anionic species, should be also used for neutral species when the topology of the system is in accordance with the definition (see ref. [1b]).
- [3] Crystal structure analysis of **2**: $\text{H}_{492}\text{C}_{24}\text{Mo}_{102}\text{O}_{534}$; $M = 19114.06 \text{ g mol}^{-1}$, space group $C2/c$, $a = 44.586(1)$, $b = 26.365(1)$, $c = 44.565(1) \text{ Å}$, $\beta = 104.21(1)^\circ$, $V = 50782 \text{ Å}^3$, $Z = 4$, $\rho = 2.500 \text{ g cm}^{-3}$, $\mu = 2.550 \text{ mm}^{-1}$, $F(000) = 36768$, crystal size $= 0.20 \times 0.08 \times 0.06 \text{ mm}^3$. Crystals of **2** were removed from the mother liquor and immediately measured at 183(2) K on a Bruker axis SMART diffractometer (three-circle goniometer with a 1 K CCD detector, MoK_α radiation, graphite monochromator; hemisphere of data collection at 0.3° wide ω scans over three runs of 606, 435, and 230 frames ($\phi = 0^\circ, 88^\circ, 180^\circ$) from a 5.00 cm-distant detector). A total of 148391 reflections ($1.54 < \theta < 26.99^\circ$) were collected, of which 54698 unique reflections ($R(\text{int}) = 0.0811$) were used. An empirical absorption correction on the basis of symmetry-equivalent reflections was performed with the SADABS program. The structure was solved and refined with the SHELXS-97 and SHELXL-97 programs (G. M. Sheldrick, University of Göttingen, **1997**) to $R = 0.0713$ for 23929 reflections with $I > 2\sigma(I)$ and a max./min. residual electron density of $2.816/-3.078 \text{ e Å}^{-3}$. Structure graphics were produced with the DIAMOND 2.1 program (K. Brandenburg, Crystal Impact GbR, **1999**). Due to disorder, not all positions of the water molecules inside the sphere and in the crystal lattice were localized. The same note applies to the acetate ligands. 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-138289. 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).
- [4] a) M. B. Robin, P. Day, *Inorg. Chem. Radiochem.* **1967**, *10*, 247–422; to emphasize the significance of the relevant class of species, see also: b) *Mixed Valence Systems: Application in Chemistry, Physics and Biology* (Ed.: K. Prassides), Kluwer, Dordrecht, **1992**.
- [5] a) This is in agreement with the presence of a neutral cluster. b) The EHMO calculations are based on the atomic positions from the X-ray structure analysis (the proton positions were modeled and disordered acetate ligands were replaced by water ligands) using standard parameters of the *bind* program (G. A. Landrum, W. V. Glassey, *bind* (version 3.0); <http://overlap.chem.cornell.edu:8080/yaehmop.html>). Detailed data on the electronic structure and the magnetism in the context of the dominating Temperature-Independent Paramagnetism (TIP), and the extremely strong exchange interactions responsible for the ESR behavior will be published elsewhere (A. Müller, D. Gatteschi, W. Jeitschko et al., unpublished results).
- [6] a) A. Müller, S. Q. N. Shah, H. Bögge, M. Schmidtmann, *Nature* **1999**, *397*, 48–50; b) A. Müller, M. Koop, H. Bögge, M. Schmidtmann, C. Beugholt, *Chem. Commun.* **1998**, 1501–1502; c) A. Müller, S. K. Das, V. P. Fedin, E. Krickemeyer, C. Beugholt, H. Bögge, M. Schmidtmann, B. Hauptfleisch, *Z. Anorg. Allg. Chem.* **1999**, *625*, 1187–1192; d) A. Müller, S. K. Das, H. Bögge, C. Beugholt, M. Schmidtmann, *Chem. Commun.* **1999**, 1035–1036; e) A. Müller, C. Beugholt, M. Koop, S. K. Das, M. Schmidtmann, H. Bögge, *Z. Anorg. Allg. Chem.* **1999**, *625*, 1960–1962.
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A Molecular Knot with Twelve Amide Groups—One-Step Synthesis, Crystal Structure, Chirality**

Oliver Safarowsky, Martin Nieger, Roland Fröhlich, and Fritz Vögtle*

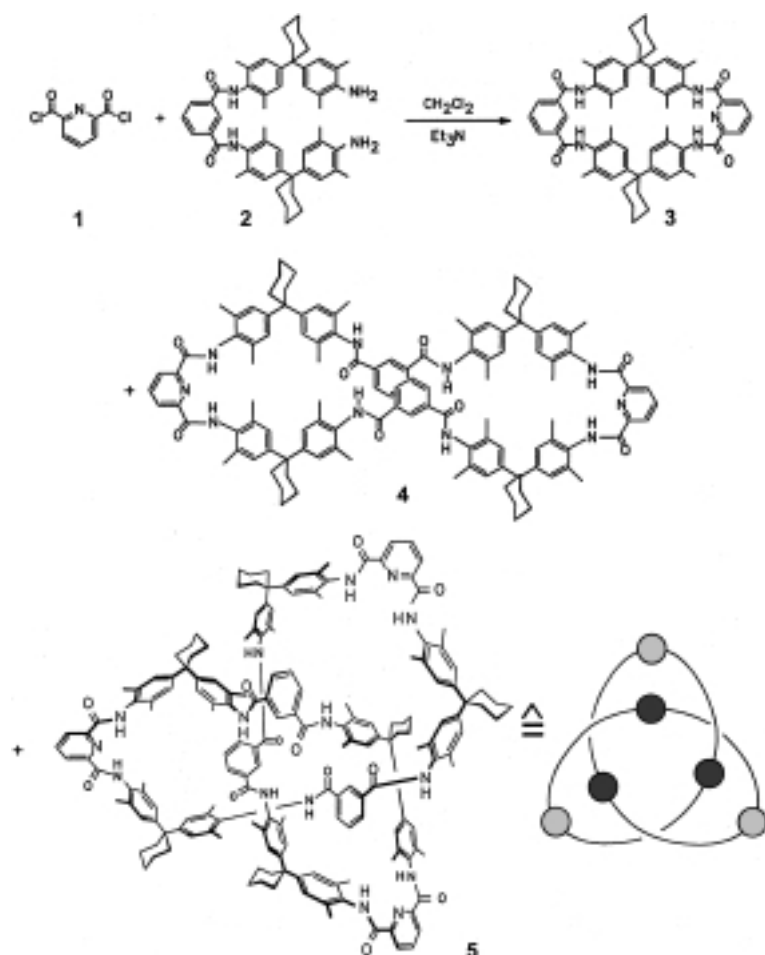
In memory of Eberhard Steckhan

Molecular knots are a little known class of substances.^[1] Hitherto only some of the (historically first) phenanthroline type (Dietrich-Buchecker and Sauvage, 1989),^[2] of the nucleic-acid type (Seeman, 1992),^[3] and of the crown/quat type (Stoddart et al., 1997)^[4] have been synthesized. We report here on probably the simplest synthesis of a new molecular trefoil knot in 20% yield, which proceeds under self-organization. Besides a 96-membered araliphatic skeleton this knot only includes twelve CONH groups.

In the course of the synthesis^[5] of higher $[n]$ catenanes^[1]—with more than two interlacing wheels—we planned to prepare larger amounts of macrocycle **4**,^[6] which should be favorable as a (ditopic) concave (host) template in the synthesis of [2]- and [3]catenanes.^[7] For this purpose we treated the proven substrates 2,6-pyridinedicarboxylic acid dichloride **1** and diamine **2**^[6] under dilution conditions (concentration 10^{-3} mm)^[5] in dichloromethane together with the auxiliary base triethylamine. This reaction gave besides **3** (yield 15%) and **4** (yield 23%) a colorless product in 20% yield which had a molecular weight of m/z 2718.6 (MALDI-TOF-/FAB-MS), a melting point of $> 325^\circ\text{C}$, and an R_f value

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[**] Extracts were presented during a talk at the Universität Düsseldorf on January 11, 2000. We thank Dr. Christian Seel and Dr. Rudolf Hartmann for suggestions and measurements.



of 0.075 (TLC on HPTLC plates, eluent dichloromethane/methanol 35:1). The latter product of this reaction thus corresponds to that from a 3:3 macrocyclization. The formation of the catenane of the same weight consisting of the two cycles **3** and **4** can be excluded, as the corresponding fragment peaks at m/z 906.2 and m/z 1812.4 are absent.

Encouraged by our recent successful crystallization of amide catenanes and rotaxanes,^[8] we also tried in this case to examine the hydrogen-bonding pattern (in the crystal) which is important for the template interaction and a prerequisite for high-yield syntheses of new mechanically linked assemblies.^[9] The X-ray crystal structure analysis^[10] of the crystals obtained by slow crystallization from trichloromethane/methanol over several weeks did not, however, lead to the non-knotted macrocycle, but surprisingly to the molecular knot **5** (Figure 1). The knot connectivity as well as entrapped peripheral solvent molecules (CH_3OH , H_2O , CHCl_3) can be discerned—similar to peptides. Only four of the twelve NH hydrogen atoms in the knot molecule participate in intramolecular

hydrogen bonds. The hydrogen-bonding pattern resembles that recently found in a [2]rotaxane.^[8b]

Despite the regular alternating sequence of its building blocks (P1-I1-P2-I2-P3-I3; P: pyridine dicarbamide, I: isophthaloyl diamide, linked by diphenylmethane units), the crystal of the trefoil clover knot has no C_3 symmetry. This is due to four hydrogen bonds between the building blocks and to the conformation of one of the three isophthaloyl amides (I1). In this moiety both carbonyl groups point towards the inside, whereas in the other five isophthaloyl units the diamide groups are all directed towards the outside. The carbonyl oxygen atom of I2 (I2-CO_b), second in terms of the sequence, forms a bifurcated hydrogen bond to both amide protons of P1 (303 and 335 pm, respectively). Hence, this leaf of the knot is narrowed, whereas in the two other loops each cavity is occupied by a methanol molecule, which is also fixed by a bifurcated hydrogen bond between its oxygen atom and the amide protons of P2 and P3, respectively. Both of the “inverted” carbonyl groups of I1 form hydrogen bonds to the amide protons of the two other isophthaloyl moieties (I1-CO_a...I2-NH_b, I1-CO_b...I3-NH_b), causing a stronger deformation. Additionally, the typical bifurcated hydrogen bonds between NH hydrogen atoms and the pyridine nitrogen atoms are formed for all pyridine dicarbamide groups. Furthermore, a third methanol molecule is

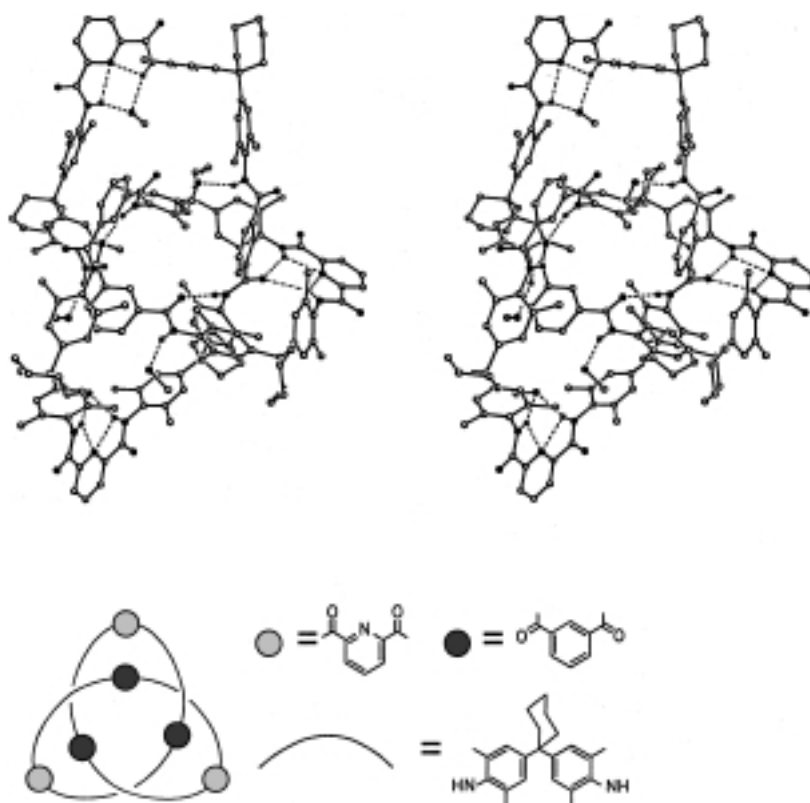


Figure 1. X-ray crystal structure analysis of **5** (stereoview). Apart from the amide protons, hydrogen atoms are omitted, hydrogen bonds are shown by dashed lines. Solvent molecules: methanol.

bound to I₂-NH_a through hydrogen bonds. The carbonyl groups not involved in the intramolecular hydrogen-bonding pattern form hydrogen bonds with solvent molecules, leading to an intermolecular cross-linkage of the individual knots.^[10]

The ¹H NMR spectra of **5** show more signals than the spectra of comparable catenanes and macrocycles.^[5, 7, 12]

The preferred formation of knot **5** over formation of a topologically isomeric catenane or the non-knotted topologically isomeric macrocycle (with 12 CONH groups each) is attributed to hydrogen bonds between amide groups, as in comparable template syntheses of catenanes and rotaxanes.^[12, 13] Instead of the usual macrocyclic tetralactam host (of type **3**) the middle loop of the knot could, however, act as a noncyclic concave template for a CONH guest group.^[14]

Molecular trefoil knots, for which we propose the name “knotanes”, are topologically chiral, and in some cases Sauvage succeeded in the resolution of racemates.^[2] The centrosymmetric unit cell of **5** proves that both enantiomers exist. Orientating attempts to separate the enantiomers of the new knot **5** by means of HPLC using cellulose carbamate column material (retention times *R_t* = 8 and 9 min, eluent: *n*-hexane/ethanol 85/15), which we successfully performed for catenanes, rotaxanes, and pretzelanes with similar structure elements,^[15] revealed that more effort is required for a quantitative separation, as for Sauvage’s knots.^[2]

Sauvage’s hope in 1999 that^[2] “hopefully, chemical knots will expand to other fields than transition metal chemistry in the future” has come true surprisingly soon. The results obtained should be interesting not only for higher mechanically linked assemblies but also for combinations with knots of the phenanthroline and other types^[16, 17]—a treasury for topological stereochemistry and topological chirality.

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ured, 35794 independent reflections of which were used for all calculations. The structure was solved by direct methods (SHELXS-97^[11a]) and refined anisotropically against *F*², whereby the hydrogen atoms (of the knot) were refined with a riding model (SHELXL-97^[11b]). The final *R* value *wR2*(*F*²) was 0.485 with a conventional *R*(*F*) = 0.177 (for 25159 reflections with *I* > 2σ(*I*)) for 2359 parameters and 1064 restraints. Approximately 30% of the structure consists of partly disordered solvent, for which the hydrogen atoms cannot be localized. 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-139484. 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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Highly Regioselective Oxygenation of C–H Bonds: Diamidomanganese Constructs with Attached Substrates as Catalyst Models**

Rayane F. Moreira, Paul M. Wehn, and Dalibor Sames*

The functionalization of the hydrocarbon framework of an organic compound is an exciting challenge of wide-reaching consequences.^[1] The regioselective functionalization of C–H bonds of complex organic compounds is of significant synthetic potential.^[2] The catalytic or reagent-driven transfer of an oxygen,^[3] carbon,^[4] or boron atom^[5] into C–H bonds

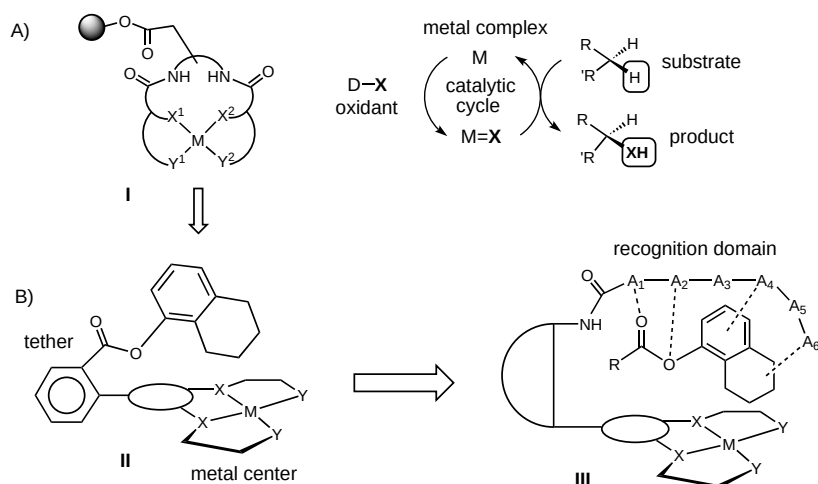
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would be of particular preparative value. To achieve such challenging goals, programmable compounds are required that possess the capacity for both recognition and derivatization of organic substrates.^[6]

For this we chose the combination of metal-centered catalysis and molecular recognition and have designed systems containing a metal coordination core and a recognition domain supported by a suitable molecular scaffold (**III**, Scheme 1). We began our search for novel metal catalysts



Scheme 1. Development of reagents and catalysts for selective C–H bond functionalization. A) Generation of novel metal complexes suitable for atom group transfer to C–H bonds by screening of solid-bound metal complexes. B) Covalent tether as a mimic of molecular recognition forces.

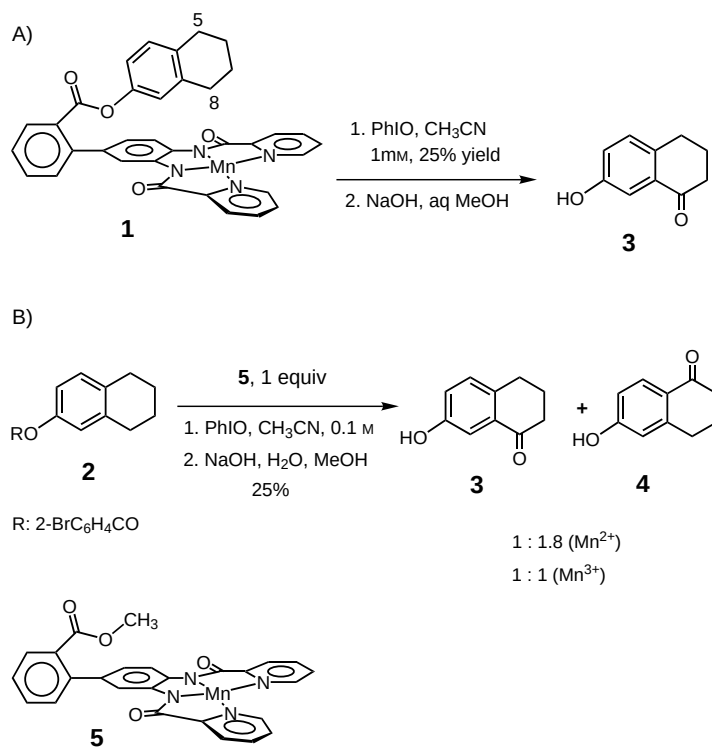
capable of atom transfer, by screening solid-bound metal complexes.^[7] Promising metal complexes emerging from the screening process will ultimately be incorporated into metal complex/receptor constructs of general type **III**. During the initial studies we learned to appreciate the full magnitude of the problem and realized the need for simpler model systems, which would allow the facile evaluation of the characteristics of metal complexes (under conditions mimicking the substrate proximity found in enzymes). As a consequence, we proposed constructs of type **II** consisting of a substrate attached, through a designed tether, to a metal complex.^[8] The covalent tether is viewed as a mimic for a noncovalent recognition event. The simplicity and synthetic accessibility of these models were considered as pivotal factors not only for the rapid analysis of products (by substrate functionalization), but also for the deduction of degradative processes occurring within the ligand sphere. Herein we report on the highly selective oxygenation of tetrahydro-2-naphthol and 4-aminomethylcyclohexylmethanol on covalent attachment to a metal complex unit.

The screening of solid-supported diamidomanganese complexes identified several systems capable of C–H bond oxidation in the presence of iodosylbenzene, of which the 1,2-bis(picolinamido)benzene ligand proved to be most efficient.^[9] We designed a rigid biphenyl tether for the attachment of a substrate to the ligand (**1** and **5**, Scheme 2).^[10] Owing to the well-known lability of benzylic C–H bonds to oxidants, we selected 5,6,7,8-tetrahydro-2-naphthol as the first substrate.^[11]

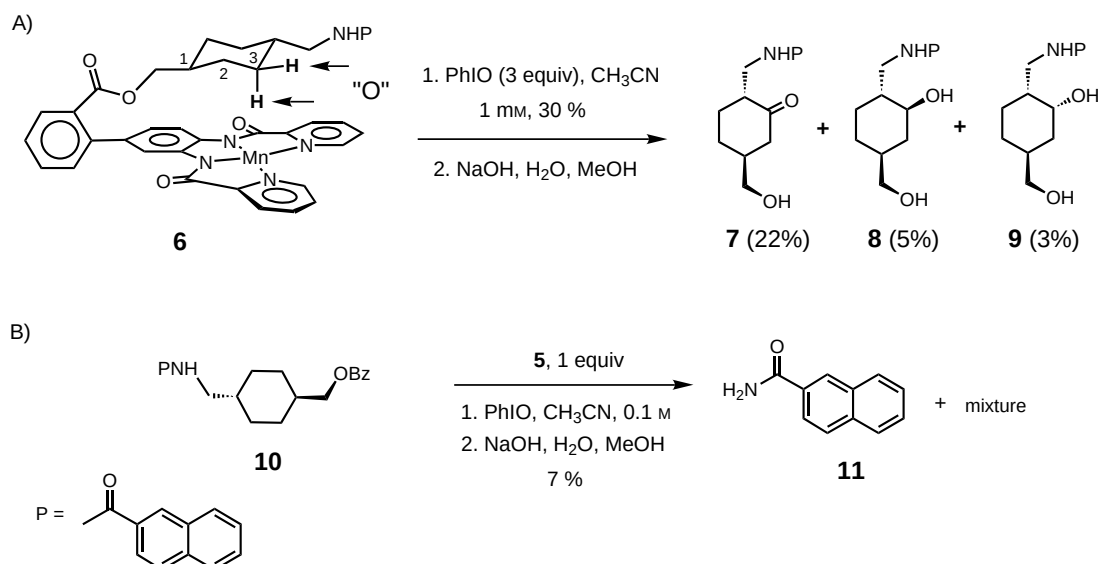
The rigidity of construct **1** augured well for the selective presentation of the benzylic C–H bonds at position 8 to the metal center. We predicted that oxidation at position 5 should be suppressed, provided the intramolecular mechanism was operative. This proved to be the case, as treatment of the manganese(II) or manganese(III) complex **1** (the Mn^{III} complex contains AcO[−] as counterion) with PhIO under high dilution conditions (1 mM) yielded a single product, which upon basic hydrolysis afforded ketone **3** exclusively. The mass balance amounted to 80% (25% product, 55% starting material).

The intramolecular nature of this reaction was secured by appropriate control experiments (Scheme 2B): 1) The intermolecular reaction of 2-bromobenzoate **2** with PhIO in the presence of one equivalent of complex **5** did not yield the corresponding oxidation product under identical dilution conditions (1 mM). 2) A concentrated solution of **2** and **5** (0.1 M) afforded a mixture of ketones **3** and **4**. Interestingly, the Mn^{II} complex **5** provided ketone **4** as the major product, a result similar to the known oxidation of 2-acetoxytetralin with CrO₃.^[12] Presumably, the C–H bonds at position 5 are more electron rich, and hence more vulnerable to electrophilic metal oxidants. In contrast, such electronic preferences are completely overridden by restricting the approach of the substrate to the metal center.

We then turned to the oxidation of unactivated aliphatic C–H bonds. In this instance, a substituted cyclohexylmethanol was linked to



Scheme 2. Selective oxidation of tetrahydro-2-naphthol.



Scheme 3. Highly selective oxidation of unactivated C–H bonds by a diamidomanganese complex.

the biphenylic backbone providing system **6** (Scheme 3). The installation of the naphthoyl group proved necessary for HPLC analysis of reaction mixtures. In analogy to the above case, reaction of a solution of **6** in acetonitrile (1 mM) in the presence of three equivalents of PhIO, followed by hydrolysis, afforded a mixture of ketone **7** (22 %), equatorial alcohol **8** (5 %), and axial alcohol **9** (3 %), and the starting material (50 %, determined by HPLC). Again, the intramolecular mechanism of this reaction was confirmed by appropriate dilution as well as intermolecular control experiments. 1) The reaction of benzoate **10** in the presence of one equivalent of complex **5** under identical conditions yielded no detectable oxidation, whereas the same reaction performed at saturation led to formation of naphthylamide **11** and intractable mixtures of side products (Scheme 3B); 90 % of starting material **10** was recovered in this case. 2) Cyclohexylmethyl benzoate was not oxidized under identical conditions. Apparently, C–H bonds at α -position to the amide moiety are particularly activated toward oxidation by an electrophilic manganese oxidant (presumably metal–oxo species).^[13]

Remarkably, the cyclohexane ring in **6** was oxidized exclusively in position 3, despite the presence of more reactive C–H bonds (C–H bonds adjacent to the amide and ester moiety; two tertiary C–H bonds). Inspection of a molecular model of **6**, founded on the

X-ray crystal structure of **12** (Figure 1), shows that all reasonable “productive conformations”, in which the cyclohexane ring is located over the metal complex, permit selective proximity of the methylene groups in position 3 to the metal.^[14] A crude qualitative analysis explained the experimental results well even in the absence of detailed mechanistic knowledge.

In conclusion, the oxidation of model systems **1** and **6** provided the following information: 1) a free radical mechanism can be ruled out; 2) in the transition state the C–H bond is found in the proximity of the metal–oxo moiety; 3)

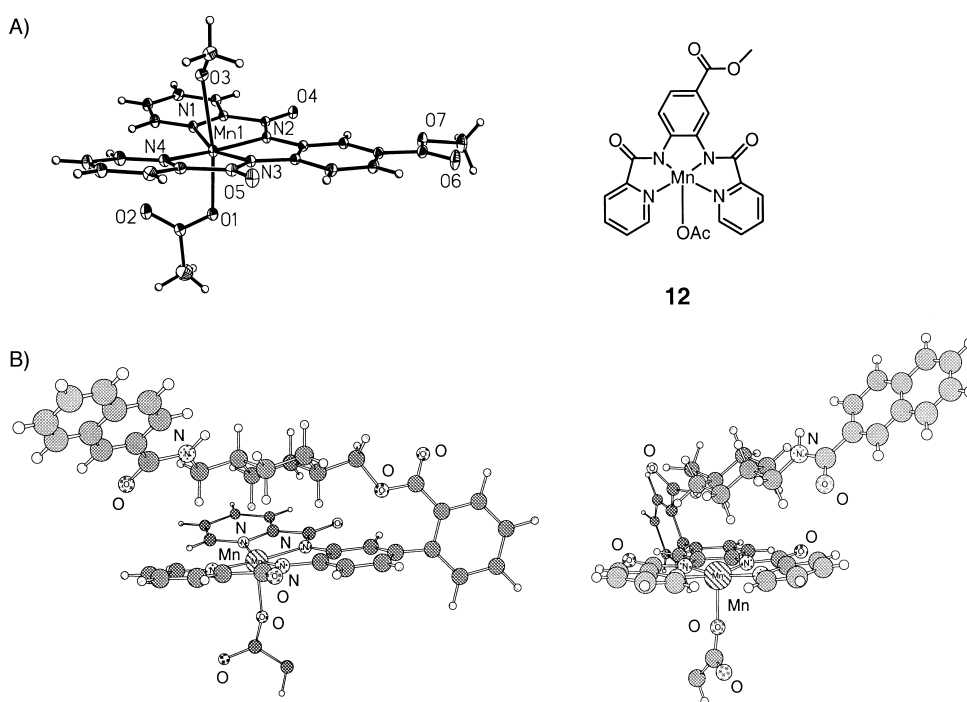
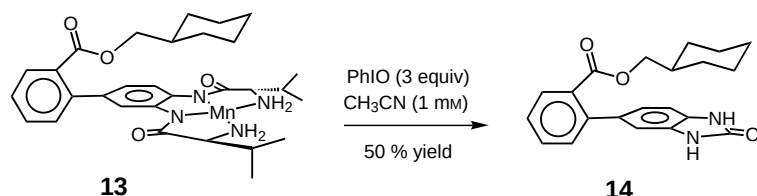


Figure 1. A) ORTEP representation of **12**: The pyridyl and deprotonated amide nitrogen atoms occupy the equatorial sites in the octahedral ligand sphere. B) Molecular model of **6** (side and front view, Chem3D), which indicates the proximity of hydrogen atoms at position 3 of the cyclohexyl ring to the metal center. This is true for all reasonable conformations in which the ring is placed over the metal complex.

the ligands are stable under the oxidation conditions. For instance, system **5** was not oxidized under the reaction conditions, suggesting that the deactivation of the metal complex is not the result of ligand degradation. In contrast, the bis(valine) complex **13**, when submitted to the same reaction conditions (3 equiv PhIO), led to complete degradation of the ligand segment yielding the cyclic urea derivative **14** as the major product (Scheme 4).^[15]



Scheme 4. Complete degradation of the bis(valine)manganese complex **13** in the presence of iodosylbenzene.

The simplicity of covalently assembled models of this type render them suitable probes for the rapid evaluation of novel metal complexes with regard to their capability to functionalize C–H bonds. We are currently studying possibilities for predictable positioning of the substrate to the metal through noncovalent recognition forces in order to attain a truly catalytic oxidation species.

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Solid-Phase Synthesis of Unprotected N-Glycopeptide Building Blocks for SPOT Synthesis of N-linked Glycopeptides

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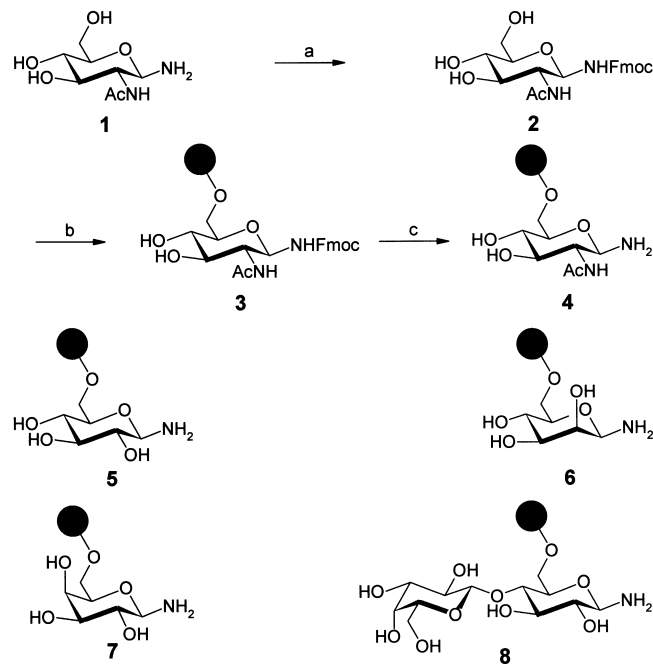
Several approaches to the chemical synthesis of N-linked glycopeptides have been reported.^[1] For the synthesis of glycosylated amino acids, the carbohydrate moiety is usually protected but unprotected glycosylamines have also been used.^[2,3] Using unprotected glycosylamines generally results in low yields^[4,5] and the compounds have to be purified by column chromatography. We present here a new and efficient method for the solid-phase synthesis of unprotected N-glycopeptide building blocks on a continuous surface (SPOT synthesis). SPOT synthesis on cellulose^[6] is a highly effective

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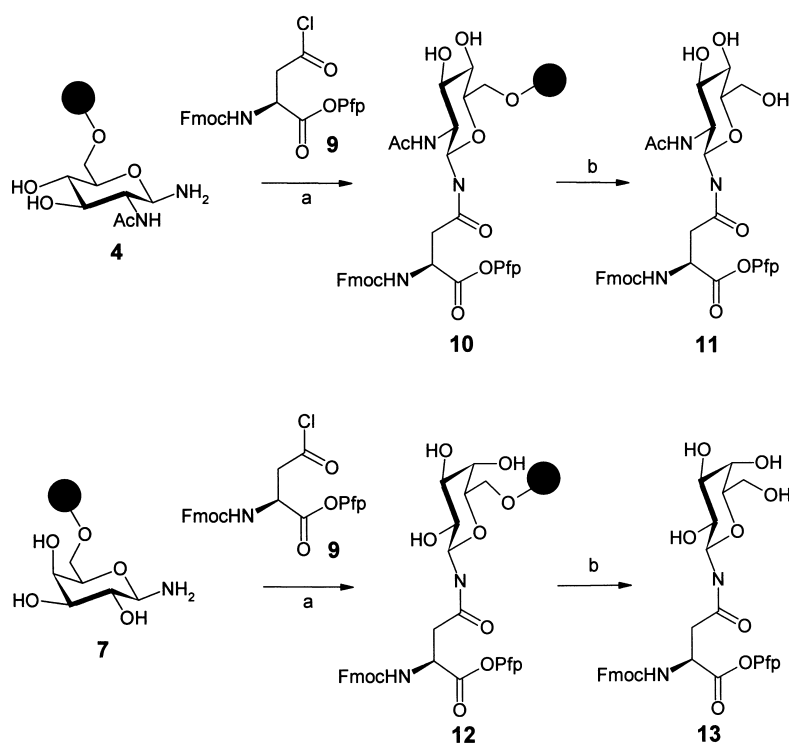
method for the rapid preparation of spatially addressed peptides.

D-glucose, D-mannose, D-galactose, D-lactose, and *N*-acetyl-D-glucosamine were treated as previously reported^[4, 7–10] to give the corresponding β -D-glycosylamines. For temporary amine protection, the glycosylamines were treated with fluoren-9-ylmethoxycarbonyl succinimide ester (Fmoc-Osu) in pyridine. The protected derivatives were obtained after trituration with a mixture of water and dichloromethane. Each of the unprotected sugar derivatives was immobilized on a triphenylmethyl (trityl) chloride derivatized polystyrene resin (1.6 mmol g⁻¹) (shown for GlcNAc, Scheme 1).^[11] The loading of the glycosylamines on the solid support was determined by UV spectrophotometric analysis of the 9-fluorenylmethyl-piperidine adduct and ranged from 0.4 to 0.8 mmol g⁻¹ depending on the glycosylamine. Removal of the Fmoc protecting group with piperidine in DMF gave compounds **4** to **8**.

In order to prepare glycosylated asparagine building blocks on the solid support, we decided to use the acid chloride *N*^α-Fmoc-Asp(Cl)-OPfp described by Bock et al.^[12, 13] (Pfp = pentafluorophenol). Condensation of the unprotected glycosylamines **4** and **7** with the acid chloride **9** gave the corresponding derivatives **10** and **12**; no reaction with the Pfp ester was observed (Scheme 2). In contrast to the solution phase synthesis, the glycosylamine hydroxyl groups had to be protected prior to this reaction in order to provide sufficient solubility.^[13] After cleavage from the resin by treatment with 2% trifluoroacetic acid (TFA) in CH₂Cl₂, the glycosylated asparagine building blocks **11** and **13** were obtained in high yield (70–80%) and purity (>90%) (NMR and MS data are given in Table 1).



Scheme 1. Reagents and conditions: a) Fmoc-Osu, pyridine, RT, 18 h; b) trityl chloride resin, pyridine, 60 °C, 8 h; c) 20% piperidine, DMF, RT, 30 min. RT = room temperature.



Scheme 2. Reagents and conditions: a) *N*-ethylmorpholine, THF, 0 °C–RT, 2 h; b) 2% TFA, CH₂Cl₂, 20 °C, 10 min.

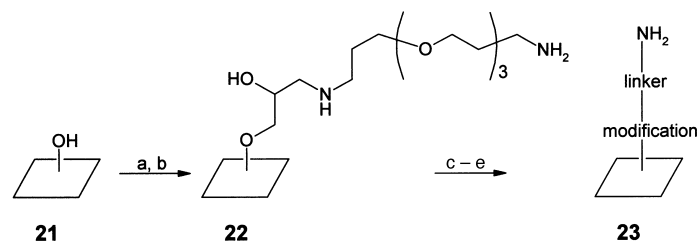
Table 1. Selected ¹H NMR signals (300 MHz, CD₃OD) and electrospray ionization (ESI) MS data.

11 : ¹ H NMR: δ = 1.93 (s, 3 H, CH ₃), 2.05 (m, 2 H, Asp H _{β} , H _{β}), 3.63 (m, 1 H, Fmoc-CH), 3.80 (m, 2 H, Fmoc-CH ₂), 4.19 (m, 1 H, 6-H), 4.37 (m, 1 H, Asp H _{α}), 4.46 (d, 1 H, $J_{1,2}$ = 9.3 Hz, 1-H), 7.33, 7.65, 7.78 (m, 8 H, Fmoc arom. H); MS: m/z : 723.9 [M^+]
13 : ¹ H NMR: δ = 1.85 (m, 2 H, Asp H _{β} , H _{β}), 3.60 (m, 1 H, Fmoc-CH), 3.87 (m, 2 H, Fmoc-CH ₂), 4.20 (m, 1 H, 6-H), 4.38 (m, 1 H, Asp H _{α}), 4.40 (d, 1 H, $J_{1,2}$ = 7.4 Hz, 1-H), 7.34, 7.65, 7.78 (m, 8 H, Fmoc arom. H); MS: m/z : 682.8 [M^+]
16 : ¹ H NMR: δ = 1.95 (s, 3 H, CH ₃), 2.04 (m, 2 H, Glu H _{β} , H _{β}), 2.39 (m, 2 H, Glu H _{γ} , H _{γ}), 3.65 (m, 1 H, Fmoc-CH), 3.81 (m, 2 H, Fmoc-CH ₂), 4.19 (m, 1 H, 6-H), 4.24 (m, 1 H, Gly H _{α}), 4.40–4.48 (m, 2 H, Gly H _{α} , Glu H _{α}), 4.96 (d, 1 H, $J_{1,2}$ = 9.7 Hz, 1-H), 7.35, 7.68, 7.79 (m, 8 H, Fmoc arom. H); MS: m/z : 629.0 [M^+]
17 : ¹ H NMR: δ = 1.96 (m, 1 H, Glu H _{β}), 2.06 (m, 1 H, Glu H _{β}), 2.40 (m, 2 H, Glu H _{γ} , H _{γ}), 3.60 (m, 1 H, Fmoc-CH), 3.80 (m, 2 H, Fmoc-CH ₂), 4.09 (m, 1 H, 6-H), 4.23 (m, 1 H, Gly H _{α}), 4.37–4.50 (m, 2 H, Gly H _{α} , Glu H _{α}), 4.90 (d, 1 H, $J_{1,2}$ = 8.3 Hz, 1-H), 7.35, 7.69, 7.79 (m, 8 H, Fmoc arom. H); MS: m/z : 587.9 [M^+]
18 : ¹ H NMR: δ = 2.00 (m, 1 H, Glu H _{β}), 2.06 (m, 1 H, Glu H _{β}), 2.32 (m, 2 H, Glu H _{γ} , H _{γ}), 3.68 (m, 1 H, Fmoc-CH), 4.00 (m, 2 H, Fmoc-CH ₂), 4.18 (m, 1 H, 6-H), 4.22 (m, 1 H, Gly H _{α}), 4.34–4.44 (m, 2 H, Gly H _{α} , Glu H _{α}), 4.42 (d, 1 H, $J_{1,2}$ = 8.0 Hz, 1-H), 7.34, 7.66, 7.79 (m, 8 H, Fmoc arom. H); MS: m/z : 587.9 [M^+]
19 : ¹ H NMR: δ = 1.96 (m, 1 H, Glu H _{β}), 2.07 (m, 1 H, Glu H _{β}), 2.40 (m, 2 H, Glu H _{γ} , H _{γ}), 3.30 (m, 1 H, Fmoc-CH), 3.90 (m, 2 H, Fmoc-CH ₂), 4.14 (m, 1 H, 6-H), 4.22 (m, 1 H, Gly H _{α}), 4.34–4.44 (m, 2 H, Gly H _{α} , Glu H _{α}), 4.74 (d, 1 H, $J_{1,2}$ = 1.0 Hz, 1-H), 7.35, 7.69, 7.79 (m, 8 H, Fmoc arom. H); MS: m/z : 587.9 [M^+]
20 : ¹ H NMR: δ = 1.98 (m, 1 H, Glu H _{β}), 2.08 (m, 1 H, Glu H _{β}), 2.40 (m, 2 H, Glu H _{γ} , H _{γ}), 3.50 (m, 1 H, Fmoc-CH), 3.90 (m, 2 H, Fmoc-CH ₂), 4.08 (m, 1 H, 6-H), 4.23 (m, 1 H, Gly H _{α}), 4.34 (d, 1 H, $J_{1,2}$ = 7.3 Hz, 1-Hb), 4.38–4.47 (m, 2 H, Gly H _{α} , Glu H _{α}), 4.92 (d, 1 H, $J_{1,2}$ = 8.8 Hz, 1-H), 7.36, 7.70, 7.79 (m, 8 H, Fmoc arom. H); MS: m/z : 749.9 [M^+]

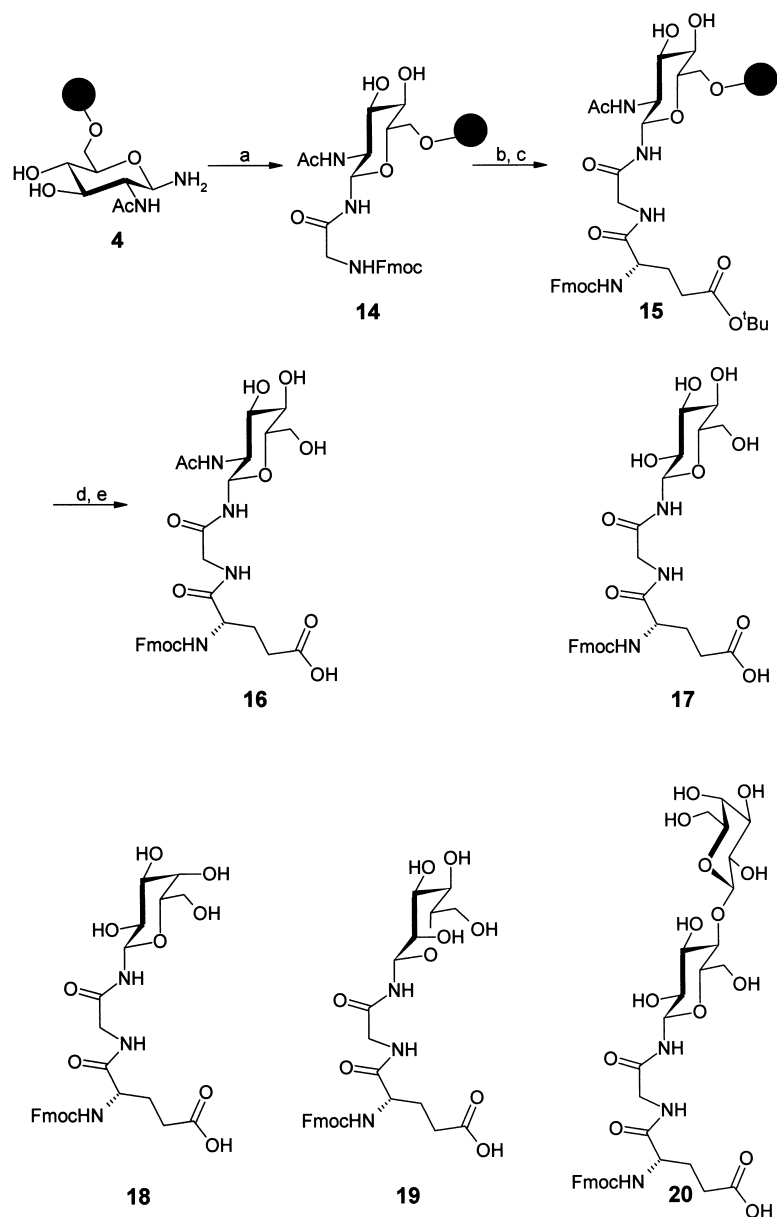
In order to introduce diversity in the array of saccharides, glycosylated glutamine building blocks were also prepared (shown for GlcNAc, Scheme 3). Glycosylamines **4** to **8** were coupled with commercially available *N*^α-Fmoc-Gly-OPfp in DMF. After 3 hours, the resin was washed, and treatment with piperidine in DMF gave the corresponding amines. A second coupling with commercially available *N*^α-Fmoc-Glu(O-*t*Bu)OPfp was performed as described above. After cleavage from the resin with 2% TFA in CH₂Cl₂ and deprotection of the *tert*-butyl esters with 50% TFA in CH₂Cl₂, derivatives **16** to **20** were obtained in good yields (75–90%) and high purity (>95%) (NMR and MS data are given in Table 1).

To demonstrate the suitability of the new building blocks, they were used in the SPOT synthesis on cellulose of an N-linked glycopeptide library. Cellulose membranes (Whatman 50) were modified by treatment with epibromohydrin

and 4,7,10-trioxa-1,13-tridecanediamine to provide homogeneous amino functionalization (**22**, Scheme 4).^[14] For analytical purposes, the photo-labile linker system 4-[4(1-Fmoc-



Scheme 4. Reagents and conditions: a) epibromohydrin, RT; b) 4,7,10-trioxa-1,13-tridecanediamine, RT; c) photo-labile linker (0.5M in NMP), HATU, NMI, RT, 2 × 15 min; d) 10% Ac₂O, 20% DIPEA, DMF, RT, 30 min; e) 20% piperidine, DMF, RT, 2 × 10 min. DIPEA = *N,N'*-diisopropylethylamine.

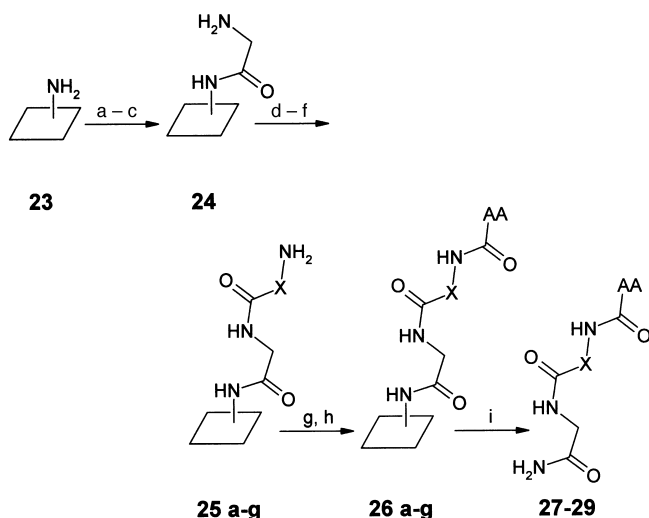


Scheme 3. Reagents and conditions: a) *N*^α-Fmoc-Gly-OPfp, DMF, RT, 3 h; b) 20% piperidine, DMF, RT, 30 min; c) *N*^α-Fmoc-Glu(O-*t*Bu)-OPfp, DMF, RT, 3 h; d) 2% TFA, CH₂Cl₂, RT, 10 min; e) 50% TFA, CH₂Cl₂, RT, 30 min.

aminoethyl)-2-methoxy-5-nitrophenoxyl]-butanoic acid was coupled with the amine by activation with *N*-[(dimethylamino)-1*H*-1,2,3-triazol[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU) and *N*-methyl-imidazole (NMI) in *N*-methyl-2-pyrrolidone (NMP). After acetylation of the remaining free amine functional groups, the Fmoc-protected photo-labile linker was treated with piperidine in DMF to give **23**.

The first amino acid *N*^α-Fmoc-Gly-OPfp was coupled on the continuous surface in NMP (Scheme 5). The remaining free amine functions were acetylated with a solution of 10% acetic anhydride in MeOH. Fmoc deprotection yielded derivative **24**. In the second coupling step, the seven sugar building blocks described above were used. Pfp-activated sugar derivatives **11** and **13** were coupled to the free amine in NMP. The free acids **16** to **20** were coupled in the presence of PfpOH and diisopropylcarbodiimide (DIC) in NMP. After acetylation and Fmoc deprotection, derivatives **25a–g** were obtained (**a–g** are the corresponding derivatives of compounds **11**, **13**, and **16–20**). The last amino acid was also coupled as described. The side-chain protective groups were removed with TFA in CH₂Cl₂. For analytical purposes, derivatives **27a–g**, **28a–g**, and **29a–g** were cleaved from the continuous surface by UV irradiation and obtained in high purity (>90%) (MS data are given in Table 2).

In conclusion, a practical way for the stereoselective synthesis of unprotected N-linked glycopeptide building blocks has been described. SPOT synthesis on a continuous surface allowed the rapid nanomolar preparation of N-glycopeptide libraries which can be used in solid- and solution-phase screening systems and can be applied to the synthesis of bigger libraries.



Scheme 5. Reagents and conditions: a) *N*^α-Fmoc-Gly-OPfp (0.6 M in NMP), RT, 2 × 15 min; b) 10% Ac₂O, MeOH, RT, 1 h; c) 20% piperidine, DMF, RT, 2 × 10 min; d) coupling of sugar building blocks: 1) if activated with Pfp, 0.6 M solution of the sugar in NMP, RT, 2 × 15 min; 2) if free of acid functionality, 0.6 M solution of the sugar in NMP, PfpOH, DIC, RT, 2 × 15 min; e) 10% Ac₂O, MeOH, RT, 1 h; f) 20% piperidine, DMF, RT, 2 × 10 min; g) *N*^α-Fmoc-AA-OPfp (0.6 M in NMP), RT, 2 × 15 min; h) TFA, CH₂Cl₂, RT, 2.5 h; i) UV light at 365 nm, 2 h. X = sugar building blocks 11, 13, 16–20, AA = different amino acids: *N*^α-Fmoc-Glu-(OH) **27 a–g**, *N*^α-Fmoc-Thr-(OH) **28 a–g**, *N*^α-Fmoc-Tyr-(OH) **29 a–g**.

Table 2. ESI MS data.

Compound	<i>m/z</i> [<i>M</i> ⁺]	Compound	<i>m/z</i> [<i>M</i> ⁺]	Compound	<i>m/z</i> [<i>M</i> ⁺]
27 a	743.1	28 a	715.1	29 a	777.1
27 b	702.0	28 b	674.1	29 b	736.1
27 c	841.1	28 c	786.1	29 c	848.1
27 d	773.0	28 d	745.0	29 d	807.0
27 e	773.0	28 e	745.0	29 e	807.0
27 f	773.0	28 f	745.0	29 f	807.0
27 g	935.1	28 g	907.1	29 g	969.1

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Can a Homometallic Chain Be Ferrimagnetic?*

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Dedicated to Professor Harald Krischner
on the occasion of his 70th birthday

One-dimensional homometallic magnetic systems can behave either as antiferromagnetic (AF) or as ferromagnetic (F) chains depending on the sign of the nearest-neighbor exchange interactions.^[1] The recent synthesis of molecular materials, however, has extended the range of magnetic behaviors that can be observed. For instance, regular alternating AF/F chains have been reported that show an overall AF behavior.^[2] However, ferrimagnetic behavior has not been reported for homometallic chains because, in this case, the condition for the noncompensation of the individual spin moments is difficult to achieve. We have now found that the versatility of the azide ligand affords chains with Mn^{II} in which ferrimagnetic behavior is clearly observed.

From methanolic solutions of manganese(II) nitrate and the appropriate pyridine derivative, *trans*-[Mn(N₃)₂(3-Mepy)₂]_n **1** and *trans*-[Mn(N₃)₂(Menic)₂]_n **2** were obtained upon addition of aqueous solutions of sodium azide (3-Mepy = 3-methylpyridine, Menic = methylnicotinate). Compounds **1** and **2** consist of one-dimensional systems^[3] in which each manganese atom is coordinated by two *trans*-oriented pyridinic ligands and four azido ligands. Two azido bridges, oriented either end-to-end (EE) or end-on (EO), between neighboring manganese atoms build the one-dimensional system. Compound **1** shows azido bridges in the sequence (-EE-EE-EO-)_n but compound **2** shows the sequence (-EE-EO-EO-EO-EO-)_n (Figure 1). Bond lengths and angles in the bridging region lie in the range of values reported for conventional EE or EO bridges.^[2, 4, 5] For the Mn^{II}-azido system, double EE azido bridges give AF interactions with

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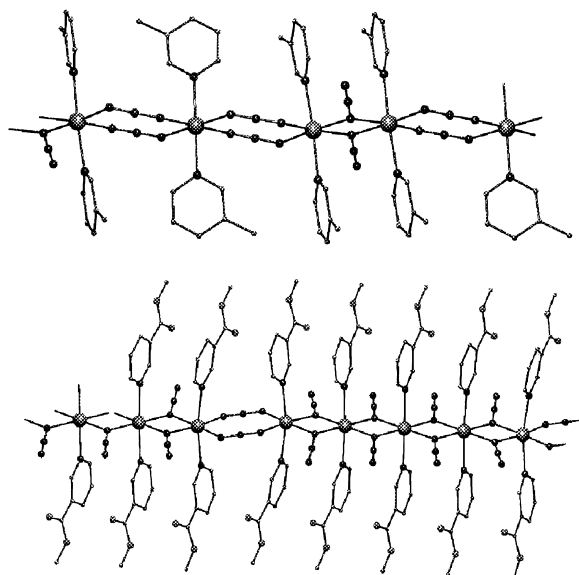


Figure 1. A view of chain structures of *trans*-[Mn(N₃)₂(3-Mepy)₂]_n **1** and *trans*-[Mn(N₃)₂(Menic)₂]_n **2**.

reported J values ranging between $J = -7$ to $J = -13$ cm⁻¹ as a function of the bond parameters,^[2, 4] whereas double EO azido bridges give F interactions with reported values of $J \leq 2$ cm⁻¹.^[5] For compounds **1** and **2** the expected interaction pattern should be the (-AF-AF-F)_n and (-AF-F-F-F)_n sequences, respectively, and $J_{AF} \gg J_F$ may be assumed.

Compound **1** shows the typical features of ferrimagnetic behavior: on cooling $\chi_M T$ decreases from 3.63 cm³ K mol⁻¹ at room temperature to a minimum of 2.01 cm³ K mol⁻¹ at 40 K then an increase to 13.1 cm³ K mol⁻¹ at 2 K (Figure 2).

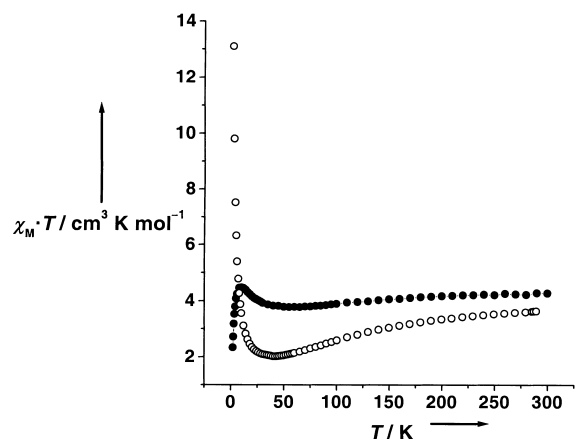


Figure 2. The product $\chi_M T$ versus T plot for **1** (○) and **2** (●).

Magnetization measurements indicate a saturation value of $S = 5/6$ per Mn^{II} atom (5/2 for each Mn₃ unit; Figure 3). These results are consistent with the expected ground state derived from the (-AF-AF-F)_n interaction sequence, which at very low temperature may be envisaged as a ferrimagnetic system with $S_A = 5/2$ and $S_B = 10/2$ (Scheme 1).

Compound **2** shows an unprecedented behavior: on cooling $\chi_M T$ slowly decreases from 4.26 cm³ K mol⁻¹ at room temperature to 3.77 cm³ K mol⁻¹ at 65 K. Below this broad minimum,

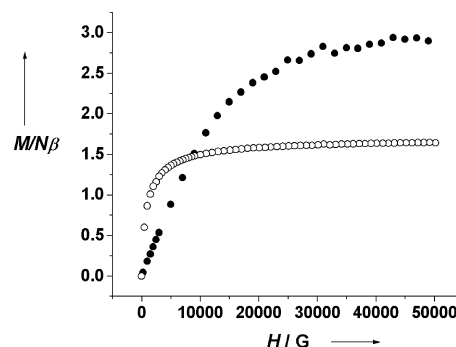
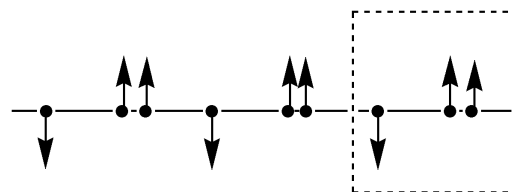
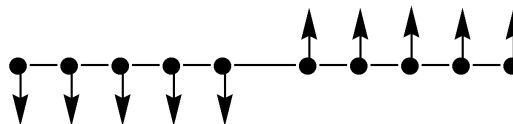


Figure 3. Molar magnetization (at 2 K) for **1** (○) and **2** (●).



Scheme 1. Ground state of an (-AF-AF-F)_n interaction sequence. $S_T = n/5/6$ (5e per Mn₃ unit).

$\chi_M T$ increases to a maximum of 4.47 cm³ K mol⁻¹ at 10 K and then falls to 2.34 cm³ K mol⁻¹ at 2 K (Figure 2). The shape of the $\chi_M T$ curve indicates ferrimagnetic-like behavior between 300–10 K, immediately followed by a strong decay of the magnetic moment. Magnetization measurements show a saturation value close to $S = 3/2$ per manganese atom (Figure 3). This value is striking as the ground state of this chain should be $S = 0$ (Scheme 2). The $\chi_M T$ decay observed below



Scheme 2. Ground state of an (-AF-F-F-F)_n interaction sequence. $S_T = 0$.

10 K clearly corresponds to the population of the ground state but the shape of the plot and the magnetization results need further study to understand their unprecedented behavior. Formally, this ground state is the result of AF interactions between units of $S = 25/2$ that correspond to ferromagnetic coupling of each five-Mn^{II}-center unit.

The magnetic properties of compounds **1** and **2** indicate that some current definitions of magnetic systems are too narrow to include increasingly complex systems. Compound **1** shows a ferrimagnetic response although the system is homometallic; the interactions are either F or AF, and the ground state is equal to one S_A for each basic three-Mn^{II}-center unit. Compound **2** is an antiferromagnetic, homometallic system with a ground state $S = 0$ but not all the interactions are AF. The ferrimagnetic behavior down to 10 K and the magnetization response are far from those of a conventional antiferromagnet or even a regular alternating system. These systems show that complicated topologies with complicated alternating sequences of F/AF interactions are an unexplored tool to design materials with new magnetic properties.

Further study of the magnetic properties of these irregular alternating systems are planned but a general law may be easily envisaged for homometallic systems with sequences of more than one F/AF interaction. Ferromagnetism emerges, as observed for **2**, if $2n+1$ AF interactions are followed by one or more F interactions; the ground state here is always $S=0$. An alternative possibility consists of an even number of AF interactions ($2n$) followed by one or more (m) F interactions, as observed for **1**, which induces net ferrimagnetic behavior with ground state $S_T=mS$ for each $(2n+m)$ local S spin carrier.

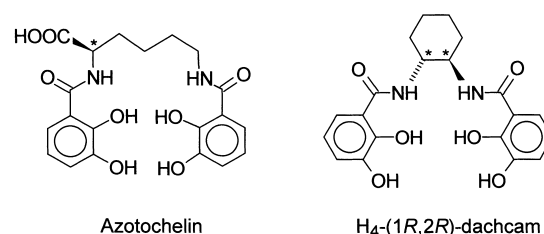
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Stereoselectivity in the Formation of a Cyclic Trinuclear *cis*-Dioxomolybdenum(vi) Complex of a Chiral Siderophore Analogue**

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The stereoselective synthesis of coordination compounds can be achieved by using enantiomerically pure ligands, which, on metal binding, transfer their chiral information to the metal center.^[1] Siderophores, high-affinity chelators synthesized by microorganisms to solubilize iron(III) for uptake into the cell, represent a biologically important example of this ligand type.^[2] Most siderophores are enantiomerically pure amino acid derivatives, and the chirality of the molecules can play an important role in their biological activity. This is well documented for enterobactin, the native siderophore of *Escherichia coli*: Only the naturally occurring complex, having an L-seryl ligand backbone and a Δ configuration at the metal center, is able to supply iron to the cells.^[3, 4] Interestingly, the N₂-fixing cells of *Azotobacter vinelandii* secrete azotochelin (Scheme 1), a tetradentate iron



Scheme 1.

siderophore which also binds molybdenum.^[5, 6] The structures of relevant model complexes have been reported.^[7, 8] Molybdenum, as well as iron, is a component of the conventional nitrogenase, and in *A. vinelandii* the siderophore production depends not only on the amount of iron in the environment but also on the concentration of molybdenum.^[5b, 6b] We report here that the L-lysine derivative azotochelin shows a high diastereoselectivity in forming the two possible Δ and Λ *cis*-dioxomolybdenum complexes. Use of the azotochelin analogue H₄-(1R,2R)-dachcam (Scheme 1) allowed us to investigate the chiral induction on molybdenum binding in the solid state and to compare the CD spectra of the model complex

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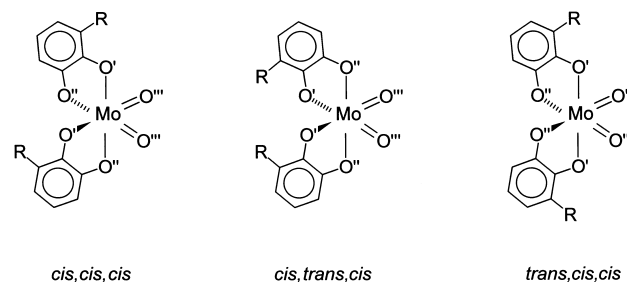
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with the spectra obtained for the naturally occurring azotochelin complex under analogue conditions.

The reaction of a solution of H_4 -(1*R*,2*R*)-dachcam in DMSO with an aqueous solution of sodium or potassium molybdate in a 1:1 ratio resulted in the formation of orange complexes which could be precipitated by addition of acetone and THF. Microanalyses of the isolated solids were consistent with a 1:1:2 ratio of molybdenum, ligand, and counterions. The electrospray (ES) mass spectrum of a solution of the sodium salt of the complex in acetonitrile showed three peaks at m/z 533, 811 (base peak), and 1645 corresponding to a trinuclear complex $[MoO_2((1R,2R)\text{-dachcam})_3]^{6-}$ (**1**) associated with three, four, and five sodium counterions, respectively. The 1/3, 1/2, and 1 spacing between isotopic components of the peaks confirmed the charges of the species involved. An additional peak at m/z 1090 originating from a dinuclear complex $[MoO_2((1R,2R)\text{-dachcam})_2]^{4-}$ associated with three sodium cations was also observed.

Suitable single crystals for X-ray diffraction could be obtained from the potassium salt of **1**. The crystal structure showed the complex to be trinuclear in the solid state (Figure 1).^[9] The molybdenum atoms form an approximately



Scheme 2. Schematic representation of the three possible *cis/trans* isomers that can be formed on coordination of two asymmetrically substituted catecholate ligands to a *cis*-dioxomolybdenum(vi) unit (all shown in *A* configuration).

field of supramolecular coordination chemistry^[10] examples of molecular triangles with metal atoms in vertex positions are still relatively rare and have so far been concentrated on noble metals,^[11–15] copper,^[16] and ligands based on nitrogen-containing heterocycles. In contrast, the novel molecular triangle **1** consists of catecholate ligands in combination with *cis*- MoO_2^{2+} units, demonstrating the versatility of these components as building blocks in supramolecular assemblies.^[17] On complex formation the enantiomerically pure ligand (1*R*,2*R*)-dachcam predetermines the chirality of the metal centers, giving rise to an entirely homochiral cyclic trimer $\Delta\Delta\Delta$ -**1**. The absolute configuration at the metal centers could be assigned unambiguously since the absolute configuration of the ligand is known.

To investigate if the intramolecular chiral induction observed for $\Delta\Delta\Delta$ -**1** in the solid state also occurs in aqueous solution at pH 7, a CD spectroscopic investigation has been carried out. A time-dependent study revealed that **1** rapidly inverts its configuration on dissolution of the crystalline solid in water. After equilibration in 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer at pH 7 the Λ -configured complex dominates, giving rise to a CD band with a minimum at around 360 nm (Figure 2). Since the Δ - and Λ -

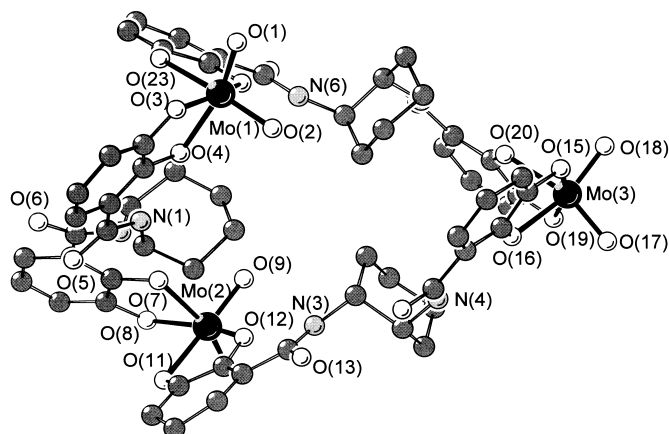


Figure 1. Structure of $\Delta\Delta\Delta$ - $[MoO_2((1R,2R)\text{-dachcam})_3]^{6-}$ showing the atom labeling scheme. Projection along the *a* axis. Hydrogen atoms have been omitted for clarity. Selected interatomic distances [Å] and angles [°]: Mo(1)–O(2) 1.71(2), Mo(1)–O(1) 1.72(2), Mo(1)–O(3) 2.02(2), Mo(1)–O(24) 2.04(2), Mo(1)–O(4) 2.10(2), Mo(1)–O(23) 2.12(2), Mo(2)–O(10) 1.70(2), Mo(2)–O(9) 1.70(2), Mo(2)–O(12) 2.02(2), Mo(2)–O(8) 2.02(2), Mo(2)–O(7) 2.13(2), Mo(2)–O(11) 2.16(2), Mo(3)–O(17) 1.71(2), Mo(3)–O(18) 1.72(2), Mo(3)–O(15) 1.98(2), Mo(3)–O(19) 2.02(2), Mo(3)–O(16) 2.12(2), Mo(3)–O(20) 2.13(2); O(23)–Mo(1)–O(24) 75.1(6), O(3)–Mo(1)–O(4) 75.7(7), O(1)–Mo(1)–O(2) 101.1(8), O(7)–Mo(2)–O(8) 75.2(7), O(11)–Mo(2)–O(12) 76.2(6), O(9)–Mo(2)–O(10) 102.5(9), O(19)–Mo(3)–O(20) 75.2(6), O(15)–Mo(3)–O(16) 75.5(6), O(17)–Mo(3)–O(18) 103.5(8).

equilateral triangle with intramolecular Mo(1)–Mo(2), Mo(1)–Mo(3), and Mo(2)–Mo(3) distances of 11.221(4), 11.104(4), and 11.236(4) Å, respectively. Atom Mo(3) lies on a pseudo-twofold axis of symmetry, and the coordination mode of the two catecholamide units corresponds to the C_2 -symmetrical *cis,trans,cis* isomer shown in Scheme 2. In contrast, the catecholamide units coordinated to Mo(1) and Mo(2) are bound in *cis,cis,cis* orientation, thereby allowing the formation of the cyclic structure. In the rapidly developing

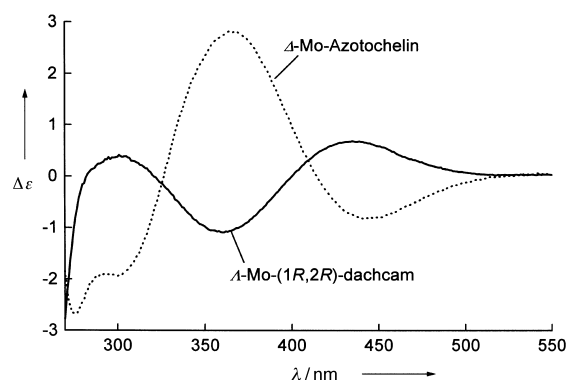
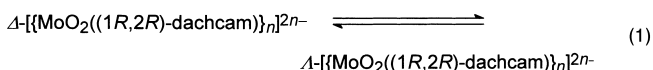


Figure 2. CD spectra of the molybdenum complexes of H_4 -(1*R*,2*R*)-dachcam and azotochelin in buffered aqueous solution (0.2 mM) at neutral pH.

configured complexes of (1*R*,2*R*)-dachcam are diastereomers [Eq. (1)], not enantiomers, they have different physical



properties, including solubilities.^[18] Consequently, the (+)₃₆₀ diastereomer present in the solid state inverts its configuration on dissolution to form the (−)₃₆₀ diastereomer, which is the more stable form in aqueous solution. In solution, however, the trimer appears to dissociate partially. The diastereomerisation process does not exhibit first-order kinetics and, in accordance with the ES mass spectrum, a molecular weight distribution analysis by gel filtration (LH20, methanol) shows evidence for the presence of a minor amount of a dinuclear species in solution.

An intramolecular chiral induction was also observed on binding of molybdenum by the naturally occurring L-lysine derivative azotochelin. In this case the CD spectrum of the equilibrium mixture in aqueous solution at pH 7 shows a strong band with a maximum at 360 nm (Figure 2). According to this comparison, the preferred configuration of the molybdenum complex of the naturally occurring L-lysine derivative azotochelin in aqueous solution and at neutral pH is likely to be the Δ form. Interestingly, this would correspond to the biologically active Δ form of the iron(III)–enterobactin complex.

Experimental Section

H₄-(1R,2R)-dachcam: The ligand was synthesized by analogy to published procedures^[19] by activation of 2,3-di(benzyloxy)benzoic acid with 2-(1-*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium (HBTU) hexafluorophosphate and subsequent reaction with (1R,2R)-diaminocyclohexane. Removal of the protecting groups was achieved by hydrogenation (catalyst: 5% Pd on charcoal). Yield: 85%. Satisfactory elemental analysis for C₂₀H₂₂N₂O₆; ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.13 (m, 2H; C-CH₂-C), 1.53 (m, 2H; C-CH₂-C), 1.75 (m, 2H; C-CH₂-C*), 1.92 (m, 2H; C-CH₂-C*), 3.76 (m, 2H; C-CH-N), 6.61 (t, 2H; ArH), 6.84 (d, 2H; ArH), 7.17 (d, 2H; ArH), 8.48 (d, 2H; NH); MS (70 eV): *m/z* (%): 386 (94) [*M*]⁺.

K₆[(MoO₂((1R,2R)-dachcam))₃] and Na₆[(MoO₂((1R,2R)-dachcam))₃]: The molybdenum complexes were synthesized by addition of a solution of H₄-(1R,2R)-dachcam (0.25 mmol) in DMSO (2 mL) to a solution of potassium or sodium molybdate (0.25 mmol) in water (2 mL). After addition of acetone (10 mL) and THF (20 mL) microcrystalline products precipitated which could be isolated in 78 and 80% yield, respectively. Satisfactory elemental analyses for C₆₀H₅₄N₆K₆Mo₃O₂₄·7 C₂H₆OS·6 H₂O and C₆₀H₅₄N₆Na₆Mo₃O₂₄·7 C₂H₆OS·6 H₂O; IR (KBr): $\tilde{\nu}$ = 870, 897 cm^{−1} (*cis*-MoO₂); MS (ES, Na salt in acetonitrile): *m/z* (%): 533 (50) [*M*_{trimer}+3Na]^{3−}, 811 (100) [*M*_{trimer}+4Na]^{2−}, 1090 (25) [*M*_{dimer}+3Na][−], 1645 (10) [*M*_{trimer}+5Na][−].

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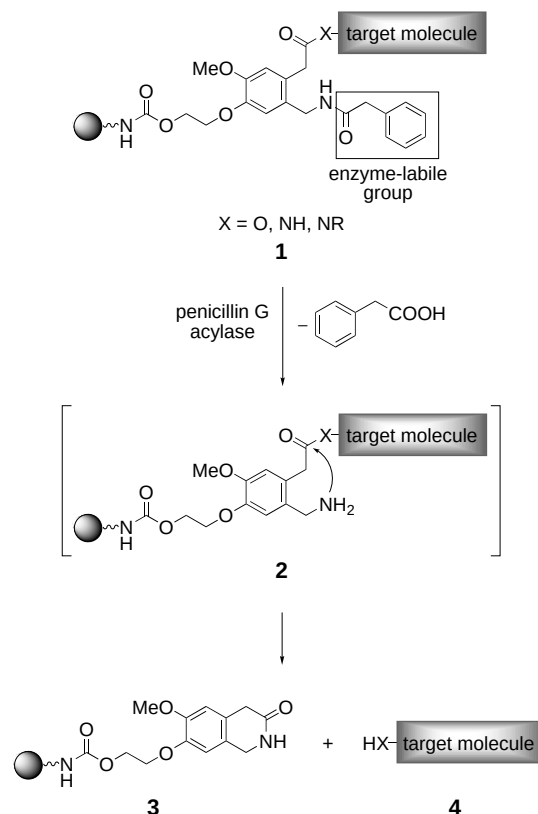
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An Enzyme-Labile Safety Catch Linker for Combinatorial Synthesis on a Soluble Polymeric Support**

Uwe Grether and Herbert Waldmann*

Combinatorial chemistry and parallel synthesis of compound libraries on polymeric supports are efficient methods for the generation of new substances with a predetermined profile of properties.^[1] Paramount to the success of this approach is the availability of suitable polymers and widely applicable linker groups for the attachment of the desired compounds to the polymeric carrier. Recent research in this field has focused on and achieved the successful transfer of a steadily growing number of reaction types to synthesis on solid supports, and the demands on the linker groups concerning their stability under different reaction conditions and selective cleavage have risen accordingly. Therefore, new and broadly applicable linkers which are stable under a variety of reaction conditions, but which at the same time allow release of the synthesized products under the mildest conditions, are of great interest in organic synthesis and combinatorial chemistry.^[2] Enzymatic methods may open up advantageous alternatives to classical chemical techniques since enzyme-catalyzed transformations often proceed under very mild conditions (pH 5–8, 25–37 °C) and with very high chemo-, regio-, and stereoselectivity.^[3] We now report on the development of a new enzyme-labile safety catch linker for combinatorial chemistry^[4] on a soluble polymeric support, allowing for the release of the target compounds in high yields and under neutral conditions.

In the design of the new linker groups a biocatalyzed transformation was combined with a subsequent intramolecular cyclization reaction, according to the principle of “assisted removal”^[5] of the desired target molecules. To this end the linker embodies a functional group which is recognized and attacked by the biocatalyst. The enzyme liberates an intermediate which cyclizes, with release of the target compounds. Furthermore, the linker carries an additional functional group for attachment to the polymeric support. The realization of this principle is shown in Scheme 1. The linker group is attached to an amino-functionalized carrier as a urethane ($\rightarrow 1$). It allows for the attachment of, for example, alkyl halides, alcohols, or amines as carboxylic acid esters and amides and their subsequent conversion to product libraries. The enzyme-labile functional group, a phenylacetamide, is remote from the structures to be generated by combinatorial



Scheme 1. Principle for the development of the enzyme-labile safety catch linker.

synthesis. Thereby possible steric or electronic interactions of the biocatalyst with the synthesis products, which might lead to a reduction of the substrate tolerance of the enzyme, are minimized. The release of the target molecules proceeds according to the safety catch principle in a two-step process. In the first step, the amidase penicillin G acylase hydrolyses the phenylacetamide with complete chemo- and regioselectivity and under exceptionally mild conditions (pH 7.0, room temperature or 37 °C).^[6] Subsequently benzylamine **2**, thereby generated as an activated intermediate, cyclizes to polymer-bound lactam **3** and releases the corresponding target molecule **4**.

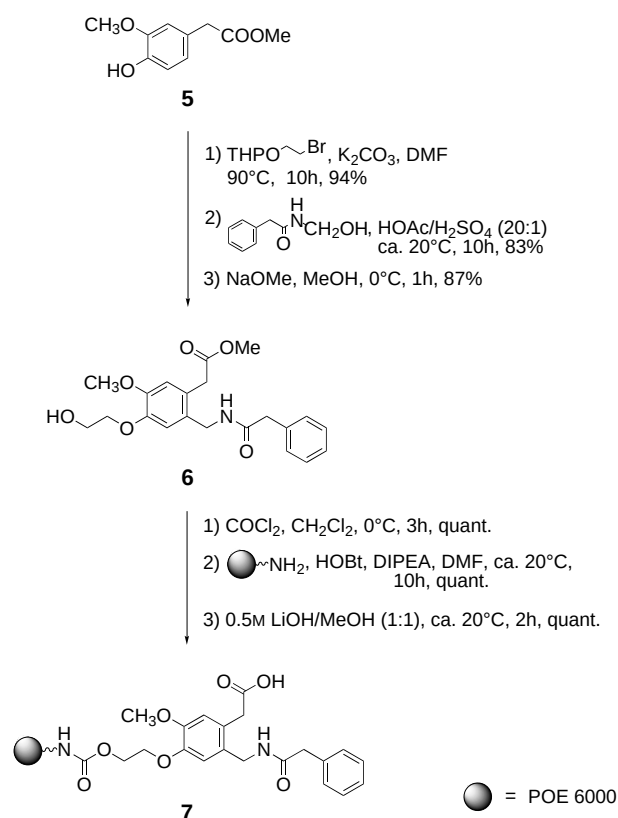
The linker was synthesized from commercially available homovanillic acid methyl ester **5** (Scheme 2). After alkylation of the phenolic hydroxyl group with THP-protected bromoethanol in high yield, the resulting trisubstituted aromatic compound was subjected to a completely regioselective electrophilic amidoalkylation with *N*-hydroxymethyl-phenylacetic acid amide.^[7] Under the acidic reaction conditions the THP ether was simultaneously converted into the corresponding acetate which was then saponified. By means of this three-step sequence, linker **6** is accessible in an overall yield of 67%.

The polymeric carrier chosen for attachment to the linker was a soluble polyethyleneglycol functionalized at both termini with an amino group and with an average molecular mass of 6000 Da (POE 6000).^[8] POE 6000 is soluble in numerous organic solvents but can be precipitated, filtered off, and washed after addition of diethyl ether, thereby

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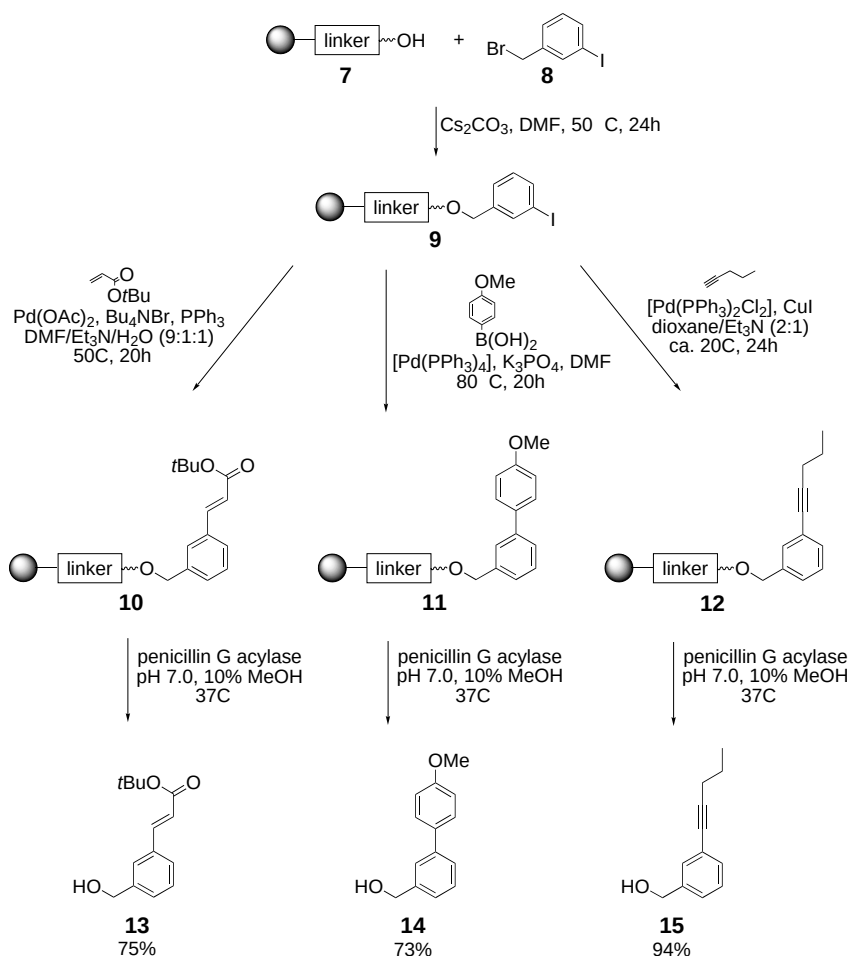
Scheme 2. Synthesis of the linker and coupling to the soluble polymer POE 6000. DIPEA=diisopropylethylamine, HOBt=1-hydroxy-1*H*-benzotriazole, THP=tetrahydropyranyl.

facilitating the separation of surplus reagents and side products. It allows for NMR spectroscopic monitoring of the reactions and, due to its pronounced solubility in water, for biocatalyzed transformations it offers the advantage that the substrates are accessible to the biocatalyst in homogeneous phase. For the attachment of **6** to POE 6000 the primary hydroxyl group was first converted into the corresponding chloroformic acid ester with phosgene and then the aminofunctionalized polymer was acylated with this intermediate quantitatively.^[9] Basic hydrolysis of the methyl ester was also quantitative and yielded functionalized polymer **7**.

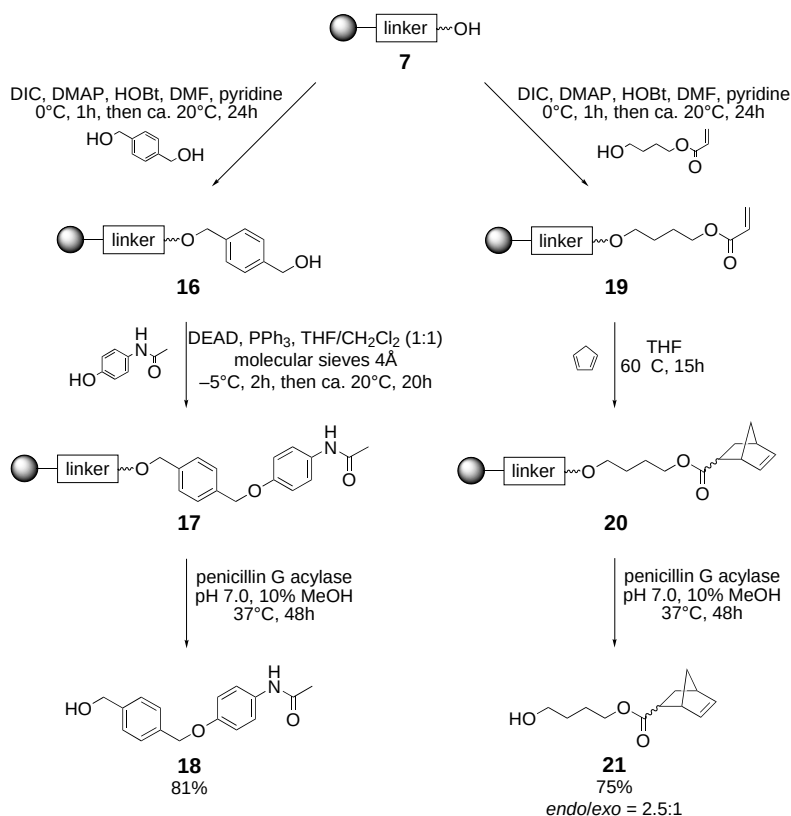
The suitability of the polymer–linker conjugate **7** for combinatorial syntheses and, thereby, also the scope of its applicability were investigated for a variety of different transformations. To this end, first the carboxyl group of the linker was esterified with *m*-iodobenzylbromide **8** and the polymer-bound aryl iodide **9** generated was then further transformed by Heck^[10], Suzuki^[11] or Sonogashira^[12] reactions (Scheme 3). NMR spectroscopic analysis revealed that these transformations proceeded quantitatively. Compounds **10**–**12** were then

incubated with penicillin G acylase at pH 7 and 37 °C. After 48 hours, benzyl alcohols **13**–**15** were isolated in high yields and with a purity of >95 % by simple extraction with diethyl ether (the phenylacetic acid remains in the aqueous phase).

In a further series of experiments Mitsunobu esterification and Diels–Alder reactions were investigated (Scheme 4). For the Mitsunobu reaction, the polymer was esterified quantitatively with 1,4-bis(hydroxymethyl)benzene. The obtained polymer-bound benzyl alcohol **16** was then treated with 4-acetamidophenol in the presence of the Mitsunobu reagent to give phenyl ether **17** in quantitative yield. By subsequent treatment of polymeric substrate **17** with penicillin G acylase, aryl benzyl ether **18** could be obtained in 81 % yield. For the Diels–Alder reaction, 4-hydroxybutyl acrylate was coupled to the linker and the polymer-bound acrylic acid ester **19** was treated with cyclopentadiene. This reaction was carried out at 60 °C at ambient pressure, and at 100 °C in a closed glass vial to investigate the pressure and temperature stability of the polymer-bound linker. According to NMR spectroscopic analysis cycloaddition product **20** was formed with an *endo/exo* ratio of 2.5:1 and with quantitative conversion. Subsequent enzymatic release delivered alcohol **21** in high yield and purity. The examples shown in Scheme 4 impressively prove the chemoselectivity of penicillin G acylase since the enzyme



Scheme 3. Palladium-catalyzed reactions on polymer **7** and enzyme-catalyzed release of the coupling products from the polymeric carrier.



Scheme 4. Mitsunobu and Diels–Alder reactions on polymeric carrier **7** and penicillin G acylase mediated release of the target molecules. DEAD = diethylazodicarboxylate, DIC = diisopropylcarbodiimide, DMAP = 4-(dimethylamino)-pyridine.

attacks only the phenylacetamide unit and not the ester and amide groups which are also present.

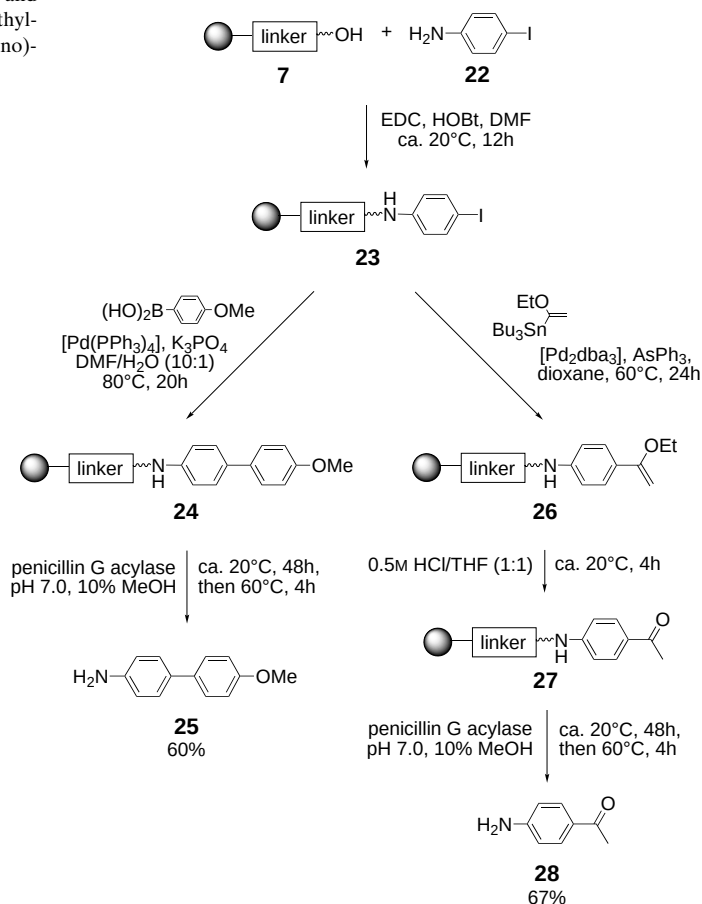
In a third series of experiments we investigated whether the enzymatic method also gives access to target molecules that are coupled to the linker as amides. To this end, 4-iodoaniline **22** was coupled quantitatively to linker **7** and the polymer-fixed aryl iodide **23** obtained thereby was subjected to a Suzuki reaction^[11] with 4-methoxyphenyl boronic acid or a Shille reaction^[13] to give enol ether **26** (Scheme 5). Upon treatment with 0.5 M hydrochloric acid, enol ether **26** yielded acetophenone **27**, thereby proving the acid stability of the linker. In order to release the coupling products, polymers **24** and **27** were incubated with penicillin G acylase at pH 7.0 and room temperature. As expected under these conditions the phenylacetamide was hydrolyzed. Due to the higher stability of amides relative to esters, however, the desired cyclization did not occur at room temperature. Upon warming of the reaction mixture to 60°C, the expected lactam was formed and amines **25** and **28** were released from the polymer.

These results demonstrate that the new enzyme-labile safety catch linker allows for the synthesis of different classes of compounds and the executions of various reaction types. The release of the products proceeds under particularly mild conditions with pronounced selectivity and delivers the desired products in high yield and purity. The linker is stable under different conditions, even at elevated temperature. Beyond the development of a new linker system for combi-

natorial chemistry our results prove that enzymes, in general, are valuable reagents for transformations on polymeric supports.

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Scheme 5. Palladium-catalyzed synthesis of anilines on the polymeric carrier and their enzymatic release. dba = *trans,trans*-dibenzylidenacetone, EDC = *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide.

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The First Structurally Characterized Metal Complex with the Molecular Unit $M=C=C=C=CR_2$ **

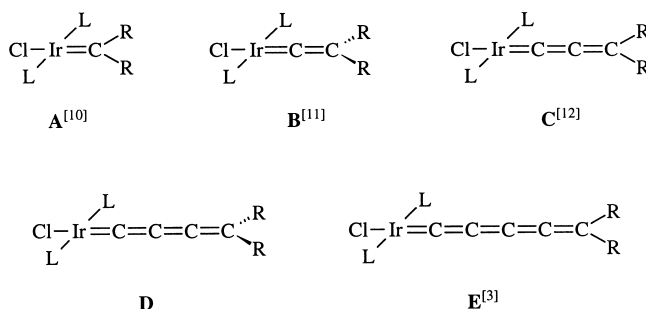
Kerstin Ilg and Helmut Werner*

Dedicated to Professor Henri Brunner on the occasion of his 65th birthday

The chemistry of metallacumulenes of the general composition $[L_xM=C(=C)_nRR']$, which could be considered as near relatives of metal carbenes, continues to receive a great deal of attention. While species with $n = 1$ and 2 have already been extensively investigated,^[1] not too much is known about the compounds with $n = 3$ and 4. In 1994, Dixneuf and co-workers reported the synthesis of the first cationic complex with $Ru=C=C=C=C=Ph_2$ as the building block,^[2] and a few months later we described the isolation of the first neutral compound with $Ir=C=C=C=C=Ph_2$ as the core unit.^[3] In the meantime, the field of metallahexapentaenes $[L_xM=C=$

$=C)_4RR']$ has further been developed, mainly due to the work by Fischer et al.^[4]

Earlier attempts to prepare *metallapentatetraenes*, that is compounds with $n = 3$ in the above-mentioned formula, date back to Lompfrey and Selegue^[5] and somewhat later to Bruce and co-workers.^[6] The latter group, by using $[(\eta^5-C_5H_5)Ru(PPh_3)_2(thf)]PF_6$ and buta-1,3-diyne as the starting materials, generated in situ a cationic complex containing the fragment $Ru=C=C=C=CH_2$ and supported the existence of this species by trapping reactions with nucleophiles such as $NHPh_2$, PPh_3 , H_2O , and imines. More recently, both the groups of Dixneuf^[7] and Winter^[8] reported about the in situ formation of cationic intermediates with the molecular unit $Ru=C=C=C=CHR$ and revealed that these can be converted to corresponding acylvinylidene, acylalkynyl, butenylnyl, and allenylidene ruthenium derivatives. In 1999, a dinuclear cationic compound with the core fragment $[M]=C=C=C=CH[M']$ ($[M] = (\eta^5-C_5Me_5)Fe('P_2')$, $'P_2' = 1,2$ -bis(diphenylphosphanyl)ethane (dppe), 1,2-bis(diisopropylphosphanyl)ethane (dippe); $[M'] = (\eta^5-C_5Me_5)Fe(CO)_2$) was prepared by Lapinte and co-workers, using the butadiynediyl complex $[M]C\equiv C\equiv C[M']$ as the precursor.^[9] We have now succeeded with the isolation and structural characterization of the first stable neutral compound of the type $[L_xM=C=C=C=CR_2]$ with $L_xM = IrCl(PiPr_3)_2$, which fills the gap in the system of the metallacumulenes **B–E** ($L = PiPr_3$).

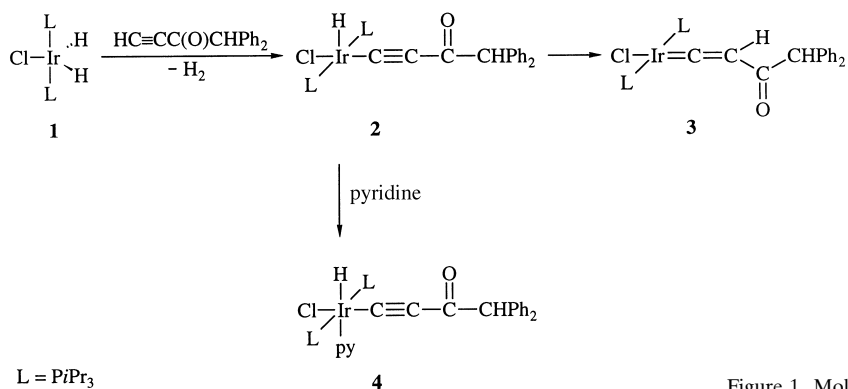


$L = PiPr_3$

The synthetic route for the iridium complex of type **D** follows the methodology which we used for the corresponding allenylidene derivatives *trans*- $[IrCl(=C=C=CRR')(PiPr_3)_2]$.^[11d, 12] Since the C_3 ligand in the compounds of type **C** was generated from propargylic alcohols $HC\equiv CCR'OH$, for the preparation of a species with a homologous C_4 unit we had to find a precursor with an additional carbon atom in the C_n chain. The best choice seemed to be the ethynyl ketone $HC\equiv CC(O)CHPh_2$.^[13] On reaction of this substrate with the dihydride **1**, the alkynyl(hydrido) complex **2** is formed which, however, is unstable in solution and isomerizes to the corresponding vinylidene derivative **3**. The existence of **2** can be confirmed by trapping the intermediate with pyridine, which results in the formation of the octahedral complex **4**. In contrast to the ^1H NMR spectrum of **3**, those of **2** and **4** display a triplet resonance in the high-field region at $\delta = -40.96$ (for **2**) and -21.68 (for **4**), the chemical shift of which is

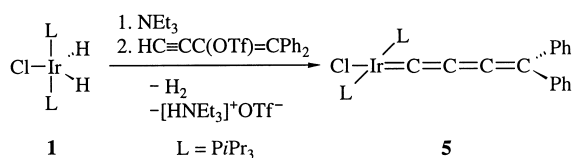
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characteristic for five- and six-coordinate hydrido-iridium(III) complexes, respectively.^[14]

In reactions in which **2** or **3** are used as the starting material, the elimination of water can be induced neither by base nor by acid catalysis. Therefore, it was necessary to bind a better leaving group to the γ -carbon atom of the substrate and at the same time to shift the keto–enol equilibrium to the side of the enol. Attempts to convert the keto function in the coordination sphere of the complex to the corresponding enol ester by using $(\text{CF}_3\text{SO}_2)_2\text{O}$ in the presence of 4-dimethylaminopyridine led only to the decomposition of the starting material **2**. The key to success was the use of the functionalized 1-alkyne $\text{HC}\equiv\text{CC}(\text{OTf})=\text{CPh}_2$ ($\text{Tf} = \text{F}_3\text{CSO}_2$), which reacts with **1** in hexane even at -100°C in the presence of one equivalent of triethylamine. The reaction is accompanied both by an evolution of gas and by a change of color from yellow to olive. After separation of the ammonium salt and recrystallization of the crude product from acetone, the butatrienylidene complex **5** is isolated as an olive-green, moderately air-sensitive solid in 77 % yield. With respect to the color, we note that a solution of **5** in benzene appears red.



The presence of a cumulated C_4 chain in **5** is indicated both by the IR spectrum, which displays an absorption at 1993 cm^{-1} , and by the ^1H NMR spectrum, which shows a splitting pattern for the signals of the phenyl protons that is typical for a system with a rotational symmetry around the $\text{Ir}-\text{C}_4$ axis. The ^{13}C NMR spectrum of **5** displays four triplet resonances for the carbon atoms of the cumulene moiety, the assignment of which is supported by the size of the $^{13}\text{C}-^{31}\text{P}$ coupling constant. The proposed structure of **5** was finally confirmed by a single-crystal X-ray structure analysis (Figure 1).^[16] The unsaturated carbon chain is nearly linear and deviates only weakly at C1 from the ideal value of 180° . The bond length $\text{Ir}-\text{C1}$ is $1.816(1)\text{ \AA}$ and thus somewhat shorter than the $\text{Ir}-\text{C}$ bond lengths in *trans*- $[\text{IrF}(\text{C}=\text{C}=\text{CPh}_2)(\text{P}^i\text{Pr}_3)_2]$ ($1.853(19)\text{ \AA}$)^[12] and *trans*- $[\text{IrCl}(\text{C}=\text{C}=\text{C}=\text{CPh}_2)(\text{P}^i\text{Pr}_3)_2]$ ($1.834(5)\text{ \AA}$).^[3] The lengths of the two internal $\text{C}-\text{C}$

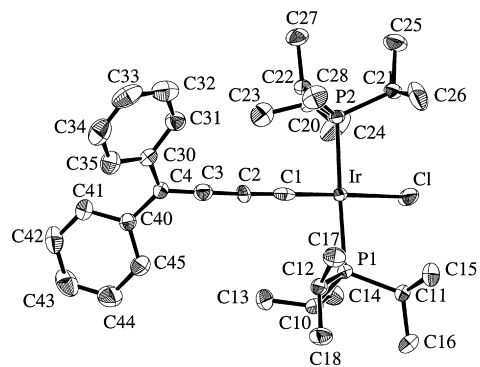
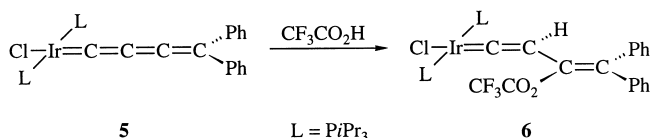


Figure 1. Molecular structure of **5** in the crystal. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: $\text{Ir}-\text{C1}$ $1.816(6)$, $\text{C1}-\text{C2}$ $1.283(8)$, $\text{C2}-\text{C3}$ $1.275(8)$, $\text{C3}-\text{C4}$ $1.339(8)$, $\text{Ir}-\text{P1}$ $2.350(1)$, $\text{Ir}-\text{P2}$ $2.356(1)$; $\text{P1}-\text{Ir}-\text{P2}$ $177.82(5)$, $\text{Cl}-\text{Ir}-\text{C1}$ $172.9(2)$, $\text{P1}-\text{Ir}-\text{C1}$ $90.0(2)$, $\text{P2}-\text{Ir}-\text{C1}$ $90.7(2)$, $\text{Ir}-\text{C1}-\text{C2}$ $175.1(5)$, $\text{C1}-\text{C2}-\text{C3}$ $178.1(6)$, $\text{C2}-\text{C3}-\text{C4}$ $178.7(7)$.

double bonds are almost identical ($1.283(8)\text{ \AA}$ and $1.275(8)\text{ \AA}$), whereas the terminal bond $\text{C3}-\text{C4}$ is slightly longer ($1.339(8)\text{ \AA}$).

To receive a first hint about the reactive centers of the neutral butatrienylidene compound **5**, we treated this species with $\text{CF}_3\text{CO}_2\text{H}$ and isolated the vinylvinylidene complex **6**. Evidently, instead of an attack of the proton at the nucleophilic metal center a regioselective addition of HX at the



$\text{C}_\beta=\text{C}_\gamma$ bond takes place. Therefore, the reactivity of the neutral compound **5** differs from that of the above-mentioned cations with the core fragment $\text{Ru}=\text{C}=\text{C}=\text{CH}_2$, which upon treatment with protic nucleophiles afford methyl-substituted allenylidene complexes by addition of HX at the $\text{C}_\gamma=\text{C}_\delta$ bond.^[6a,c]

Experimental Section

2: A solution of **1**^[13a] (113 mg, 0.22 mmol) in hexane (15 mL) was treated at -78°C with $\text{HC}\equiv\text{CC}(\text{O})\text{CHPh}_2$ (48 mg, 0.22 mmol). After the mixture had been warmed to room temperature, the solvent was evaporated and the beginning crystallization was completed at -78°C . The red microcrystalline solid was separated from the mother liquor and dried in vacuo; yield: 150 mg (90 %); m.p. 96°C (decomp); IR (C_6H_6): $\tilde{\nu} = 2310$ (IrH), 2062 ($\text{C}\equiv\text{C}$), 1683 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (200 MHz, C_6D_6)^[16]: $\delta = 7.42$ (m, *ortho*-H of C_6H_5), 7.08 (m, *meta*- and *para*-H of C_6H_5), 5.34 (s, CHPh_2), 2.89 (m, PCHCH_3), 1.15 (dvt, $N = 14.2$, $^3J(\text{H},\text{H}) = 7.1\text{ Hz}$, PCHCH_3), 1.07 (dvt, $N = 14.5$, $^3J(\text{H},\text{H}) = 7.3\text{ Hz}$, PCHCH_3), -40.96 (t, $^2J(\text{P},\text{H}) = 11.6\text{ Hz}$, IrH); $^{31}\text{P}\{^1\text{H}\}$ NMR (81.0 MHz, C_6D_6): $\delta = 39.2$ (s).

3: A solution of **2** (62 mg, 0.08 mmol) in benzene (10 mL) was stirred for 3 h at room temperature. After removal of the solvent the residue was suspended in pentane (2 mL) and the suspension was stored for 12 h at -78°C . The red-violet solid was separated from the mother liquor and dried in vacuo; yield: 57 mg (92 %); m.p. 142°C (decomp); IR (KBr): $\tilde{\nu} = 1654$ ($\text{C}=\text{O}$), 1544 cm^{-1} ($\text{C}=\text{C}$); ^1H NMR (200 MHz, C_6D_6): $\delta = 7.30$ (m, *ortho*-H of C_6H_5), 7.06 (m, *meta*- and *para*-H of C_6H_5), 4.84 (s, CHPh_2), 2.78 (m, PCHCH_3), 1.28 (dvt, $N = 14.5$, $^3J(\text{H},\text{H}) = 7.3\text{ Hz}$, PCHCH_3), -1.45 (t, $^4J(\text{P},\text{H}) = 2.9\text{ Hz}$, $=\text{CH}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (50.3 MHz, C_6D_6): $\delta = 255.2$ (t, $^2J(\text{P},\text{C}) = 11.6\text{ Hz}$, $\text{Ir}=\text{C}$), 181.3 (s, CO), 140.9 (s, *ipso*- C_6H_5), 129.6, 128.4,

126.9 (all s, C₆H₅), 112.4 (t, ³J(P,C) = 3.5 Hz, Ir=C=C), 64.3 (s, CHPh₂), 23.5 (vt, N = 26.8 Hz, PCHCH₃), 20.1 (s, PCHCH₃); ³¹P{¹H} NMR (81.0 MHz, C₆D₆): δ = 37.1 (s).

4: A solution of **2** (66 mg, 0.09 mmol) in diethyl ether (10 mL) was treated with pyridine (7 μL, 0.09 mmol) and stirred for 5 min at room temperature. After removal of the solvent, the off-white residue was dissolved in refluxing hexane (2 mL) and the solution then cooled to -78 °C. The resulting microcrystalline solid was separated from the mother liquor and dried in vacuo; yield: 67 mg (93 %); m.p. 127 °C (decomp); IR (KBr): $\tilde{\nu}$ = 2252 (IrH), 2054 (C=C), 1620 cm⁻¹ (C=O); ¹H NMR (400 MHz, C₆D₆): δ = 10.24, 9.90 (both br s, *ortho*-H of C₅H₅N), 7.49 (m, *ortho*-H of C₆H₅), 7.05 (m, *meta*- and *para*-H of C₆H₅), 6.82 (m, *para*-H of C₅H₅N), 6.56 (m, *meta*-H of C₅H₅N), 5.43 (s, CHPh₂), 2.84 (m, PCHCH₃), 1.06 (dvt, N = 14.0, ³J(H,H) = 7.3 Hz, PCHCH₃), 1.01 (dvt, N = 14.0, ³J(H,H) = 7.3 Hz, PCHCH₃), -2.168 (t, ²J(P,H) = 16.0 Hz, IrH); ¹³C NMR (100.6 MHz, C₆D₆): δ = 182.3 (s, CO), 140.8 (s, *ipso*-C₆H₅), 154.9, 152.3, 136.7, 129.7, 129.4, 128.5, 128.3, 126.7 (all s, C₆H₅ and C₅H₅N), 110.8 (t, ³J(P,C) = 4.1 Hz, Ir=C=C), 67.1 (s, CHPh₂), 23.8 (vt, N = 26.4 Hz, PCHCH₃), 19.2, 19.1 (both s, PCHCH₃), resonance of IrC=C not observed; ³¹P{¹H} NMR (162.0 MHz, C₆D₆): δ = 10.4 (s).

5: A solution of **1** (110 mg, 0.22 mmol) in hexane (15 mL) was treated at -100 °C with NEt₃ (24 μL, 0.22 mmol) and subsequently with a solution of HC=CC(OTf)=CPh₂ (77 mg, 0.22 mmol) in hexane (20 mL). After the reaction mixture had been warmed to room temperature, the solvent was evaporated, the residue was extracted with pentane (30 mL), and the extract was evaporated to dryness in vacuo. Recrystallization from acetone at -78 °C yielded an olive-green solid which was dried in vacuo; yield: 123 mg (77 %); m.p. 62 °C (decomp); IR (KBr): $\tilde{\nu}$ = 1993 cm⁻¹ (C=C=C=C); ¹H NMR (400 MHz, C₆D₆): δ = 7.50 (m, *ortho*-H of C₆H₅), 7.21 (m, *meta*-H of C₆H₅), 6.82 (m, *para*-H of C₆H₅), 2.89 (m, PCHCH₃), 1.28 (dvt, N = 13.8, ³J(H,H) = 7.0 Hz, PCHCH₃); ¹³C{¹H} NMR (100.6 MHz, C₆D₆): δ = 255.7 (t, ²J(P,C) = 13.7 Hz, Ir=C=C=C=C), 174.6 and 164.1 (both t, ³J(P,C) = ⁴J(P,C) = 3.6 Hz, Ir=C=C=C=C and Ir=C=C=C=C), 132.1 (s, *ipso*-C₆H₅), 130.2, 128.5, 127.3 (all s, C₆H₅), 105.9 (t, ²J(P,C) = 2.5 Hz, Ir=C=C=C=C), 23.6 (vt, N = 26.4 Hz, PCHCH₃), 20.1 (s, PCHCH₃); ³¹P{¹H} NMR (162.0 MHz, C₆D₆): δ = 26.7 (s).

6: A solution of **5** (53 mg, 0.07 mmol) in benzene (5 mL) was treated with CF₃CO₂H (5.5 μL, 0.07 mmol) at room temperature and the resulting red-violet solution stirred for 5 min. The solvent was removed in vacuo and the residue recrystallized from pentane (2 mL) at -60 °C; red-violet crystals; yield: 52 mg (87 %); m.p. 106 °C (decomp); IR (KBr): $\tilde{\nu}$ = 1795 (OCO)_{as}, 1626 (C=C), 1457 cm⁻¹ (OCO)_{sym}; ¹H NMR (200 MHz, C₆D₆): δ = 7.27 (m, *ortho*-H of C₆H₅), 6.93 (m, *meta*-H of C₆H₅), 2.88 (m, PCHCH₃), 1.28 (dvt, N = 13.4, ³J(H,H) = 6.7 Hz, PCHCH₃), -2.81 (t, ⁴J(P,H) = 2.1 Hz, =CH); ¹³C{¹H} NMR (50.3 MHz, C₆D₆): δ = 255.6 (t, ²J(P,C) = 12.1 Hz, Ir=C=C), 154.6 (q, ²J(F,C) = 43.2 Hz, CF₃CO₂), 148.1 (br s, C(O₂CCF₃)=CPh₂), 140.0, 138.8, 130.2, 129.3, 123.3, 120.2 (all s, C₆H₅), 138.7 (s, =CPh₂), 115.3 (q, ¹J(F,C) = 268.0 Hz, CF₃CO₂), 104.9 (t, ³J(P,C) = 3.8 Hz, Ir=C=C), 23.4 (vt, N = 26.7 Hz, PCHCH₃), 20.0 (s, PCHCH₃); ¹⁹F{¹H} NMR (188.0 MHz, C₆D₆): δ = -74.4 (s); ³¹P{¹H} NMR (162.0 MHz, C₆D₆): δ = 32.2 (s).

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- [16] Crystal structure analysis of **5**: Crystals from diethyl ether at 5 °C, C₃₄H₅₂ClIrP₂ (750.35); crystal dimensions 0.21 × 0.20 × 0.05 mm; triclinic, space group *P* $\bar{1}$ (no.2), *a* = 8.7412(17), *b* = 12.309(2), *c* = 16.213(3) Å, α = 96.425(12), β = 91.125(13), γ = 103.352(11)°, *Z* = 2, *V* = 1684.8(6) Å³, ρ_{calc} = 1.479 g cm⁻³; *T* = 193(2) K; 2 θ = 45°; 4931 reflections measured; 4391 were unique (*R*_{int} = 0.0260), and 3947 observed (*I* > 2 σ (*I*)); Enraf-Nonius-CAD4 diffractometer, Mo_{K α} radiation (λ = 0.71073 Å), graphite monochromator, zirconium filter (factor 15.2); Lp- and empirical absorption correction (Ψ scan, min. transmission 67.21 %). The structure was solved by Patterson method, refinement with full-matrix, least-squares method; *R*₁ = 0.0277, *wR*₂ = 0.0627 (for 3947 reflections with *I* > 2 σ (*I*)), *R*₁ = 0.0346, *wR*₂ = 0.0667 (for all 4391 data); data-to-parameter ratio 12.37; residual electron density +1.015/–0.919 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-138491. 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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Homoleptic Carbonyl Ni–Pd Clusters: Synthesis of $[\text{Ni}_{16}\text{Pd}_{16}(\text{CO})_{40}]^{4-}$ and $[\text{Ni}_{26}\text{Pd}_{20}(\text{CO})_{54}]^{6-}$ and Structural Characterization of $[\text{NnBu}_4]_4[\text{Ni}_{16}\text{Pd}_{16}(\text{CO})_{40}]^{4-}$ **

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Recent collision-induced dissociation studies on the gas-phase $[\text{Pd}_3(\text{CO})_6]^-$ cluster^[1] supplement other experimental observations,^[2–7] which seem to suggest the feasibility of homoleptic carbonylpalladium derivatives. Thus, although the measured average Pd–CO bond dissociation energy (ca. 134 kJ mol^{−1}) is weaker than that measured for the $[\text{Pt}_3(\text{CO})_6]^-$ congener (ca. 173 kJ mol^{−1}), its value does not seem, however, sufficient to rule out the possible existence of binary palladium carbonyl compound in solution, unless their formation is hindered by some competing reaction.^[1] The belief that the preassembly of a Pd kernel of critical size could ultimately favor the synthesis of a binary palladium carbonyl compound in solution led us to tackle the synthesis of Ni–Pd homoleptic carbonyl bimetallic clusters (HCBCs) as potential precursors of the former. So far, only the related phosphane-substituted derivative $[\text{Ni}_9\text{Pd}_{33}(\text{CO})_{41}(\text{PPh}_3)_6]^{4-}$ ^[8] and the trimetallic derivative $[\text{Au}_6\text{Ni}_6(\text{Pd}_{6-x}\text{Ni}_x)\text{Ni}_{20}(\text{CO})_{44}]^{6-}$ ^[9] have been reported. To our knowledge, the only Ni–Pd HCBC cited in literature is the incompletely characterized $[\text{Ni}_{30-x}\text{Pd}_x(\text{CO})_y]^{4-}$ ($x \approx 16$; $y \approx 36$) species, which has been used as precursor for the synthesis of the giant complex $[\text{Pd}_{59}(\text{CO})_{32}(\text{PMe}_3)_{21}]^{10}$

Investigation of the reaction of $[\text{Ni}_6(\text{CO})_{12}]^{2-}$ with Pd^{II} compounds in miscellaneous molar ratios and reaction solvents displayed the existence of wide series of Ni–Pd HCBCs. We report here our first results on the synthesis, chemical properties, and X-ray structural characterization of the tetraanion $[\text{Ni}_{16}\text{Pd}_{16}(\text{CO})_{40}]^{4-}$ (**1**), as well as preliminary details of the closely related hexaanion $[\text{Ni}_{26}\text{Pd}_{20}(\text{CO})_{54}]^{6-}$ (**2**).

The tetrabutylammonium salt of **1** separated out in about 50% yield (based on Pd) as a microcrystalline dark precipitate directly from the reaction of $[\text{NnBu}_4]_2[\text{Ni}_6(\text{CO})_{12}]$ with $[\text{Pd}(\text{SEt}_2)_2\text{Cl}_2]$ in THF and was recrystallized by extraction in acetone and precipitation with *n*-hexane. Crystals of $[\text{NnBu}_4]_6[\text{2}]$ were obtained in low yields (5–10%) from the filtered THF reaction solution upon layering with *n*-hexane. The structure of **1**^[11] is shown in Figure 1; its metal skeleton is represented in Figure 2 (left) as deriving from condensation of two Ni_8Pd_8 vertex-truncated ν_3 -tetrahedra through their

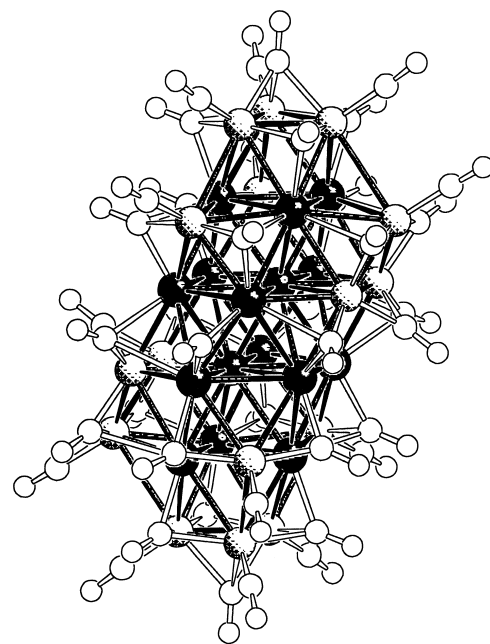


Figure 1. The structure of **1**: black spheres represent the palladium atoms. Range of M–M bonds [Å]: Ni–Ni 2.426(1)–2.473(1), Ni–Pd 2.582(1)–2.825(1), Pd–Pd 2.674(1)–2.930(1). The Ni–Ni inter-layer separations of the outer pair of layers are outside of the above range (mean value 3.07 Å).

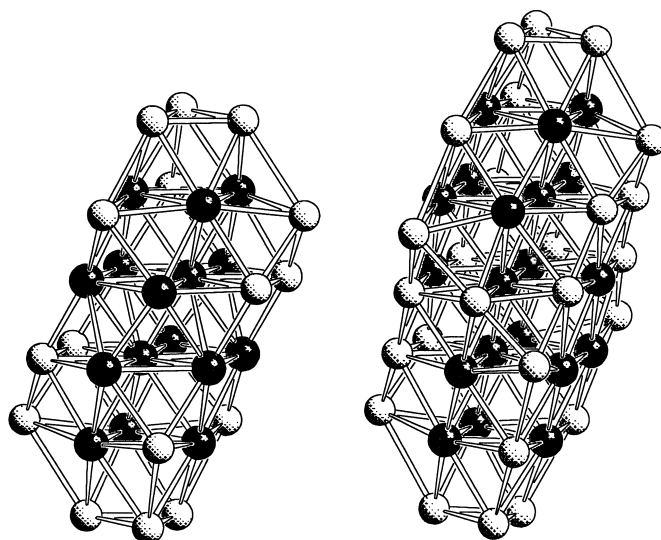


Figure 2. Comparison between the *cp* metal framework of **1** (left; oriented as an *abcba* sequence of compact layers) and the *ccp* metal framework of **2** (right; as an *abcbca* sequence).

Ni_2Pd_5 hexagonal faces, giving rise to a six-layer close-packed metal framework. Two Pd atoms are encapsulated in two $\text{Ni}_2\text{Pd}_{10}$ twinned cubooctahedral moieties and the cluster surface solely comprises triangular faces with all possible combinations of the two metals. The forty carbonyl groups display most possible CO coordination modes. They comprise linear, and symmetrical edge- and face-bridging ligands, as well as unsymmetrical and semibridging carbonyl groups with sub-van-der-Waals Pd–C contacts of 2.3–2.5 Å. Only nickel atoms bind terminal carbonyl groups. Both homo- and heterometallic edges are spanned by bridging CO groups. Notably, only the Pd_3 triangles of the miscellaneous $\text{Ni}_{3-x}\text{Pd}_x$

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($x=0-3$) triangular faces are not capped by a face-bridging carbonyl group. CO binding to Pd only as a bridging ligand in **1** is in keeping with its preferential coordination as a bridging adsorbate on Pd surfaces of different topologies.^[15] Such preferential coordination has been explained by a theoretical study.^[16]

The HCBC **2**^[17] displays a metal structure closely related to that of **1** and a similar carbonyl distribution comprising also capped Pd₃ faces. As shown in Figure 2 (right), its metal framework formally derives by sandwiching a Ni₆Pd₄ layer between the two Ni₈Pd₈ vertex-truncated ν_3 -tetrahedra and addition of four capping Ni atoms. As a result, four Pd atoms are encapsulated in the cubooctahedral moieties.

The Ni-decorated palladium kernels of **1** and **2** (Figure 3) bear little structural resemblance with the so far known Ni–Pt HCBCs, namely $[H_{4-n}Ni_9Pt_3(CO)_{21}]^{n-}$ ($n=2-4$), $[Ni_{36}Pt_4(CO)_{45}]^{6-}$, and $[H_{6-n}Ni_{38}Pt_6(CO)_{48}]^{n-}$ ($n=4-6$).^[18] The only similarity is shown by the metal atoms of the Ni₆Pd₃ outer moieties, which are arranged as the related moieties of $[H_{4-n}Ni_9Pt_3(CO)_{21}]^{n-}$.

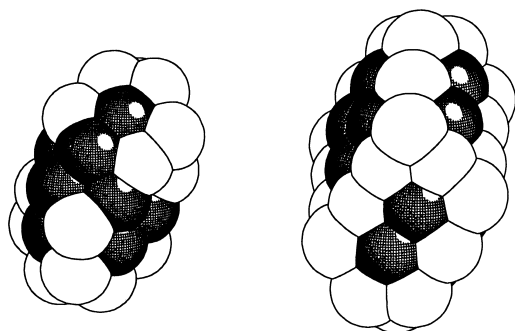


Figure 3. Space-filling model of the nickel-decorated Pd frameworks of **1** (left) and **2** (right).

Extended Hückel(EH) MO calculations with the CACAO program^[19] on **1** and **2** disclose neat energy gaps after the 360th and 500th (from bottom) molecular orbitals, respectively. The four and six additional valence electrons, respectively, present in **1** and **2**, populate closely spaced weakly antibonding molecular orbitals delocalized over the inner metal core and carbonyl ligands. The nature of the frontier orbitals and the energy separations between them suggest that **1** and **2** could have several valence electrons and be magnetic.^[20, 21] However, preliminary magnetic measurements at room temperature with the Gouy method did not substantiate the presence of unpaired electrons in **1** and **2**.

Both **1** and **2** readily eliminate Ni(CO)₄ under a carbon monoxide atmosphere and afford unstable species that contain insignificant amounts of nickel; their solutions display IR patterns almost coincident with those of the smallest carbonylated crystalline Pd/poly(vinylpyrrolidone) colloids,^[22] and absorption wavenumbers influenced by their redox state (terminal and bridging CO in the 2040–1990 (mw) and 1930–1890 (s) cm^{−1} range, respectively). If nothing more, the Ni–Pd HCBC may turn out to be possible precursors of palladium carbonyl colloids of tailored size.

Experimental Section

$[Pd(SET_2)_2Cl_2]$ (1.80 g, 5.04 mmol) was added in portions to a solution of $[NnBu_4]_2[Ni_6(CO)_{12}]$ (3.54 g, 3.02 mmol) in THF (60 mL) under stirring over a period of 6 h. The mixture was left to react for 12 h. The resulting dark brown suspension was filtered. The microcrystalline precipitate was thoroughly washed with water (40 mL) and THF (40 mL), extracted in acetone (40 mL), and precipitated by layering of *n*-hexane (60 mL) to give black prisms of $[NnBu_4]_4[1]$ (743 mg, 49.8% based on Pd). The salt is soluble in acetone, acetonitrile, dimethylformamide, and dimethyl sulfoxide, sparingly soluble or insoluble in THF, alcohols, and nonpolar solvents. IR (acetonitrile): $\bar{\nu}_{CO}=2016$ (s), 1883 (m), and 1820 (m) cm^{−1}.

Layering of *n*-hexane on the filtered THF reaction solution afforded black crystals of $[NnBu_4]_6[2] \cdot x C_6H_{14}$ (94 mg). The salt is soluble in acetone, acetonitrile, dimethylformamide, and dimethyl sulfoxide, sparingly soluble in THF, and insoluble in alcohols and nonpolar solvents. IR: (acetonitrile): $\bar{\nu}_{CO}=2015$ (s), 1863 (ms), and 1800 (w) cm^{−1}.

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$[\text{Li}(\text{thf})_4]_2^+[\text{Ga}_{12}(\text{C}_{13}\text{H}_9)_{10}]^{2-}$: The First Molecular Compound with an Icosahedral Ga_{12} Framework**

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Starting from metastable AlX and GaX solutions ($\text{X} = \text{Cl}$, Br, I), which can be prepared by using a cocondensation method,^[1] metalloid clusters such as Al_7R_6^- ,^[2] $\text{Al}_{12}\text{R}_8^-$,^[3] $\text{Al}_{17}\text{R}_{20}^{2-}$,^[4] ($\text{R} = \text{N}(\text{SiMe}_3)_2$) and Ga_{22}R_8 ^[5] ($\text{R} = \text{Si}(\text{SiMe}_3)_3$, $\text{Ge}(\text{SiMe}_3)_3$) have recently been synthesized in metathesis reactions. In contrast, there are only a few examples in which polyhedral species such as $(\text{AlR})_n^{x-}/(\text{GaR})_n^{x-}$ ($x = 0, 1, 2$) have been prepared from AlX/GaX solutions or similar routes. In addition to tetrahedral $(\text{MR})_4$ compounds, for example B_4R_4 ,^[6] Al_4Cp_4^* ,^[7] and $\text{Ga}_4[\text{C}(\text{SiMe}_3)_3]_4$,^[8] as icosahedral species for the two lightest elements of Group 13, besides numerous boron compounds, only the following aluminum species have been structurally characterized: $\text{Al}_{12}\text{iBu}_{12}^{2-}$ ^[9] and $\text{Al}_{12}(\text{AlBr}_{10}) \cdot 2\text{THF}$.^[10, 11] A corresponding

molecular gallium compound is as yet unknown,^[12] although there are numerous examples of icosahedral partial structures for gallium in solid-state chemistry.^[13] We report here on the first molecular compound with an icosahedral Ga_{12} unit.

A metastable GaBr solution, which was obtained by the simultaneous condensation of the high-temperature molecule GaBr with a toluene/THF mixture, was treated with a fluorenyllithium/toluene solution at -78°C . Allowing the mixture to warm to room temperature, followed by removal of the solvent in vacuo gave a dark red oil, which was subsequently dissolved in THF. Crystals of $[\text{Li}(\text{thf})_4]_2^+[\text{Ga}_{12}(\text{C}_{13}\text{H}_9)_{10}]^{2-}$ (**1**) were obtained from the resulting dark red THF solution. The result of an X-ray crystal structure analysis of the anionic Ga_{12} unit is shown in Figure 1.

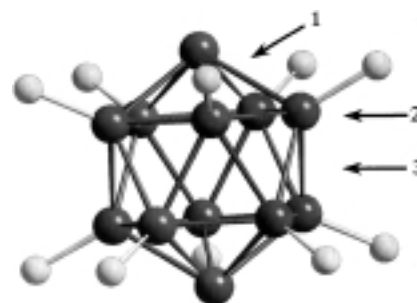


Figure 1. Molecular structure of $\text{Ga}_{12}(\text{C}_{13}\text{H}_9)_{10}^{2-}$ in **1**: For clarity only the carbon atom directly bound to the gallium atom is shown in each case for the fluorenyl ligands. Bond lengths (min./av./max.) [pm] in the different regions labeled by numbered arrows: $d(\text{Ga}-\text{Ga})_1 = 264.72(7)/265.3/265.87(7)$, $d(\text{Ga}-\text{Ga})_2 = 258.27(7)/258.9/259.14(6)$, $d(\text{Ga}-\text{Ga})_3 = 267.33(9)/268.4/269.69(8)$.

The structure reveals that fluorenyl ligands are only bound to ten of the twelve gallium atoms, which are arranged in the form of an icosahedron. This icosahedron is slightly elongated in the direction of the “naked” gallium atoms, thus the longest Ga–Ga contacts (268.4 pm) are found between the two Ga_5 rings. The distances between the “naked” Ga atoms and the Ga atoms of the respective Ga_5 rings (265.3 pm) are only slightly shorter. The shortest Ga–Ga distances (258.9 pm) of the Ga_{12} framework are found in the Ga_5 rings. The ten fluorenyl ligands are each bound to one gallium atom (205.9 pm) in a σ -like fashion and are tilted in a regular fashion in one direction, which is particularly evident on inspection of **1** along an axis running through the two “naked” Ga atoms (Figure 2).

Since the question of whether the “naked” Ga atoms are each saturated by a H atom could not be answered unambiguously from the X-ray structure analysis, we recorded IR spectra on the crystals; however, these revealed no indications of a Ga–H bond. These experimental findings were confirmed by quantum-chemical calculations,^[14] which showed that the Ga–Ga and Ga–C distances calculated for the model compound $\text{Ga}_{12}(\text{CH}_3)_{10}^{2-}$ are in good agreement with those measured in **1**.^[12]

In order to compare the bonding in **1** with the Wade-like bonding in polyhedral boranes by using simple MO diagrams, we performed additional density functional theory (DFT) calculations for $\text{Ga}_{12}\text{H}_{12}^{2-}$ (**1a**), $\text{Ga}_{12}\text{H}_{10}^{2-}$ (**1b**), $\text{B}_{12}\text{H}_{12}^{2-}$ (**1a'**),

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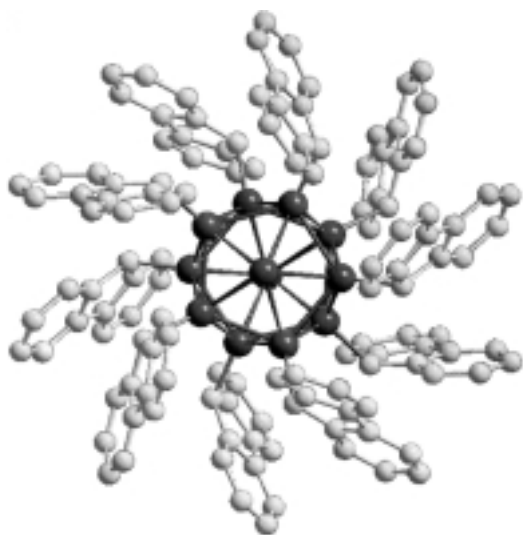


Figure 2. Molecular structure (hydrogen atoms omitted) of $\text{Ga}_{12}(\text{C}_{13}\text{H}_9)_{10}^{2-}$ in **1**. View along one of the axes running through the two “naked” Ga atoms.

and $\text{B}_{12}\text{H}_{10}^{2-}$ (**1b'**). These revealed that the M_{12}^{2-} frameworks in **1a** and **1a'** are held together by 26 electrons and those in **1b** and **1b'** by 28 electrons. The principle difference between the boron and gallium species is that in the boron clusters four (**1a'**) and five MOs (**1b'**), respectively, lie above the MOs for the B–H bonds, whereas the number of framework MOs lying above the Ga–H bonding MOs for the corresponding gallium compounds are eight (**1a**) and nine (**1b**), respectively. This means that the framework MOs found in the gallium compounds are more diffuse, which is a clear indication of the greater “metalloid” character of the gallium compounds (see below) and their expected spontaneous decomposition with metal deposition.^[15] The preference of a $\text{Ga}_{12}\text{R}_{10}^{2-}$ species over a hypothetical $\text{B}_{12}\text{H}_{10}^{2-}$ species (each in D_{5d} symmetry) is likewise clearly evident from DFT calculations: The HOMO (a_{2u}) in $\text{B}_{12}\text{H}_{10}^{2-}$ is destabilized by about 3.8 eV compared to the next lower lying MO (e_{2u}), whereas the HOMO (e_{2u}) for $\text{Ga}_{12}\text{H}_{10}^{2-}$ is only about 0.1 eV above the MO (e_{1u}) lying directly below it. This means that a hypothetical icosahedral $\text{B}_{12}\text{H}_{10}^{2-}$ species with the 28 framework electrons necessary for a *nido* framework and an energetically high-lying HOMO (see above) should be stabilized by oxidation or reduction of the symmetry in the boron framework. In contrast, the observation of the distorted icosahedral $\text{Ga}_{12}\text{R}_{10}^{2-}$ ion in **1** is strong evidence for the different bonding in such Ga_n polyhedra. Similar bonding to that in **1** might be present in $\text{Al}_{12}(\text{AlBr}_2)_{10}$ (**2**), which we prepared recently, although in **2** a distortion different to that in **1** is observed in the Al_{12} icosahedron ($d(\text{Al}–\text{Al})_1 = 265.0$, $d(\text{Al}–\text{Al})_2 = 276.7$, $d(\text{Al}–\text{Al})_3 = 269.2$ pm; numbering as in Figure 1). The $\text{Al}_{12}\text{iBu}_{12}^{2-}$ icosahedron **3**^[9] is a “true” *closo* cluster as defined by Wade, since here all the distances are almost the same (267.9–269.6 pm). As expected the average Ga–Ga distances in **1** are significantly shorter than the Al–Al distances in **3**, since Ga_2R_4 species also display a shortening of about 3% of these distances over those in Al_2R_4 compounds.^[16]

The results presented here show that in contrast to the Wade-like bonding system of **3**, a different description of the

bonding is necessary for **1**. An interpretation which appears to us to be plausible is briefly presented as follows: In a hypothetical cleavage of two R[−] groups from $\text{Ga}_{12}\text{R}_{10}^{2-}$, a neutral Ga_{12}R_8 compound would be formed with the same average oxidation state of the Ga atoms as in **1**. Thus, the relationship to the recently published metalloid clusters In_{12}R_8 ^[17] and $\text{Al}_{12}\text{R}_8^{3-}$ ^[3] is clearly apparent. Whereas the latter two compounds are intermediates with “metallic” partial structures on the route to the metal, an icosahedral structure is observed for **1**, however, with an electronic structure unexpected for polyhedra (see above). This finding is nevertheless plausible because gallium, in contrast to the more typical metals Al and In, contains icosahedral units in the δ -modification of the element.^[18] Thus, the formation of element-like, metalloid structures appears in the cases considered here ($\text{Ga}_{12}\text{R}_{10}^{2-}$, In_{12}R_8 , $\text{Al}_{12}\text{R}_8^{3-}$) to be the main driving force in the disproportionation. This conclusion, however, does not mean that Wade-like species do not form in such reactions as precursors, which, however, have only been isolated in a few cases to date (e.g. $\text{Al}_{12}\text{iBu}_{12}^{2-}$ ^[9]).

Experimental Section

Fluorenyllithium (225 mg, 1.33 mmol) was placed in toluene (15 mL) and cooled to -78°C . GaBr solution (4.2 mL; 1.25 mmol of a 0.3 M solution in toluene/THF (3/1)) was added slowly to this suspension at -78°C by using a steel cannula. The solution was subsequently allowed to warm to room temperature slowly with stirring. This gave a pale red solution and a black residue. After removal of the solvent in vacuo, a black residue remained, which was washed with pentane and toluene and then taken up in THF. This gave a dark red extract and a yellow-orange residue. The residue was identified by qualitative methods as LiBr. The product **1** was obtained in crystalline form from the THF extract by layering the solution with heptane. Yield: 40 mg of dark red crystals, 0.013 mmol, 12.5 %.

Since the resulting crystals could not be redissolved either in benzene or in THF, no NMR data have been obtained to date. The IR spectrum (KBr disk) shows no other absorption bands apart from those for the fluorenyl ligand.

Crystal structure data of **1**: $[\text{Li}(\text{thf})_4]_2[\text{Ga}_{12}(\text{C}_{13}\text{H}_9)_{10}]$, $M_r = 3077.99$, crystal dimensions $0.2 \times 0.2 \times 0.3$ mm, triclinic, space group $P\bar{1}$, $a = 17.565(2)$, $b = 17.694(2)$, $c = 17.737(2)$ Å, $\alpha = 63.45(1)$, $\beta = 85.54(1)$, $\gamma = 62.71(1)^\circ$, $V = 4325.8(8)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.379$ g cm^{−3}, μ_{Mo} = 1.8976 mm^{−1}, $2\theta_{\text{max}} = 51.74^\circ$, 33 554 measured reflections, 15 572 independent reflections ($R(\text{int.}) = 0.0416$), absorption correction: numerical (min./max. transmission 0.527/0.709), $R_1 = 0.0453$, $wR_2 = 0.1208$. Stoe IPDS diffractometer ($\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å), 200 K). The structure of **1** was solved by direct methods and refined against F^2 for all observed reflections. Programs applied: Shelxs and Shelxtl (G. M. Sheldrick, Universität Göttingen). 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-138288. 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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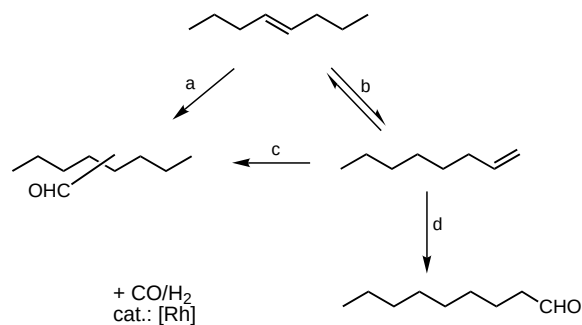
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Novel Oxyfunctionalized Phosphonite Ligands for the Hydroformylation of Isomeric *n*-Olefins

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Hydroformylation (oxo synthesis) is one of the most important industrial procedures carried out under homogeneous catalysis. The high economic significance of this C–C coupling reaction results from the successful production of over six million tonnes per year of aldehydes and subsequent

products for the plasticizer industry, with propylene as the most important reagent.^[1] Knowledge gained from experience demonstrates the advantages of ester plasticizers with a low degree of branching and C-numbers from nine upwards for the alcohol components. An olefin raw material for this application is a technical octene mixture, for which complete conversion of all isomers present and control of regioselectivity to the benefit of terminal aldehyde products are of equal importance (Scheme 1). Hitherto, these two parameters could



Scheme 1. Isomerizing hydroformylation of internal olefins with the example of 4-octene. a) hydroformylation, b) isomerization, c), d) hydroformylation.

only be fulfilled by cobalt catalysis under severe reaction conditions. Characteristic productivities are $0.1\text{--}0.4\text{ t m}^{-3}\text{ h}^{-1}$ and selectivities for the terminal aldehyde of 50–85 %, which are achieved with 0.1–1 % Co at pressures of 80–350 bar and temperatures of 160–190 °C, as well as an undesirable and extensive hydrogenation activity.^[1]

The elimination of these disadvantages by, for example, the use of novel metal complexes, ligands, and technologies is one of the current demands placed upon this area. Highly selective rhodium catalysts based upon bidentate aryl phosphites and diphosphanes with a large coordination angle already exist for the conversion of terminal, long-chain olefins.^[2] However, where internal olefins are concerned, technically useful activity is exhibited only with short-chain homologues such as 2-butene.^[1,3] Thermally more stable diphosphanes with rigid, bidentate structure and a bias towards *trans* coordination give *n*-selectivities of up to 86 % *n*-nonanal from *trans*-octene-4 at very low turnover frequencies of 15 h^{-1} .^[4] In the case of terminal olefins the regioselectivity targeted through the use of diphosphanes of selected structure under the assumption of irreversible olefin insertion may also be reasoned on theoretical grounds.^[5] On the other hand, structure prediction for ligands which induce *n*-selectivity and, within the context of target position, necessarily also olefin isomerization is still nonexistent.

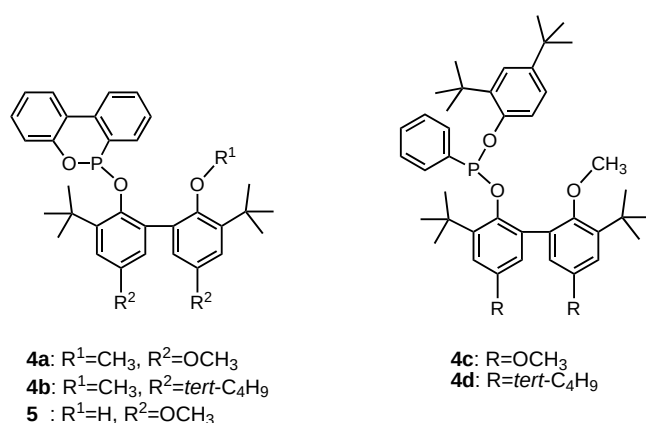
Esters of phosphonous acids have hitherto found little application as ligands in homogeneous catalysis.^[6] There are examples of oxo reactions with the highly reactive propylene as reagent.^[6c] Here we demonstrate that compounds of this class are highly suitable for the hydroformylation of long-chain olefins.

For our investigations we chose the readily available and conformationally flexible phosphonites **4a–d** and **5**, which in each case contain a second donor function in the 2'-position.

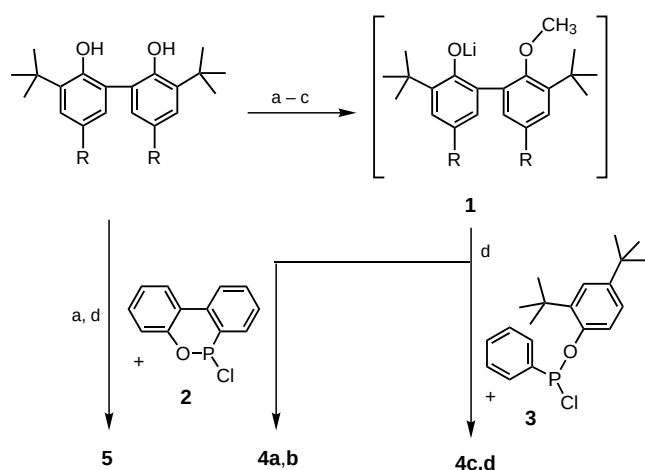
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The phosphonite ethers **4a–d** are obtainable from the corresponding bisphenols by partial deprotonation with benzyl potassium, subsequent etherification with methyl iodide, in situ formation of the lithium phenolate **1** with *n*-butyllithium, and finally reaction with 6-chloro-6*H*-di-benz[*c,e*]-1,2-oxaphosphorine (**2**)^[7] or (2,4-di-*tert*-butylphenyl)phenylphosphonityl chloride (**3**; Scheme 2). Phenol **5** was prepared by reaction of the monopotassium salt of the corresponding bisphenol with **2**. The formation of diastereoisomers was confirmed spectroscopically for **4a–d** and **5**.^[8]



Scheme 2. Synthesis of **4a–d** and **5**: a) C_7H_7K (1 equiv), THF, 30 min at 0 °C; b) CH_3I , THF, 8 h at 55 °C; c) *n*BuLi, THF/hexane, 30 min at –20 °C; d) reaction with **2** or **3**; 4 h at 25 °C; 55–85 %. Compound **2** was prepared as described in ref. [7], **3** by reaction of $PhPCl_2$ with 2,4-di-*tert*-butylphenol in the presence of pyridine in THF/ Et_2O (85/15).

The catalytic properties of the new ligands was first tested for the hydroformylation of 1-octene (Table 1). Even at low rhodium concentrations of about 14 ppm, reactions with exceptionally high initial activities and almost quantitative conversions were obtained without detectable olefin hydrogenation and alcohol formation. With respect to the ligand effect, the most active catalysts proved to be the derivatives **4a,b**, and **5**, derived from the rigid oxaphosphorine **2**. Particularly notable is the catalyst with the phosphonite phenol **5**, a further prototype of a ligand class that has not yet been established in hydroformylation. On the basis of GC

Table 1. Hydroformylation of 1-octene:^[a] effect of the ligand.

Ligand	<i>t</i> [h]	Yield [%] ^[b]	<i>n</i> / <i>iso</i> ^[b]	TOF [h ^{–1}] ^[c]
4a	1.5	97	1.22	> 46 000 ^[d]
4b	1.5	93	0.90	> 46 000 ^[d]
4c	3	89	0.66	17 570
4d	3	98	0.61	> 46 000 ^[d]
5	1	94	1.03	> 83 600 ^[d,e]

[a] The reactions were carried out in a 200-mL autoclave with $[1\text{-octene}]_0 = 1.692\text{ M}$ at 120 °C in toluene under a constant pressure of 50 bar CO/H_2 (1/1) with $[(\text{acac})Rh(1,5\text{-cyclooctadiene})]$ (acac = acetylacetonate anion) as catalyst precursor. $[Rh] = 0.1078\text{ mM}$, $Rh:P:(1\text{-octene}) = 1:5:15\,700$. [b] Determined by gas chromatography, by *iso* all branched aldehydes are meant. [c] Turnover frequency in mol aldehyde per mol catalyst per hour at 20 % turnover, calculated on the basis of gas consumption measured with a Hitec gas flow meter from the company Bronkhorst (NL). [d] Limit of measurement range. [e] 71 % turnover in 8 min.

analysis and within the effective range of the recorded gas uptake an average turnover frequency of over 83 000 h^{–1} at up to 71 % conversion was measured. Additional information on the activity of the catalyst formed with **5** was provided by the investigation of temperature dependency (Table 2). Even at 60 °C a quantitative conversion with negligible double-bond isomerization of the substrate is realizable. The maximum *n*-selectivity at 80 °C can be explained by the different effects of *T* on the rate of isomerization of the substrate and the ratio of the rates of hydrogenolysis of the intermediate acylrhodium complexes (r_t/r_{iso}), should this be the rate-determining step of the catalysis.^[9]

Table 2. Hydroformylation of 1-octene with **5**: temperature dependency.^[a]

<i>T</i> [°C]	<i>t</i> [h]	Yield [%]	<i>n</i> / <i>iso</i>	Int. aldehyd. ^[b]	TOF [h ^{–1}] ^[c]
120	1	94	1.03	+	83 600 ^[d,e]
100	1	96	1.30	+	> 46 000 ^[d]
80	1	92	1.57	(+) ^[f]	45 370
70	2	93	1.43	(+) ^[f]	24 020
60	4	98	1.39	– ^[g]	7 070

[a] For the reaction conditions, except temperature, see Table 1. [b] 3,4-Aldehydes after double-bond isomerization (determined by gas chromatography). [c]–[e] See footnotes [c]–[e] in Table 1. [f] 1.6 % (at 80 °C) or 0.5 % (at 70 °C) 2-ethylheptanal, no 2-propylhexanal. [g] 2-Octene chemoselectivity: 1.2 %.

Investigations on isomerizing hydroformylation were carried out with an *n*-octene mixture containing 3.3 % 1-octene, obtained by butene dimerization. At 140 °C and 20 bar—favorable conditions for olefin isomerization—about 35 % *n*-pelargonaldehyde was obtained with the catalyst formed with **4a**, with activity increasing in parallel with the P:Rh ratio used (Table 3).

A surprising result came from exchange of methyl ether **4a** with phenol **5** (Table 4). The *n*-selectivity increased above P:Rh ratios of 10:1 to more than 45 %.^[10] The conversion rate measured at threefold olefin concentration corresponds to aldehyde yields of 287 kg m^{–3} h^{–1}.

The properties of the catalyst formed from **5** are currently being investigated in more detail. Of interest in this context are literature references on the inhibition of hydroformylation as well as on the increase in olefin isomerization activity

Table 3. Hydroformylation^[a] of isomeric *n*-octenes^[b] with **4a**: effect of the ligand:metal ratio.

P:Rh	Yield [%]	TOF [h ⁻¹] ^[c]	<i>n</i> -Nonanal [%] ^[d]	ROH [%] ^[e]
1:1	66	2270	35.1	2.2
2:1	82	3550	35.2	2.2
5:1	88	5350	35.1	2.2
10:1	93	7390	35.4	1.6

[a] For the procedure see footnote [a] in Table 1. Conditions: $T = 140^{\circ}\text{C}$; $p = 20$ bar CO/H_2 (1/1); $t = 6$ h. [b] 3.3% 1-octene, 48.4% (*Z*)- and (*E*)-2-octene, 29.2% (*Z*)- and (*E*)-3-octene, 16.4% (*Z*)- and (*E*)-4-octene, 2.1% skeletal octene isomers, 0.6% octane. [c] Turnover frequency at 20% conversion. [d] Fraction of the total amount of aldehydes (four isomers). [e] Total alcohol yield relative to the amount of olefin used. *n*-Octane selectivity: < 1.4%.

Table 4. Hydroformylation^[a] of isomeric *n*-octenes^[b] with **5**: effect of the ligand:metal ratio.

P:Rh	Yield [%]	TOF [h ⁻¹] ^[c]	<i>n</i> -Nonanal [%] ^[d]	ROH [%] ^[e]
1:1	21	540	31.7	0.6
5:1	38	1000	41.0	1.4
10:1	52	1320	47.8	1.4
20:1	77	3120	45.9	2.0
50:1	86	2840	47.9	0.8
50:1 ^[f]	73	18710	41.8	0.8

[a]–[e] See footnotes [a]–[e] in Table 3. [f] [Octene isomers]₀ = 5.08 M.

upon use of rhodium catalysts with phosphane ligands that were functionalized with Brønsted acids.^[11, 12] Variation of the active proton group in **5** with respect to donor capability and acidity (SH, COOH, etc.) and the ring size of a potentially hemilabile chelate complex offers potential for further ligand modification.^[13]

The results presented here show for the first time that the productivities and selectivities of the technically established high-pressure processes with rhodium catalysts can be achieved with greatly reduced metal concentration and mild reaction conditions (ca. 20–50° lower in temperature and ca. 60–330 bar lower in pressure) and even exceeded with respect to suppression of hydrogenation activity. The introduction of additional oxy groups into monodentate phosphorus ligands ensures at the same time the necessary high isomerization activity of the catalyst and the tendency towards hydroformylation at the chain end. This generally exceeds the optimistic estimates of the potential development of rhodium catalyst for the isomerizing hydroformylation of internal olefins.^[4, 10]

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First Noncovalently Bound Calix[4]arene–Gd^{III}–Albumin Complex

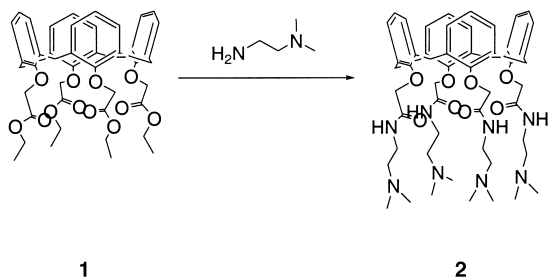
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Gadolinium(III) in its chelated form has long-been recognized as being useful as a contrast enhancement agent in magnetic resonance imaging (MRI) because of its f^7 electronic configuration and long relaxation time. Noncovalent attachment of low molecular weight Gd^{III} complexes to serum

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albumin provides macromolecular MR blood pool agents with enhanced efficacy and extended times in the blood-pool without attendant clearance problems.^[1] Lauffer et al.^[2] and others have reported the synthesis and relaxivity (relaxation rate per mM concentration of Gd^{III}) of noncovalently bound adducts of Gd^{III} complexes.^[3] The chelates used have been either diethylenetriaminepentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) derivatives, in which a lipophilic moiety has been attached to the DTPA or DOTA core. Surprisingly, despite all the considerable interest in the development of water-soluble calix[4]-arenes capable of binding lanthanide ions for numerous applications,^[4, 5] no aqueous solution data are yet available to evaluate their potential as MR contrast agents. Roundhill et al. reported the relaxivity for a calix[4]arene-tetraamide–Gd^{III} complex at 400 MHz.^[5] However, their measurement was done in a water/DMSO mixture and therefore is not necessarily valid for biomedical evaluations. Herein, we present the first example of a calix[4]arene–Gd^{III} complex which noncovalently binds to human serum albumin (HSA), as confirmed from its magnetic relaxation dispersion (MRD) profiles.

The novel tetraamidotetraamine compound, 25,26,27,28-tetrakis-*N*-(*N*,*N*-dimethyl-2-aminoethyl)carbamoyloxymethoxycalix[4]arene (**2**) is produced in excellent yield in the single-step reaction of the corresponding tetraethyl ester **1** with *N*,*N*-dimethylethylenediamine at ambient temperature. It is obtained as a white solid and the structure was confirmed



by elemental analysis, ¹H and ¹³C NMR data, and FAB mass spectrometry. The stability constant for the complexation of Gd^{III} in the cavity formed by the eight oxygen atoms on the lower rim of **2** was found to be $2 \times 10^5 \text{ M}^{-1}$ as determined by calorimetric titrations.^[6] This number is higher than the previously reported value of $1.0 \times 10^3 \text{ M}^{-1}$ for another calix[4]arene–Gd^{III} complex.^[5]

The $1/T_1$ and $1/T_2$ MRD data for samples containing 0.001 M Gd(NO₃)₃·5 H₂O and 0.001 M of tetraamide **2** in the absence and after the addition of 2% or 10% HSA are shown in Figure 1 and Figure 2, respectively. The $1/T_1$ MRD profile of [Gd^{III}(**2**)] is similar to that of the previously reported DTPA–Gd^{III} and DOTA–Gd^{III} complexes.^[7] This indicates that the Gd^{III} ion is probably nine-coordinate in solution, with one coordination site occupied by a water molecule. The addition of HSA results in a characteristic peak relaxivity in the MRD profile,^[8] which is a result of the increase in the rotational correlation time (tumbling time) of the [Gd^{III}(**2**)] complex caused by its noncovalent interaction with HSA.

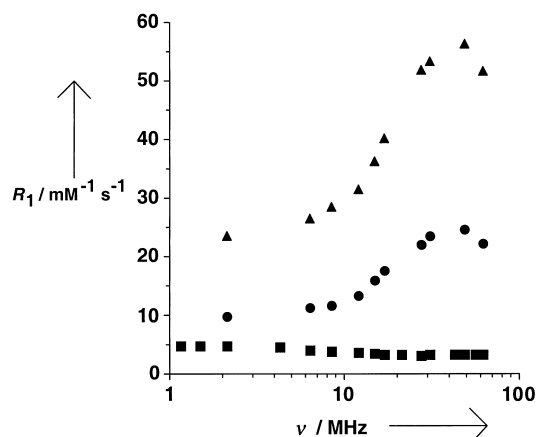


Figure 1. $1/T_1$ ¹H MRD profiles of [Gd^{III}(**2**)] in the absence (■) and in the presence of 2% (●) and of 10% HSA (▲) at 23 °C after subtraction of the HSA contribution. ν = proton Larmor frequency, R_1 = spin–lattice (longitudinal) water proton relaxivity.

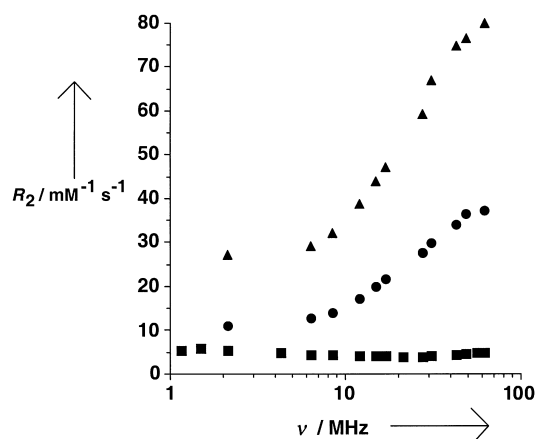


Figure 2. $1/T_2$ ¹H MRD profiles of [Gd^{III}(**2**)] in the absence (■) and in the presence of 2% (●) and 10% HSA (▲) at 23 °C after subtraction of the HSA contribution. ν = proton Larmor frequency, R_2 = spin–spin (transverse) water proton relaxivity.

Upon noncovalent binding to HSA, the Gd^{III} complex behaves as a macromolecule; the binding leads to longer rotational correlation times in solution. Thus, the electron spin relaxation time, which is dependent on the strength of the external magnetic field, dominates and an increase in the relaxivities results with a maximum for [Gd^{III}(**2**)] at a Larmor frequency of about 45 MHz. That the relaxivity for [Gd^{III}(**2**)] in the presence of 10% HSA is higher than in the presence of 2% HSA is due to the additional increase in the rotational correlation time and consequently more pronounced domination of the electron spin relaxation time for [Gd^{III}(**2**)] in the 10% HSA solution. The noncovalent interaction of [Gd^{III}(**2**)] with HSA produces dramatic increases in the $1/T_1$ and $1/T_2$ relaxivities at all field strengths studied compared to those of the unbound complex.

HSA is the most abundant protein in plasma and the noncovalent interaction of [Gd^{III}(**2**)] with HSA in vitro may have strong implications for the future use of calix[4]arene–Gd^{III} complexes in vivo as MR contrast agents. The noncovalent interaction of [Gd^{III}(**2**)] with HSA in vivo would allow its application in dynamic and steady-state MR

angiography and furthermore indicates the potential to develop a whole new class of MR contrast agents based on water-soluble calixarene chelates.

Experimental Section

The reaction was carried out under argon. The tetraethyl calix[4]arene-tetraacetate **1** was prepared according to the literature procedure.^[9] The *N,N*-dimethylethylenediamine and $\text{Gd}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ were purchased from Aldrich Chemical Co., Milwaukee, WI. Chemical shifts δ are given relative to the relevant standard tetramethylsilane. The stability constant of the $[\text{Gd}^{\text{III}}(\text{2})]$ complex was determined by MicroCal Inc., Northampton, MA.^[6]

2: Compound **1** (10.0 g) was added in small portions to *N,N*-dimethylethylenediamine (30 mL) and the resulting solution was stirred for 18 h under argon. The unconverted amine was removed by evaporation under reduced pressure and the residue treated with diethyl ether. The white precipitate was filtered, rinsed with diethyl ether, and dried in vacuo. Yield: 11.2 g (92%). m.p. 213 °C. Elemental analysis (%) calcd for $\text{C}_{52}\text{H}_{72}\text{N}_8\text{O}_8$: C 66.6, H 7.74, N 12.0; found: C 66.7, H 7.86, N 11.8; FAB-MS: m/z : 937.5 $[\text{M}^+]$; ^1H NMR (CDCl_3): δ = 2.19 (s, 24H; NCH_3), 2.44 (t, 8H; NCH_2), 3.22 (d, 4H; CH_2), 3.41 (q, 8H; CH_2NH), 4.44 (s, 8H; CH_2O), 4.47 (d, 4H; CH_2), 6.58 (m, 12H; ArH), 7.57 (br.s, 4H, D_2O exchangeable; NH); ^{13}C NMR (CDCl_3): δ = 31.03, 37.04, 45.29, 58.11, 74.13, 123.31, 129.02, 134.48, 155.98, 169.76.

MR dispersion measurements: A HSA stock solution (20% w/v) was prepared in deionized water from 96%–99% albumin (fraction V, Sigma Chemical Co., St. Louis, MO). Relaxation measurements were made on a custom-designed variable field T_1 - T_2 analyzer (Southwest Research Institute, San Antonio, TX) at 23 °C. The magnetic field strength was varied from 0.02 to 1.5 T (corresponding to a proton Larmor frequency of 1–64 MHz). T_1 was measured by using a saturation recovery pulse sequence with 32 incremental recovery times. The relaxivities (relaxation rates per mM Gd concentration) were obtained after subtracting the water contribution or the appropriate diamagnetic 2% or 10% HSA solution contribution, respectively. T_2 was measured by using a Carr–Purcell–Meiboom–Gill pulse sequence of 500 echoes and a time interval of 2 msec between echos.

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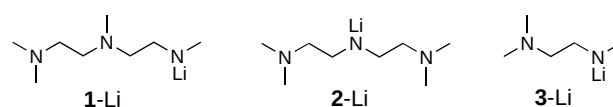
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Lithium Amides: Intra-Aggregate Complexation of Lithium and Entropy Control of Basicity

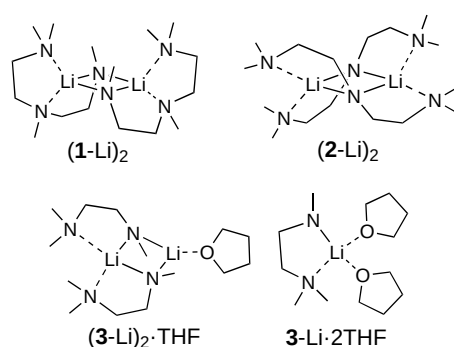
Gerbert L. J. van Vliet, Henri Luitjes, Marius Schakel, and Gerhard W. Klumpp*

Lithium amides (LiNR_2 , LiA) are the most widely used reagents for the generation of enolates and their cognate species from carbonyl compounds and related CH acids.^[1] This practical importance has led to extensive lists of pK values of secondary amines (HA).^[2] However, interpretation of ΔpK values in terms of enthalpy and entropy effects, fundamental to understanding the basicity of lithium amides, is severely limited. Commonly, pK values are determined at a single temperature, usually around 25 °C. This permits only correlation of ΔpK with differences in relative free energy, $\Delta G_{\text{rel}}(\text{LiA}(2), \text{LiA}(1))$, at that temperature.^[3] We now report on the prominent influence of entropy on the basicity towards triphenylmethane (TPMH) in THF of lithium *N*-(3,6-diaza-3,6-dimethyl)heptyl-*N*-methylamide (**1-Li**), lithium bis(*N,N*-dimethyl-2-aminoethyl)amide (**2-Li**), and lithium *N*-(*N,N*-dimethyl-2-aminoethyl)-*N*-methylamide (**3-Li**).^[4] Despite the rather special nature of **1-Li**–**3-Li**, our findings have some bearing on the thermodynamics of lithium amides in general.

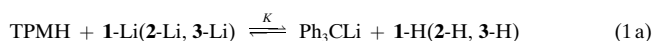


1-Li and **2-Li** were shown^[4] to exist in toluene or THF exclusively as the dimers (**1-Li**)₂ and (**2-Li**)₂, with exhaustive intra-aggregate complexation of lithium. Their congener **3-Li** lacks one of the amino groups of **1-Li** and **2-Li** and forms an equilibrium mixture (THF, –108 °C: 2.3:1) of a monomer and a dimer, for which the structures **3-Li** · 2 THF and (**3-Li**)₂ · THF were suggested by THF titration,^[4] MNDO calculations,^[5] and reaction kinetics.^[6]

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The equilibria of **1**-Li, **2**-Li, and **3**-Li with triphenylmethane [TPMH, Eq. (1a)] in THF were measured in the temperature range -20 to 15°C .^[7] Values of the TPMH-based pK of the conjugate acids **1**-H–**3**-H at 30°C [the temperature at which numerous pK values were determined;^[2] $pK_{\text{Li,THF},30^\circ\text{C}}$, Eq. (1b); $30.4 = pK_{\text{Li,THF},30^\circ\text{C}}(\text{TPMH})$ ^[2] and of ΔH [Eq. (1a)] and ΔS [Eq. (1a)] are given in Table 1 (entries 1–3).^[9]



$$pK_{\text{Li,THF},30^\circ\text{C}}(\text{1-H (2-H, 3-H)}) = 30.4 + \lg K(\text{1-H (2-H, 3-H)}, 30^\circ\text{C}) \quad (1b)$$

Table 1. Values of $pK_{\text{Li,THF},30^\circ\text{C}}$ of the conjugate acids of **1**-Li–**3**-Li [Eq. (1b)]; ΔH [Eq. (1a)] [kJ mol^{−1}] and ΔS [Eq. (1a)] [J K^{−1} mol^{−1}].^[a]

Entry		$pK_{\text{Li,THF},30^\circ\text{C}}$	ΔH [Eq. (1a)]	ΔS [Eq. (1a)]
1	1 -Li ^[b]	25.4 ± 0.3	-36.9 ± 3	-220 ± 20
2	2 -Li ^[b]	23.8 ± 0.6	-35.7 ± 10	-240 ± 40
3	3 -Li ^[c]	27.9 ± 0.1	-33.8 ± 6	-160 ± 20
4	1 -Li + 1 equiv 1 -H ^[d]	27.7 ± 0.4	-20.7 ± 3	-120 ± 20
5	1 -Li + 2 equiv 1 -H ^[d]	27.9 ± 0.4	-22.6 ± 3	-120 ± 20

[a] [**1**-Li]₂–[**3**-Li]₂ ≈ [TPMH] ≈ 0.03 M, THF. [b] Average of three determinations. [c] Average of two determinations. [d] Single experiment.

Disregarding intra-aggregate complexation of lithium by the dimethylamino groups, one would expect $pK_{\text{Li,THF},30^\circ\text{C}}$ of **2**-H, **3**-H, and Me₂NH to follow the same order as those^[2] of Et₂NH (31.7) > EtMeNH (30.9) > Me₂NH (29.7), for which successive replacements of ethyl by methyl groups change $pK_{\text{Li,THF},30^\circ\text{C}}$ by roughly the same amount ($\Delta pK_{\text{Li,THF},30^\circ\text{C}} = -0.8, -1.2$). In fact, the values of $pK_{\text{Li,THF},30^\circ\text{C}}$ of **2**-H and **3**-H are considerably lower than those of Et₂NH and EtMeNH, respectively, and their order runs counter to that of the simple dialkylamines: compared to Et → Me, replacement of CH₂CH₂N(Me)₂ by Me affects $pK_{\text{Li,THF}}$ in the opposite sense by amounts that distinctly differ for the two steps ($\Delta pK_{\text{Li,THF},30^\circ\text{C}} = 4.1, 1.8$ ^[10]).

The values of ΔH [Eq. (1a)] and ΔS [Eq. (1a)] provide a clue to the mode by which intra-aggregate complexation of lithium by (alkyl)(methyl)amino groups influences $pK_{\text{Li,THF}}$.^[11] The strongly negative reaction entropies are most telling. They indicate that the reactions of **1**-Li–**3**-Li with TPMH in THF involve the binding of a considerable number of THF molecules, that is, the actual reaction product is Ph₃C[−][Li(thf)_{*n*}]⁺.^[12] Detailed analysis is impossible. However, because THF is already bonded to lithium in the reacting **3**-Li species—probably **3**-Li·2THF and (**3**-Li)₂·THF (see

above)^[13]—fewer THF molecules are immobilized in the reaction of **3**-Li than in the reactions of **1**-Li and **2**-Li, the (**1**-Li)₂ and (**2**-Li)₂ constituents of which do not contain bound THF. Consequently, in the case of **3**-Li, the decrease in entropy is smaller and the basicity $pK_{\text{Li,THF},30^\circ\text{C}}$ is higher, even though the reaction of **3**-Li with TPMH is (slightly) less exothermic than those of **1**-Li and **2**-Li. We recognize a clear case of basicity control by the entropy of THF complexation. The decrease in entropy is smaller, the cost in ΔG [Eq. (1a)] is lower, and the basicity $pK_{\text{Li,THF},30^\circ\text{C}}$ is higher, if **1**-H–**3**-H act as ligands towards lithium. Owing to the polydentate nature of these ligands, the decrease in the number of particles upon complexation/chelation is lower than with THF. Accordingly, when one or two equivalents of **1**-H were added to the equilibrium reaction mixture of **1**-Li (Table 1, entries 4 and 5), $pK_{\text{Li,THF},30^\circ\text{C}}$ rose by approximately 2.4 units, and less negative values of ΔS [Eq. (1a)] and ΔH [Eq. (1a)] were found. This is ascribed to chelation by **1**-H of both Ph₃CLi and a dimer of **1**-Li.^[14] Again, the effect on $pK_{\text{Li,THF},30^\circ\text{C}}$ of the (**1**-H)-induced lowering of $|\Delta S$ [Eq. (1a)] is stronger than the counteracting influence of the decrease in $|\Delta H$ [Eq. (1a)]|. ^[15, 16]

Clearly, entropies of LiA reactions are strongly influenced by the interdependent modes of aggregation and Lewis base complexation of both the reactant and the product lithium species. This led to the working hypothesis that reactions of lithium amides having the same type of aggregation and complexation (e.g., dimers of lithium amides with tricoordinate lithium such as (*i*Pr₂NLi)₂·2THF)^[17] with the same substrate (e.g., TPMH) have about the same entropy. Consequently, their $\Delta pK_{\text{Li,THF}}$ should approximately reflect differences in reaction enthalpies and relative enthalpies^[3] [ΔH_{rel}^0 ; Eq. (2)].^[18]

$$2.3 RT \Delta pK_{\text{Li,THF}}(\text{HA(2)}, \text{HA(1)}) \approx \Delta H(\text{LiA(2)}) - \Delta H(\text{LiA(1)}) = \Delta H_{\text{rel}}^0(\text{LiA(1)}) - \Delta H_{\text{rel}}^0(\text{LiA(2)}) \quad (2)$$

The enthalpies of reaction with TPMH of **1**-Li–**3**-Li (ΔH [Eq. (1a)], Table 1) are rather similar, and that of **3**-Li is smallest.^[13] This shows that intra-aggregate tetracoordination of lithium by (alkyl)(methyl)amino groups in LiA dimers has no enthalpic advantage over the THF-induced modes of aggregation/coordination (**3**-Li·2THF and (**3**-Li)₂·THF) that are ascribed to **3**-Li in THF.^[19] What, then, is the cause of the special stability of **2**-Li, that is, the strong decrease in basicity on going from Et₂NLi to **2**-Li, and from EtMeNLi to **3**-Li, as well? An important role is played by the entropically unfavorable structure of **2**-Li. On the simplifying assumption that ΔS [Eq. (1a)] depends solely on the number of THF molecules that are immobilized by formation of Ph₃C[−][Li(thf)_{*n*}]⁺ and that this number is approximately the same for (Et₂NLi)₂·2THF^[17] and (EtMeNLi)₂·2THF^[17] (immobilization of *n* − 1 molecules of THF per lithium atom) and **3**-Li (average of **3**-Li·2THF and (**3**-Li)₂·THF: ca. *n* − 1.25 molecules of THF immobilized per lithium atom), about four units of $\Delta pK_{\text{Li,THF},30^\circ\text{C}}(\text{Et}_2\text{NH}, \text{2-H}) = 7.9$ are caused by the entropy effect (cf. Table 1, entries 2 and 3). We attribute a large part of the remaining four units to inductive stabilization of N[−] in **2**-Li by its two dimethylamino groups. In the case of **3**-Li, about the total of $\Delta pK_{\text{Li,THF},30^\circ\text{C}}(\text{EtMeNH}, \text{3-H}) = 3$

would be due to this effect. The supposition that two dimethylamino groups per lithium atom in **2**-Li lead to a lowering of $pK_{\text{Li,THF},30^\circ\text{C}}$ by about four units, while nearly the same effect is produced by a single such group in **3**-Li, implies nonadditivity of these inductive interactions in lithium amides with intra-aggregate complexation.

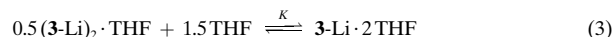
In conclusion, the values of $pK_{\text{Li,THF},30^\circ\text{C}}$ (based on that of TPMH) of the conjugate acids of **1**-Li–**3**-Li are 4.3, 5.9, and 1.8 units lower than that of dimethylamine. The differences in basicity of **1**-Li–**3**-Li are due to the entropic consequences of the differences in Lewis base complexation of these lithium amides and Ph_3CLi . The rather similar reaction enthalpies of **1**-Li–**3**-Li indicate that intra-aggregate tetracoordination of lithium in LiA dimers has no enthalpic advantage over THF-induced modes of aggregation/coordination. Besides entropy, inductive stabilization by dimethylamino groups is proposed as a major cause of the basicity differences between **2**-Li, **3**-Li and Et_2NLi , EtMeNLi , respectively. In the wider realm of LiA properties, our findings suggest that within a family of lithium amides of the same aggregation and complexation type, $\Delta pK_{\text{Li,THF}}$ provides an approximate value of the difference in relative LiA enthalpies.

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- [6] In *pentane*, the reaction order of THF, added to the system 2-*exo*-bromonorbornane + **3**-Li, is close to one-half. This indicates the presence, in the transition state, of one molecule of THF per two atoms of lithium (G. L. J. van Vliet, unpublished results).
- [7] Nearly equivalent amounts of TPMH and LiA ($[\text{TPMH}] (=Q) \approx [\text{LiA}] (=R$; formal concentration as obtained by titration) were mixed in an evacuated (4×10^{-6} mbar) and sealed UV cell. $[\text{Ph}_3\text{CLi}]$ was measured at $\lambda = 500$ nm, $\epsilon = 28300 \text{ L mol}^{-1} \text{ cm}^{-1}$,^[8] and equilibrium constants were calculated as $K[\text{Eq. (1a)}] = [\text{Ph}_3\text{CLi}]^2 / (Q - [\text{Ph}_3\text{CLi}])^{-1} (R - [\text{Ph}_3\text{CLi}])^{-1}$.
- [8] Compare I. S. Antipin, R. F. Gareev, A. N. Vedernikov, A. I. Konovalov, *Zh. Org. Khim.* **1989**, 25, 1153–1160.
- [9] While the values of $\Delta H[\text{Eq. (1a)}]$ and $\Delta S[\text{Eq. (1a)}]$ in entries 1–3 of Table 1 are specific for reaction with TPMH, the values of $pK_{\text{Li,THF},30^\circ\text{C}}$ are applicable to all reactions with substrates whose $pK_{\text{Li,THF},30^\circ\text{C}}$ is based on that of TPMH.
- [10] $\Delta pK_{\text{Li,THF},30^\circ\text{C}}$ between piperidine (30.7)^[2] and morpholine (28.8)^[2] is nearly the same as that between Me_2NH and **3**-H and may have similar origins.

- [11] For the effects of intramolecular complexation on alkyl lithium compounds, see R. F. Schmitz, M. Schakel, M. Vos, G. W. Klumpp, *Chem. Commun.* **1998**, 1099–1100, and references therein.
- [12] From the similarity of the entropies in entries 1 and 2 with that of another case of lithium salt formation in THF and ascribed—in accord with known structures of THF-complexed lithium salts—to the formation of $[\text{Li}(\text{thf})_4]^+$ (see A. H. J. F. de Keijzer, F. J. J. de Kanter, M. Schakel, R. F. Schmitz, G. W. Klumpp, *Angew. Chem.* **1996**, 108, 1183–1184; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1127–1128), we speculate that $\text{Ph}_3\text{C}^-[\text{Li}(\text{thf})_4]^+$ is formed in solution, although Ph_3CLi is solvated in the solid state. (For a discussion of Ph_3CLi solvation, see C. Lambert, P. von R. Schleyer, *Methoden Org. Chem. (Houben-Weyl)*, 4th ed. 1952–, Vol. E19d, **1993**, p. 68.)
- [13] A more refined analysis would focus on $pK_{\text{Li,THF},30^\circ\text{C}}$, $\Delta H[\text{Eq. (1a)}]$, and $\Delta S[\text{Eq. (1a)}]$ of **3**-Li·2 THF and $(\text{3-Li})_2 \cdot \text{THF}$, respectively. This requires knowledge of $\Delta H[\text{Eq. (3)}]$ and $\Delta S[\text{Eq. (3)}]$ which can only be speculated on.



- [14] a) Recent work (P. I. Arvidsson, G. Hilmersson, P. Ahlberg, *J. Am. Chem. Soc.* **1999**, 121, 1883–1887) showed that secondary amines of the type $\text{HN(R)CHR'CH}_2\text{NR}_2$ stabilize by chelation dimers of lithium amides more strongly than does $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$ (TMEDA), and we presume that under the conditions of entries 4 and 5, **1**-H analogously chelates a dimer of **1**-Li. Exhaustive chelation may already be achieved at a 1:1 (equiv) ratio, and the differences between entries 4 and 5 are probably due to experimental error. b) We have not yet succeeded in detecting such species by ^{13}C NMR spectroscopy. At -106°C , a 1:2 (equiv) mixture of $(\text{1-Li})_2$ and **1**-H exhibited separate spectra of the two species. Warming led to extensive coalescence that prevented identification of any new species.
- [15] Under the conditions of entries 1–3, **1**-H–**3**-H, present in the same (low) concentrations as Ph_3CLi , seem to be unable to compete for the latter with THF, the concentration of which is 10^5 – 10^6 times higher.
- [16] The effect of addition of polydentate HA' might be put to advantage in asymmetric synthesis based on the use of LiA' with intra-aggregate complexation (e.g., D. Sato, H. Kawasaki, I. Shimada, Y. Arata, K. Okamura, T. Date, K. Koga, *J. Am. Chem. Soc.* **1992**, 114, 761–763).
- [17] According to, both experimental results and calculations, the lithium atom in dimers of lithium amides is tricoordinate: F. E. Romesberg, D. B. Collum, *J. Am. Chem. Soc.* **1992**, 114, 2112–2121; B. L. Lucht, D. B. Collum, *J. Am. Chem. Soc.* **1995**, 117, 9863–9874.
- [18] a) By using Equation (2), $(\text{Et}_2\text{NLi})_2 \cdot 2 \text{THF}$ ^[17] ($pK_{\text{Li,THF},30^\circ\text{C}} = 31.7$ ^[2]) is calculated to be stabilized enthalpically with respect to $i\text{Pr}_2\text{NLi}$ ($pK_{\text{Li,THF},30^\circ\text{C}} = 34.4$ ^[2]) by 15.6 kJ mol^{-1} , which is just 0.8 kJ mol^{-1} outside the lower error limit of the value obtained from the difference of their heats of protonation ($i\text{PrOH}$, hexane/diethyl ether 90/10, $\Delta\Delta H = (21.8 \pm 5.4) \text{ kJ mol}^{-1}$, E. M. Arnett, K. D. Moe, *J. Am. Chem. Soc.* **1991**, 113, 7068–7069). b) The (near) additivity of the α -methyl effect on $pK_{\text{Li,THF},30^\circ\text{C}}$ observed^[2] for a substantial number of lithium dialkylamides of the $(\text{R}_2\text{NLi})_2 \cdot 2 \text{THF}$ family^[17] supports our guideline. In its light, the $pK_{\text{Li,THF},30^\circ\text{C}}$ difference of 0.8 units^[2] between $(\text{Et}_2\text{NLi})_2 \cdot 2 \text{THF}$ and $(\text{EtMeNLi})_2 \cdot 2 \text{THF}$ ^[17] indicates that the ligand change methyl $\rightarrow$ ethyl increases ΔH^0 of a THF-solvated LA dimer by about 5 kJ mol^{-1} per lithium atom.
- [19] The tetracoordination of lithium calculated^[5] and found^[4] for $(\text{1-Li})_2$ and $(\text{2-Li})_2$ and calculated for one lithium atom of $(\text{3-Li})_2 \cdot \text{THF}$ ^[5] is exceptional. Due to the intra-aggregate mode of complexation, adverse effects of entropy loss and steric crowding, both disfavoring intermolecular tetracoordination of THF to LiA dimers, are minimal.

Synthesis, Crystal Structure, and Magnetic Behavior of Linear $M_2^{\text{II}}U^{\text{IV}}$ Complexes ($M = \text{Co, Ni, Cu, Zn}$)

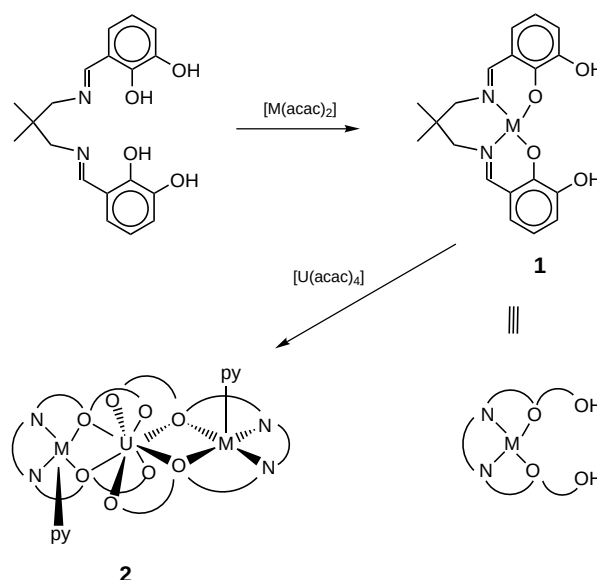
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In memory of Olivier Kahn

Much attention has been paid to the design of novel molecular compounds containing both $3d^n$ transition metal and $4f^n$ lanthanide(III) ions in order to discover and/or understand rather unexpected magnetic and optical properties.^[1] Most of the studies have been focused on the ferromagnetic $M - \text{Gd}^{\text{III}}$ pairs, M being usually Cu^{II} ,^[2] but also Co^{II} , Ni^{II} , Fe^{III} , and V^{IV} .^[3] Very recent work has been devoted to the interaction between Cu^{II} and lanthanide(III) ions other than Gd^{III} , which, because of the orbital contribution, is much more difficult to analyze and is subject to debate.^[4, 5] In contrast, molecular compounds containing simultaneously paramagnetic $3d^n$ transition metal and $5f^n$ actinide ions are very rare,^[6] and nothing is known about their magnetic behavior. In this context, we planned to prepare a series of new heteropolymetallic compounds in which the transition metal is in close proximity to uranium.

One of the methods for the synthesis of polymetallic compounds consists in utilizing compartmental ligands derived from Schiff base condensation.^[7] By adopting this strategy, we succeeded in preparing unique examples of trimetallic complexes of general formula $[\{\text{LM}^{\text{II}}(\text{py})\}_2\text{U}^{\text{IV}}]$ ($M = \text{Co, Ni, Cu}$; $\text{py} = \text{pyridine}$) in which the three metals are held together by the hexadentate compartmental ligand N,N' -bis(3-hydroxysalicylidene)-2,2-dimethyl-1,3-propanediamine^[8] (L) in a linear fashion. Our attempts to prepare U^{III} complexes which would be the analogues of known $M^{\text{II}}\text{Ln}^{\text{III}}$ species have so far been unsuccessful.

The synthesis of the U^{IV} compounds is represented in Scheme 1. The first step—the formation of complexes **1** by coordination of the transition metal into the inner N_2O_2 chamber of the hexadentate compartmental Schiff base—is similar to that used in the synthesis of the $M^{\text{II}}\text{Ln}^{\text{III}}$ compounds. Treatment of **1** with $[\text{U}(\text{acac})_4]$ ($\text{acac} = \text{acetylacetonate}$) afforded complexes **2**, which were isolated as red ($M = \text{Co}$) or green microcrystals ($M = \text{Ni, Cu}$). In fact, only 0.5 equiv of



Scheme 1. Synthesis of the U^{IV} complexes. $M = \text{Co, Ni, Cu, Zn}$.

$[\text{U}(\text{acac})_4]$ was necessary for the total conversion of **1** into **2**, indicating that trinuclear complexes would be formed by chelation of a central uranium atom with two metalloligands **1**. Complexes **2** were characterized by elemental analysis (C, H, N) and ^1H NMR spectroscopy; the spectra exhibited six resonances in a 3:2:1:1:1:1 intensity ratio, corresponding to equivalent L ligands.^[9]

The structure of complexes **2** was confirmed by the X-ray crystallographic study of the cobalt derivative $[\{\text{LCo}(\text{py})\}_2\text{U}]$ (Figure 1).^[10] Each LCo unit is linked to the central uranium atom through two Co–O–U bridges, which are ensured by the oxygen atoms of the salicylidene fragments (O2, O3 and O6, O7), and also by two bonds between the uranium and the phenolate oxygen atoms at the 3-position of the L ligand (O1, O4 and O5, O8). The uranium atom is therefore surrounded by eight oxygen atoms in a dodecahedral arrangement defined by the two trapezia O1–O2–O3–O4 and O5–O6–O7–O8 intersecting at an angle of $88.2(3)^\circ$. The equivalent sites A and B of the dodecahedron are occupied by the bridging and terminal oxygen atoms at an average distance from uranium of 2.45(1) and 2.31(3) Å, respectively. The pseudo D_{2d} symmetry of the complex is broken by the presence of a single pyridine molecule attached to each cobalt atom. The cobalt ion thus adopts a square-pyramidal coordination mode, being displaced from the N_2O_2 base by 0.38(2) Å towards the axial pyridine ligand. The three metal centers are almost linear (Co1–U–Co2 $171.84(2)^\circ$), with intramolecular U–Co separations of 3.68(2) Å. To our knowledge, species **2** represent unique examples of trinuclear complexes with a hexadentate Schiff base ligand; more generally, these are the only molecular compounds in which an f element is associated with two d transition metals in a linear arrangement.

For the purpose of magnetic studies, it was of interest to have at our disposal complexes **2** in which the paramagnetic centers have been replaced with diamagnetic ions. The orange $[\{\text{LZn}(\text{py})\}_2\text{U}]$ and dark red $[\{\text{LCu}(\text{py})\}_2\text{Zr}]$ compounds were prepared by the same synthetic route shown in Scheme 1. The Zn_2U complex is isostructural with $[\{\text{LCo}(\text{py})\}_2\text{U}]$.

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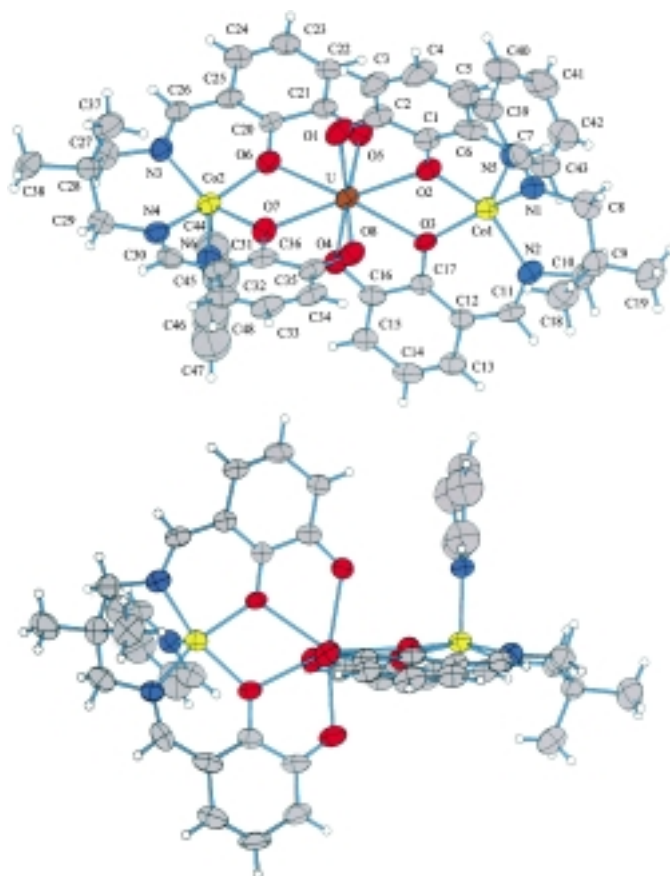


Figure 1. Structure of $[\text{LCo}(\text{py})_2]\text{U}$ in the crystal (ORTEP; thermal vibrational ellipsoids 30%). Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: U–O1 2.325(7), U–O2 2.450(8), U–O3 2.455(6), U–O4 2.286(7), U–O5 2.333(8), U–O6 2.457(7), U–O7 2.459(8), U–O8 2.316(7); O1–U–O4 167.5(3), O2–U–O3 60.4(2), O5–U–O8 165.3(3), O6–U–O7 60.4(2). The bottom view shows the orthogonality of the Schiff base ligands.

The magnetic behavior of the Cu_2U , Zn_2U , and Cu_2Zr complexes is shown in Figure 2 in the form of $\chi_M T$ versus T (χ_M = molar magnetic susceptibility, T = temperature). For the Cu_2Zr complex, $\chi_M T$ is essentially constant and equal to $0.77 \text{ cm}^3 \text{ K mol}^{-1}$, a value which corresponds to that expected for two noninteracting Cu^{II} ions; no ferromagnetic coupling is observed despite the orthogonality of the Cu^{II} magnetic orbitals. The magnetic susceptibility of the Cu_2U and Zn_2U complexes decreases with the temperature, and in the latter compound this deviation from the Curie law results entirely from the crystal field effect of the U^{IV} ion.

If it is assumed that the two Cu^{II} ions are not coupled in the Cu_2U complex, as found in the Cu_2Zr analogue, the difference $\Delta = (\chi_M T)_{\text{Cu}_2\text{U}} - (\chi_M T)_{\text{Zn}_2\text{U}}$ should be due to the U–Cu interaction. At 300 K, the value of Δ corresponds to the contribution of two isolated Cu^{II} ions, and this difference increases as T is lowered to reach a maximum and then decreases at very low temperature. With this empirical approach, which has been designed recently for determining the nature of the $\text{Ln}^{\text{III}}-\text{Cu}^{\text{II}}$ interaction,^[4, 5] the profile of the Δ versus T curve might suggest that the $\text{U}^{\text{IV}}-\text{Cu}^{\text{II}}$ interaction in **2** is ferromagnetic. This amazing result, which cannot be explained with a simple theory, has to be confirmed, in particular by the study of discrete bimetallic U–Cu com-

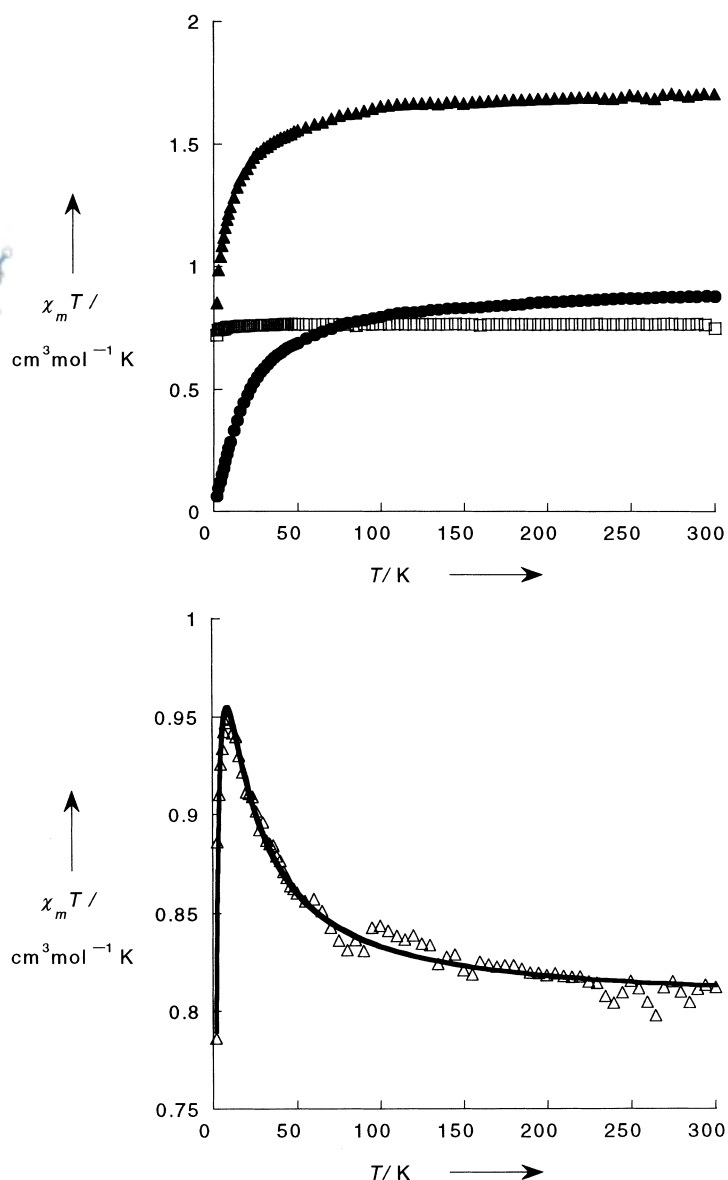


Figure 2. Thermal dependence of $\chi_M T$ for the Cu_2U ($\blacktriangle$), Zn_2U ($\bullet$), and Cu_2Zr ($\square$) compounds (top) and the difference $\Delta = (\chi_M T)_{\text{Cu}_2\text{U}} - (\chi_M T)_{\text{Zn}_2\text{U}}$ (bottom). The solid curve was calculated as discussed in the text.

plexes. If it is now considered that the two copper(II) ions are coupled in **2**, it is most striking that the experimental Δ curve fits quite perfectly to the magnetic susceptibility equation valid for a Cu^{II} dimer; the parameters corresponding to the best fit are $J_{\text{CuCu}} = 13.6 \text{ cm}^{-1}$, $g = 2.07$, and $\theta = 0.7 \text{ K}$ with an agreement factor R of 4.5×10^{-5} .

These data strongly suggest that the U^{IV} center is able to mediate the ferromagnetic interaction between the two Cu^{II} ions! This coupling exchange would involve the f orbitals of the U^{IV} ion that have the appropriate energy and symmetry to overlap with the $d_{x^2-y^2}$ type magnetic orbitals centered on each Cu^{II} ion; these are the $f_{x(x^2-z^2)}$ and $f_{y(x^2-z^2)}$ orbitals, which belong to the e irreducible representation in the symmetry group D_{2d} (Figure 3). The ferromagnetism in **2** could then be explained either by a) the presence of two degenerate molecular orbitals of type e which would accommodate the two unpaired electrons

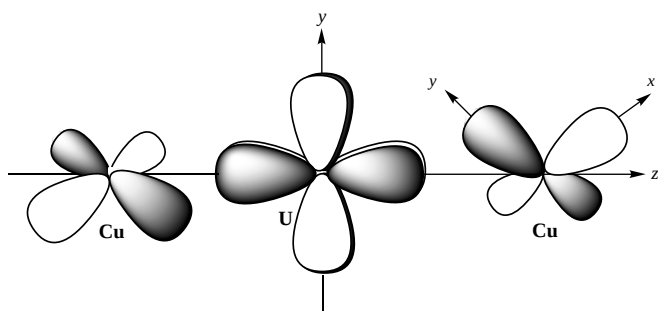


Figure 3. Role of the $f_{x(y^2-z^2)}$ U^{IV} orbital in coupling the two $d_{x^2-y^2}$ orbitals containing the two Cu^{II} unpaired electrons. The planes of the Cu orbitals are 45° above and below the horizontal plane.

from the Cu^{II} ions, leading to a triplet state,^[11] or b) within a more localized picture and in line with the proposed mechanism of the $Ln^{III}-Cu^{II}$ interaction,^[12] the transfer of the unpaired electron of Cu^{II} towards an empty 5f orbital of U^{IV} . This process would force the d and f electrons to align parallel and, in the case of a Cu-U-Cu triad, would lead to the parallel alignment of the Cu^{II} electrons.

In conclusion, the use of a hexadentate compartmental Schiff base ligand permitted the synthesis of the first complexes in which an uranium(IV) ion is located between two paramagnetic divalent metallic ions—these are unique molecular compounds exhibiting a linear arrangement of an f element and two d transition metals. The comparative magnetic study of the Cu_2U , Zn_2U , and Cu_2Zr compounds revealed that the f orbitals of the U^{IV} center would mediate ferromagnetic interaction within the Cu-U-Cu triad.

Experimental Section

All experiments were carried out under argon (<5 ppm oxygen and water) using standard Schlenk-vessel and vacuum-line techniques or in a glove box. Solvents were thoroughly dried and deoxygenated by standard methods and distilled immediately before use.

[$LiCo(py)_2$] U : A mixture of LH_4 (306 mg, 0.89 mmol) and $[Co(acac)_2]$ (230 mg, 0.89 mmol) in THF (50 mL) was stirred for 1 h at $20^\circ C$. The red solution was evaporated to dryness, leaving **1** ($M=Co$), which was then treated with $[U(acac)_4]$ (283 mg, 0.44 mmol) in THF (50 mL). After 2 h at $20^\circ C$, the red powder of $[LiCo(THF)_2]U$ was filtered off, washed with THF, and dried under vacuum. This powder was dissolved in pyridine (5 mL), and the red microcrystals of **2** ($M=Co$) that deposited after 12 h at $110^\circ C$ were filtered off and dried under vacuum (441 mg, 83%).

The Ni_2U , Cu_2U , Zn_2U , and Cu_2Zr analogues were synthesized by the same procedure.

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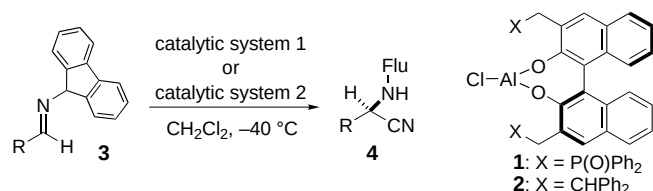
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- [9] ^1H NMR data for complexes **2** (200 MHz, $[D_5]$ pyridine, $30^\circ C$, TMS): $M=Co$: $\delta=402$ (4H, $W_{1/2}=160$ Hz; $N=CH$), 133.0 (8H, $W_{1/2}=200$ Hz; CH_2), 48.7, 9.6, and -2.4 ($3 \times 4H$; aromatic CH), -11.8 (12H, $W_{1/2}=95$ Hz; CH_3); $M=Ni$: $\delta=409$ (4H, $W_{1/2}=2500$ Hz; $N=CH$), 102 (8H, $W_{1/2}=540$ Hz; CH_2), 46.5, 10.7, and 9.6 ($3 \times 4H$, aromatic CH), -4.3 (12H, $W_{1/2}=135$ Hz; CH_3); $M=Cu$: $\delta=423$ (4H, $W_{1/2}=3000$ Hz; $N=CH$), 96 (8H, $W_{1/2}=325$ Hz; CH_2), 47.5, 16.0, and 4.38 ($3 \times 4H$; aromatic CH), -7.0 (12H, $W_{1/2}=50$ Hz; CH_3); $M=Zn$: $\delta=24.0$, 14.2, 5.1, and 0.3 ($4 \times 4H$; CH), -7.4 (8H; CH_2), -7.9 (12H; CH_3). When not specified, $W_{1/2}=5-40$ Hz.
- [10] Crystal structure analysis of **2** ($M=Co$): Siemens diffractometer, MoK_{α} radiation, measurement temperature 296(2) K, crystal dimensions $0.28 \times 0.24 \times 0.22$ mm³, orthorhombic, space group $Pna2$ (no. 1), $a=27.4586(2)$, $b=13.8515(2)$, $c=13.9874(2)$ Å, $V=5320.01(11)$ Å³, $Z=4$, $\rho=1.487$ g cm⁻³, $\mu(MoK_{\alpha})=3.705$ mm⁻¹, $2.96 < 2\theta < 59.26^\circ$; of 34624 measured reflections, 12594 were independent and 7380 with $I > 2\sigma(I)$; 566 parameters, multiscan absorption correction (R. H. Blessing, *Acta Cryst. Sect. A* **1995**, 51, 33; $T_{max}=0.453$, $T_{min}=0.336$), $R1=0.0520$, $wR2=0.1324$, $GOF=0.986$; max./min. residual electron density 1.179/−0.517 e Å⁻³. The structure was solved with direct methods and refined against F^2 for all observed reflections. Hydrogen atoms were introduced at calculated positions and constrained to ride on their parent carbon atom. Software used: SHELXTL94, SHELXS86, SHELXL93 (G. M. Sheldrick, Universität Göttingen). 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-136721. 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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A Catalytic Asymmetric Strecker-Type Reaction: Interesting Reactivity Difference between TMSCN and HCN**

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The catalytic asymmetric Strecker-type reaction^[1] is one of the most direct and efficient methods for the asymmetric synthesis of natural and unnatural α -amino acids. Recently, several excellent reactions of this type were reported, which reflects the importance of this field.^[2] However, as far as we know, the reaction is not yet satisfactory in terms of the generality of the imine substrates. Although aromatic aldimines give excellent selectivities and yields, aliphatic aldimines, specifically *n*-aldimines, do not afford satisfactory results.^[3] Furthermore, no examples of α,β -unsaturated imines, which should give products that are versatile precursors of functionalized α -amino acids, have been reported so far. Herein we disclose a general asymmetric Strecker-type reaction that is controlled by the bifunctional Lewis acid–Lewis base catalyst **1** (9 mol %; Scheme 1).^[4] The reaction



Scheme 1. Catalytic system 1: **1** (9 mol %), TMSCN (2 mol equiv); PhOH (20 mol %, slow addition over 17 h). Catalytic system 2: **1** (9 mol %), TMSCN (20 mol %); HCN (1.2 mol equiv, slow addition over 24 h).

proceeds with good to excellent enantioselectivities toward various imines, including *n*-aldimines and α,β -unsaturated imines, in the presence of a catalytic amount of phenol (20 mol %; catalytic system 1). Furthermore, we have found that TMSCN is more reactive than HCN in the reaction catalyzed by **1**, which led to the idea for developing a novel catalytic system composed of **1** (9 mol %), TMSCN (20 mol %), and HCN (120 mol %; catalytic system 2).

We reported previously that the Lewis acid–Lewis base bifunctional catalyst **1** promotes the addition of TMSCN to a

variety of aldehydes with high enantioselectivities.^[4] The origin of the highly enantioselective catalysis by **1** is the simultaneous activation of aldehydes and TMSCN by the Lewis acid (Al) and the oxygen atom of the phosphane oxide, respectively. Therefore, it seemed to be a rational extension to apply this catalyst to the development of an asymmetric Strecker-type reaction. We started this project by observing that the nature of the substituent on the nitrogen atom of imines had a dramatic effect on the enantioselectivity of the reaction. Although the reaction of TMSCN (2 mol equivalents) with the *N*-allyl benzaldehydeimine catalyzed by 9 mol % of **1** at -40°C gave the product with only 4% *ee* in 67% yield (62 h), the reaction of *N*-benzhydrylimine gave the product with 78% *ee* in 84% yield (85 h). The *ee* value was further increased up to 95% (97% yield) by the reaction with *N*-fluorenylimine (**3a**, 111 h). The fluorenyl group is also effective in forming the aminonitrile **4m** in 75% *ee* in 94% yield (192 h) from the corresponding aliphatic pivalaldehydeimine (**3m**).

We investigated the effect of additives in the reaction and found that protic additives such as alcohols and phenol afforded a beneficial effect on the reaction rate.^[5,6] Thus, all the reactions using **3m** were completed in 22 h by slowly (12 h) adding 110 mol % of MeOH, *i*PrOH, *t*BuOH, or PhOH, to give the products **4m** with 66, 68, 72, and 78% *ee*, respectively (>94% yield). Although the *ee* values of the products varied from 66 to 78% depending on the additives, the following results suggested that the additive did not perform a major role in the enantioface selection step. First, when the chiral alcohol 2-phenylethanol was used as an additive, both the *R* and *S* isomer afforded (*R*)-**4m** in almost the same enantioselectivity (64 and 67% *ee*, respectively) and yield (90 and 91%). Second, the ³¹P NMR spectra of the catalyst in the absence or presence of PhOH (20 mol %) was exactly the same under the reaction conditions used, thus suggesting a negligible interaction between the catalyst and the additive.^[7] Therefore, the protic additive seems to facilitate the reaction without changing the catalytic species. We next investigated the possibility of promoting the reaction by using a catalytic amount of the best additive (PhOH) without diminishing the synthetic utility of this reaction. Gratifyingly, even when the amount of PhOH was reduced to 20 mol %, the reaction was completed in 44 h to give **4m** in 97% yield with 78% *ee*. Consequently, the effective reaction conditions were found to involve the slow (17 h) addition of PhOH (20 mol %) to a mixture of **1** (9 mol %), the imine, and TMSCN (2 mol equivalents; catalytic system 1).

A variety of *N*-fluorenylaldimines were examined as substrates for this optimized catalytic asymmetric Strecker-type reaction, and the results are shown in Table 1. Aromatic aldimines including heterocyclic aldimines, α,β -unsaturated aldimines, as well as aliphatic aldimines can be converted into Strecker products in excellent yields with good to excellent enantioselectivities. The Strecker products were successfully converted into the corresponding amino acid derivatives in high yields without loss of enantiomeric purity, and the absolute configurations of these products were determined to be *R* (Scheme 2).^[8] Furthermore, hydrogenation or dihydroxylation^[9] of the products from α,β -unsaturated imines afford-

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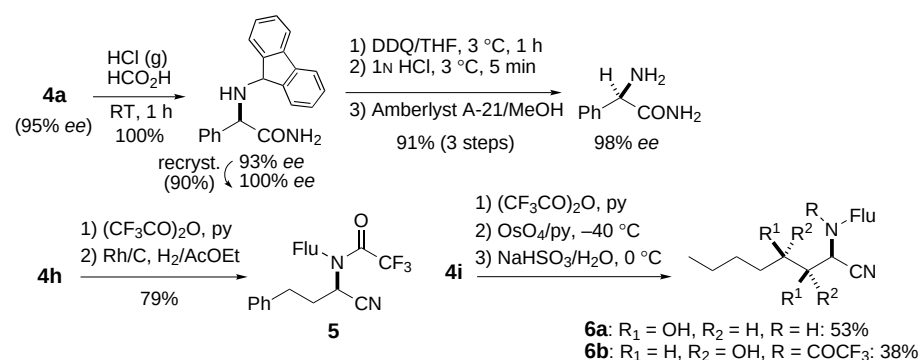
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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Table 1. Catalytic asymmetric Strecker-type reaction of various imines.^[a]

entry	R	3a–m	System 1			System 2		
			time [h]	yield [%] ^[b]	ee [%] ^[c]	time [h]	yield [%] ^[b]	ee [%] ^[c]
1	Ph	a	44	92	95	36	92	95
2	<i>p</i> -ClPh	b	44	92	95			
3	<i>p</i> -MeOPh	c	44	93	93			
4	1-naphthyl	d	68	95	89			
5	2-furyl	e	44	93	79			
6	3-furyl	f	44	92	90	36	92	87
7		g	58	90	89			
8	<i>trans</i> -PhCH=CH	h	41	80	96	36	78	92
9	<i>trans</i> -CH ₃ (CH ₂) ₃ CH=CH ₂	i	24	66	86 ^[d]			
10	CH ₃ (CH ₂) ₅	j	24	80	80 ^[e]	36	75	81
11	CH ₃ CH ₂	k	44	84	70			
12	<i>i</i> Pr	l	44	89	72	36	92	71
13	<i>t</i> Bu	m	44	97	78	36	98	77

[a] See Experimental Section for the preparation of the catalyst and the general reaction procedure. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] 50 mol % of PhOH was used. The aminonitrile was isolated as the corresponding trifluoroacetamide. [e] Without PhOH.



Scheme 2. Conversion to α -amino acid derivatives and functionalization of α,β -unsaturated Strecker products.

ed saturated or functionalized aminonitriles without loss of enantiomeric purity.

The kinetic profile of this reaction was investigated to gain further insight into the reaction mechanism.^[10] After adding PhOH in one portion the reaction was monitored by NMR spectroscopy by observing the disappearance of the imine proton of **3a** (δ = 8.58, Figure 1). The initial reaction rate in

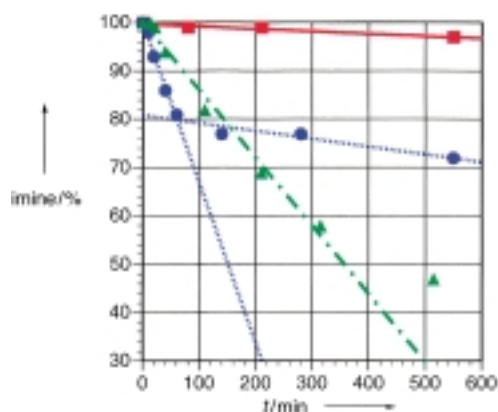


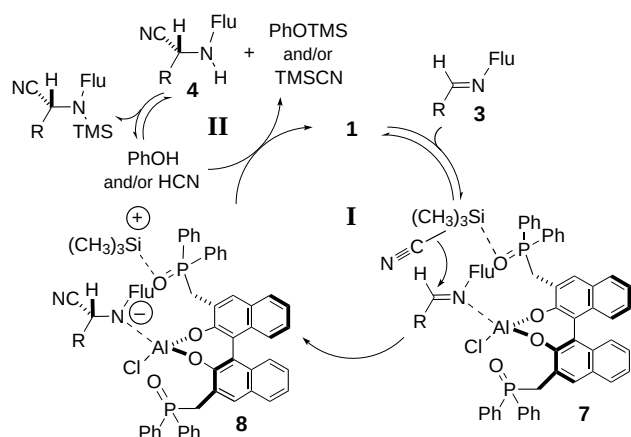
Figure 1. Initial reaction rate of **3a**. The disappearance of **3a** was monitored by ¹H NMR spectroscopy. For the experimental details, see the Supporting Information: the reaction of TMSCN in the absence (red ■) and in the presence of 20 mol % of PhOH (blue ●), and the reaction of HCN (green ▲) are shown.

the presence of 20 mol % of PhOH was 82 times faster than in the absence of PhOH. After about 20 % of the starting imine had been consumed, which corresponds to the complete conversion of PhOH into TMSOPh,^[11] the reaction entered a slower phase. However, even in this slower phase, the reaction rate was approximately two times faster than in the absence of PhOH. This result may be a consequence of the regeneration of a very small amount of PhOH from TMSOPh and the product amine. This regeneration of the

proton source was also suggested from the fact that the initial reaction rate in the presence of 20 mol % of **4a** and TMSOPh was approximately twice that in the absence of these additives.

Another interesting question is whether the reactive nucleophile is TMSCN or HCN.^[12] When HCN (2 mol equivalents) was added in one portion, the initial reaction rate was 0.4 times slower than when TMSCN was used in the presence of 20 mol % of PhOH (Figure 1), and the ee value of the product **4a** was 53 %. Furthermore, under the slow addition (26 h) conditions of HCN, **4a** was obtained in 54 % yield with 28 % ee after 85 h.^[13] These results reveal the reactive nucleophile to be TMSCN. Although HCN may be generated under the reaction conditions by the reaction of TMSCN with PhOH,^[14] the highly enantioselective pathway with TMSCN as an active nucleophile predominates, since the reaction rate with TMSCN is faster than that with HCN in this catalytic system. Thus, this reaction is the first example of a catalytic asymmetric Strecker-type reaction with TMSCN as an active nucleophile. This unique feature of the catalytic system using **1** may be derived from the ability of the Lewis-basic phosphane oxide moiety of the bifunctional catalyst **1** to activate TMSCN.^[4] These mechanistic studies suggest that PhOH and/or HCN work as a proton source to protonate the negative charge on the nitrogen atom that is generated by the

addition of CN to the imine, thus accelerating the formation of **4** (Scheme 3).^[15] A small amount of the proton source would be re-generated by cycle II, thus significantly accelerating the reaction rate when even a catalytic amount of PhOH is used.



Scheme 3. Working model for the catalytic cycle.

By taking advantage of the intriguing reactivity difference between TMSCN and HCN in this catalytic reaction, we expected that it would be possible to reduce the amount of TMSCN needed if HCN was used instead of PhOH, since TMSCN should be regenerated in catalytic cycle I (Scheme 3). Thus, by using 20 mol % of TMSCN and slowly adding the solution of HCN (120 mol %) in CH₂Cl₂ (system 2) we could obtain the products with comparable results as by the TMSCN–PhOH system (system 1, Table 1).

Although further investigation of the reaction mechanism is needed, the absolute configuration of the products may be explained from the working model **7** (Scheme 3), from analogy with the cyanosilylation of aldehydes. The Lewis acid (Al) and the Lewis base (phosphane oxide) activate the imine and TMSCN, respectively, at defined positions thus affording *R* products. The dual activation mechanism is supported by a control experiment using catalyst **2**, containing a diphenylmethyl group which should work only as a steric hindrance, instead of the diphenylphosphane oxide moiety. Catalyst **2** afforded the opposite enantiomer (*S*)-**4a** with 15 % *ee* in 100 % yield (42 h), in the presence of 20 mol % of PhOH. Therefore, in the case of **1**, TMSCN seems to attack the activated imine from the side of the phosphane oxide moiety.

In summary, the Lewis acid–Lewis base bifunctional catalyst **1** is shown to be a very general catalyst for the catalytic asymmetric Strecker-type reaction. Specifically, highly enantioselective α,β -unsaturated aminonitriles were obtained for the first time and successfully converted into the *n*- or functionalized aminonitriles. It was found that TMSCN is more reactive than HCN in the presence of 20 mol % of PhOH, which made it possible to use the unique catalytic system with a catalytic amount of TMSCN and a stoichiometric amount of HCN. Further investigations toward the reaction mechanism as well as developing a catalyst with higher activity are currently under investigation.

Experimental Section

The general procedures for the Strecker reaction are described. System 1: Et₂AlCl (17 μ L, 16 μ mol, 0.96 M in hexane) was added at room temperature to a solution of the chiral ligand (13 mg, 18 μ mol) in CH₂Cl₂ (0.5 mL), and the mixture was stirred for 1 h. The resulting solution of **1** was cooled to –40 °C and the solution of the imine (0.17 mmol) in CH₂Cl₂ (0.6 mL) was added. After 30 min, TMSCN (45 μ L, 0.34 mmol) was added to this solution. After another 30 min, the solution of PhOH (3 μ L, 34 μ mol) in CH₂Cl₂ (0.2 mL) was added slowly over 17 h. The reaction was monitored by thin-layer chromatography and after the time shown in Table 1, saturated NaHCO₃ solution was added. Extraction, usual workup, and purification by flash column chromatography on SiO₂ gave the pure product.

System 2: A solution of the imine (0.352 mmol) in CH₂Cl₂ (1 mL) and TMSCN (70 μ mol) were added to the solution of the catalyst (33 μ mol) in CH₂Cl₂ (1 mL) prepared as above at –40 °C. The solution of HCN (0.422 mmol) in CH₂Cl₂ (0.26 mL) was slowly added over 24 h to this mixture. The reaction was worked up as described above after 12 h (total 36 h).

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- [7] Two ³¹P NMR signals were observed at δ = 42.2 and 51.2 in the presence of TMSCN and **3a** in CD₂Cl₂.
- [8] For the conversion of products from aliphatic imines into α -amino acid derivatives, see the Supporting Information.
- [9] The relative configuration of **6a** was determined by X-ray crystallographic analysis of the cyclic carbonate derived from **6a**. See Supporting Information.
- [10] When PhOH was added in one portion, the reaction pathway seemed to be nearly the same as under the best reaction conditions. Thus, the *ee* values of the product **4a** in these kinetic studies were 95 % (in the absence of PhOH) and 88 % (20 mol % of PhOH).
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Metric Engineering of Crystalline Inclusion Compounds by Structural Mimicry**

K. Travis Holman and Michael D. Ward*

Considerable effort has been devoted to crystal engineering—the skillful contrivance of crystal architecture—of host frameworks capable of guest inclusion.^[1] The molecular-scale cavities of inclusion hosts can potentially serve as miniaturized reaction chambers,^[2] catalytic environments,^[3] and storage compartments^[4] in a manner that resembles^[5] more well established zeolites. Though interpenetration^[6] and the unpredictability of molecular assembly complicate the design of low-density host frameworks, strategies that rely on modular design^[7]—using robust supramolecular building blocks—promise improved control of solid-state structure. However, modular strategies also require elucidation of the intermolecular forces and molecular recognition factors that govern host–guest organization, so that crystal architecture and specific metric parameters can be reliably predicted and ultimately controlled. We herein report a rare example of crystal engineering in which the host–guest organization and specific structural features of a series of new inclusion compounds can be anticipated from the known crystal structures of the pure guests.

Recent efforts in our laboratory have produced a family of lamellar inclusion compounds based upon a persistent two-dimensional quasihexagonal hydrogen-bonding sheet comprising guanidinium cations (G) and the sulfonate (S) moieties of organodisulfonate anions,^[8] the latter serving as “pillars” that connect opposing GS sheets to create porous galleries, occupied by guest molecules, between the sheets (Figure 1). The use of different pillars—for example, 1,4-butanedisulfonate, 1,5-naphthalenedisulfonate, 2,6-naphthalenedisulfonate (NDS), 4,4'-biphenyldisulfonate (BPDS), azobenzene-4,4'-disulfonate, or 2,6-anthracenedisulfonate (ADS; Scheme 1)^[9]—permits adjustment of pore size and character.^[10] Two compositionally equivalent architectural isomers, a discrete bilayer and a continuous “brick”, can be generated, with the more open, lower density brick architecture templated by larger guest molecules.^[10c, 11]

The GS inclusion frameworks possess an intrinsic “softness” associated with conformational and turnstilelike rotational freedom of the pillars, as well as accordionlike puckering of the GS sheets about an axis defined by hydrogen bonds that join 1D N–H⋯O hydrogen-bonded ribbons. These features enable the GS host framework to “shrink-wrap” about a variety of differently sized guest molecules so

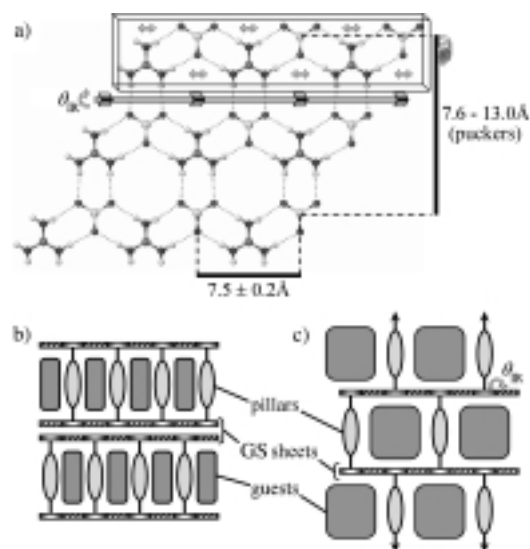
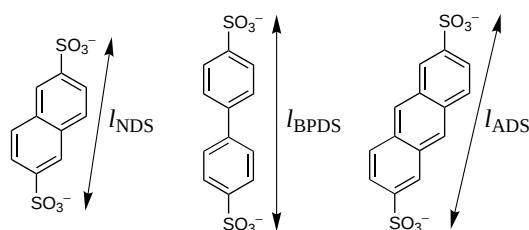


Figure 1. a) The quasihexagonal 2D hydrogen-bonded GS sheet consisting of connected 1D ribbons (boxed) that can pucker by angle θ_{IR} . b) Pillared discrete bilayer. c) Pillared continuous “brick” architecture.



Scheme 1. Pillars of 2,6-naphthalenedisulfonate (NDS), 4,4'-biphenyldisulfonate (BPDS), and 2,6-anthracenedisulfonate (ADS) with the corresponding S–S distances l (8.5, 10.6, and 10.8 Å for NDS, BPDS, and ADS, respectively).

that dense packing, which provides the cohesive energy required for crystallization, can be achieved.

The range of repeat distances within each GS ribbon for the GS host frameworks and their related guanidinium organomonosulfonates is rather narrow (7.5 ± 0.2 Å), reflecting the stiffness of these ribbons. However, the repeat distance normal to the ribbon direction varies with the interribbon puckering angle (θ_{IR}),^[12] and ranges from 7.6 Å for highly puckered sheets (e.g. $\theta_{IR} = 81^\circ$ for G_2 (BPDS)·1,4-dibromobenzene)^[10c] to 13.0 Å for perfectly flat sheets (e.g. $\theta_{IR} = 180^\circ$ for $[G][\text{triflate}]$).^[8a] Interestingly, the dimensions of the 2D herringbone motifs observed in some crystalline aromatic hydrocarbons—such as naphthalene, biphenyl, and anthracene (Figure 2a–c)^[13]—are within the range of lattice parameters that can be achieved by the flexible GS sheet. This prompted us to examine GS inclusion compounds in which the organic portion of the pillar and the guest were identical so that pillar–guest ensembles, mimicking the herringbone motif of the crystalline guests alone, would form within the galleries. Simple steric and geometric considerations dictate that such a herringbone motif is not sterically possible in the bilayer GS framework. Consequently, this structural mimicry would require the host framework to adopt the more open brick architecture (Figure 2d).

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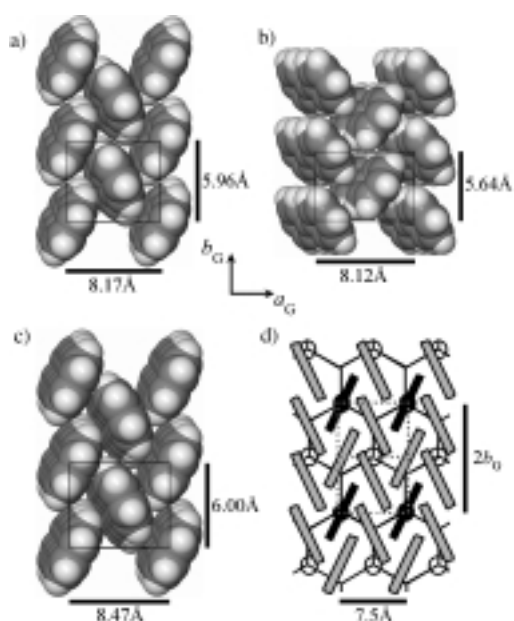


Figure 2. The 2D herringbone motif in a) naphthalene, b) biphenyl, and c) anthracene as viewed normal to the ab plane. d) Anticipated herringbone pillar-guest packing in the brick framework, as viewed normal to a GS sheet, with a 1:3 stoichiometry of pillar (black) to guest (gray). The pillars projecting below the sheet are depicted as open circles. The correspondence between the GS structure and that of the pure guest crystals is depicted by the dashed rectangles, which represent two unit cells of the herringbone-packed guests.

Compounds $G_2(\text{NDS}) \cdot 3$ naphthalene (**1**), $G_2(\text{BPDS}) \cdot 3$ biphenyl (**2**), and $G_2(\text{ADS}) \cdot 3$ anthracene (**3**) precipitate as single crystals when saturated methanolic solutions of the host components are treated with saturated solutions of the guests. The composition of each compound was confirmed by ^1H NMR spectroscopy, thermogravimetric analysis (TGA),^[14] and single-crystal X-ray diffraction.^[15] These compounds are essentially isostructural, the host frameworks adopting the continuous brick architecture with the guests and their isostructural pillars packing between the GS sheets in a manner nearly identical to that observed in the crystal

structures of the respective pure guests (Figure 3a). As expected, the organodisulfonate pillars effectively replace every fourth molecule in the herringbone motif of the pure guests to afford a pillar:guest stoichiometry of 1:3.

The herringbone pillar-guest ensembles in **1–3** can be described by the in-plane lattice dimensions of the pillar-guest ensembles, defined by two lattice constants: b_1 , coinciding with the relatively stiff GS ribbons, and b_2 , the repeat distance normal to the ribbons, which through puckering can conform to optimize the pillar-guest packing so that $b_2 \approx 2b_G$, where b_G is the b axis of the pure guest structure ($b_1 = a$ and $b_2 = c$ for **1** and **2**; $b_1 = a$ and $b_2 = b$ for **3**). The herringbone motif can also be described by the average dihedral angles ϕ between the mean planes of the arenes. Though the stiffness of the GS ribbons along the ribbon direction prevents b_1 from conforming exactly with a_G of the corresponding pure guests, the 7.5 ± 0.2 Å repeat distance along the GS ribbon is within 8% of a_G , with **3** having the largest mismatch. However, the values of b_2 , the variable puckering lattice parameter, are nearly identical to $2b_G$ of the respective guests (Table 1). The pillar-guest ensemble in each inclusion compound exhibits more than one value of ϕ , but the average of these values is nearly identical to the arene-arene dihedral angle in the respective pure guests.^[16] This reflects the ability of the pillars to rotate about their long axes, which is crucial to achieving the herringbone motif.

All the unit cell angles in **1–3** are equal to, or very near, 90° . The angle subtended by b_1 and b_2 in **1** and **2** (β in the monoclinic cell) deviates slightly from 90° ($\beta = 91.61^\circ$ and 90.46° , respectively) because of a small misregistry, along the ribbon direction, between adjacent hydrogen-bonded ribbons. In contrast, the angle subtended by b_1 and b_2 in **3** (γ for this compound) is exactly 90° . We note that the brick framework enforces a near-orthorhombic structure in which the long axes of the pillars are normal, or nearly so, to the GS sheets.

The value of θ_{IR} , reflecting the degree of host puckering required to achieve the value of b_2 necessary for herringbone packing, can be predicted by Equation (1), which only requires b_G (the 6.5 Å term in the denominator corresponds

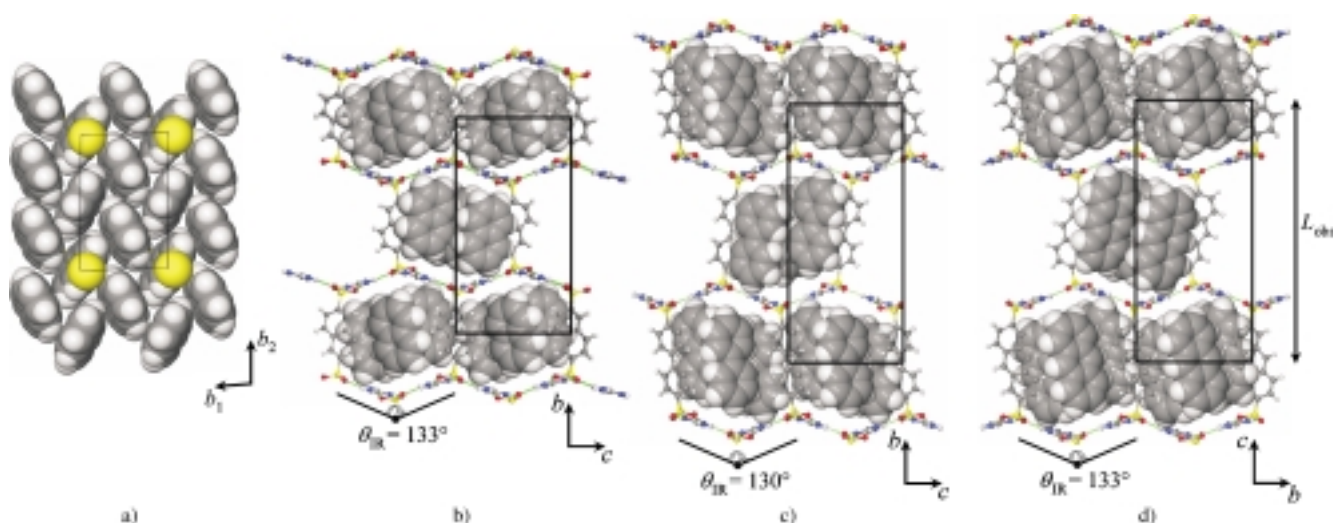


Figure 3. a) Herringbone pillar-guest packing in the ab plane of **1**. The G ions and sulfonate oxygen atoms have been removed for clarity. Sulfur atoms are yellow. b)–d) The crystal structures of **1**, **2**, and **3** as viewed along the a axis. The observed interribbon puckering angles θ_{IR} are provided below each structure.

Table 1. Comparison of the structural parameters of GS inclusion compounds and pure guest structures.

Compound	$b_{1,\text{obs}}$ and a_{G} [Å]	$b_{2,\text{obs}}$ and $2b_{\text{G}}$ [Å]	$\theta_{\text{IR,obs}}$ [°]	$\theta_{\text{IR,calcd}}$ [°]	L_{obs} [Å]	L_{calcd} [Å]	ϕ [°]
1	$b_1 = 7.64$	$b_2 = 11.82$	133	133	22.04	22.2	54
naphthalene	$a_{\text{N}} = 8.17$	$2b_{\text{N}} = 11.92$					52
2	$b_1 = 7.66$	$b_2 = 11.49$	130	120	26.31	27.7	62
biphenyl	$a_{\text{B}} = 8.12$	$2b_{\text{B}} = 11.28$					67
3	$b_1 = 7.56$	$b_2 = 11.96$	133	135	26.85	26.6	51
anthracene	$a_{\text{A}} = 8.47$	$2b_{\text{A}} = 12.00$					51

$$\theta_{\text{IR,calcd}} = 2 \sin^{-1}(b_{\text{G}}/6.5 \text{ Å}) \quad (1)$$

to one-half of the in-plane 13.0 Å repeat distance normal to the ribbons in a flat GS sheet). With the b_{G} lattice parameters of the pure naphthalene, biphenyl, and anthracene guests, Equation (1) affords $\theta_{\text{IR,calcd}}$ values of 133°, 120°, and 135°, which compare favorably to $\theta_{\text{IR,obs}}$ values measured from the crystal structures of **1–3** (Table 1).

The lattice constant normal to the GS sheets (L , given in Å), which defines two lamellae, can be calculated with Equation (2), using $\theta_{\text{IR,calcd}}$ and l , the S–S distance of the organodisulfonate pillar measured from known compounds (see Scheme 1). The bilamellar spacings for **1–3**, calculated with Equation (2), agree to within 1 % of the observed values (L_{obs}) for **1** and **3**, and to within 6 % for **2** (Table 1).

$$L_{\text{calcd}} = 2b_{\text{G}}/\tan(\theta_{\text{IR,calcd}}/2) + 2l \quad (2)$$

The agreement of b_2 and ϕ with the corresponding values in the pure guest structure, and of $\theta_{\text{IR,obs}}$ and L_{obs} with calculated values based on the pure guest lattice constant b_{G} , strongly argues that the major driving force for pillar–guest organization in the inclusion compounds is the achievement of an innate herringbone motif that mimics molecular organization in the pure guests. The intermolecular forces amongst the guest molecules and their isostructural pillars are sufficient to cause puckering, to a predictable extent, of the soft hydrogen-bonded GS sheets so that the herringbone motif is achieved.

Recently, it was suggested that a 2D pyrene guest network, interpenetrated with a 2D transition metal coordination network, exhibited edge-to-face interactions between the pyrene molecules in a manner reminiscent of molecular packing in many aromatic compounds.^[17] The brick inclusion compounds described here, as well others reported previously by our laboratory,^[10c] also can be described as interpenetrated 2D networks. However, compounds **1–3** are distinct—the existence of isostructural framework components, in this case freely rotating pillars, allows the ensemble of pillars and guests to mimic, almost exactly, the molecular packing in the crystal structures of the guests alone.

The ability to tune the guest environment in inclusion cavities of the GS frameworks suggests that crystallization-based separations can be developed in which guest inclusion selectivity is governed by carefully designed host frameworks that permit molecular organization mimicking innate packing motifs, such as the herringbone structures described above. We note the extremely low density of the host frameworks in these clathrates. Indeed, the packing fractions of **1**, **2**, and **3** in the absence of the guests (framework only) are 0.31, 0.29, and

0.29, respectively.^[18] The guests, in fact, occupy more volume than the host frameworks, with packing fractions of 0.38, 0.39, and 0.43. The corresponding guest mass fractions are 48.6, 51.7, and 54.0 %, illustrating that high separation efficiencies are feasible with protocols based on these inclusion frameworks.

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- Numerous examples of $G_2(\text{BPDS}) \cdot n\text{guest}$ inclusion compounds suggest a critical guest volume for the bilayer-to-brick conversion of about 128 Å³.
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- [15] A full hemisphere of data was collected on a Siemens SMART diffractometer with Mo α_K radiation ($\lambda = 0.71073$ Å). Data were corrected for Lorentz polarization, absorption, and decay using SADABS. Structures were solved by direct methods (SHELXS) and refined with full-matrix least squares based on $|F^2|$ (SHELXL-97-2). Hydrogen atoms were placed in calculated positions using a riding model. X-ray data for **1** (C₂₁H₂₁N₃O₃S): 0.42 × 0.36 × 0.21 mm, monoclinic, $P2_1/n$ (no. 14), $a = 7.6376(1)$, $b = 22.0442(4)$, $c = 11.8162(1)$ Å, $\beta = 91.611(1)^\circ$, $Z = 4$, $V = 1988.65(5)$ Å³, $\rho_{\text{calcd}} = 1.321$ g cm⁻³, $\mu = 0.190$ mm⁻¹, $1.8 < 2\theta < 24.0^\circ$, $T = 173$ K, $R_1 = 0.0351$ and $wR_2 = 0.0819$ for 2621 ($I > 2\sigma[I]$) of 3107 unique reflections and 253 parameters. X-ray data for **2** (C₂₅H₂₅N₃O₃S): 0.49 × 0.22 × 0.22 mm, monoclinic, $P2_1/n$ (no. 14), $a = 7.6612(6)$, $b = 26.306(2)$, $c = 11.4887(9)$ Å, $\beta = 90.458(2)^\circ$, $Z = 4$, $V = 2315.3(3)$ Å³, $\rho_{\text{calcd}} = 1.284$ g cm⁻³, $\mu = 0.171$ mm⁻¹, $1.5 < 2\theta < 25.0^\circ$, $T = 173$ K, $R_1 = 0.0359$ and $wR_2 = 0.0920$ for 3086 ($I > 2\sigma[I]$) of 4084 unique reflections and 289 parameters. X-ray data for **3** (C₂₉H₃₀N₃O₃S): 0.24 × 0.09 × 0.03 mm, monoclinic, $P2_1/n$ (no. 14), $a = 7.559(5)$, $b = 11.96(1)$, $c = 26.85(2)$ Å, $\beta = 94.17(8)^\circ$, $Z = 4$, $V = 2422(3)$ Å³, $\rho_{\text{calcd}} = 1.36$ g cm⁻³, $\mu = 0.171$ mm⁻¹, $1.9 < 2\theta < 24.0^\circ$, $T = 173$ K, $R_1 = 0.2791$ and $wR_2 = 0.5839$ for 2704 ($I > 2\sigma[I]$) of 3801 unique reflections and 186 parameters. The highly mosaic nature of all samples made accurate integration of the reflection intensities difficult and precluded the possibility of a more accurate single-crystal structure determination for compound **3**. We surmise that the high mosaicity can be attributed to the larger lattice mismatch (8%), compared to **1** and **2**, between the host structure and the native anthracene structure. X-ray powder diffraction of the bulk material (see the Supporting Information) reveals a unit cell identical to that determined from the single-crystal data and, based upon extensive studies of closely related compounds, confirms the structural assignment of the brick architecture for **3**. Importantly, the metric parameters with which this manuscript is principally concerned (i.e., b_1 and b_2) can be obtained from the lattice constants. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-136727 (**1**), -136728 (**2**), and -136729 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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The Eight Stereoisomers of LNA (Locked Nucleic Acid): A Remarkable Family of Strong RNA Binding Molecules**

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For more than a decade, chemists have searched the chemical space in order to obtain nucleic acid analogues with certain desirable properties, such as increased stability towards nucleolytic degradation and increased binding affinity (and specificity) towards complementary natural nucleic acid targets.^[1] A strong impetus for this research has been, and continues to be, the therapeutic promises of the antisense strategy.^[2] Unprecedented thermal affinities of duplexes involving the nucleic acid analogue “LNA” (Locked Nucleic Acid, **T^L**, β -D-ribo isomer, Figure 1) have recently been reported by us^[3,4] and others.^[5] The furanose ring of LNA, being part of a dioxabicyclo[2.2.1]heptane skeleton, is efficiently locked in a C-3'-endo (N-type) conformation and we have initiated a program which focuses on the synthesis and properties of the likewise conformationally locked configurational isomers of LNA. Recently we have published the syntheses of the two first diastereoisomeric forms of LNA, namely “xylo-LNA” (**xT^L**, β -D-xylo isomer) and “ α -L-LNA” (**α T^L**, α -L-ribo isomer, Figure 1).^[6,7]

In this report, the RNA binding of all eight possible stereoisomers of LNA is evaluated. Synthesis of “ α -L-xylo-LNA” (**α xT^L**, α -L-xylo isomer,^[7] Figure 1) has been accomplished and the remaining four stereoisomers (Figure 1), all enantiomers of the four synthesized diastereoisomers, are indirectly evaluated by hybridization studies of the four synthesized stereoisomers towards enantiomeric RNA targets (ent-RNA, also known as L-RNA or mirror-image RNA).^[8]

In Table 1 the results from hybridization studies towards RNA complements for homo-thymine derivatives are shown. Whereas the remarkable binding affinities of fully modified^[7] LNA, α -L-LNA, and xylo-LNA have been reported earlier,^[3,6b] it can be seen that fully modified α -L-xylo-LNA [5'-(**α xT^L**)₉T] is unable to hybridize towards both RNA and ent-RNA.^[9] The reason for this is presently unclear but the

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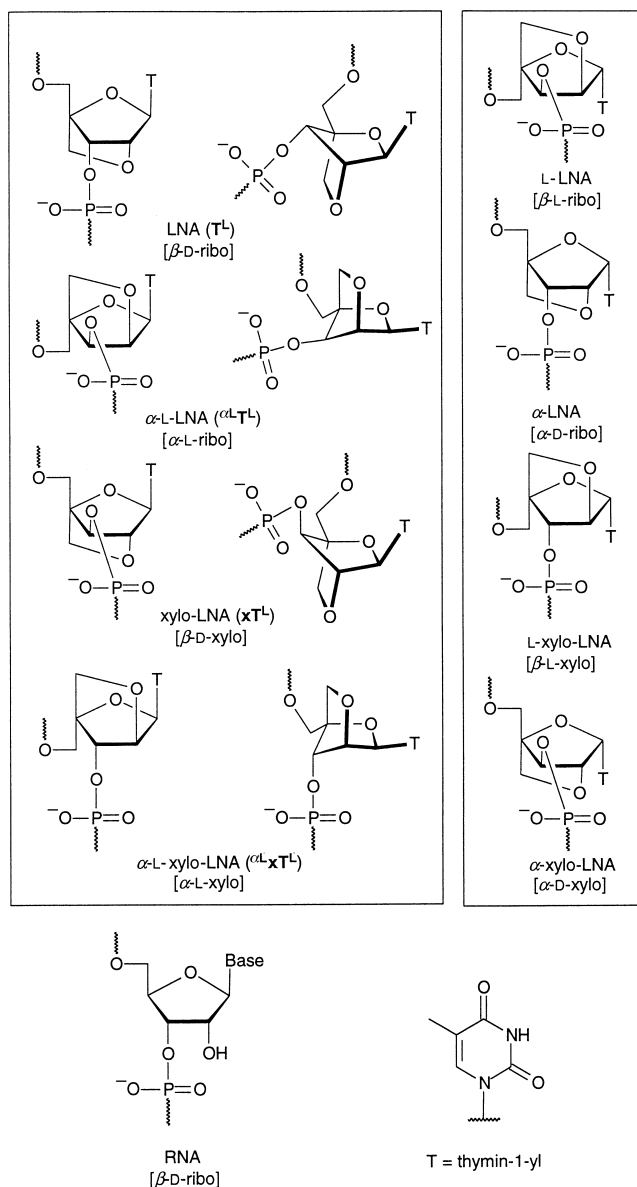


Figure 1. The four synthesized diastereoisomeric LNAs are shown to the left together with their locked furanose conformations, as obtained from molecular modeling studies. To the right, the structures of the indirectly evaluated remaining four LNA stereoisomers are depicted. Also shown are the structure of RNA and the thymine base (T). The configurations are indicated in the square brackets.

unnatural configuration may in this case prevent a suitable positioning of the thymine base for hybridization. Interestingly, the formation of very stable complexes with *ent*-RNA was detected for LNA, α -L-LNA, and xylo-LNA as indicated by the T_m values of 52 °C, 40 °C, and 39 °C, respectively.

Table 1. Binding studies of homo-thymine diastereoisomeric LNAs towards RNA (rA₁₄), singly mis-matched RNA (5'-r(A₆CA₇)), enantiomeric RNA (*ent*-rA₁₄), and singly mismatched enantiomeric RNA (*ent*-5'-r(A₆CA₇)) as shown by melting temperatures (T_m values [°C]).^[a]

Sequence	rA ₁₄	5'-r(A ₆ CA ₇)	<i>ent</i> -rA ₁₄	<i>ent</i> -5'-r(A ₆ CA ₇)
T ₁₀	18 ^[b]	no T_m ^[c]	no T_m ^[c]	no T_m ^[c]
5'-(T ^L) ₉ T	71 ^[b]	61	52	51
5'-(α T ^L) ₉ T	66 ^[d]	49	40	no T_m ^[c]
5'-(xT ^L) ₉ T	57 ^[d]	47	39	36
5'-(α xT ^L) ₉ T	no T_m ^[c]	no T_m ^[c]	no T_m ^[c]	no T_m ^[c]

[a] T_m values obtained from the maxima of the first derivatives of the melting curves (absorbance at 260 nm (A_{260}) versus temperature; gradient 0.5 °C min⁻¹); recorded in medium salt buffer (10 mM sodium phosphate, 100 mM sodium chloride, 0.1 mM ethylenediaminetetraacetate (EDTA), pH 7.0); 1.5 mM concentrations of the two complementary strands assuming identical extinction coefficients for modified and unmodified thymine (oligo)nucleotides. [b] See reference [3a]. [c] No cooperative transition above 10 °C. [d] See reference [6b].

Experiments towards the singly mismatched RNA target [5'-r(A₆CA₇)] showed the hybridization of LNA, α -L-LNA, and xylo-LNA towards RNA to be selective (changes in T_m values of -10 °C, -17 °C, and -10 °C, respectively). Using the singly mismatched *ent*-RNA target [*ent*-5'-r(A₆CA₇)], LNA and xylo-LNA displayed only slightly reduced T_m values compared to the fully matched situation. However, the selectivity of α -L-LNA:*ent*-RNA hybridization appears significant. Taken together, the melting results shown in Table 1 are quite remarkable, as illustrated by the ΔT_m values (change in T_m value per modification) ranging from +2.3 to +5.9 °C for the six hybridizing LNAs. The decisive factor for binding towards the RNA and *ent*-RNA targets for the LNAs shown in Table 1 is anticipated to be the nine consecutive LNA-type monomers. However, the fact that all sequences contain a 3'-end natural thymidine monomer could have a minor influence on the T_m data, as this monomer interacts differently with the RNA and the *ent*-RNA targets. It is noteworthy that only a very few of the large number of oligonucleotide analogues so far synthesized, such as the phosphodiester analogues HNA (hexitol nucleic acid)^[10] and tricyclo-DNA,^[11] have displayed binding affinities towards complementary RNA comparable with those obtained with the six stereoisomeric LNAs.

Especially fascinating is the fact that the binding affinity of α -L-LNA towards RNA is comparable to that of the parent LNA. This prompted us to further study the hybridization properties of a 9-mer mixed sequence α -L-LNA, containing three α -L-LNA thymine monomers (α T^L) and six unmodified deoxynucleotide monomers (Table 2, entry 3) in comparison with the corresponding DNA (Table 2, entry 1) and LNA (Table 2, entry 2). From the results shown in entry 3 it can be extracted that the binding affinity of the α -L-LNA is excellent

Table 2. Binding studies of mixed sequence 9-mer DNA, LNA, and α -L-LNA as shown by melting temperatures (T_m values [°C]).^[a]

Entry		N = A	5'-d(GXGAXXGC):3'-d(CACTNTACG)		5'-d(GXGAXXGC):3'-r(CACUNUACG)	
			C	T	A	C
1	X = T	28/28 ^[b]	11/13 ^[b]	12/15 ^[b]	28/29 ^[b]	10/no T_m ^[b]
2	X = T ^L	44 ^[c]	23 ^[c]	27 ^[c]	50 ^[c]	33 ^[c]
3	X = α T ^L	37	19	19	45	23

[a] For experimental details, see footnote [a] of Table 1. [b] These T_m values varied between two experimental series; the first value relates to the data in entry 2; the second value relates to the data in entry 3. [c] See reference [3b].

towards both complementary DNA ($\Delta T_m = +3.0^\circ\text{C}$) and RNA ($\Delta T_m = +5.3^\circ\text{C}$), though lower than that of LNA ($\Delta T_m = +5.3^\circ\text{C}$ towards DNA and $\Delta T_m = +7.3^\circ\text{C}$ towards RNA). The binding affinities obtained towards the singly mismatched sequences prove the excellent binding specificity of α -L-LNA towards both RNA and DNA targets (Table 2, entry 3 relative to entries 1 and 2).

CD spectra were recorded in order to evaluate the overall conformation of the duplexes involving LNA, xylo-LNA and α -L-LNA. In Figures 2 and 3, the CD spectra of these diastereoisomeric LNAs hybridized towards complementary RNA (rA_{14}) and *ent*-RNA (*ent*- rA_{14}), respectively, are shown. From the CD spectra in Figure 2 it can be seen that the

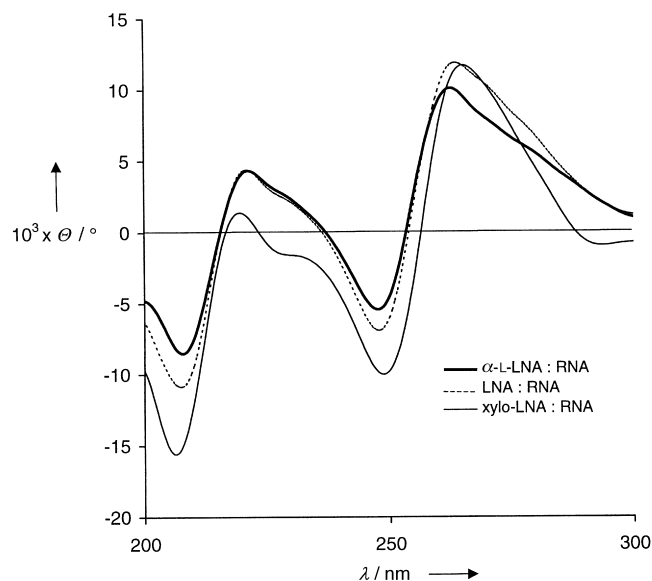


Figure 2. CD spectra recorded at 20°C of α -L-LNA:RNA [$5'-(^{\alpha}\text{L}\text{T})_9\text{-T:rA}_{14}$], LNA:RNA [$5'-(\text{T})_9\text{T:rA}_{14}$], and xylo-LNA:RNA [$5'-(\text{xT})_9\text{T:rA}_{14}$] duplexes. Conditions otherwise as described in footnote [a] of Table 1.

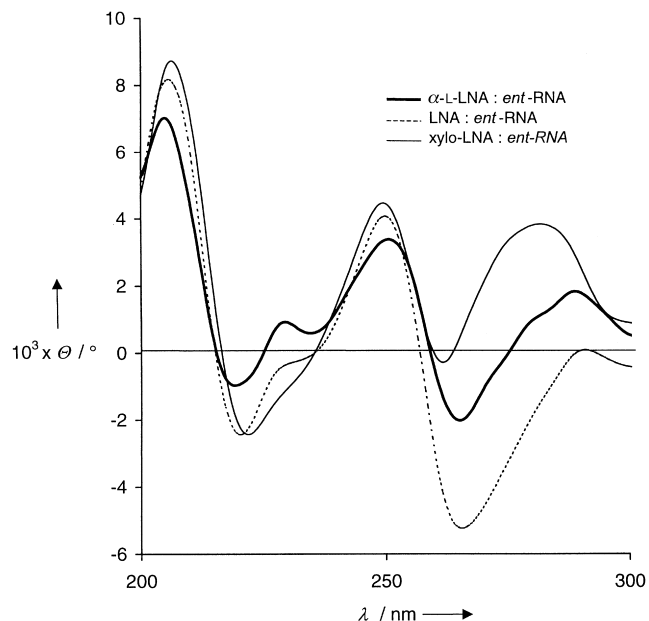


Figure 3. CD spectra recorded at 20°C of α -L-LNA:*ent*-RNA [$5'-(^{\alpha}\text{L}\text{T})_9\text{T:ent-rA}_{14}$], LNA:*ent*-RNA [$5'-(\text{T})_9\text{T:ent-rA}_{14}$], and xylo-LNA:*ent*-RNA [$5'-(\text{xT})_9\text{T:ent-rA}_{14}$] duplexes. Conditions otherwise as described in footnote [a] of Table 1.

conformations of the LNA:RNA and α -L-LNA:RNA duplexes are strikingly similar whereas the xylo-LNA:RNA duplex displays somewhat deviating characteristics (for example, a reduced ellipticity value at 220 nm). The CD spectra of the LNA:RNA and α -L-LNA:RNA duplexes closely resemble the CD spectrum of a reference A-type DNA:RNA ($\text{T}_{14}:\text{rA}_{14}$) duplex.^[12] This strongly suggests that LNA and α -L-LNA bind with complementary RNA in the antiparallel duplex mode which was likewise indicated by the hybridization data shown in Table 2. Figure 3 demonstrates a structural similarity, especially between the LNA:*ent*-RNA and α -L-LNA:*ent*-RNA duplexes and, for example, a characteristic positive ellipticity values above 240 nm for the xylo-LNA:*ent*-RNA duplex. These CD spectra reveal that α -L-LNA, like LNA,^[3c] can be regarded as an RNA mimic.

Both the T_m experiments and the CD spectra point to a structural similarity between an LNA monomer and an α -L-LNA monomer, such as T^{L} and $^{\alpha}\text{T}^{\text{L}}$ (Figure 1), having an identical constitution but different configuration at three out of the four asymmetric carbon atoms. This is further illustrated in Figure 4 which displays energy-minimized structures of the corresponding thymine nucleosides aligned to show the close three-dimensional fit between three key atoms in relation to nucleic acid structure, namely N-1, O-3' and C-5'.^[13]

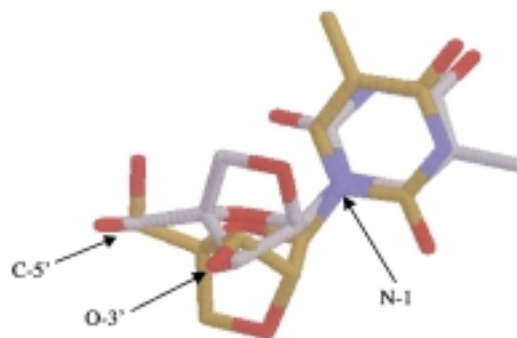


Figure 4. Energy-minimized structures of the LNA thymine nucleoside (yellow) and the α -L-LNA thymine nucleoside (gray) (HyperChem program, Polak-Ribiere algorithm).

Remarkably increased binding affinities towards RNA, compared to the DNA reference, have been documented for six out of the eight stereoisomeric LNAs which contain conformationally locked furanose moieties. This indicates that the potential for efficient hybridization is not restricted to the natural β -D-ribofuranosyl nucleic acids (RNA) and that the position of the conformational equilibria for the different potentially natural pentofuranose stereoisomers could have played a role in nature's choice^[14] of the β -ribofuranosyl isomer.^[15] The remarkable binding affinities and specificities obtained for LNA and α -L-LNA, both in a fully and in a partly modified context, establish these molecules as unique nucleic acid mimics.

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Metal Incorporation into and Dimerization of M_3E_4 Clusters (M = Mo, W; E = S, Se) in Supramolecular Assemblies with Cucurbituril: A Molecular Model of Intercalation**

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Incorporation of transition and post transition elements M' into trinuclear M_3^IV incomplete cuboidal clusters $[M_3E_4(H_2O)_9]^{4+}$ (M = Mo, W; E = S, Se), first reported in 1986,^[1] has developed into a field of considerable research interest.^[2, 3] The most fascinating aspect is that the zero oxidation state heteroatom can in many cases be used as the source of M' . Thus with $[Mo_3S_4(H_2O)_9]^{4+}$, direct incorporation of Hg, Ga, In, Tl, Sn, Pb, Sb, Bi, Fe, Co, Ni, Cu, and Pd has been achieved.^[3] Characterization has, however, remained a serious problem, and in many cases, in particular with the highly charged double cubes (e.g. $M' = Hg, In, Sn, Sb$), crystallization has only been possible as the pts^- salt of the aqua ion $[Mo_6M'S_8(H_2O)_{18}](pts)_8 \cdot xH_2O$ ($pts^- = p$ -toluenesulfonate).^[2, 4, 5] This may also be regarded as a supramolecular approach, since the pts^- ion is responsible for hydrogen bonding which holds the structure together.

Here we report rational syntheses of examples of a potentially rich and versatile class of supramolecular structures based on cucurbituril adducts. These can be prepared with the trinuclear clusters and heterometal-containing double cubes obtained as derivatives of $[M_3E_4(H_2O)_9]^{4+}$. Both the trinuclear and double cube products have a molecular C_3 axis. Cucurbituril ($C_{36}H_{36}N_{24}O_{12}$) is a macrocyclic cavitand with D_{6h} symmetry, having two identical carbonyl-fringed portals.^[6] We have identified as potential hydrogen-bond donors six coordinated water molecules, *cis* to the unique μ_3 -E group capping the triangle of Mo or W atoms, as complementary to six cucurbituril portal oxygen acceptor atoms. Crystallization should therefore be facilitated by the formation of hydrogen-bonded supramolecular aggregates. Coordination of cucurbituril to Na^+ , Rb^+ , and Cs^+ has been reported.^[7] Also, aliphatic and aromatic ammonium ions show high affinity towards cucurbituril.^[8]

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Crystals of $[\text{M}_6\text{HgE}_8(\text{H}_2\text{O})_{14}\text{Cl}_4](\text{C}_{36}\text{H}_{36}\text{N}_{24}\text{O}_{12})\text{Cl}_4 \cdot 14\text{H}_2\text{O}$, where the double cube component can be written as $[\{\text{M}_3\text{E}_4(\text{H}_2\text{O})_7\text{Cl}_2\}_2\text{Hg}]^{4+}$ ($\text{M} = \text{Mo}$, $\text{E} = \text{S}$ (**1**); $\text{M} = \text{Mo}$, $\text{E} = \text{Se}$ (**2**); $\text{M} = \text{W}$, $\text{E} = \text{Se}$ (**3**)), have been prepared by reaction of $[\text{M}_3\text{E}_4(\text{H}_2\text{O})_9]^{4+}$ with metallic Hg in hydrochloric acid and further crystallization in the presence of cucurbituril.^[9, 10] X-ray single-crystal analyses have revealed that **1**,^[11] **2**,^[12] and **3**^[13] are isostructural and have cluster cations $[\text{M}_6\text{HgE}_8(\text{H}_2\text{O})_{14}\text{Cl}_4]^{4+}$ sandwiched between two cucurbituril units; the cation and cucurbituril are held together by complementary hydrogen bonds ($\text{O} \cdots \text{O}$, 2.665–2.768 Å for **1**; $\text{O} \cdots \text{O}$, 2.679 Å–2.797 Å for **2**) to form an infinite chain structure (Figure 1 a). The Hg–S distances in **1** are unusually long, with two at 2.768(2) Å and four longer at 2.903(2) Å. This is in good agreement with the value of 2.84(12) Å reported for $[\text{Mo}_6\text{HgS}_8(\text{H}_2\text{O})_{18}](\text{pts})_8 \cdot 20\text{H}_2\text{O}$.^[2] In the closest structural analogue of **1**, $[\text{Hg}(\text{[9]-aneS}_3)_2]^{2+}$,^[14] the six Hg–S distances vary between 2.638(3) and 2.728(3) Å, and this seems to be the upper limit for Hg^{II} –S bond lengths ([9]-aneS₃ = 1,4,7-trithiacyclononane). This means that upon formation of the heterometallic double cube Hg retains a large part of its formal Hg^0 oxidation state.^[14] The Hg–Se distances in **2** vary between 2.795(1) and 2.9683(9) Å. The chlorides are all *trans* in respect to the unique μ_3 -E (capping Mo_3) so that on each Mo_3E_4 unit two chlorides are disordered between the three available positions.

The most striking feature of **1–3** is that they are isostructural with the cucurbituril assembly incorporating the incomplete cuboidal dimer adduct, $[\{\text{W}_3\text{Se}_4(\text{H}_2\text{O})_8\text{Cl}_2\}_2]^{2-}(\text{C}_{36}\text{H}_{36}\text{N}_{24}\text{O}_{12})\text{Cl}_6 \cdot 12\text{H}_2\text{O}$ (**4**).^[15] Here dimeric aggregates $(\text{W}_3\text{Se}_4)_2$, held together by rather short (compared to the sum of the van der Waals radii) $\text{Se} \cdots \text{Se}$ interactions (3.617–

3.740 Å), are embedded between cucurbituril molecules ($\text{O} \cdots \text{O}$, 2.719–2.779 Å) in exactly the same way as are heterometallic double cubes **1–3**, (Figure 1). Such dimeric aggregates have been reported previously for $[\text{W}_3\text{Se}_4(\text{NCS})_9]^{5-}$, $[\text{W}_3\text{Se}_4(\text{CN})_9]^{5-}$, as well as for other M_3E_4 derivatives ($\text{M} = \text{Mo}$, W ; $\text{E} = \text{S}$, Se).^[16] Moreover, in binary ME_2 chalcogenides of the early transition metals the chalcogen atoms of the neighboring layers interact with each other in the same way. Metal atoms and small molecules can intercalate between the layers.^[17] Thus the structures of **1–3**, and of **4**, are formally related as those of a matrix and of an intercalate. This means that the two W_3Se_4 trinuclear units, sandwiched between two cucurbituril molecules in **4**, mimic rather closely two neighboring layers $\text{EME} \cdots \text{EME}$ in solid ME_2 (in which M_3 units may be regarded as building blocks). This result shows that solid-state chemistry is related to the chemistry of small molecular clusters in a more intimate way than might have been expected. Even secondary effects such as specific noncovalent attractions between chalcogen atoms are important structure-organizing factors, both for solid-state materials like binary chalcogenides, and for packing together of smaller discrete clusters like M_3E_4 .

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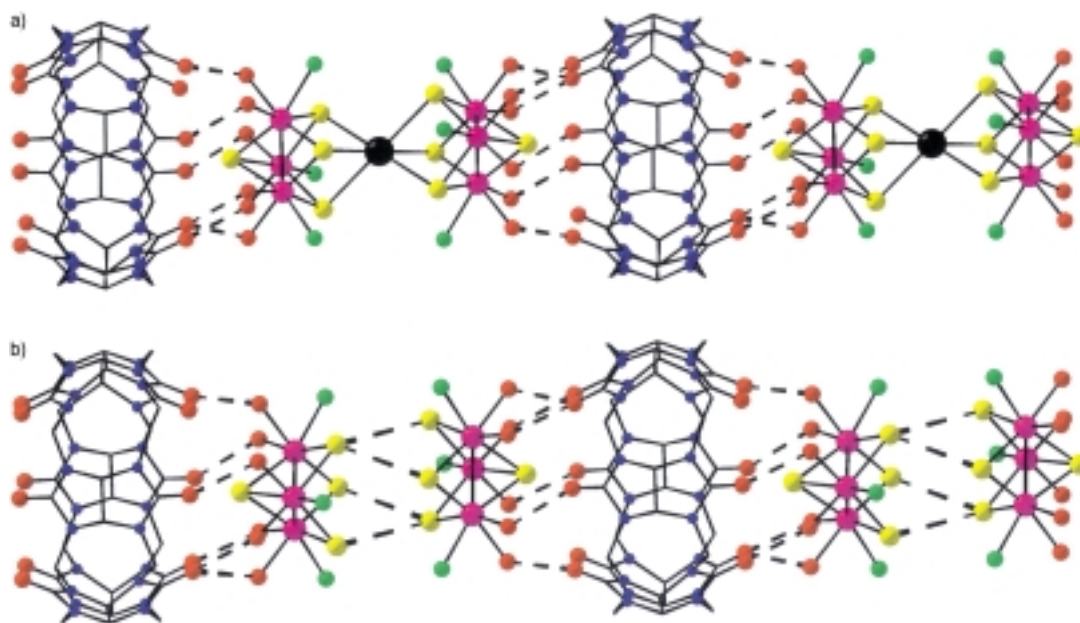


Figure 1. a) Structure of the $[\{\text{Mo}_3\text{Se}_4(\text{H}_2\text{O})_7\text{Cl}_2\}_2\text{Hg}](\text{C}_{36}\text{H}_{36}\text{N}_{24}\text{O}_{12})^{4+}$ polymeric chain in **2**. All hydrogen atoms, chloride ions, and water molecules in the lattice are omitted for clarity. Hydrogen-bonding interactions are indicated by dashed lines; Hg: black; Mo: purple; Se: yellow; O: red; disordered position of $\frac{1}{2}\text{Cl} + \frac{1}{2}\text{O}$: green; N: blue; C: no spheres. Main bond distances (Å): Mo–Mo, 2.762(1)–2.799(1); Mo–Se, 2.415(1)–2.460(1); Hg–Se, 2.795(1)–2.9683(9). b) Structure of the $[\{\text{W}_3\text{Se}_4(\text{H}_2\text{O})_8\text{Cl}_2\}_2](\text{C}_{36}\text{H}_{36}\text{N}_{24}\text{O}_{12})^{2+}$ polymeric chain in **4**. All hydrogen atoms, chloride ions, and water molecules in the lattice are omitted for clarity. Hydrogen-bonding interactions and $\text{Se} \cdots \text{Se}$ interactions are indicated by dashed lines; W: purple; Se: yellow; O: red; disordered position of $\frac{1}{2}\text{Cl} + \frac{1}{2}\text{O}$: green; N: blue; C: no spheres.

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- [9] A drop of metallic Hg (2–3 g) was added to a solution of $[\text{Mo}_3\text{S}_4(\text{H}_2\text{O})_9]^{4+}$ (2 mmol) in 4 M HCl (20 mL) under nitrogen. As the reaction proceeded, the color changed to royal blue. The resulting solution (10 mL) was added to cucurbituril (20 mg) in 4 M HCl (20 mL). After 4 d at room temperature, dark blue well-formed crystals of **1** appeared (yield 66%). Elemental analysis (%): calcd for $[\text{Mo}_6\text{S}_8\text{Hg}(\text{H}_2\text{O})_{14}\text{Cl}_4](\text{C}_{36}\text{H}_{36}\text{N}_{24}\text{O}_{12})\text{Cl}_4 \cdot 14\text{H}_2\text{O}$: C 15.35, H 3.29, N 11.93, S 9.10, Cl 10.07; found: C 15.44, H 3.33, N 12.01, S 9.12, Cl 9.93.
- [10] The Se analogues **2** and **3** were prepared similarly. Satisfactory analytical data (C, H, N, Cl) were obtained.
- [11] Crystal data for **1**:^[18] Crystal dimensions $0.12 \times 0.10 \times 0.06 \text{ mm}^3$, monoclinic, space group $C2/m$, $a = 16.775(1)$, $b = 18.298(1)$, $c = 15.268(1)$ Å, $\beta = 102.128(1)^\circ$, $V = 4581.9(5)$ Å³, $\rho_{\text{calcd}} = 2.042 \text{ g cm}^{-3}$, $\lambda(\text{MoK}\alpha) = 0.71073$ Å, $T = 160$ K, total/unique reflections 18445/5645 collected with Bruker SMART CCD diffractometer, $R_{\text{int}} = 0.0644$. Final refinement converged with $R_1 = 0.0450$ for 3399 reflections with $F_o \geq 4\sigma(F_o)$ and $wR_2 = 0.1197$ for all reflections.
- [12] Crystal data for **2**:^[18] Crystal dimensions $0.14 \times 0.08 \times 0.04 \text{ mm}^3$, monoclinic, space group $C2/m$, $a = 16.832(2)$, $b = 18.340(2)$, $c = 15.287(2)$ Å, $\beta = 101.842(2)^\circ$, $V = 4619(1)$ Å³, $\rho_{\text{calcd}} = 2.296 \text{ g cm}^{-3}$, $\lambda(\text{MoK}\alpha) = 0.71073$ Å, $T = 160$ K, total/unique reflections 14341/5631 collected with Bruker SMART CCD diffractometer, $R_{\text{int}} = 0.0646$. Final refinement converged with $R_1 = 0.0476$ for 3226 reflections with $F_o \geq 4\sigma(F_o)$ and $wR_2 = 0.1218$ for all reflections.
- [13] Due to insufficient size of the crystals only cell parameters could be determined for **3**: $a = 16.705(7)$, $b = 18.382(9)$, $c = 15.268(9)$ Å, $\beta = 101.93(4)^\circ$, $V = 4578(6)$ Å³.
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- [15] a) Preparation of **4**: To a saturated (about 5 mm) solution of cucurbituril in 2.5 M HCl (3 mL), a 10 mm solution of $[\text{W}_3\text{Se}_4(\text{H}_2\text{O})_9]^{4+}$ in 2.5 M HCl (3 mL) was added. The mixture was stirred and left for 4 d at room temperature. Dark green crystals suitable for X-ray analysis were obtained (yield 72%). Elemental analysis (%): calcd for $[\text{W}_3\text{Se}_4(\text{H}_2\text{O})_8\text{Cl}_2](\text{C}_{36}\text{H}_{36}\text{N}_{24}\text{O}_{12})\text{Cl}_6 \cdot 12\text{H}_2\text{O}$: C 12.29, H 2.63, N 9.55, Cl 8.06; found: C 12.18, H 2.75, N 9.30, Cl 8.10. b) Crystal data for **4**:^[18] Crystal dimensions $0.12 \times 0.05 \times 0.03 \text{ mm}^3$, monoclinic, space group $C2/m$, $a = 16.825(1)$, $b = 8.558(2)$, $c = 15.167(1)$ Å, $\beta = 105.364(2)^\circ$, $V = 4566.5(6)$ Å³, $\rho_{\text{calcd}} = 2.560 \text{ g cm}^{-3}$, $\lambda(\text{MoK}\alpha) = 0.71073$ Å, $T = 160(1)$ K, total/unique reflections 20050/5663 collected with Bruker SMART CCD diffractometer, $R_{\text{int}} = 0.0697$. Final refinement converged with $R_1 = 0.0635$ for 3558 reflections with $F_o \geq 4\sigma(F_o)$ and $wR_2 = 0.1909$ for all reflections.
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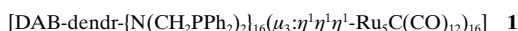
Nanoscale Super Clusters of Clusters Assembled around a Dendritic Core**

Neil Feeder, Junfeng Geng, Peter G. Goh, Brian F. G. Johnson,* Caroline M. Martin, Douglas S. Shephard,* and Wuzong Zhou

The construction of nanoscale molecular architectures is of considerable current interest.^[1–4] The development of dendrimer-based clusters of clusters as quantum dots should provide unique advantages, for example, in the preparation of monodispersed particles with well-defined molecular structures and surface functionalities. In the course of our studies on synthesis, deposition, and ordering of platinum group clusters,^[5, 6] we have prepared novel dendrimers based on an “inside-out” approach.

Here we describe the synthesis and characterization of nanoscale super clusters of clusters assembled around a dendritic core. High-resolution transmission electron microscopy (HRTEM) in conjunction with molecular modeling using force-field calculations have been employed to establish the morphology of these nanoparticles. In contrast to the “magic-number” synthesis^[7] of colloids wherein metal particles are stabilized by a “passivating” external layer of organic ligands, we have used a large internal organic scaffold, [DAB-dendr-[N(CH₂PPh₂)₂]₁₆],^[8] to construct an array of sixteen clusters, thereby forming a nanoscale self-ordering molecule (DAB = diaminobutane).

Compounds **1** and **2** (Figure 1) were prepared by binding the 16[P-N-P] tridentate terminal functionalities of the



organic third-generation dendritic core to cluster units $[\text{Ru}_5\text{C(CO)}_{12}]$ or $[\text{Au}_2\text{Ru}_6\text{C(CO)}_{16}]$. Both **1** and **2** show a molecular multiple-layer structure (Figure 2). They may be viewed as a sphere consisting of a nonconducting organic core with a sheath of conducting metal particles over the surface, which in turn is covered by a further outer layer of insulating carbonyl ligands. For conduction to occur, an electron introduced into the molecule would first have to tunnel through the carbonyl sheath to the “metallic layer”, move through the metallic layer to an exit point, and then tunnel again out of the molecule.

In addition to compounds **1** and **2**, we have also prepared and characterized the respective dimeric compounds **3** and **4** as

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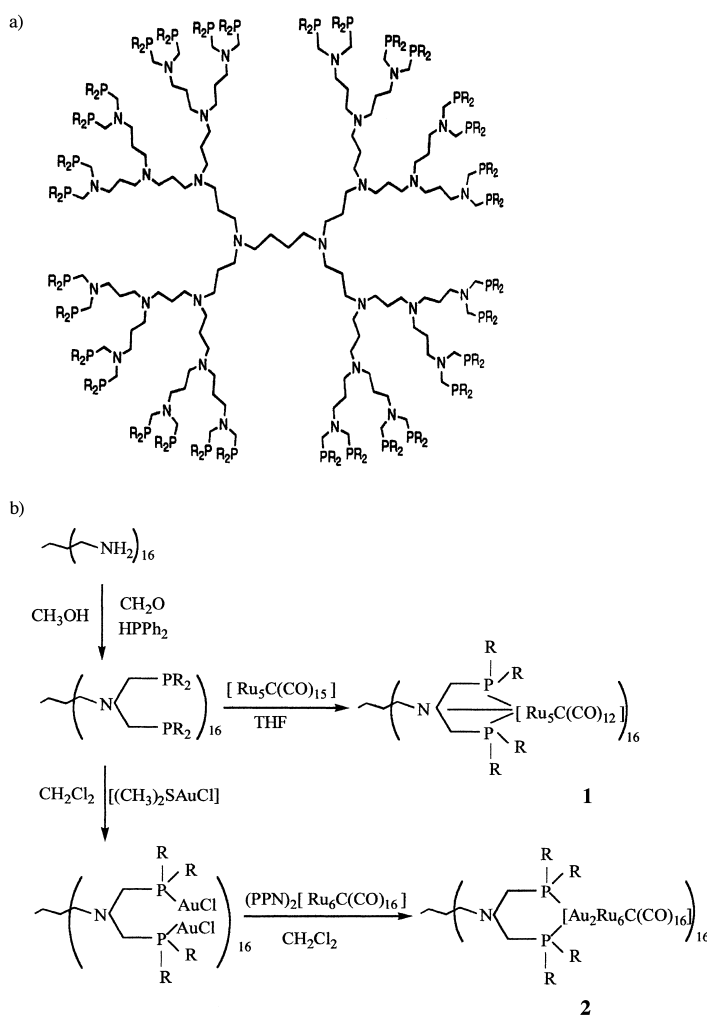


Figure 1. a) Chemical formula of the dendrimer molecule used for assembling the super clusters of clusters. b) The synthetic route to compounds **1** and **2**. R = C₆H₅ (Ph); PPN = [PPh₃NPPh₃]⁺.

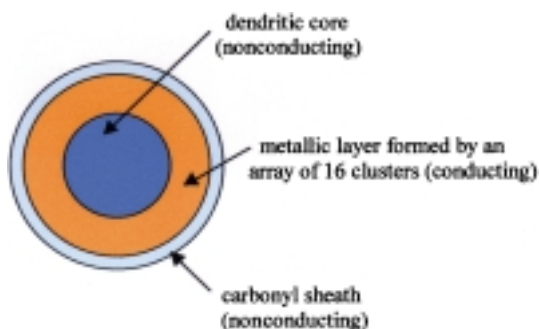
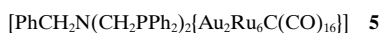
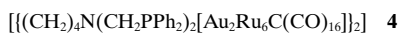
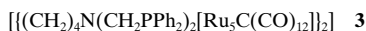


Figure 2. Representation of the molecular "multilayer" structure of compounds **1** and **2**.

well as the model compound **5**. Crystals of **3** suitable for single-crystal X-ray crystallography were grown from a chloroform solution by slow evaporation. The determined molecular structure is shown in Figure 3a. Two pentaruthenium clusters, related by a center of inversion, are linked by the bis-tridentate ligand. The amino nitrogen and the two phosphorus atoms of each terminal unit coordinate to three basal ruthenium atoms of the cluster, displacing three axial carbonyl ligands from the parent cluster. The pyramidal



geometry of the pentaruthenium carbido cluster is retained. Single crystals of **5** were obtained from dichloromethane by addition of hexane. The resulting X-ray structure (Figure 3b) shows precisely how the P-N-P chelating ligand binds and organizes the Au₂Ru₆ cluster core. The same bonding mode is therefore anticipated in the dendritic compound.

Compounds **1** and **3** display almost identical IR spectra in the CO region, strongly suggesting the coordinated clusters adopt a similar bonding mode. Evidence for the coordination of all the tridentate P atoms to clusters was provided by the observed single peak in the ³¹P NMR spectrum.^[9] Elemental analyses for both **1** and **2** as well as TGA measurement for **1** are in good agreement with those calculated for each dendrimer molecule containing sixteen [Ru₅C(CO)₁₂] or [Au₂Ru₆C(CO)₁₆] cluster units.

Initial attempts to record HRTEM images of **1** deposited on a carbon film revealed that the material was highly perturbed by the electron beam, probably because of CO ejection causing movement. Despite this, good HRTEM images (Figures 4a and 4b) were recorded by careful control of the beam current and exposure time. In Figure 4a a single approximately cubic molecule of dimensions 46 × 46 Å is shown on the carbon surface. A second image taken some 10 s later (Figure 4) shows the molecule to have collapsed inwardly to give a smaller, denser particle. This may be explained by decarbonylation and agglomeration of the carbonyl clusters covering the perimeter of the dendrimer as we have observed previously. In direct contrast, Figure 5 shows an essentially spherical single molecule (ca. 8 nm in diameter) of **2** supported on the carbon film. The large contrast observed is consistent with the large metal content and may be compared to the molecular model (Figure 6) generated with Chem 3D based on modified MM2 parameters. These giant molecules of **2** show no further change to the electron beam even after several minutes of intense irradiation.

In conclusion, we have developed a route to a new family of giant molecules which display self-ordering and which may be used in the production of nanoscale metal particles. The assembly of different, as well as similar, clusters onto successive generations of dendrimers should also be possible. Their properties suggest that they may be of use in gas delivery/storage systems (CO, NO, ethene, etc.) switched thermally or electrochemically,^[10] delivering metal particles of precise nuclearity to surfaces for nanoelectronics, and catalysis.

Experimental Section

Syntheses: Compounds **1** and **3** were synthesized by the addition of stoichiometric amounts of [Ru₅C(CO)₁₅] to a solution of [DAB-dendr-[N(CH₂PPh₂)₂]₁₆] (48 h) or [(CH₂)₄N(CH₂PPh₂)₂]₂ (10 h), respectively, in THF. Products **1** and **3** may be isolated in good yield (90% and 40%) by

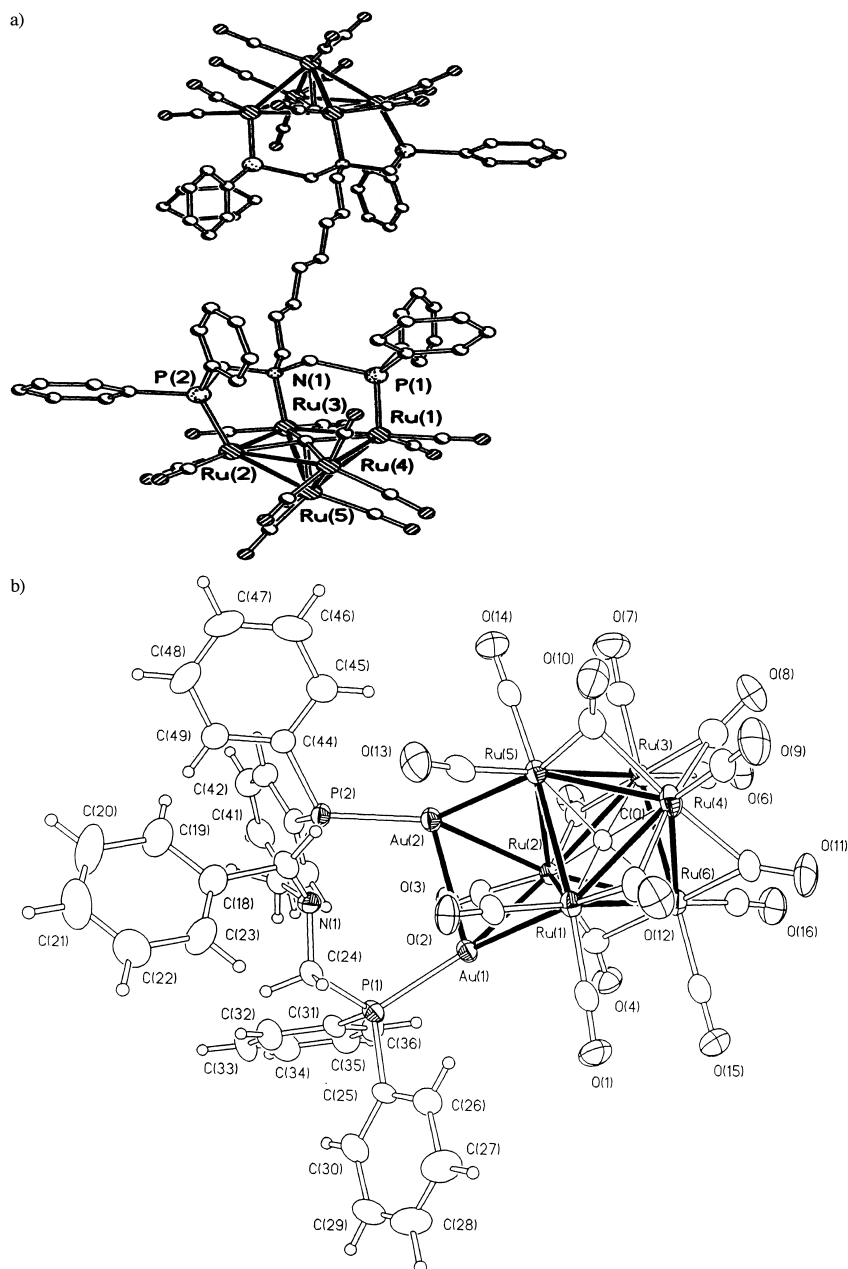


Figure 3. a) Solid-state molecular structure of **3**.^[11] Selected bond lengths [Å]: P(1)–Ru(5) 2.294(2), N(2)–Ru(1) 2.211(5), P(2)–Ru(2) 2.301(2), Ru(5)–Ru(1) 2.8218(8), Ru(1)–Ru(2) 2.8127(7), Ru(2)–Ru(4) 2.8966(8), Ru(4)–Ru(5) 2.8617(7). b) Solid-state molecular structure of **5**.^[11] Selected bond lengths [Å]: Au(1)–Au(2) 2.9362(6), P(1)–Au(1) 2.301(2), P(2)–Au(2) 2.314(2), Au(1)–Ru(1) 2.8213(6), Au(1)–Ru(2) 2.7451(6), Au(2)–Ru(2) 2.8200(6), Au(2)–Ru(5) 2.7725(6).

precipitation (hexane) and thin layer chromatography on silica gel. To obtain **2**, **4**, and **5**, we firstly synthesized intermediate compounds [DAB-dendr-[N(CH₂PPh₂AuCl)₂]₁₆], [(CH₂)₄N(CH₂PPh₂AuCl)₂]₂, and [PhCH₂N(CH₂PPh₂AuCl)₂] by the addition of [(CH₃)₂SAuCl] to a solution of [DAB-dendr-[N(CH₂PPh₂)₂]₁₆] (2 h), [(CH₂)₄N(CH₂PPh₂)₂] (2 h) or [PhCH₂N(CH₂PPh₂)₂] (1 h), respectively, in dichloromethane. Further reactions with (PPN)₂[Ru₆C(CO)₁₆] for about 48 h in freshly distilled CH₂Cl₂ produced compounds **2**, **4**, and **5** (yield: 60, 70, and 80%, respectively), which were then purified by recrystallization.

IR absorption measurements (CH₂Cl₂): $\tilde{\nu}(\text{C}=\text{O})$ [cm⁻¹] for **1**: 2055.4(s), 2014.4(s), 2003.0(sh), 1985.4(sh), 1968.8(sh); **2**: 2065.0(w), 2025.7(vs), 1998.0(m); **3**: 2056.2(s), 2014.3(s), 2003.6(sh), 1983.3(sh), 1970.3(sh); **4**: 2065.6(m), 2025.1(vs), 1987.2(m); **5**: 2066.4(m), 2026.3(vs).

Elemental analysis (%): **1**: found: C 39.18, H 2.80, N 1.89, P 4.77; calcd: C 39.43, H 2.58, N 1.94, P 4.58; **2**: found: C 31.32, H 2.09, N 1.18; calcd: C 29.67, H 1.78, N 1.34; **4**: found: C 30.10, H 1.98, N 0.45; calcd: C 29.24, H 1.66, N 0.73.

³¹P NMR measurements: single, sharp peak for **1**: δ = 30.0, **3**: δ = 30.5 in CDCl₃; **2**: δ = 21.6, **4**: δ = 17.4, **5**: δ = 21.6 in CD₂Cl₂.

TGA analysis for **1** (298–600 K) under argon gas gave a residual mass corresponding to the calculated Ru content of the sample.

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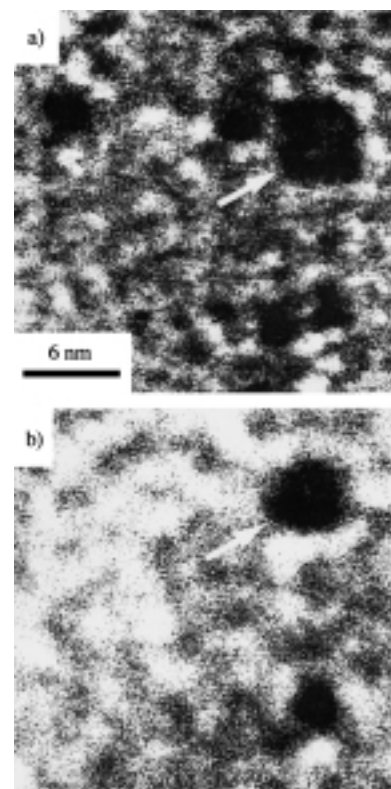


Figure 4. HRTEM images of **1** deposited on a holey carbon film: a) An intact molecule (indicated by an arrow) at $t \approx 0$. b) The same molecule (indicated by an arrow) 10 s later after decarbonylation and collapse.

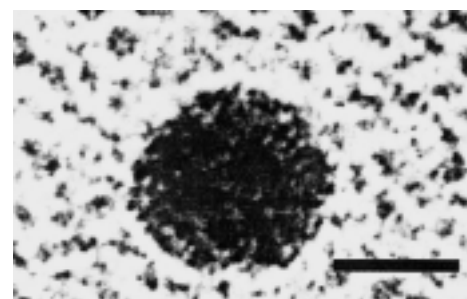


Figure 5. HRTEM image of a single molecule of **2** deposited on a holey carbon film. The length of the bar is 5 nm.

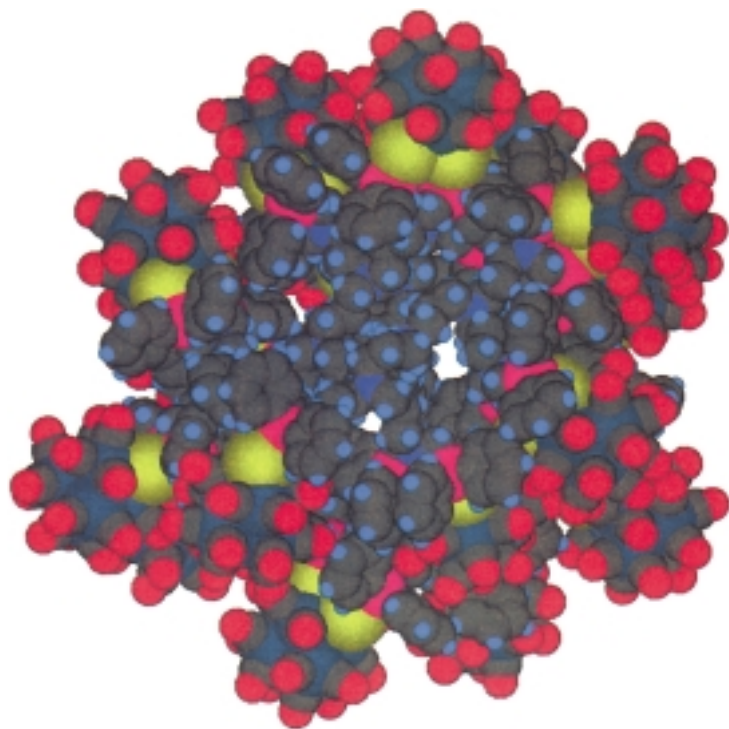


Figure 6. Chem 3D model of **2** (minimized by using modified MM2 parameters and molecular dynamics). Color code: Oxygen (red), hydrogen (light blue), ruthenium (dark green), carbon (black), phosphorus (violet), nitrogen (dark blue), gold (yellow).

The Synthesis of Streptogramin Antibiotics: (–)-Griseoviridin and Its C-8 Epimer**

Curt A. Dvorak, William D. Schmitz, Daniel J. Poon, David C. Pryde, Jon P. Lawson, Richard A. Amos, and Albert I. Meyers*

The streptogramin antibiotics are a family of compounds that were isolated from a variety of soil organisms belonging to the genus *Streptomyces*.^[1] On isolation they can be separated into two distinct groups, one of which is termed Group A containing a 23-membered unsaturated ring such as that found in griseoviridin (**1**),^[1] madumycin II (**2**),^[2] and virginiamycin M₂ (**3**).^[3] Also isolated from this family of mold metabolites are macrocyclic depsipeptides (e.g. etamycin (**4**)),^[4] known as Group B, which usually contain five to seven amino acids in a cyclic array (Figure 1). The antibiotics in

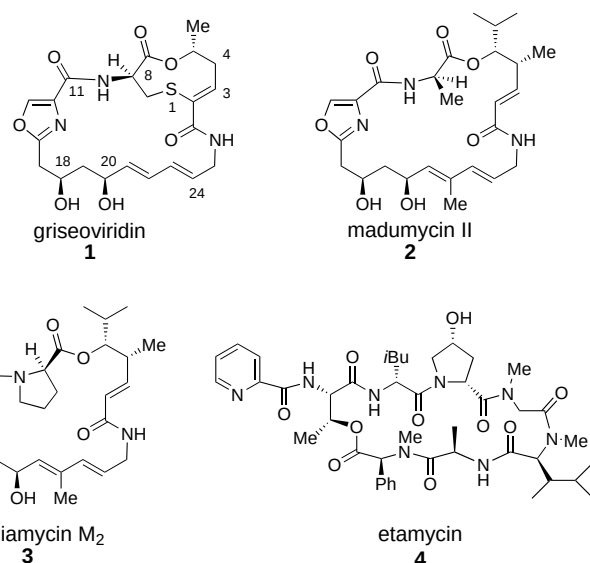


Figure 1. Streptogramin antibiotics.

Group A (**1–3**) exhibit a strong synergism when combined with those in Group B with respect to their activity toward Gram-positive bacteria. Recently, the Food and Drug Administration (FDA) (USA) has approved a combination of Group A and Group B to be used against bacteria which have already shown resistance toward vancomycin.^[5]

In 1996 we described^[2] the synthesis of madumycin II (**2**) and Schlessinger and Li^[3] simultaneously reported the total synthesis of virginiamycin M₂ (**3**). Pattenden et al. subsequently reported the synthesis of 14,15-anhydropristinamycin.

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

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cin II_B.^[6] The presence of the properly substituted nine-membered ring lactone containing an ene–thio linkage in **1** adds considerably to the complexity of the synthetic problem for reaching griseoviridin (**1**). A number of groups^[7] have attempted the synthesis of griseoviridin over the past 20 years and none have met with success until this current report.

The structure of griseoviridin was determined in 1976 by X-ray studies^[8, 9] but was reported in error with regard to the relative C-18,C-20 configuration. The correct configuration of the 1,3-diol system in **1** and **2** is *syn* as shown in Figure 1. Here we report the first successful synthesis of (–)-griseoviridin (**1**) as well as its C-8 epimer which were obtained from parallel syntheses starting with D-cystine for griseoviridin and L-cystine for C-8 *epi*-griseoviridin.

The synthetic plan to (–)-**1** hinged on the two crucial fragments, **5**^[10] and **6**, which had to be prepared in high enantiomeric purity and then coupled to provide the proper precursor to (–)-**1** (Figure 2). This would require, in a retrosynthetic manner, disconnection of **1** at C-11 (amide bond) and an attempt at an unprecedented olefin metathesis at C-24–C-25, using the diene present in **6**.

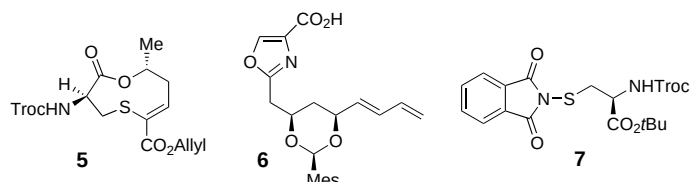
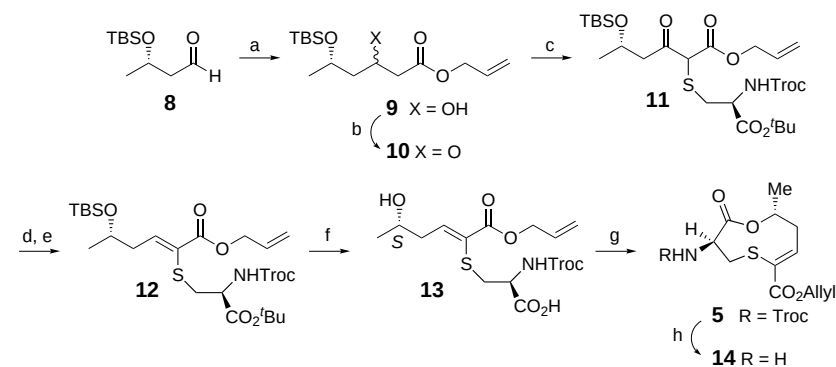


Figure 2. Key coupling fragments for griseoviridin and *S*-phthalimide **7**. Troc = trichloroethoxycarbonyl, Mes = mesityl.

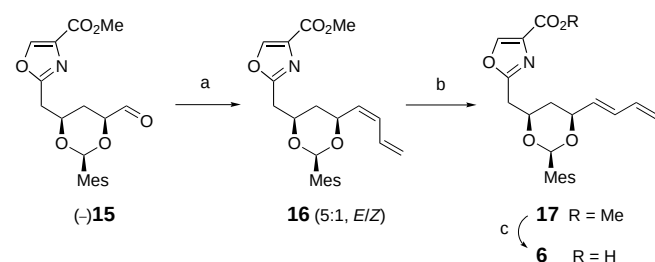
The lactone **5** was assembled in the following manner (Scheme 1). Known aldehyde **8**^[11] was treated with the lithium enolate of allyl acetate providing a diastereomeric mixture of β -hydroxy allyl esters **9**, which were directly oxidized with the Dess–Martin reagent^[12] to give the β -keto ester **10**. Preparation of the *S*-phthalimido compound **7** (see Figure 2) from commercially available D-cystine was effected by using a procedure adapted from the work of Miller et al.^[7c] The key carbon–sulfur bond in **11** was then constructed by treatment



Scheme 1. Synthesis of lactone **5**. a) Allyl acetate, LDA, Et₂O, –78 °C, 83%; b) Dess–Martin periodinane, CH₂Cl₂, 78%; c) NaH, THF, 0 °C, then **7**; 86%; d) NaBH₄, dioxane:aq pH 7 buffer: iPrOH (12:3:1), 83%; e) MsCl, Et₃N, CH₂Cl₂, 96%; f) 10% aq HCl, DME, 65 °C, 74%; g) DIAD, Ph₃P, THF, 50–70%; h) 10% Cd/Pb, 1 M NH₄OAc, THF, 96%. TBS = *tert*-butyldimethylsilyl, LDA = lithium diisopropylamide, Ms = mesyl = methanesulfonyl, DME = 1,2-dimethoxyethane, DIAD = diisopropylazodicarboxylate.

of **10** with sodium hydride and *S*-phthalimide **7** in THF. The vinyl sulfide linkage in **12** was then installed by reduction of the β -keto ester **11** with NaBH₄ followed by treatment with CH₃SO₂Cl. This resulted in the elimination of the in situ formed mesylate providing the required vinyl sulfide **12** as a 20:1 mixture of olefin isomers (*Z/E*). Removal of the secondary TBS silyl ether and the *tert*-butyl ester could be effected simultaneously to give hydroxy acid **13** in good overall yield. Lactonization, under Mitsunobu conditions,^[13] proceeded with inversion^[14] at the secondary hydroxy groups to give the appropriately substituted ene–thiol lactone **5** in 50–70% yield. Removal of the Troc group^[15] by Cd–Pb reduction provided the primary amine **14** to be used in the coupling with the diene oxazole moiety **6**.

To reach the oxazole-containing subunit, aldehyde (–)-**15** was prepared from (*S*)-malic acid as previously described^[2] (Scheme 2). Wittig olefination of aldehyde **15** with allyl

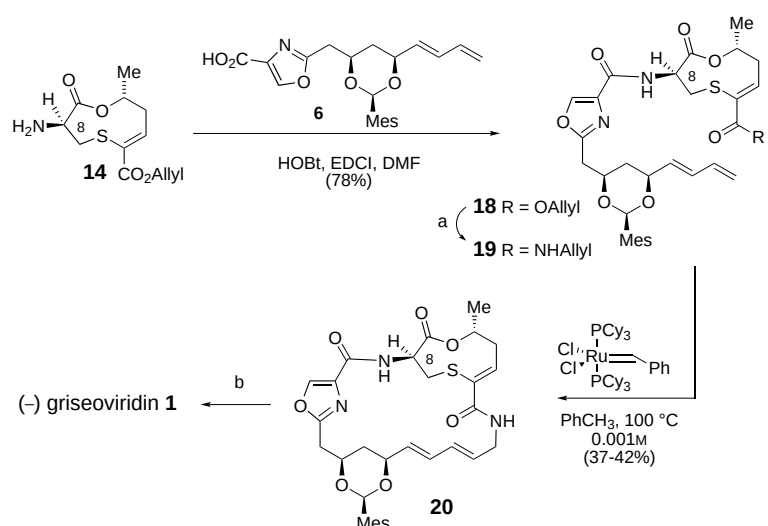


Scheme 2. Synthesis of oxazole diene **6**. a) Allyltriphenylphosphonium bromide, KHMDS, THF, 62%; b) benzene, I₂, *h* ν , 84%; c) LiOH THF/H₂O, 88%. KHMDS = potassium bis(trimethylsilyl) amide.

triphenylphosphorane gave the corresponding diene **16** as a mixture of stereoisomers (5:1, *Z/E*) in 62% yield. Although the olefination reaction was *Z*-selective, the mixture could be smoothly photoisomerized to the required *E*-diene **17** in the presence of iodine.^[16] Removal of the methyl ester in **17** using lithium hydroxide gave the requisite acid **6** to be coupled with lactone **14**.

The amide bond at C-11 was formed from oxazole acid **6** and lactone amine **14** using EDCI and HOBt^[17] to afford **18** in good yield. It now became necessary to convert the allyl ester **18** into the allyl amide **19**, since the latter will serve as the properly substituted olefin in the ring-closing metathesis process. To initiate this sequence, the allyl group was removed with [Pd(Ph₃P)₄]^[18] affording the crude carboxylic acid, and thereafter, coupled with allyl amine (HOBt-EDCI) to afford the cyclization precursor **19** in 82% overall yield (Scheme 3).

The ring-closing metathesis of **19** using 30% Grubbs' catalyst^[19] furnished **20** as a single product in 37–42% yield. After a number of additional attempts, the metathesis yield remained within this range. The ¹H NMR spectrum showed no sign of olefin isomers during the metathesis cyclization. Acidic removal of the diol protecting group gave (–)-griseoviridin (**1**) as a single diaster-



Scheme 3. Synthesis of griseoviridin (**1**). a) $[\text{Pd}(\text{PPh}_3)_4]$, pyrrolidine; allyl amine, HOBT, EDCI, DMF, 82%; b) PPTS, acetone/ H_2O , 68%. HOBT = 1-hydroxy-1*H*-benzotriazole, EDCI = *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, PPTS = pyridinium-*p*-toluenesulfonate.

eomer in 68% yield. The entire sequence was performed in 24 linear steps from (*S*)-malic acid. The material thus obtained was shown to be identical in all respects to natural griseoviridin^[20] (^1H , ^{13}C NMR, $[\alpha]_D$, etc.).

The sequence leading to C-8 *epi*-griseoviridin^[21] was performed in exactly the same manner and led to a product, in comparable yields, that was distinctly different from natural griseoviridin in its spectroscopic properties. Attempts to ascertain whether ene–thiol lactone **5** could be interconverted to its C-8 epimer proved fruitless due to decomposition when strong bases were employed. Further, attempts to incorporate deuterium into the C-8 position of **5** also failed. In summary, griseoviridin and its C-8 epimer have been synthesized for the first time employing a novel ring-closing metathesis which involved a highly diastereoselective triene to diene macrocyclic ring formation.

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- [21] A sample of the heretofore unknown C-8 *epi*-griseoviridin has been submitted for antibacterial screening (Aventis) and found to be only very poorly active (courtesy of Dr. S. Dutka-Malen).

A Structural Model for the Galactose Oxidase Active Site which Shows Counteranion-Dependent Phenoxy Radical Formation by Disproportionation**

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Galactose oxidase (GO) contains one copper ion at its active site and performs a two-electron oxidation of primary alcohols to aldehydes, coupled with a reduction of O_2 to

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H_2O_2 .^[1] Structural studies of the inactive form of GO have revealed that there exist two distinct tyrosine residues in the active site, one of which is a cysteine-modified phenol moiety of tyrosine 272 (Y_{272}) coordinated to the copper center as an equatorial ligand, while the other is a phenol group of tyrosine 495 (Y_{495}) bound at an apical position.^[2] The Cu^{II} ion and a phenoxyl radical together effect the two-electron oxidation reaction.^[3] The proposed mechanism of catalysis involves a cycle of the Cu^{I} –phenol and Cu^{II} –phenoxyl radical states; no Cu^{II} –phenolate form has been detected during catalysis.^[1, 2, 4]

Recent synthetic studies afforded well-characterized mononuclear Cu^{II} –phenoxyl radical species, which provided further insights into the reactivity of the GO active site.^[5] Tripodal ligands introduced by Karlin^[6] have been developed for use as GO model ligands in a number of studies.^[5c, f, h, 7, 8] Model complexes of ligands with two or more phenol moieties have also been synthesized by several groups.^[5b, d, e, f, k–m] However, modeling of the coordination structure and roles of the two coordinated phenol moieties with monomeric Cu^{II} complexes has not yet been fully achieved, and dimerization of the complexes often occurs.^[5f, h, 7, 8] We report here the synthesis and characterization of a novel mononuclear Cu^{II} complex of a tetradentate tripodal ligand, which is similar to that prepared by Pierre et al.,^[5f] with two phenol moieties and two *tert*-butyl groups introduced. The coordination structure has been found to closely resemble that of the inactive GO form.^[2] Preliminary studies showed that, while $\text{Cu}(\text{OAc})_2$ gives a stable GO-mimicking complex with two phenol moieties coordinated, the CuCl_2 and $\text{Cu}(\text{ClO}_4)_2$ ligand systems react differently and the latter spontaneously gives the phenoxyl radical species by disproportionation.

N-(2-pyridylmethyl)-*N,N*-bis(2'-hydroxy-3',5'-di-*tert*-butylbenzyl)amine (H_2L) was treated with $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ in air at room temperature to give $[\text{Cu}(\text{HL})(\text{OAc})] \cdot \text{H}_2\text{O}$ (**1**) as brown crystals (Scheme 1). X-ray crystal

structure analysis revealed that **1** contains two phenol moieties coordinated to Cu^{II} in different ways (Figure 1), and the unit cell consists of two crystallographically independent complex molecules.^[9] The Cu^{II} center is in a distorted

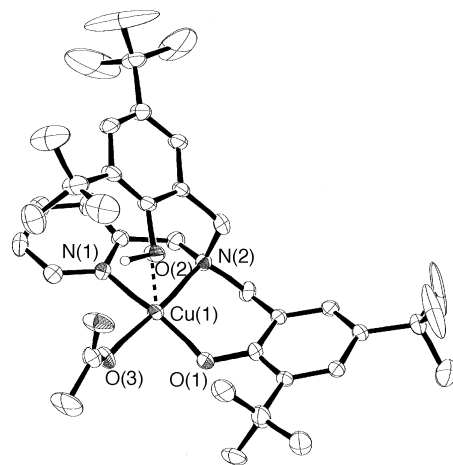
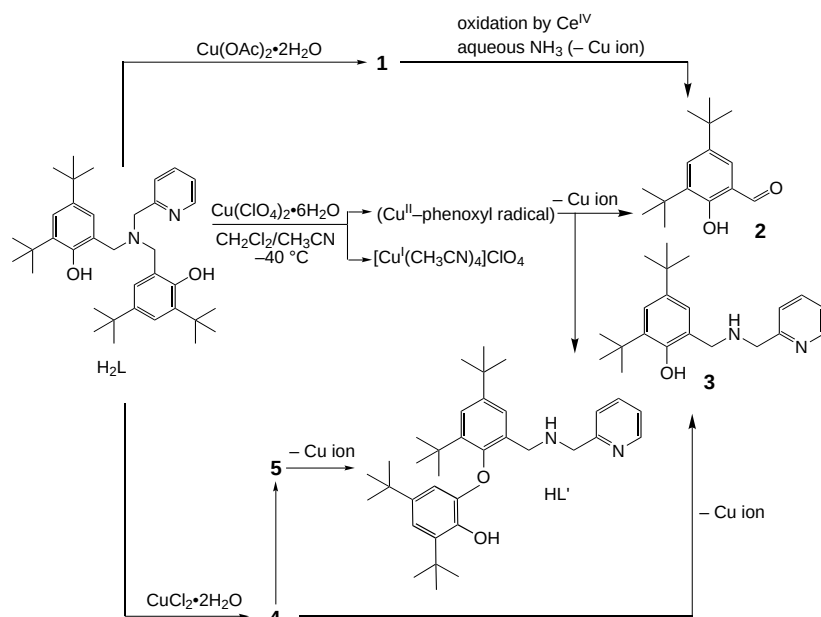


Figure 1. ORTEP view of $[\text{Cu}(\text{HL})(\text{OAc})]$ **1** (drawn with the thermal ellipsoids at the 30% probability level) and atomic labeling scheme. Selected bond lengths [Å] and angles [°]: Cu(1)–N(1) 2.001(6), Cu(1)–N(2) 2.043(5), Cu(1)–O(1) 1.883(4), Cu(1)–O(2) 2.418(5), Cu(1)–O(3) 1.957(5); N(1)–Cu(1)–N(2) 83.2(2), N(1)–Cu(1)–O(1) 159.6(2), N(1)–Cu(1)–O(2) 90.5(2), N(2)–Cu(1)–O(2) 86.6(2), N(1)–Cu(1)–O(3) 93.1(2), O(1)–Cu(1)–O(2) 109.6(2), O(1)–Cu(1)–O(3) 88.5(2).

square-pyramidal geometry formed by a phenolate oxygen, a pyridine nitrogen, a tertiary amine nitrogen, and an acetate oxygen in the coordination plane with a protonated phenol oxygen at an axial position with an average Cu–O bond length of 2.40 Å.

The brown solution of **1** exhibited the phenolate– Cu^{II} charge transfer band at 470 nm ($\epsilon = 1300$), which disappeared upon oxidation with Ce^{IV} in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ at low temperature (-40°C), but formation of the phenoxyl radical could not be detected. Decomposition products **2** and **3** were isolated from the reaction mixture, both in 15% yield (Scheme 1). Cyclic voltammetry in CH_2Cl_2 with tetrabutylammonium perchlorate revealed an irreversible oxidation at 0.62 V against Ag/AgCl (scan rate = 100 mV s^{-1}). Complex **1** was found to be inactive for oxidation of ethanol.

On the other hand, $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ underwent a reaction with H_2L in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$, to rapidly form a deep green color. After exposure to air at room temperature, the deep green reaction mixture turned colorless, and yielded colorless crystals of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4$ (yield of the first crop, 35%; subsequent small crops were also obtained). The deep green intermediate solution at -40°C exhibited an absorption band centered at 403 nm ($\epsilon = 2000$) with a shoulder and at 654 nm ($\epsilon = 400$); no X-band EPR signals were observed, which is consis-



Scheme 1. Reaction scheme for Cu^{II} – H_2L system which shows the dependence on the counterion.

tent with a Cu^{II} -phenoxyl radical species as these are known to give typical absorption peaks, for example, at 410 ($\epsilon = 4000$), 422 ($\epsilon = 3800$), and 672 nm ($\epsilon = 1000$).^[5d] The radical species was also detected under an inert gas atmosphere, and colorless crystals of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4$ were isolated, showing that the radical formation is not due to oxidation by dioxygen. The deep green reaction intermediate was short lived relative to some of the reported oxidized species,^[5] decaying by a first order process at -20°C with $k = (9.3 \pm 0.2) \times 10^{-4} \text{ s}^{-1}$ (UV-Visible monitoring). No such reactions were observed for a solution containing methanol, which gave the dimeric complex Cu_2L_2 as brown powder upon addition of triethylamine.^[5f] Decomposition products **2** and **3** (yields less than 10%) were also detected in the colorless reaction mixture of the $\text{Cu}(\text{ClO}_4)_2\text{-H}_2\text{L}$ system (Scheme 1). As they are identical with those from complex **1**, we may infer that similar reactions have occurred in both systems.

When $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ was used in place of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, it underwent a reaction with H_2L in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ /hexane in air to give $[\text{Cu}(\text{H}_2\text{L})\text{Cl}_2]$ (**4**) as green crystals, where the Cu^{II} ion binds two nitrogen atoms and two chloride ions in the coordination plane and the two phenol hydroxyl groups are protonated, one is also weakly coordinated ($\text{Cu}\text{-O}(1)$ 2.677(7) Å; Figure 2). Addition of triethylamine to **4** afforded

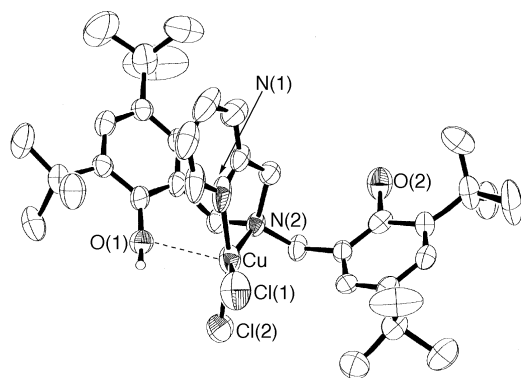


Figure 2. ORTEP view of $[\text{Cu}(\text{H}_2\text{L})\text{Cl}_2]$ **4** (drawn with the thermal ellipsoids at the 30% probability level) and atomic labeling scheme. Selected bond lengths [Å] and angles [$^\circ$]: Cu–N(1) 1.955(9), Cu–N(2) 2.099(7), Cu–Cl(1) 2.254(4), Cu–Cl(2) 2.230(3), Cu–O(1) 2.677(7); N(1)–Cu–N(2) 82.3(5), N(1)–Cu–Cl(1) 94.3(4), Cl(1)–Cu–Cl(2) 93.7(2), N(1)–Cu–O(1) 80.5(3), N(2)–Cu–O(1) 87.5(3).

the same dimeric complex as obtained from the $\text{Cu}(\text{ClO}_4)_2\text{-H}_2\text{L}$ system.^[5f] In connection with this, Cu^{II} -tripodal ligand complexes with an N_3O chromophore have been isolated with different anions.^[8] By analogy with CuCl_2 , $\text{Cu}(\text{ClO}_4)_2$ most probably initially forms a protonated complex such as **4**, and since the perchlorate ions can dissociate easily from Cu^{II} even when they are bound, Cu_2L_2 should be more rapidly formed in the $\text{Cu}(\text{ClO}_4)_2\text{-H}_2\text{L}$ system than from **4**. Upon standing at room temperature for a few weeks, **4** gave **2**, **3**, and complex **5** which coordinates a new product HL' (Figure 3); this was also detected in a small amount in the $\text{Cu}(\text{ClO}_4)_2\text{-H}_2\text{L}$ system. These results indicate that the Cu^{II} -phenoxyl radical in this system was produced together with $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4$ as a result of a disproportionation reaction,^[10] which may take

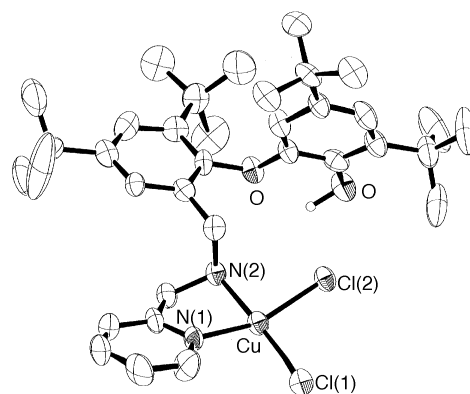


Figure 3. ORTEP view of $[\text{Cu}(\text{HL}')\text{Cl}_2]$ **5** (drawn with the thermal ellipsoids at the 30% probability level) and atomic labeling scheme. Selected bond lengths [Å] and angles [$^\circ$]: Cu–N(1) 2.002(8), Cu–N(2) 2.024(8), Cu–Cl(1) 2.266(3), Cu–Cl(2) 2.268(3); N(1)–Cu–N(2) 80.2(3), N(1)–Cu–Cl(1) 96.2(3), N(1)–Cu–Cl(2) 158.0(3), N(2)–Cu–Cl(1) 176.2(2), N(2)–Cu–Cl(2) 89.1(2), Cl(1)–Cu–Cl(2) 94.0(1).

place by rapid dimer formation from **4** where the phenol moieties are unbound or only weakly bound.

In conclusion, we obtained a new GO model Cu^{II} complex **1** of a tripodal ligand H_2L , where the two side-chain phenol moieties coordinated at an equatorial and an axial position in the phenolate and the phenol form, respectively. Different counteranions of the metal sources not only caused a large structural difference in the complexes relative to that reported earlier^[8] but also affected the reactivity of the complexes, which increases as the order of anion basicity decreases: $\text{CH}_3\text{COO}^- > \text{Cl}^- > \text{ClO}_4^-$.^[11] In the $\text{Cu}(\text{ClO}_4)_2\text{-H}_2\text{L}$ system, spontaneous formation of a phenoxyl radical species and $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4$ due to disproportionation has been observed. To the best of our knowledge, this is the first observation of Cu^{II} -phenoxyl radical formation by disproportionation of Cu^{II} complexes.

Experimental Section

Synthesis of *N*-(2-pyridylmethyl)-*N,N*-bis(2'-hydroxy-3',5'-di-*tert*-butylbenzyl)amine (H_2L): 2,4-di-*tert*-butylphenol (4.12 g, 20 mmol) and paraformaldehyde (0.60 g, 20 mmol) were added to a solution of 2-pyridylmethylamine (1.08 g, 10 mmol) in ethanol (100 mL). The reaction mixture was refluxed for two days to give a white powder which, after isolation, was recrystallized from ethyl acetate to yield 2.01 g (56.3%). ^1H NMR (300 MHz, CDCl_3): δ = 1.28 (s, 18H; $(\text{CH}_3)_3\text{C}$), 1.40 (s, 18H; $(\text{CH}_3)_3\text{C}$), 3.80 (s, 4H; phenol- CH_2), 3.84 (s, 2H; py- CH_2), 6.93 (d, 2H; phenol-H), 7.13 (d, 1H; py-H), 7.22 (d, 2H; phenol-H), 7.27 (m, 1H; py-H), 7.69 (td, 1H; py-H), 8.69 (d, 1H; py-H), 10.55 (br s, 2H; phenol-OH).

Synthesis of **1:** The complex was prepared from H_2L and $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (1:1) to give brown crystals. Elemental analysis (%) calcd for $\text{C}_{38}\text{H}_{57}\text{N}_2\text{O}_5\text{Cu}$: C 66.59, H 8.38, N 4.09; found: C 66.13, H 8.450, N 4.08.

Synthesis of the dimer Cu_2L_2 : H_2L (0.545 g, 1.0 mmol) was dissolved in CH_2Cl_2 (10 mL) which contained a few drops of triethylamine and was added to a solution of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.370 g, 1.0 mmol) in methanol (10 mL), which caused a brown powder to separate immediately. This was collected and dried. Elemental analysis (%) calcd for $\text{C}_{72}\text{H}_{100}\text{N}_4\text{O}_4\text{Cu}_2$: C 71.31, H 8.31, N 4.62; found: C 70.99; H 8.153; N 4.619.

Synthesis of **4:** Small green crystals were obtained from a solution of H_2L and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ /hexane (1/1/1). Elemental analysis (%) calcd for $\text{C}_{36}\text{H}_{52}\text{N}_2\text{O}_2\text{CuCl}_2$: C 63.66, H 7.72, N 4.12; found: C 63.29, H 7.596, N 4.07.

Typical recovery of reaction products:^[12] compound **4** (0.350 g, 0.514 mmol) was dissolved in CH₃OH/CH₃CN (1:1) and kept standing for a few weeks at room temperature. The green crystals which separated from the reaction mixture were collected, and the brown filtrate was evaporated in vacuo. The residue was dissolved in concentrated aqueous NH₃ (10 mL) and extracted with CHCl₃ (4 × 10 mL). The combined organic fractions were washed with concentrated aqueous NaCl (3 × 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to leave a brown oil. Compounds **2** and **3** were separated by column chromatography, and their structures and yields were determined by ¹H NMR. The structure of ligand HL' in **5** was determined by X-ray analysis of **5** and by ¹H NMR after removal of Cu^{II} as described above. Compound **2**: Yield, 15%; ¹H NMR (300 MHz, CDCl₃): δ = 1.33 (s, 9H; (CH₃)₃C), 1.43 (s, 9H; (CH₃)₃C), 7.34 (d, 1H; phenol-H), 7.59 (d, 1H; phenol-H), 9.87 (s, 1H; phenol-OH), 11.64 (s, 1H; CHO). Compound **3**: Yield, 15%; ¹H NMR (300 MHz, CDCl₃): δ = 1.28 (s, 9H; (CH₃)₃C), 1.43 (s, 9H; (CH₃)₃C), 3.93 (s, 2H; CH₂), 3.98 (s, 2H; CH₂), 6.84 (d, 2H; phenol-H), 7.2 (m, 3H; py-H, phenol-H), 7.66 (td, 1H; py-H), 8.58 (d, 1H; py-H). Compound **5**: Yield, 12%; elemental analysis (%) calcd for C₃₅H₅₀N₂O₂CuCl₂: C 63.19, H 7.58, N 4.21; found: C 63.07, H 7.532, N 4.27. HL': ¹H NMR (300 MHz, CDCl₃): δ = 1.11 (s, 9H, (CH₃)₃C), 1.33 (s, 9H, (CH₃)₃C), 1.37 (s, 9H, (CH₃)₃C), 1.47 (s, 9H, (CH₃)₃C), 3.47 (q, 2H; CH₂), 3.73 (q, 2H; CH₂), 6.27 (d, 1H; phenol-H), 6.90 (d, 1H; phenol-H), 7.14 (dd, 1H; py-H), 7.16 (d, 1H; phenol-H), 7.19 (d, 1H; py-H), 7.37 (d, 1H; phenol-H), 7.60 (td, 1H; py-H), 8.52 (d, 1H; py-H).

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- [9] X-ray crystal structure determination: The X-ray diffraction data were collected at 295 K with a Rigaku AFC-5R four-circle diffractometer using graphite-monochromated CuK α radiation ($\lambda = 1.54178 \text{ \AA}$). Crystal data for **1**: Formula C₇₆H₁₀₈N₄O₉Cu₂, $M_w = 1348.80$, crystal size: $0.3 \times 0.1 \times 0.1 \text{ mm}$, monoclinic, space group $P2_1/n$, $a = 26.782(4) \text{ \AA}$, $b = 10.672(2) \text{ \AA}$, $c = 26.819(3) \text{ \AA}$, $\beta = 94.33(1)^\circ$, $V = 7643(2) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.352 \text{ g cm}^{-3}$, $\mu = 12.39 \text{ cm}^{-1}$, $F(000) = 3112.00$, 13682 independent reflections, 8230 reflections used, 821 parameters, $R = 0.074$, $R_w = 0.085$ ($I > 2.00\sigma(I)$). In the asymmetric unit there were two crystallographically independent complex molecules, which have very similar structures and may be regarded as mirror images arising from the coordination of the tertiary amine nitrogen to Cu^{II}. Crystal data for **4**: Formula C₃₇H₅₆N₂O₃Cl₂Cu, $M_w = 711.31$, crystal size: $0.17 \times 0.10 \times 0.06 \text{ mm}$, triclinic, space group $P\bar{1}$, $a = 13.865(4) \text{ \AA}$, $b = 16.048(5) \text{ \AA}$, $c = 10.378(5) \text{ \AA}$, $\alpha = 98.69(5)^\circ$, $\beta = 104.67(4)^\circ$, $\gamma = 112.64(2)^\circ$, $V = 1980(1) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.193 \text{ g cm}^{-3}$, $\mu = 22.80 \text{ cm}^{-1}$, $F(000) = 758.00$, 5791 independent reflections, 5791 reflections used, 407 parameters, $R = 0.083$, $R_w = 0.128$ ($I > 2.00\sigma(I)$). Crystal data for **5**: Formula C₃₅H₅₀N₂O₂Cl₂Cu, $M_w = 665.24$, crystal size: $0.20 \times 0.15 \times 0.03 \text{ mm}$, monoclinic, space group $P2_1/a$, $a = 18.054(4) \text{ \AA}$, $b = 12.712(7) \text{ \AA}$, $c = 18.314(4) \text{ \AA}$, $\beta = 116.00(1)^\circ$, $V = 3783(2) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.168 \text{ g cm}^{-3}$, $\mu = 23.35 \text{ cm}^{-1}$, $F(000) = 2256.00$, 5357 independent reflections, 4926 reflections used, 380 parameters, $R = 0.069$, $R_w = 0.107$ ($I > 2.00\sigma(I)$). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-136595, -136596, and -136821. 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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Reaction of Organic Selenocyanates with Hydroxides: The One-Pot Synthesis of Dialkyl Diselenides from Alkyl Bromides

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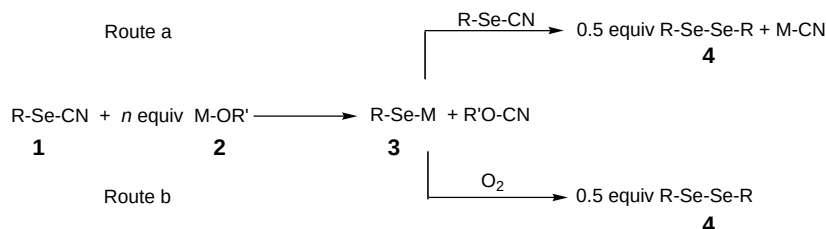
Dedicated to Professor Bernd Giese
on the occasion of his 60th birthday

Since the beginning of organoselenium chemistry, organoselenocyanates have occupied a privileged position.^[1] They are easily prepared, are stable to atmospheric conditions, and have widely contributed to the use of organoselenium compounds in synthesis due to their exceptional versatility.^[1] They react with a large variety of compounds, producing chemoselectively, in a single step and in almost quantitative

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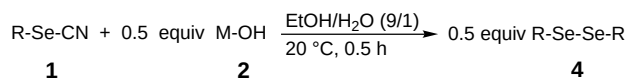
yields, selenolates (NaBH_4 ,^[2a-d, 3c,d] SmI_2 ,^[2e-g] Bu_4NF ,^[2g]), diselenides (NaBH_4 , MH),^[3] selenols (H_3PO_2),^[4] selenenyl halides or trihalides (halogens)^[5] as well as organic selenides (alcohols and Bu_3P ,^[1f,g, 6] organometallic compounds^[7]).

The reaction of organoselenocyanates with hydroxides^[8] and alkoxides^[9] has been documented over the last 110 years, but the results lack consistency since, depending upon the case, either selenolates **3**^[8a-c] or diselenides **4** are produced^[8d-k, 9] (Scheme 1). It is furthermore impossible to determine if the diselenides **4** are directly formed (route a)^[8d-f] or if



Scheme 1. Reaction of organic selenocyanates with alkaline hydroxides and alkoxides. $n = 0.5$ (route a), 1 (route b); R = Ar, Alk, R' = Me, Et, M = Na, K.

they result from oxidation of the initially formed selenolates **3**, fortuitously by air during or after the reaction^[8g-i] or intentionally by bubbling of oxygen through the medium^[8j,k] (route b). Although both conditions produce the diselenides **4**, the amount of reagent **2** required would be different



(0.5 equiv for route a and 1 equiv for route b) as are the nature and amount of the by-products formed (0.5 equiv each of HOCN and MCN for route a and 1 equiv of HOCN for route b).

The experimental conditions have not always been properly achieved and/or described. In some cases oxygen had been improperly used because the diselenide was already in the reaction medium, and oxidation of the presumed selenolate was useless. It is therefore surprising that the statement of Paulmier in his 1986 review article that “Alkaline hydrolysis of selenocyanates has never been clearly explained”^[10] has not attracted much attention.

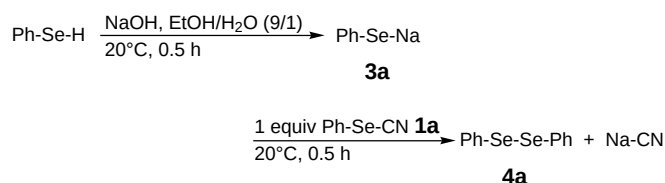
We report here our results in this field which clearly delineate the scope and limitations of the reactions involving hydroxides and phenyl or alkyl selenocyanates (see the Experimental Section). The reactions were carried out with

different amounts of reagent since formally one equivalent of hydroxide is required for the synthesis of the selenolate, whereas only 0.5 equiv is needed to produce the diselenide. It was not clear at that stage if the use of 0.5 equiv of hydroxide would produce 0.5 equiv of the selenolate besides unchanged selenocyanate or if the former would react with the latter to produce the diselenide.

To clarify this point we treated sodium phenylselenolate (**3a**) with one molar equivalent of phenyl selenocyanate (**1a**) in ethanol/water (9/1) at 20 °C. The corresponding diphenyl diselenide (**4a**) was produced in 93 % yield (Scheme 2). Successful formation of a selenolate would therefore require not only that at least an equimolecular amount of hydroxide is used, but also that the hydroxide reacts faster than the resulting selenolate with the selenocyanate.^[11]

We allowed selenocyanates **1** to react with 0.5 equiv of metal hydroxide in ethanol/water and found that they produce under mild conditions (20 °C, 0.5 h) the corresponding diselenides **4** in very high yields (82–97 %, Table 1).^[11, 12]

We ascertained the presence of sodium cyanide in the reaction mixture from butyl selenocyanate and NaOH (entry 2) by ¹³C NMR spectroscopy ($\delta = 165$) and quantified its amount (0.5 equiv).^[13]



Scheme 2. Synthesis of sodium phenylselenolate (**3a**) and subsequent reaction with phenyl selenocyanate (**1a**).

Table 1. Reaction of organic selenocyanates with 0.5 equiv of alkaline hydroxide.

Entry	R	1	Hydroxide	Product (yield [%])
1	Ph	1a	KOH	4a (90)
2	Ph	1a	NaOH	4a (86)
3	Ph	1a	LiOH	4a (85)
4	Bu	1b	KOH	4b (97)
5	Bu	1b	NaOH	4b (82)
6	Bu	1b	LiOH	4b (96)
7	<i>i</i> Pr	1c	NaOH	4c (82)

We also observed that the reactions carried out with one or more equivalents of hydroxide provide, depending upon the nature of the selenocyanate, either selenolates (from **1a** (Table 2, entries 1–3), often contaminated with **4a**) or

Table 2. Reaction of organic selenocyanates with at least one equivalent of alkaline hydroxide.

Entry	R	1	<i>n</i>	Hydroxide	<i>T</i> [°C]	<i>t</i> ¹ [h]	<i>t</i> ² [h]	Yield of 4 [%]	Yield of 6 [%]	Recovered 5 [%]
1	Ph	1a	1	KOH	20	1	20	29	70	29
2	Ph	1a	1	NaOH	20	0.5	20	0	90	0
3	Ph	1a	1	LiOH	80	2	19	35	41	57
4	Bu	1b	5	KOH	80	2	2	71	14	53
5	Bu	1b	5	NaOH	80	3	2	74	14	82
6	<i>i</i> Pr	1c	1	NaOH	80	1	20	80	5	77
7	PhCH ₂	1d	5	KOH	20	0.5	23	75	9	64

Synthesis of **4** from **1** and metal hydroxide (0.5 equiv): The organic selenocyanate **1** (2 mmol) and ethanol (5 mL) were placed in a 25-mL, two-necked flask fitted with a magnetic stirrer, a septum, and an argon-filled balloon. The hydroxide (1 mmol in 0.25 mL of water) was introduced by syringe. The resulting mixture was stirred at 20 °C for 0.5 h and then hydrolyzed (10 mL of water) and extracted with diethyl ether (2 × 20 mL). The ether fractions were combined, washed with water (2 × 20 mL), and dried over MgSO₄. The solvent was evaporated in vacuo. The crude mixture was fractionated by column chromatography on silica gel using pentane as eluent.

Synthesis of **6a** from **1a** and NaOH (1 equiv): Phenyl selenocyanate (**1a**, 2 mmol) and ethanol (5 mL) were introduced into a 25-mL, two-necked flask fitted with a magnetic stirrer, a septum, and an argon-filled balloon. Sodium hydroxide (2 mmol in 0.5 mL of water) was added by syringe. The resulting mixture was stirred for 2 h at 20 °C. *n*-Decyl bromide (**5**, 2 mmol in 1 mL of ethanol) was added. The mixture was stirred for 20 h at 20 °C and then hydrolyzed (10 mL of water) and extracted with diethyl ether (2 × 20 mL). The ether fractions were combined, washed with water (2 × 20 mL), and dried over MgSO₄. The solvent was evaporated in vacuo. The crude mixture was fractionated by column chromatography on silica gel using pentane as eluent to provide **6a** in 90 % yield.

One-pot synthesis of **4b** from *n*-butyl bromide and potassium selenocyanate: KSeCN (2 mmol) and DMF (2 mL) were introduced into a 25-mL, two-necked flask fitted with a magnetic stirrer, a septum, and a condenser connected to an argon-filled balloon. The solution was heated to 75 °C, and *n*BuBr (2 mmol in 1 mL of DMF) was added. The resulting mixture was stirred for 3 h at 75 °C. K₂CO₃ (2 mmol in 0.8 mL of water) was slowly introduced by syringe. The resulting mixture was stirred for 3 h at 75 °C and then hydrolyzed (10 mL of water) and extracted with diethyl ether (2 × 20 mL). The ether fractions were combined, washed with water (2 × 20 mL), and dried over MgSO₄. The solvent was evaporated in vacuo. The crude mixture was fractionated by column chromatography on silica gel using pentane as eluent to provide **4b** in 71 % yield.

One-pot synthesis of **4b** from *n*-butyl bromide and elemental selenium. KCN (1 mmol) and DMF (3 mL) were introduced into a 25-mL, two-necked flask fitted with a magnetic stirrer, a septum, and a condenser connected to an argon-filled balloon. The solution was heated to 75 °C. Elemental selenium (2 mmol) was added and the mixture stirred for 0.25 h at 75 °C. Then *n*BuBr (2 mmol in 1 mL of DMF) and K₂CO₃ (2 mmol in 0.5 mL of water) were introduced. The resulting mixture was stirred for 20 h at 75 °C and then hydrolyzed (10 mL of water) and extracted with diethyl ether (2 × 20 mL). The ether fractions were combined, washed with water (2 × 20 mL), and dried over MgSO₄. The solvent was evaporated in vacuo. The crude mixture was fractionated by column chromatography on silica gel using pentane as eluent to provide **4b** in 75 % yield.

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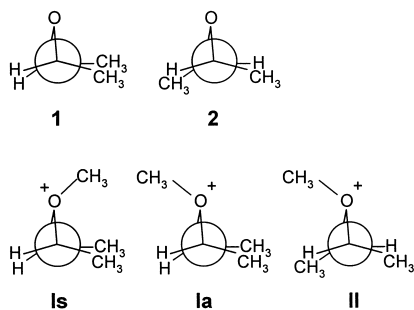
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Eliminative Ring Opening of Oxiranium Ions in the Gas Phase**

Gabriele Renzi, Graziella Roselli, Felice Grandinetti, Antonello Filippi, and Maurizio Speranza*

When a base interacts with a substrate containing a nucleofuge,^[1] two competing reactions generally take place: 1,2-elimination and nucleophilic substitution.^[2] Exceptions to this dual behavior are rare in solution.^[3] One such exception concerns the ring opening of three-membered heterocycles in acidic solutions, which normally proceeds by nucleophilic displacement and not by 1,2-elimination.^[4] This is due to the pronounced s character of the carbon atoms of the three-membered ring, which minimizes repulsive nonbonding interactions in the substitution transition structure (TS).^[5] Eliminative ring cleavage becomes observable to a limited extent in three-membered cycles only when the competing substitution is sterically inhibited, as in the reaction between *cis*-1,1,2,3-tetramethylaziridinium ions and *N*-ethyldiisopropylamine (Hünig's base).^[5a,b, 6] The bulky Hünig's base interacts only with the exocyclic hydrogen atoms of the encumbered solvated ion,^[6] so that small amounts of the corresponding Hoffmann olefin, *N,N*-dimethyl-3-aminobut-1-ene, are exclusively formed. No examples of eliminative ring cleavage of three-membered heterocycles following the Saytzeff rule have been presented to date.

Here we provide the first experimental evidence for the occurrence of this unprecedented elimination reaction in the gas phase.^[7] The reaction is induced by the attack of a powerful base, $N(CH_3)_3$, on the ions **Is/Ia** and **II**. Epimers *cis*-

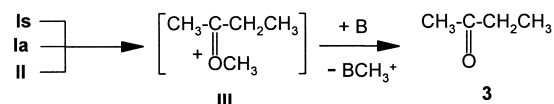


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Is/Ia and the *trans* isomer **II**^[8] are generated in the gas phase by methylation of *cis*- (**1**) and *trans*-2,3-butene oxide (**2**) with $(CH_3)_2F^+$ ions,^[9] which are formed in known yields by γ -radiolysis of CH_3F (760 torr, ^{60}Co source). If not rapidly neutralized by collision with a gaseous base, ions **Is/Ia** and **II** tend to rearrange exclusively to the more stable open-chain isomer **III**, which eventually neutralizes to ketone **3** (Scheme 1).^[9, 10]



Scheme 1. B = base.

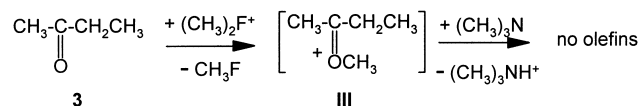
In the presence of $N(CH_3)_3$ (proton affinity (PA) = 226.8 kcal mol⁻¹),^[11] **3** is formed along with appreciable amounts of the *E* and *Z* isomers of 2-methoxy-2-butene (**4E** and **4Z**, see Scheme 3; Table 1).^[12] No production of 3-methoxy-1-butene is observed. Formation of alkenes **4E** and **4Z** requires the

Table 1. Yields of the products from the gas-phase attack of $(CH_3)_3N$ on **Is/Ia** and **II**, formed by O-methylation of **1** and **2** (see Schemes 1 and 3).^[a]

Substrate	Amount [torr] ($CH_3)_3N$	T [°C]	Yields [%]			4E:4Z	$G_{(M)}^{[b]}$
			4E	4Z	3		
1 , 1.61	1.64	37	19.0	6.2	74.8	3.07	0.24
1 , 1.49	1.54	60	21.4	4.2	74.4	5.07	0.31
1 , 1.53	1.59	80	25.9	2.0	69.2	12.80	0.49
1 , 1.58	1.62	100	28.3	1.0	70.7	27.60	0.49
2 , 1.47	1.53	37	14.9	6.4	78.7	2.31	0.25
2 , 1.53	1.61	60	17.2	5.8	77.0	3.00	0.33
2 , 1.57	1.64	80	25.0	5.8	69.2	4.28	0.43
2 , 1.46	1.52	100	26.7	5.1	68.2	5.27	0.43

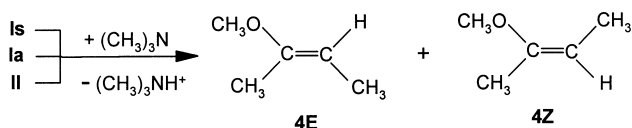
[a] Bulk gas: 760 torr CH_3F , 10 torr O_2 . Radiation dose 2×10^4 Gy (dose rate 1×10^4 Gy h⁻¹). [b] Absolute yields of products, expressed as their $G_{(M)}$ values (the number of molecules *M* produced per 100 eV of energy absorbed by the gaseous mixture). Each value is the average of several determinations, with an uncertainty level of about 5%. The detection limit for $G_{(M)}$ is 2×10^{-3} .

presence of both **Is/Ia** (or **II**) and $N(CH_3)_3$. In fact, no olefins are recovered: 1) in the gaseous mixtures if they are not submitted to irradiation; 2) in the irradiated mixtures if $N(CH_3)_3$ is replaced by the milder base NH_3 (PA(NH_3) = 204.0 kcal mol⁻¹);^[11] and 3) in the irradiated mixtures if the **Is/Ia** or **II** intermediates are replaced by ion **III**, which is directly formed in the same medium upon methylation of **3** by $(CH_3)_2F^+$ (Scheme 2).



Scheme 2.

The last point (3) excludes that olefins **4E** and **4Z** arise from deprotonation of **III**, which is an abundant intermediate in the irradiated systems of Table 1, by $N(CH_3)_3$. This is testified by the high yield of butanone **3**. On these grounds, olefins **4E** and **4Z** are thought to arise from exothermic eliminative ring opening (Scheme 3).^[13]



Scheme 3.

The exclusive recovery of the Saytzeff olefins **4E** and **4Z**, coupled with the absence of the Hoffmann isomer 3-methoxy-1-butene, indicate that in the gas phase $\text{N}(\text{CH}_3)_3$ abstracts selectively the most acidic ring protons of **Ia**, **Ib**, and **Ic**. Irrespective of the structure of the starting epoxide, whether **1** or **2**, olefin **4E** invariably prevails over the more stable isomer **4Z**^[14] to an extent which increases with reaction temperature (Table 1). This implies that the reaction in Scheme 3 is 1) kinetically controlled under all conditions and 2) governed by stereoelectronic factors, despite the quasi-orthogonality of the $\text{C}_\beta\text{--O}$ and $\text{C}_\alpha\text{--H}$ bonds involved in the process.^[15]

Quantum-chemical calculations at the B3LYP/6-31G* level of theory have been employed to gather information about the mechanism of the reaction in Scheme 3.^[13] Since the molecular complexity of the species involved makes the accurate theoretical description of this reaction computationally unfeasible, we limited our analysis to a strictly related model reaction, that is, the NH_3 -induced eliminative ring opening of O-methylated ethene oxide (**IV**) to yield NH_4^+ and methyl vinyl ether (**5**). The relevant free energy profile (298 K) is illustrated in Figure 1 along with the relevant isomer adducts and transition states. The reported energetics are not appreciably affected by upgrading the level of the calculation to B3LYP/6-31+G(d,p).

Ion **IV** interacts with ammonia to give two isomer adducts, **IVs** and **IVa**, which can interconvert either by O^+ epimerization through the **EP** TS or by backdissociation (Figure 1). Intrinsic reaction coordinate (IRC) calculations indicate that ring opening of **IVs** and **IVa** leads to complex **V** via the **SS** and **SA** (from **IVs**) and **AA** and **AS** TSs (from **IVa**). This process is characterized by extensive $\text{C}_\beta\text{--O}$ bond cleavage, negligible C_αH proton transfer to ammonia, and partial rotation of the $\text{C}_\beta\text{H}_2^+$ moiety either clockwise (**AA** and **SA**) or

counterclockwise (**SS** and **AS**). Evolution of these TSs to product **V** requires alignment of the empty orbital of the $\text{C}_\beta\text{H}_2^+$ rotor with the vicinal $\text{C}_\alpha\text{--H}$ bond prior of transfer of the proton to NH_3 . Rotation may be assisted by the CH_3O lone pair, as in the paths involving **SA** and **AS**, or may not, as in those involving **SS** and **AA**. The lower energy levels of the **SA** and **AS** TSs are due to the orbital arrangement, which is reminiscent of that of the concerted *anti* and *syn* E2 eliminations. No similar orbital arrangements is present in the higher energy **SS** and **AA** TSs.

The above picture can be qualitatively extended to the more exothermic process shown in Scheme 3.^[13] Interaction of $(\text{CH}_3)_3\text{N}$ with the ring hydrogen atoms of **II** is expected to generate the quasi-resonant *syn-IVs*^t and *anti-IVa*^t adducts.^[8] Since the TSs for ring opening of these species involve the formation of the secondary $\text{CH}_3\text{C}_\beta\text{H}^+$ moiety, the magnitude of the relevant energy barriers is expected to be substantially lower than those reported in Figure 1. As a consequence, ring opening of **IVs**^t and **IVa**^t is allowed to compete with interconversion (**IVs**^t $\leftrightarrow$ **IVa**^t).^[16] Therefore, the **IVs**^t and **IVa**^t adducts are formed in comparable proportions, which are not

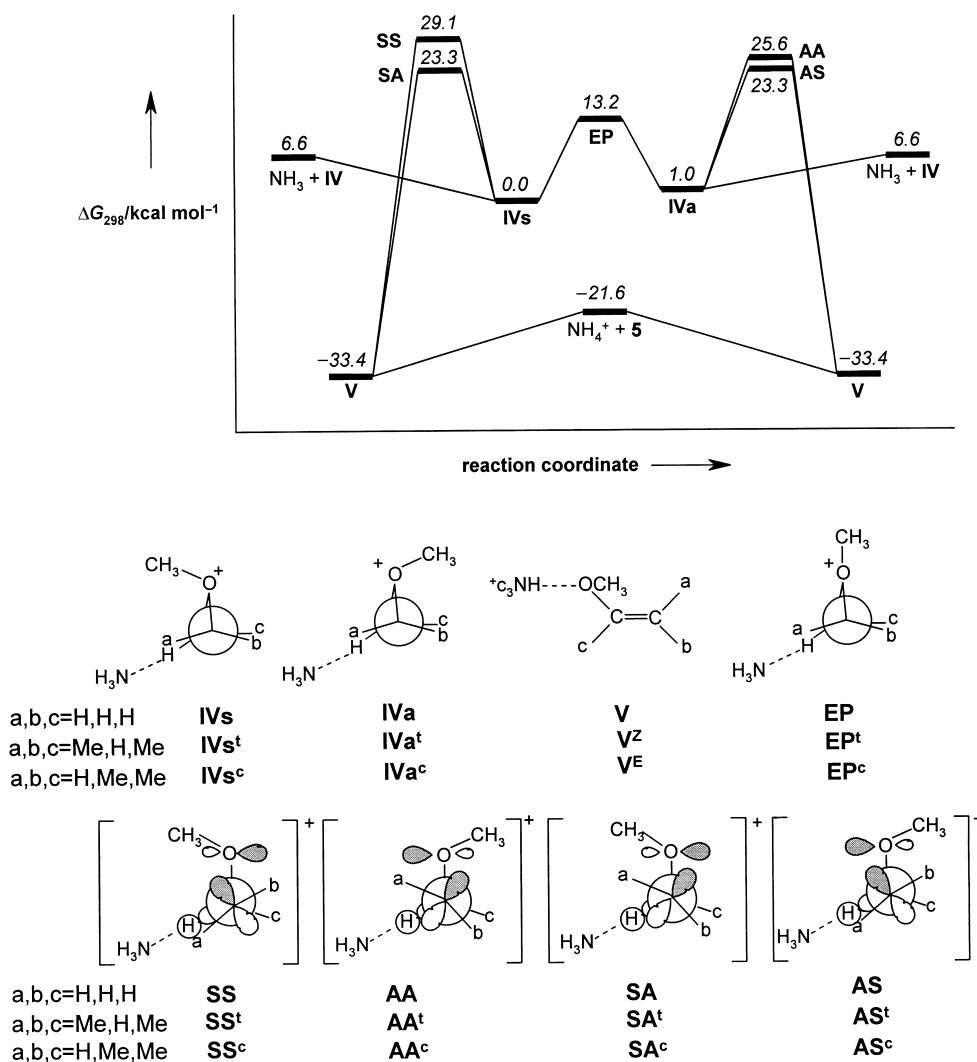


Figure 1. Top: Profile of the free energy (ΔG_{298}) of the NH_3 -induced eliminative ring opening of O-methylated ethene oxide as calculated at the B3LYP/6-31G* level of theory. The relative energies are shown in italics. Bottom: Schematic representation of the isomer adducts and transition states involved.

significantly affected by temperature.^[17] According to Figure 1, the ring opening of **IVs'** and **IVa'** should involve very similar free energies of activation corresponding to TSs **SA'** and **AS'**, respectively. Thus, a quasi-equimolar mixture of isomers of 2-methoxy-2-butene should be formed (**SA'** → **V^Z** → **4Z** + **HNMe₃⁺**; **AS'** → **V^E** → **4E** + **HNMe₃⁺**). As a matter of fact, formation of the **4E** isomer always predominates (Table 1). A plausible rationale for this lack of balance may be found in the presence of repulsive interactions in **SA'** and **AA'** between the OCH₃ group and the CH₃ moiety of the CH₃C_βH⁺ rotor, which may increase the energy barriers corresponding to **SA'** and **AA'** relative to those of **SS'** and **AS'**. In fact, no similar repulsive interactions operate in these latter TSs.

A somewhat different picture arises for the attack of (CH₃)₃N on the ring hydrogen atoms of **Is** and **Ia**. The attack gives rise to the *syn*-**IVs'** and the *anti*-**IVa'** adducts, which may interconvert only through the **EP'** TS. Since the *syn*-**IVs'** adduct is appreciably more stable than the *anti*-**IVa'** adduct,^[8] the relative population of the adducts leans more and more toward the *syn* complex as the reaction temperature increases.^[17] If, as assumed above, repulsive interactions operate between the OCH₃ group and the CH₃ moiety of the CH₃C_βH⁺ rotor, the energy barriers corresponding to **SS'** and **AS'** should increase relative to those of **SA'** and **AA'**. Thus, the energy difference between **SA'** and **SS'** should increase and that between **AA'** and **AS'** should decrease or even invert. As a result of the latter, ring opening of the *anti*-**IVa'** adduct is expected to lead to comparable proportions of **4E** and **4Z** or even to predominance of **4E** over **4Z** (**AS'** → **V^Z** → **4Z** + **HNMe₃⁺**; **AA'** → **V^E** → **4E** + **HNMe₃⁺**). Instead, ring opening of the *syn*-**IVs'** adduct would mostly lead to **4E** (**SA'** → **V^E** → **4E** + **HNMe₃⁺**). This may account for both the high selectivity of **4E** over **4Z** for the eliminative ring opening of **1**, as compared to that of **2**, and the pronounced positive temperature dependence of this selectivity (Table 1).^[17]

In conclusion, it has been demonstrated that eliminative ring opening of oxiranium ions is a relatively facile process in the gas phase. The reaction involves preliminary ring opening of the charged moiety favored by interaction of its acidic protons with the base. A combination of stereoelectronic and conformational factors accounts for the high stereoselectivity of the reaction.

Experimental Section

Quantum-chemical calculations were performed using a IBM RISC/6000 version of the GAUSSIAN94 set of programs.^[18] The 6-31G* basis set was employed for all the atoms to optimize the geometries of the investigated species at the density functional level of theory, using the B3LYP functional which combines Becke's three-parameter hybrid description of exchange and the correlation functional of Lee, Yang, and Parr.^[19] The total energies were refined by single-point calculations at the B3LYP/6-31 + G(d,p) level of theory. The correspondence between the various transition structures and the energy minima of Figure 1 was ascertained by intrinsic reaction coordinate (IRC) calculations.^[20]

The gaseous mixtures of Table 1 were prepared by conventional vacuum techniques.^[9] The irradiation was carried out at constant temperature (37, 60, 80, and 100 °C) in a 220 Gammacell (Nuclear Canada Ltd.) to a total dose of 2 × 10⁴ Gy at a rate of 1 × 10⁴ Gy h⁻¹, as determined by a

neopentane dosimeter. The irradiated mixtures were analyzed using a Hewlett-Packard 5890/II gas chromatograph equipped with a flame ionization detector. The following columns were employed: a) a 30-m (0.25 mm inner diameter) Vocol™ fused silica capillary column operated at 35–150 °C (4 °C min⁻¹); b) a 100-m (0.25 mm inner diameter) Petrocol™ fused silica capillary column operated at 35–200 °C (2 °C min⁻¹); c) a 30-m (0.32 mm inner diameter) Supelcowax fused silica capillary column operated at 50–230 °C (4 °C min⁻¹). The products were identified by coincidence of their retention volumes with those of authentic reference compounds, and their identity was confirmed by gas liquid chromatography/mass spectrometry with a Hewlett-Packard 5971A mass spectrometer. The yields were measured from the areas of the corresponding eluted peaks, using the internal standard calibration method.

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- [13] Thermochemical data of the reaction in Scheme 3 as calculated at the B3LYP/6-31G* level of theory (onium ion, neutral olefin, $-\Delta H_{298} [\text{kcal mol}^{-1}]$): **Ia**, **4E**, 28.5; **Ia**, **4Z**, 30.1; **Is**, **4E**, 32.0; **Is**, **4Z**, 33.6; **II**, **4E**, 29.1; **II**, **4Z**, 30.7. Eliminative ring opening may be accompanied by nucleophilic addition of N(CH₃)₃ to the onium ion with formation of the [Me₃NCHMeCHMeOMe]⁺ intermediate and by nucleophilic transfer of the CH₃ group from the onium ion to N(CH₃)₃ to give back the starting epoxide and N(CH₃)₄⁺ (see the Supporting Information). The hypothesis that olefins **4E** and **4Z** may be formed by elimination of HN(CH₃)₃⁺ from the [Me₃NCHMeCHMeOMe]⁺ intermediate is ruled out by the lack of any detectable products from the [Me₃NCHMeCHMeOMe]⁺ intermediate, which is generated by gas-phase methylation of *threo*-Me₂NCHMeCHMeOMe by (CH₃)₂F⁺ under conditions identical to those of Table 1.
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- [16] Back-dissociation of the hydrogen-bonded adducts opens the way for the competing nucleophilic substitutions mentioned in reference [13], involving reattack of $\text{N}(\text{CH}_3)_3$ at the carbon centers of the freed onium ion. Thus, only a fraction of the back-dissociating hydrogen-bonded adducts collapse again to another hydrogen-bonded adduct.
- [17] Interaction of $(\text{CH}_3)_3\text{N}$ with the ring hydrogen atoms of **II** generates an initial distribution of $[\text{IVa}^*] \approx [\text{IVs}^*]$ which is not far from that corresponding to the thermodynamic equilibrium ($[\text{IVa}^*]_{\text{eq}} \approx [\text{IVs}^*]_{\text{eq}}$). Thus, the slight positive temperature dependence of the **4E:4Z** ratios from **2** reflects the effect of temperature on the ring-opening processes and on the limited $\text{IVs}^* \leftrightarrow \text{IVa}^*$ interconversion. In contrast, interaction of $(\text{CH}_3)_3\text{N}$ with the ring hydrogen atoms of the **Is/Ia** pair generates the corresponding adducts in an initial distribution of $[\text{IVa}^*]$ and $[\text{IVs}^*]$ which is far away from the equilibrium distribution ($[\text{IVs}^*]_{\text{eq}} > [\text{IVa}^*]_{\text{eq}}$). In this case, the steeper positive temperature dependence of the **4E:4Z** ratios from **1** is much more sensitive to the effect of temperature on the $\text{IVa}^* \rightarrow \text{IVs}^*$ conversion, which efficiently competes with the ring-opening reactions.
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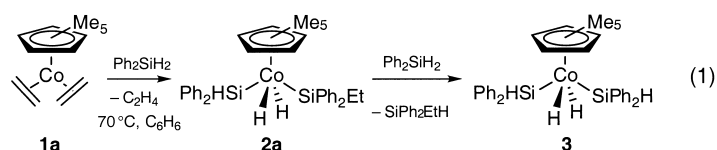
High Oxidation State Organocobalt Complexes: Synthesis and Characterization of Dihydridodisilyl Cobalt(v) Species**

Maurice Brookhart,* Brian E. Grant, Christian P. Lenges, Marc H. Prosenc, and Peter S. White

Recently there has been considerable interest in the organometallic chemistry of late transition metals in high oxidation states. Second- and third-row metals in particular were stabilized in high oxidation states by using organic ligand environments. Certain catalytic reactions mediated by these late metals were proposed to occur through high oxidation

state intermediates, as opposed to the traditionally formulated redox pairs.^[1–4] Some of the most thoroughly investigated examples in this class are the high oxidation state neutral iridium(v) and rhodium(v) complexes studied initially by Maitlis et al. such as $[(\text{C}_5\text{Me}_5)\text{IrMe}_4]$,^[5] $[(\text{C}_5\text{Me}_5)\text{Ir}(\text{H})_2(\text{SiR}_3)_2]$, and $[(\text{C}_5\text{Me}_5)\text{Rh}(\text{H})_2(\text{SiR}_3)_2]$ ^[6–10] and the Ir^{v} complex cation $[(\text{C}_5\text{Me}_5)\text{IrMe}_3\text{L}]^+$ reported later by Bergman and Aliamo.^[11] Higher oxidation states of first-row metals have been discussed as reactive intermediates, but isolated examples are rare.^[12] We showed that cationic cobalt(III) alkyl complexes $[(\text{C}_5\text{Me}_5)\{\text{P}(\text{OMe})_3\}\text{CoR}]^+$ are olefin hydrosilylation catalysts and must proceed through the Co^{v} intermediate $[(\text{C}_5\text{Me}_5)\{\text{P}(\text{OMe})_3\}\text{Co}(\text{R})(\text{H})(\text{SiR}_3)]^+$ or the Co^{III} intermediate $[(\text{C}_5\text{Me}_5)\{\text{P}(\text{OMe})_3\}\text{Co}(\text{R})(\eta^2\text{-H-SiR}_3)]^+$.^[13, 14] Here we report the synthesis and X-ray crystallographic characterization of a bis-hydrido bis-silyl cobalt(v) complex.

For cobalt-mediated bond-activation reactions we have used olefin complexes of the type $[(\text{C}_5\text{Me}_5)\text{Co}(\text{olefin})_2]$ (**1a**) as catalysts,^[13, 15–17] which provides a source of $[(\text{C}_5\text{Me}_5)\text{Co}]$ through olefin dissociation.^[18] Heating a solution of **1a** in C_6D_6 (olefin = C_2H_4) with 5 equiv of Ph_2SiH_2 (15 min, 70°C) led to a rapid disappearance of starting material and, along with the appearance of ethylene and $\text{Ph}_2(\text{Et})\text{SiH}$, the formation of two products **2a** and **3** in approximately 1:1 molar ratio, as determined by ^1H NMR spectroscopy [Eq. (1)].^[19] Equivalent hydrido ligands and silyl methylene protons support a *trans* configuration of **2a**, while a single set of ^{13}C phenyl signals indicates a *trans* configuration for **3**.



Heating **1a** with an excess of Ph_2SiH_2 (5–10 equiv) in toluene at 85°C for 60 min and removal of volatiles resulted in quantitative formation of **3**. Extraction with pentane and crystallization at -25°C produces white crystals that are stable to air in the solid state and can be stored indefinitely at 20°C in an argon atmosphere. In the temperature range of -80 to 70°C no reactivity or dynamic behavior of **3** was observed by NMR spectroscopy. No exchange or magnetization transfer between the Co-H and the Si-H groups was observed on the NMR timescale, and silicon satellites for the Co-H signals were absent. On the basis of this spectroscopic evidence, the new cobalt silyl hydrido complexes are formulated as rare examples of organocobalt(v) species which contribute to a now complete series of silyl hydride complexes of the type $[(\text{C}_5\text{Me}_5)\text{M}(\text{SiR}_3)_2(\text{H})_2]$ ($\text{M} = \text{Co}, \text{Rh}, \text{Ir}$).^[6–10]

The activation of the Si-H bond is facile in this process, as is suggested by the reactivity of the more labile cobalt(II) precursor $[(\text{C}_5\text{Me}_5)\text{Co}(\text{C}_2\text{H}_5\text{SiMe}_3)_2]$ (**1b**). The reaction of **1b** with Ph_2SiH_2 (15 equiv) in C_6D_6 at 30°C for 10 h gave a reaction mixture consisting of $[(\text{C}_5\text{Me}_5)\text{Co}(\text{SiPh}_2\text{C}_2\text{H}_4\text{SiMe}_3)(\text{SiPh}_2\text{H})(\text{H})_2]$ (**2b**) (70%) and a minor amount of **3**. Heating this reaction mixture at 80°C for 2 h resulted in quantitative formation of **3**. The reaction of Ph_2SiH_2 with

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$\text{C}_2\text{H}_3\text{SiMe}_3$ in the presence of a catalytic amount of **1b** (5 mol %, 50 °C, 24 h) resulted in only 15 % conversion to the hydrosilylation product $\text{Ph}_2\text{Si}(\text{H})\text{CH}_2\text{CH}_2\text{SiMe}_3$. During this process, **1b** is converted to **3**. This indicates that these new cobalt(v) silyl hydrides are not active at 50 °C in the catalytic hydrosilylation of olefins.^[20]

Scheme 1 outlines two possible routes for the formation of **3** from **1a, b**. Since intermediates **2a, b** are precursors to **3**, the mechanism must incorporate hydrosilylation of one of the olefin ligands of **1a, b**. Formation of **5a, b** by oxidative addition of silane to **4a, b** is certainly the first step. Silyl (path a; Scheme 1) or hydride (path b) migration may occur to produce **6a, b** or **7a, b**, respectively, which can both be converted to **9a, b**. Path b for **5b** is consistent with the previously observed regiochemistry of insertion of vinyl-trimethylsilane into a cobalt–hydrogen bond,^[21, 22a] which could be followed by α -elimination and subsequent alkyl–silylene coupling to form **9a, b**.^[22b] Alternatively, it is reasonable to suggest that the bulky SiPh_2H group might migrate to C_β (path a; Scheme 1). Conversion of **7a, b** to **9a, b** may occur via formation of the metallacycle **8a, b**. Oxidative addition of

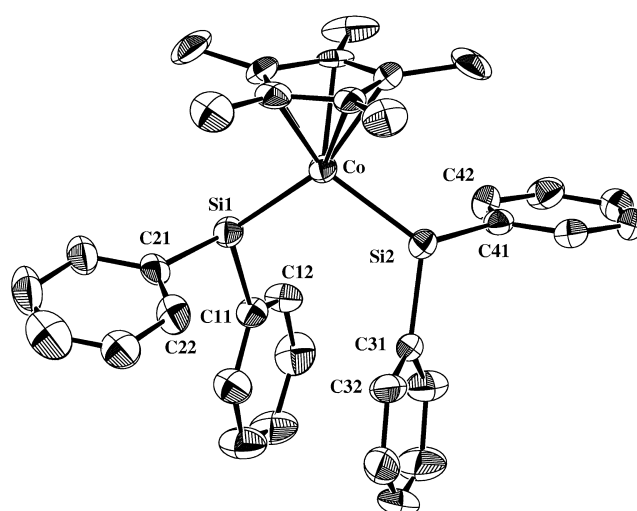
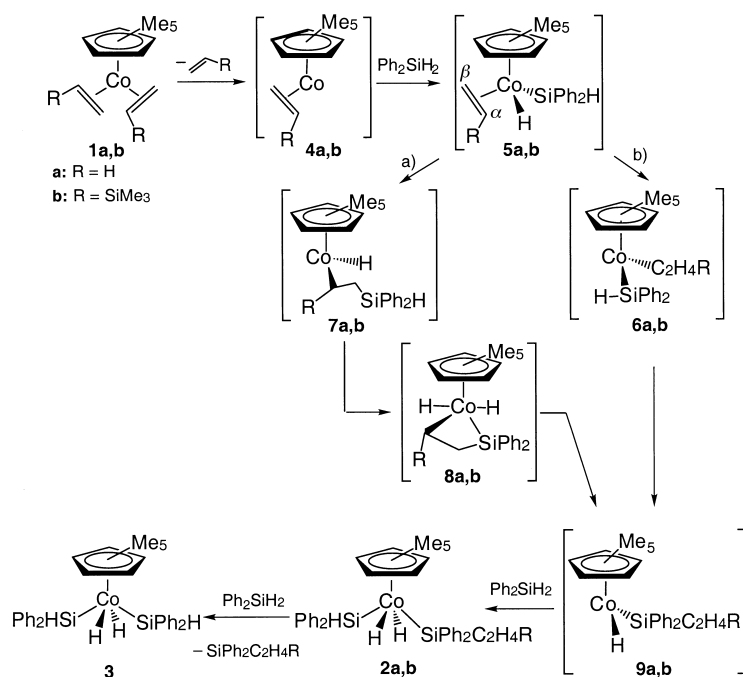


Figure 1. ORTEP diagram of complex **3** (50 % probability ellipsoids). Selected bond lengths [Å] and angles [°]: Co–Si1 2.2492(21), Co–Si2 2.2536(19), Si1–C11 1.894(6), Si1–C21 1.922(7), Si2–C31 1.885(7), Si2–C41 1.895(6); Si1–Co–Si2 107.21(8), Co–Si1–C11 117.58(21), Co–Si1–C21 116.58(21), Co–Si2–C31 119.76(21), Co–Si2–C41 117.04(20).



Scheme 1. Proposed mechanism for formation of **3** from **1a, b**.

Ph_2SiH_2 to **9a, b** results in **2a, b**.^[23] Reductive elimination of $\text{Ph}_2\text{Si}(\text{C}_2\text{H}_4\text{R})(\text{H})$ from **2a, b** followed by oxidative addition of Ph_2SiH_2 produces **3**.

To support the spectroscopic and chemical evidence for these cobalt(v) complexes, single crystals of **3** were subjected to X-ray structural analysis. The unit cell contains four independent molecules, one of which is shown in Figure 1. The X-ray structure verifies the proposed structure for **3**. The hydrido ligands attached to the cobalt center and the H atoms bound to silicon atoms could not be located in the difference Fourier map. Key structural parameters of **3** are listed in Table 1 and compared to those of related Rh and Ir complexes.

The Co–Si distances^[24] are slightly shorter than those of related Co^{III} silyl complexes (2.28–2.30 Å) as expected for the smaller ionic radius of cobalt in the higher oxidation state.^[25, 26] The Si1–Co–Si2 angle in **3** of 107.2° is slightly smaller than the corresponding angle of the rhodium complex, and this could be attributed to the larger nonbonding repulsions in the ligands around the smaller Co center. Especially interesting in **3** is the arrangement of the SiPh_2H group around the cobalt center. To reduce steric crowding, one of the phenyl groups on each Si atom is oriented parallel to the C_5Me_5 ligand. The other two phenyl groups are roughly perpendicular (105°) to the C_5Me_5 ring and parallel to each other with a distance of 3.7 Å between the best planes of the six carbon atoms of each ring. The C–Si–Co angles of 117–120° are significantly larger than 109.5°; we suppose that this also contributes to reduction of nonbonding repulsions around the Co center. Similar large C–Si–Co angles (114–120°) were also found in the calculated structure (see below) in which intermolecular interactions were not taken into account.

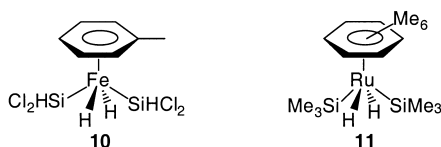
Table 1. Comparison of selected interatomic distances [Å] and bond angles [°] in $[(\text{C}_5\text{Me}_5)\text{M}(\text{H})_2(\text{SiR}_3)_2]$ (M = Rh, Ir and $\text{SiR}_3 = \text{SiEt}_3$; M = Co, $\text{SiR}_3 = \text{SiPh}_2\text{H}$).

	Ir	Rh	Co ^[a]	Co ^[b]
M–Si	2.390(1)	2.379(2)	2.256–2.261 2.243–2.247	2.29 2.28
M–H	1.581(1)	1.594(1)		1.49
Si–C	1.901(2)	1.900(1)	1.880–1.922	1.90
H1–M–H2	99.50(2)	94.84(2)		100
Si1–M–Si2	109.49(6)	107.90(8)	107.2	109
H1...Si1	2.272(2)	2.212(2)		2.24
H2...Si1	2.384(2)	2.336(2)		2.25
H1...H2	2.433(4)	2.328(4)		2.28

[a] Averaged for the four molecules in the unit cell. [b] Data are based on DFT calculations (see text).

To further investigate structural details of complex **3**, density functional theory (DFT) calculations were conducted^[27–30], as were successfully employed for related organometallic complexes.^[31–34] Some geometrical parameters obtained after geometry optimization are listed in Table 1. The main structural features of the calculated geometry of **3** and the X-ray structure of **3** are in good agreement. The Co–Si bond lengths in the calculated structure (Co–Si 2.29 Å) are slightly longer than those observed experimentally (Co–Si 2.26 Å). The pseudo-square-pyramidal structure of the ML₅ complex is clearly evident from the calculation. The calculated H–H distance for complex **3** of 2.28 Å and the H–Si distances of 2.24 and 2.25 Å indicate the complete oxidative addition of the two Ph₂SiH₂ molecules to the cobalt center.^[35]

We compared the Co^V species **3** with other high oxidation state silyl hydrido complexes. Interestingly, the rare iron(IV) complex **10** also has a *trans* configuration around the Fe center.^[36] Complex **11**, an Ru analogue of **3**, was recently reported^[37] and also structurally characterized.



In summary, we have prepared and structurally characterized rare examples of organometallic Co complexes in the formal oxidation state +5. Our DFT calculations fully support the assigned structure and oxidation state of these cobalt complexes. These species are remarkably stable towards reductive elimination, and this is consistent with the well-established ability of silyl and hydrido ligands to stabilize metals in high oxidation states.

Experimental Section

All operations were carried out under an Ar atmosphere. All solvents were degassed and purified by standard methods.

3: Ten equivalents of diphenylsilane were added to a solution of **1a** (0.15 g, 0.6 mmol) in toluene (5 mL). The mixture was stirred for 1 h at 80 °C. After cooling to 20 °C and removal of all volatile materials, the resulting solids were dissolved in pentane and filtered. The clear, pale yellow solution was cooled to –78 °C for 24 h; white crystalline material was obtained (72% yield). Crystals for the X-ray structure analysis were obtained from pentane at –25 °C.

Spectroscopic data for **3**: ¹H NMR (300 MHz, [D₆]benzene, 20 °C) δ = 1.53 (s, 15H, C₅Me₅), 5.92 (s, 2H, Si–H), 7.15 (m, 12H, Ph), 7.71 (m, 8H, Ph) –15.51 (s, 2H, Co–H); ¹³C{¹H} NMR: δ = 95.46 (C₅Me₅), 9.65 (C₅Me₅), 140.90, 136.40, 135.88, 134.99 (Ar); elemental analysis: calcd: H 6.99, C 72.57; found: H 7.11, C 72.32.

Structural data for **3**: crystals from pentane; C₃₄H₃₉Si₂Co, M_r = 562.76; monoclinic, space group C_c; Z = 16; a = 60.673(3), b = 10.0978(5), c = 20.8573(10) Å, β = 109.264(1)°, V = 12063.1(10) Å³; ρ_{calcd} = 1.235 g cm^{–3}; T = –110 °C; 2θ_{max} = 50°; MoKα radiation (λ = 0.71073 Å), 50673 reflections were measured; 21315 unique reflections were obtained, and 14248 of these with I > 3.0σ(I) were used in the refinement; data were collected on a Siemens SMART diffractometer by the Ω scan method. For significant reflections, the merging R value was 0.052; residuals: R_F = 0.046, R_w = 0.054 (significant reflections); GOF 1.42. 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-136182. 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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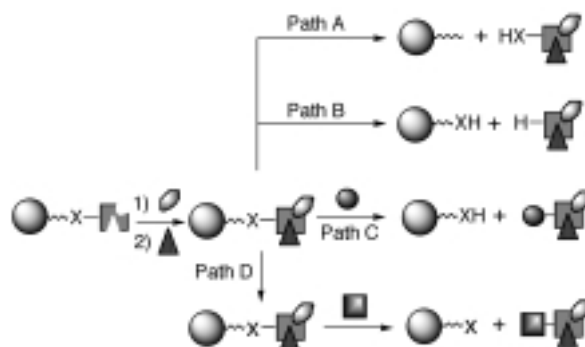
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Traceless, Solid-Phase Synthesis of Biarylmethane Structures through Pd-Catalyzed Release of Supported Benzylsulfonium Salts**

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Solid-phase synthesis (SPS) has attracted much attention from the scientific community during the past decade, particularly by pharmaceutical companies in their race to speed up drug discovery. Solid-phase chemistry evolved from peptide chemistry and gradually became a field on its own in chemistry.^[1] Multi-step processes were automated in a peptide-like fashion, and gave birth to the so-called high-throughput synthesis (HTS).

Under this impulse, new tools for SPS were rapidly developed, for example, new generations of robots and synthesizers, resins, linkers, reactions, and building blocks. However, most of the chemistry performed derives from solution and peptide synthetic studies and do not make full benefit of the use of the solid-support technique. In particular, the most frequently used linkers were designed for peptide-like synthesis. Substrates are therefore linked to the solid support through either an ester, amide, or ether bond. Thus, the cleaved products contain an acid, amide, or hydroxyl residue, respectively, at the former linkage site (Scheme 1, path A).^[2]



Scheme 1. Anchoring–cleavage strategies used in SPS.

To avoid a residual functionality on the cleaved product, traceless cleavage strategies were developed (Scheme 1 path B).^[3] These strategies result in the formation of a carbon–hydrogen or heteroatom–hydrogen bond and often rely on cyclization/cleavage or *ipso*-aromatic-substitution reactions.^[4]

Recently developed synthetic procedures for SPS have allowed the introduction of diversity concomitantly with the release of the target compound (Scheme 1, path C).^[5] These advantageous double transformations are generally achieved through nucleophilic cleavage. The resin is thus used both as a protecting group during all preliminary SPS steps, and as a leaving group during the cleavage. These two properties, stability during SPS and reactivity towards cleavage, are somewhat antinomic. The linkages so far reported for such functionalizing cleavage suffer from an enhanced reactivity that forbids the use of many reaction conditions during the SPS sequence.

To overcome this drawback a tether that is stable during SPS steps but becomes reactive after selective activation is used (Scheme 1, path D). An example of such a strategy is the safety-catch linker of Kenner et al.,^[6] which is unreactive towards nucleophiles as such, but becomes electrophilic upon activation with diazomethane. Other linkers such as the REM or hydrazide linkers were recently developed based on the same principle.^[7] Although they allow efficient cleavage, they are highly specific and can not be used generally.

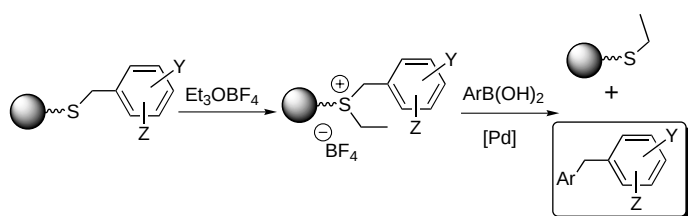
To the best of our knowledge, no strategy so far reported for the safety-catch linkers enables concomitant formation of a carbon–carbon bond and functionalization within the cleavage step. During the course of our study on the SPS of

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biaryl methane compounds, we were challenged by the problem of attachment and traceless release of these structures. Herein we describe an efficient anchoring/activation/cleavage sequence for traceless, solid-phase synthesis of biaryl methane derivatives. Of particular interest is that, in contrast to biphenyl, biaryl methane structures are rarely found in pharmaceutical compounds, which makes this process attractive for the preparation of original libraries.

A functional arene scaffold is linked to the resin through a benzylic carbon–sulfur bond. This C–S bond is known to be stable under many reaction conditions classically used in SPS, namely acidic, basic, nucleophilic, mild electrophilic, and oxophilic conditions. The activation step consists of the alkylation of the sulfur atom leading to a sulfonium salt. Cleavage from the resin is carried out subsequently by treatment of the resulting supported sulfonium salt through palladium catalysis in the presence an aryl boronic acid. This key reaction allows both the release and the synthesis of the biaryl moiety by formation of a carbon–carbon bond (Scheme 2).



Scheme 2. Coupling–release strategy, which relies on a sulfur/sulfonium switch. Y, Z = functional groups or building blocks.

Very few examples of the use of sulfonium salts as appropriate substrates for Pd-catalyzed cross-coupling reactions are reported in the literature. A recent study performed in the solution phase has demonstrated that aryl- and benzyl-substituted cyclic tetramethylenesulfonium salts can undergo a coupling reaction with boronic acids.^[8] However, no mention was made of the relative ease of palladium insertion in the aryl versus the benzyl bond and on the reactivity of acyclic sulfonium salts. Since cyclic tetramethylenesulfonium salts are prepared in one step from a thiol and 1,4-dibromobutane, this sulfonium structure could not be used in the envisioned solid-support sequence. Therefore, before running our strategy, we first carried out a series of experiments to develop and understand the chemistry of acyclic sulfonium salts. To determine a general relative reactivity of aryl-, benzyl-, and alkyl–sulfur bonds towards Pd-catalyzed cross-coupling, several sulfonium salts were synthesized and tested in solution.^[9] The most representative results are summarized in Table 1.

The phenyltetramethylenesulfonium salt (entry 1) underwent efficient Pd-catalyzed cross-coupling to give biphenyl in 85% yield, as described.^[8] When the cyclic phenylsulfonium structure was replaced by an acyclic one, namely, homobenzyl and ethyl (entry 2), no coupling reaction was observed. Only partial dealkylation by loss of the ethyl group occurred. Dealkylation of a sulfonium salt has already been reported on a solid support.^[10] Interestingly, the sulfonium salt bearing

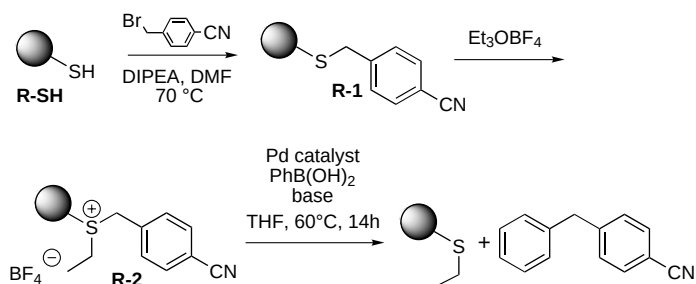
Table 1. Relative reactivity of different carbon–sulfur bonds towards Pd-catalyzed cross coupling with phenyl boronic acid.

$$\text{X}^{\ominus} \text{R}^1 \text{R}^2 \text{S}^{\oplus} \text{R}^3 \xrightarrow[\text{[Pd(dppf)Cl}_2\text{]}]{\text{PhB(OH)}_2} \text{R}^2\text{--S--R}^3 + \text{R}^1\text{--Ph}$$

Entry	R ¹	R ²	R ³	Yield
1	phenyl	–(CH ₂) ₄ –		85
2	phenyl	homobenzyl	ethyl	0
3	benzyl	phenyl	ethyl	68
4	benzyl	homobenzyl	ethyl	85

both phenyl and benzyl residues reacted exclusively at the benzylic position (entry 3). Moreover, in contrast to the arylalkylsulfonium salt (entry 2), the benzyldialkylsulfonium salt (entry 4) gave the coupling product in high yield. Thus, we have shown that acyclic benzylsulfonium salts can undergo this Pd coupling reaction and that they are ideal intermediates for the development of our original safety-catch strategy. According to these results, it appeared appropriate to link the arene scaffold through a benzylic bond to a alkylthiol resin (**R-SH**).^[11]

A series of experiments using a model system was then carried out to optimize the reaction conditions on a solid support (Scheme 3). 4-Cyano-benzylbromide was linked to



Scheme 3. Model system and optimized conditions to carry out the grafting/activation/cleavage sequence.

the alkylthiol resin under classical SPS conditions.^[12] The **R-SH** resin was swelled in DMF (1 g per 10 mL), the benzyl-bromide derivative (3 equiv/resin loading) and *N,N*-diisopropylethylamine (DIEA) (3 equiv/resin loading) were added successively and the slurry heated for 10 h at 70 °C.

To validate this first step of the SPS resin **R-1** was subjected to spectral analysis. The ¹³C NMR spectrum was recorded by using a procedure we recently reported.^[13] Each carbon atom of the linker could be identified, with the sulfur-substituted benzyl and alkyl carbon atoms at $\delta = 40.5$ and 35.5, respectively, being especially clear. Though not quantitative, NMR spectroscopy gave good evidence that both the preparation of the alkylthiol resin and the substrate grafting proceeded efficiently without any significant formation of side products.

Starting from resin **R-1**, the activation step was carried out by alkylating the sulfur atom under conditions that are analogous to those used in solution chemistry. The sulfide resin (200 mg, 1 equiv) was allowed to swell in dichloromethane (2 mL) and then cooled down to 0 °C. Five equivalents of triethyloxonium tetrafluoroborate were added. The

resulting slurry was swirled for eight hours at room temperature. The activated resin **R-2** was washed with CH_2Cl_2 and MeOH, and finally dried under vacuum.

The functionalizing release was carried out under standard palladium coupling conditions. Analysis of the resulting crude mixtures showed the presence of two compounds: the desired biaryl methane along with a biaryl product that was derived from homo-coupling of the boronic acid.^[14] Several combinations of catalyst and base were tested to optimize the yield and lower formation of the side product. Treatment of the sulfonium resin with $\text{Pd}(\text{OAc})_2$ in the presence of triphenylphosphane or triphenylphosphane sulfide, K_2CO_3 as base, and three equivalents of phenylboronic acid never gave the desired biaryl methane in more than 73 % yield after chromatographic purification, the crude product being contaminated by 50 % of the biaryl side product. A better efficiency was obtained with $[\text{Pd}(\text{dppf})\text{Cl}_2]$ in association with K_2CO_3 ($\text{dppf} = 1,1'$ -bis(diphenylphosphanyl)ferrocene). By using this catalytic system the yield of the desired product was raised to 97 %, the crude product still being contaminated by 50 % of the biaryl product. Although it was not possible to completely avoid formation of the biphenyl derivative, the use of only two equivalents of phenylboronic acid enabled its amount to be reduced to only 20 % in the cleavage mixture without decreasing the yield in the biaryl methane. The crude cleavage product was purified by preparative layer chromatography using ethyl acetate/hexane (1/9) as eluant and the biphenyl methane was recovered in 97 % yield. An additional confirmation of the efficacy of the cleavage was given by IR analysis of the resulting resin where no IR band corresponding to the nitrile group could be detected.

Different combinations of resin-bound benzylic substrates and boronic acids were tested under the optimized conditions to determine the scope of this process (Table 2).

To establish the limitations of this novel, traceless linker strategy, we focused on two areas. First, we wanted to determine if the reaction proceeded both with electron-rich and electron-deficient benzyliothiols. Second, we explored which type of functional groups would tolerate the cleavage reaction. Therefore, we introduced several electron-withdrawing and electron-donating groups (entries 1–8) onto the resin as mimics for the potential building blocks and we prepared resins with readily derivatizable aromatic structures: acetal (entries 9, 10), ester (entries 11, 12), amide (entry 13), and nitrile moieties (entries 14, 15).

Since the activation is carried out using triethyloxonium tetrafluoroborate one might fear alkylation of the linked substrate might occur. Miscellaneous functions such as ether (Table 2, entries 7, 8), acetal (entries 9, 10), nitro (entry 5), ester (entries 11, 12), or nitrile (entries 14, 15) were compatible with these conditions. None of them were affected by the triethyloxonium tetrafluoroborate. Interestingly, the

Table 2. Coupling–release of various functionalized resins.

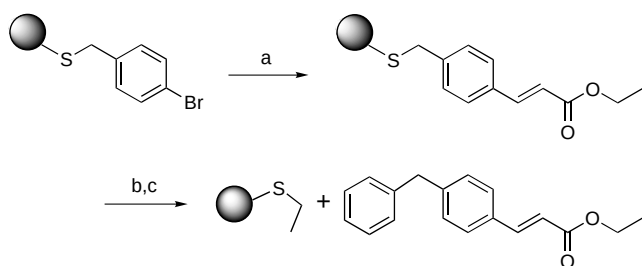
Entry	Resin	Boronic acid	Product	Yield [%] ^[a]
1		$\text{PhB}(\text{OH})_2$		46
2				99
3		$\text{PhB}(\text{OH})_2$		96
4				80
5		$\text{PhB}(\text{OH})_2$		55
6		$\text{PhB}(\text{OH})_2$		42
7		$\text{PhB}(\text{OH})_2$		82.5
8				62
9		$\text{PhB}(\text{OH})_2$		79
10				24
11		$\text{PhB}(\text{OH})_2$		98
12				99 ^[b]
13		$\text{PhB}(\text{OH})_2$		80
14		$\text{PhB}(\text{OH})_2$		97
15				63

[a] Yields of isolated products based on the loading of the **R-SH** resin (0.8 mmol g^{-1}). All compounds were purified by flash chromatography on silica gel. [b] The ester was hydrolyzed to the corresponding acid with LiOH in $\text{H}_2\text{O}/\text{dioxane}$ (1/1) and the undesired homo-coupling product was extracted with diethyl ether. The aqueous phase was acidified and the acid was extracted with EtOAc.

primary amide and the nitrile also proved to be compatible with our procedure (Table 2, entries 13, 14, 15).

The cleavage reaction proceeds under conditions very similar to those already described and extensively used in SPS. Moreover, since the boronic acid is never in contact with the alkylating reagent there is no problem of compatibility. Thus, an important diversity can be introduced through this functionalizing cleavage. For instance, substituted aromatic and heteroaromatic boronic acids could be used without any difficulty (Table 2, entries 4, 8, 12) and the coupling was shown not to be affected by steric hindrance (entries 8, 15).

Finally, to illustrate the versatility of this activation/cleavage sequence, two successive Pd-catalyzed reactions (widely used in SPS to introduce further diversity) were carried out. 4-Bromobenzylbromide was linked to the alkylthiol resin **R-SH**. A Heck coupling reaction involving ethyl acrylate was then performed under standard conditions (Scheme 4), to afford the supported ethyl cinnamate. The sulfide link was activated with triethyloxonium tetrafluoroborate and subsequent cleavage gave the biaryl methane cinnamate derivative in 57% yield.



Scheme 4. Pd-catalyzed Heck coupling performed in the presence of the sulfide link and Pd-catalyzed cleavage after activation of the sulfide bond. Reagents and conditions: a) Pd(OAc)₂ (0.2 equiv), PPh₃ (0.4 equiv), ethyl acrylate (4 equiv), K₂CO₃ (2 equiv), DMF, 70°C, 14 h. b) Et₃O⁺BF₄⁻ (5 equiv), CH₂Cl₂, 0°C → RT, 8 h. c) [Pd(dppf)Cl₂] (0.2 equiv), PhB(OH)₂ (1 equiv), K₂CO₃ (3 equiv), THF, 60°C, 14 h.

As no cleavage was observed during the Heck reaction, it emphasizes that, prior to the activation step, the sulfide link is totally stable towards the Pd-catalyzed coupling reaction, while after alkylation, the resin-bound sulfonium group undergoes efficient cleavage.

In conclusion, a reactivity study of acyclic sulfonium salts toward Pd-catalyzed cross coupling has been reported. The reaction allowed us to develop an original and useful safety-catch linker for the SPS of biaryl methane structures. We have shown that the benzyl carbon–sulfur bond is an advantageous link for organic synthesis on a solid support. Since the sulfide bond is compatible with most SPS reaction conditions this resin–substrate linkage is suitable for use in various types of reactions. Moreover, since Pd-catalyzed cross-couplings are well established reactions for the introduction of diversity in SPS and since the pool of commercially available boronic acids is increasing, this new protocol appears to be a powerful tool that might be employed for the synthesis of many libraries.

Experimental Section

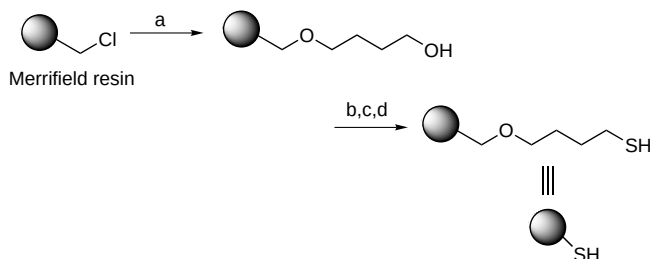
Typical procedure for the traceless cleavage: A conical flask was successively charged under argon, with [Pd(dppf)Cl₂] (0.2 equiv), aryl boronic acid (2 equiv), resin **R-2** (200 mg, 1 equiv), potassium carbonate (3 equiv), and THF (2 mL). The resulting suspension was degassed by gently bubbling argon and the flask was hermetically closed. The reaction was carried out at 60°C for 14 h. After cooling the resin, it was filtered and washed successively with THF (2 × 5 mL), and then 5 times alternately with CH₂Cl₂ (5 mL) and MeOH (5 mL). The combined filtrates were evaporated to dryness to yield a redish brown solid, which was filtered over a bed of silica with dichloromethane and methanol used to remove palladium residues.

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- [9] The phenyltetramethylenesulfonium salt was synthesized by the reaction of thiophenol (1 equiv) with 1,4-dibromobutane (2 equiv) in the presence of triethylamine (1.5 equiv) in diethyl ether. The insoluble salt was purified by titration with ethanol/diethyl ether. All other salts were prepared by alkylation (methylation or ethylation) of the corresponding sulfide. Several alkylating agents were

tested. The use of methyl iodide, even in large excess, gave very slow and incomplete reactions. Very good results were obtained with methyl triflate. However, this method was found to be expensive and not practical to carry out. Thus, triethyloxonium tetrafluoroborate was preferred for a quick (1 or 2 h) and quantitative synthesis of sulfonium salts. Purifications of the salts were performed by trituration in ethanol/diethyl ether.

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 [11] This resin was prepared from commercially available Merrifield resin (1.2 mmol g⁻¹, 200–400 mesh) in four steps. a) 1,4-Butanediol (10 equiv), NaH (5 equiv), DMF, RT, 14 h (an analogous transformation is described in ref. [4f]); b) methanesulfonyl chloride (5 equiv), Et₃N (5 equiv), CH₂Cl₂, RT, 15 h; c) thiourea (5 equiv), DMF, 70 °C, 17 h; d) benzylamine (3 equiv), toluene, 70 °C, 14 h.



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A Highly Soluble Luminescent Decanuclear Gold(I) Complex with a Propeller-Shaped Structure**

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The chemistry of polynuclear d¹⁰ metal systems has attracted numerous studies in the past few decades, and many of them involved the investigation of their structure and their photoluminescent behavior.^[1] These properties are often affected by the presence of weak metal–metal interactions as a result of a relativistic effect that leads to the contraction of the *ns* orbital of the d¹⁰ metal center.^[2] This effect is most

prominent for gold and leads to the phenomenon of aurophilicity commonly found in gold complexes, in which aggregation through short sub-van-der-Waals gold–gold contacts of around 3.05 Å occurs.^[3] Chalcogenides, with their propensity to bridge metal atoms, could serve as ideal candidates for polynuclear metal complex formation. Although chalcogenido copper(I) and silver(I) clusters are known and a number of them have been structurally characterized, most are insoluble or have low solubility in common organic solvents.^[4] Examples of soluble polynuclear d¹⁰ metal chalcogenides are scarce, especially those of gold.^[5–7]

Recently, we reported the isolation of a series of soluble tetranuclear copper(I) and silver(I) chalcogenido complexes with the general formula [M₄(μ-dppm)₄(μ₄-E)]X₂ (M = Cu, Ag; dppm = bis(diphenylphosphanyl)methane; E = S, Se, Te; X = PF₆, OTf = trifluoromethanesulfonate),^[8] as well as the dodecanuclear gold(I) sulfido complex [Au₁₂(μ-dppm)₆(μ₃-S)₄](PF₆)₄.^[6] All were structurally characterized and shown to exhibit rich photophysical properties. Structurally related gold(I) complexes with the general formulas [E(AuPPh₃)₃]⁺ (E = S, Se, Te) and [E(AuPPh₃)₄]²⁺ (E = S, Se) were also reported.^[7] Here we report the synthesis and the structural characterization of a novel soluble, high-nuclearity luminescent μ₃-sulfidogold(I) complex with bridging diphenylamine ligands, namely, [Au₁₀(μ-PNP)₄(μ₃-S)₄](PF₆)₂ (PNP = Ph₂PN(*n*Pr)PPh₂).

Reaction of H₂S with a suspension of [Au₂Cl₂(PNP)]^[9] in ethanol/pyridine followed by metathesis reaction with NH₄PF₆ in methanol and recrystallization from acetone/diethyl ether afforded [Au₁₀(μ-PNP)₄(μ₃-S)₄](PF₆)₂ (**1**) as yellow crystals in 72% yield. The formulation of **1** was confirmed by elemental analyses, positive FAB and ESI mass spectrometry, ¹H and ³¹P NMR spectroscopy, ¹H–¹H COSY experiments, and measurement of the molar conductivity.^[10] The solid-state structure was established by X-ray crystallography (Figure 1).^[11]

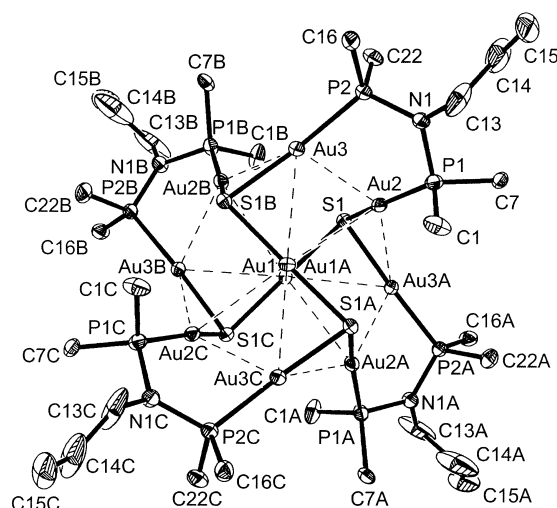


Figure 1. Perspective view of the complex cation of **1** with the atomic numbering scheme. Only the *ipso*-C atoms of the phenyl rings are shown and hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at the 30% probability level. Atoms with the notations A have coordinates at (–y + 1/2, x + 1/2, –z + 1/2), B at (y – 1/2, –x + 1/2, –z + 1/2), and C at (–x, –y + 1, z).

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Complex **1** is composed of four PNP-Au₂ units linked together by four S atoms, whereby opposite pairs of S atoms are bonded to the two Au1 and Au1A atoms at the core in a linear fashion. Significant intramolecular Au...Au interactions exist; most of the Au–Au distances lie in the range of 3.026–3.278 Å, and the Au1–Au1A distance is 3.1553(5) Å. These values are comparable to those in [Au{S(AuPPh₃)₂}]₂[(CH₃)₃SnCl₂] (3.030(2)–3.213(2) Å)^[12] and [Au₁₂(μ-dppm)₆(μ₃-S)₄](PF₆)₄ (2.905(2)–3.272(2) Å).^[6] Exceptionally long Au–Au distances of 3.613 Å are found for Au1A–Au2, Au1–Au2B, Au1A–Au2C, and Au1–Au2A. The Au–S bond lengths of about 2.3 Å are in the range generally observed for Au^I–μ₃-S compounds.^[6, 7a, 13] All the Au^I centers are two-coordinate, with P–Au–S angles of 165.60(3) and 173.88(3)°, and S–Au–S angles of 170.32(4)° that deviate from ideal linear geometry. The Au–S–Au angles range from 81.67(2) to 102.97(3)° and thus deviate from the 90° expected for bonding that involves sulfur 3p orbitals. Similar findings were reported for other related μ₃-sulfidogold(II) systems.^[6, 7a, 13] The coordination geometry about the nitrogen atom of the diphosphanylamine ligand is almost trigonal-planar, and the atoms N1, P1, P2, and C13 all lie approximately on the same plane. Such a planar geometry is commonly found in compounds involving this class of ligands.^[9, 14]

The ³¹P{¹H} NMR spectrum of **1** at ambient temperature showed a pair of doublets at δ = 83.1 and 85.5 (*J*_{PP} = 115 Hz), and this indicates the presence of two different phosphorus environments, P_A and P_B. The observation of a two-spin AB pattern is in line with the results predicted when the difference in chemical shifts has the same order of magnitude as the coupling constant *J*_{PP}.^[15a] The inequivalence of the two P environments supports the assignment of a local S₄ symmetry in solution, with the principal symmetry axis coincident with the Au1–Au1A bond axis, such that the two P environments could not be interchanged by any symmetry operations of the S₄ point group. The four *n*Pr groups are magnetically equivalent in solution. From the room-temperature ¹H NMR spectrum, five multiplets at δ = 2.80, 2.33, 0.85, 0.27, and 0.04 with integral ratios of 1:1:1:1:3 were observed for the protons of the *n*-propyl groups, namely, {H_A, H_B}, {H_C, H_D}, and H_E, respectively (Figure 2). The splitting of the H_A–H_B and H_C–H_D signals may be explained by their diastereotopic relationship, which is induced by the slow inversion at the nitrogen

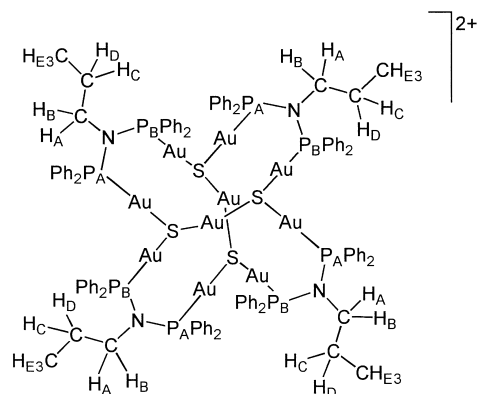


Figure 2. The proposed structure of the complex cation of **1** in solution on the NMR timescale.

atom. Similar findings were reported for a number of compounds with a chiral nitrogen center or a ring structure with restricted rotation.^[15] The H_E protons are much less affected on the NMR timescale simply as a result of their greater distance from the nitrogen atom. A ¹H–¹H COSY experiment confirmed the diastereotopic relationship between the protons rather than the presence of two different *n*-propyl environments, as the five proton environments are correlated with the protons on the adjacent carbon atoms (Figure 3). It further suggests that, in solution, the nitrogen atom may have a nonplanar geometry that allows an inversion process to occur and is different from that in the solid state.

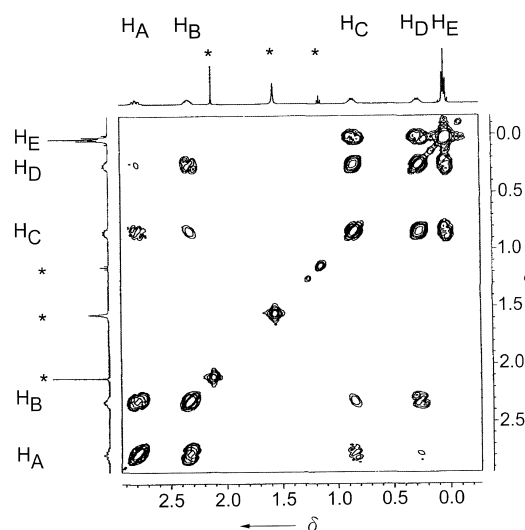


Figure 3. The ¹H–¹H COSY spectrum of **1** at 298 K in CD₂Cl₂, showing the correlations between the *n*-propyl protons. * = solvent peak.

The electronic absorption spectrum of **1** in CH₂Cl₂ shows low-energy absorption bands at about 336 and 400 nm (Table 1). The low-energy band at 400 nm, which is absent in the Au^I precursor [Au₂Cl₂(PNP)], is likely to originate from

Table 1. Photophysical data for **1**.

λ _{abs} [nm] (ε [dm ³ mol ^{−1} cm ^{−1}])	Medium	<i>T</i> [K]	λ _{em} [nm]	τ ₀ [μs]
268 (71620), 336 (24920), 400 (3930)	CH ₂ Cl ₂	298	510, 759	0.10
	(CH ₃) ₂ CO	298	509, 768	0.11
	Solid	298	522, 657	0.23, 1.28 ^[a]
	Solid	77	526, 662	3.77

[a] Biexponential decay.

a ligand-to-metal charge transfer transition modified by an Au...Au interaction (LMMCT; S → Au). The higher energy absorptions at about 268 and 336 nm, which are also exhibited by the PNP ligand and [Au₂Cl₂(PNP)], are assigned to an intraligand transition and a metal-perturbed intraligand transition, respectively. Excitation of **1** in the solid state or in solution with visible light at room temperature and at 77 K results in intense dual luminescence in the green and orange-red regions. The radiative lifetimes in the microsecond range are suggestive of a triplet parentage. With reference to previous spectroscopic work on d¹⁰ chalcogenido systems,^[6, 8, 9] the low-energy emission is tentatively assigned to originate

from triplet states of a ligand-to-metal charge transfer character that mix with metal-centered (ds/dp) states modified by Au...Au interactions (LMMCT; S → Au), whereas the high-energy emission at ca. 500 nm is attributed to metal-perturbed intraligand phosphorescence.

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- [10] **1**: Elemental analysis calcd for $[\text{Au}_{10}(\mu\text{-PNP})(\mu_3\text{-S})_4](\text{PF}_6)_2 \cdot (\text{CH}_3)_2\text{CO}$ (found): C 32.08 (32.34), H 2.76 (2.75), N 1.38 (1.43); positive FAB-MS: m/z : 1903 $[\text{M} - 2\text{PF}_6]^{2+}$; positive ESI-MS: m/z : 1903 $[\text{M} - 2\text{PF}_6]^{2+}$; ^1H NMR (300 MHz, CD_2Cl_2 , 298 K): δ = 0.04 (m, 12H, CH_3), 0.27 (m, 4H, CCH_2C), 0.85 (m, 4H, CCH_2C), 2.33 (m, 4H, NCH_2), 2.80 (m, 4H, NCH_2), 6.83 (m, 8H, Ph), 7.12–7.83 (m, 72H, Ph); $^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz, CD_2Cl_2 , 298 K): δ = 83.1, 85.5 (dd, J_{PP} = 115 Hz); molar conductivity (acetone, 298 K): $\Lambda_{\text{M}} = 262 \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$ (1:2 electrolyte).
- [11] a) Crystal data for **1**: $\text{Au}_{10}\text{S}_4(\text{C}_{27}\text{H}_{27}\text{P}_2\text{N})_4 \cdot 2\text{PF}_6$, $M_r = 4097.59$, tetragonal, space group $I4$ (no. 82), $a = 18.9950(14)$, $c = 17.7282(19)$ Å, $V = 6396.5(10)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 2.127$, $\mu(\text{MoK}\alpha) = 11.670 \text{ mm}^{-1}$, $F(000) = 3792$, $T = 293$ K; $R = 0.0347$, $wR = 0.0870$ for 7314 reflections with $I > 2\sigma(I)$. Crystal dimensions $0.20 \times 0.14 \times 0.12$ mm; Bruker CCD area detector diffractometer, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å); collection range $2\theta = 3-55^\circ$; Φ and Ω oscillation frames $0-180^\circ$; 1321 frames taken in four shells. Absorption correction applied by using the program SADABS^[11b]; the structure was determined by direct methods and subsequent difference Fourier syntheses, and refined by full-matrix least-squares on F^2 by using the programs of the Bruker Smart and Bruker Shelxtl package^[11b]. All non-hydrogen atoms were refined anisotropically. Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary

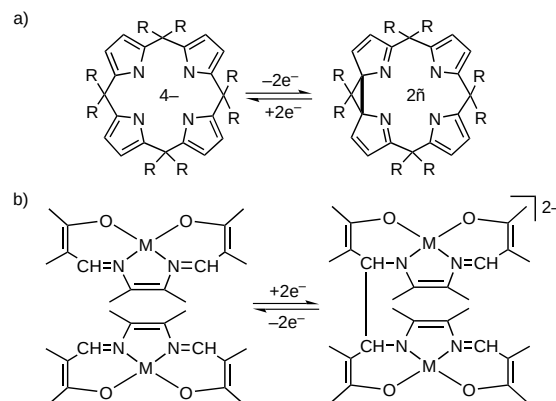
publication no. CCDC-138838. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.); b) SADABS, Bruker Smart and Bruker Shelxtl Package, Bruker AXS GmbH, **1998**.

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Metal-Mediated Transfer of Electrons between Two Different C–C Single Bonds That Function as Electron-Donor and Electron-Acceptor Units**

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Two complementary electron-storage and -releasing units are the fundamental constituents of storage cells^[1] and molecular devices devoted to long-range electron-transfer processes.^[2] The C–C single bonds formed by oxidative (Scheme 1a)^[3] or reductive coupling^[4] (Scheme 1b) can be



Scheme 1. Reversible two-electron oxidative (a) and reductive coupling (b) to form C–C bonds. R = Et.

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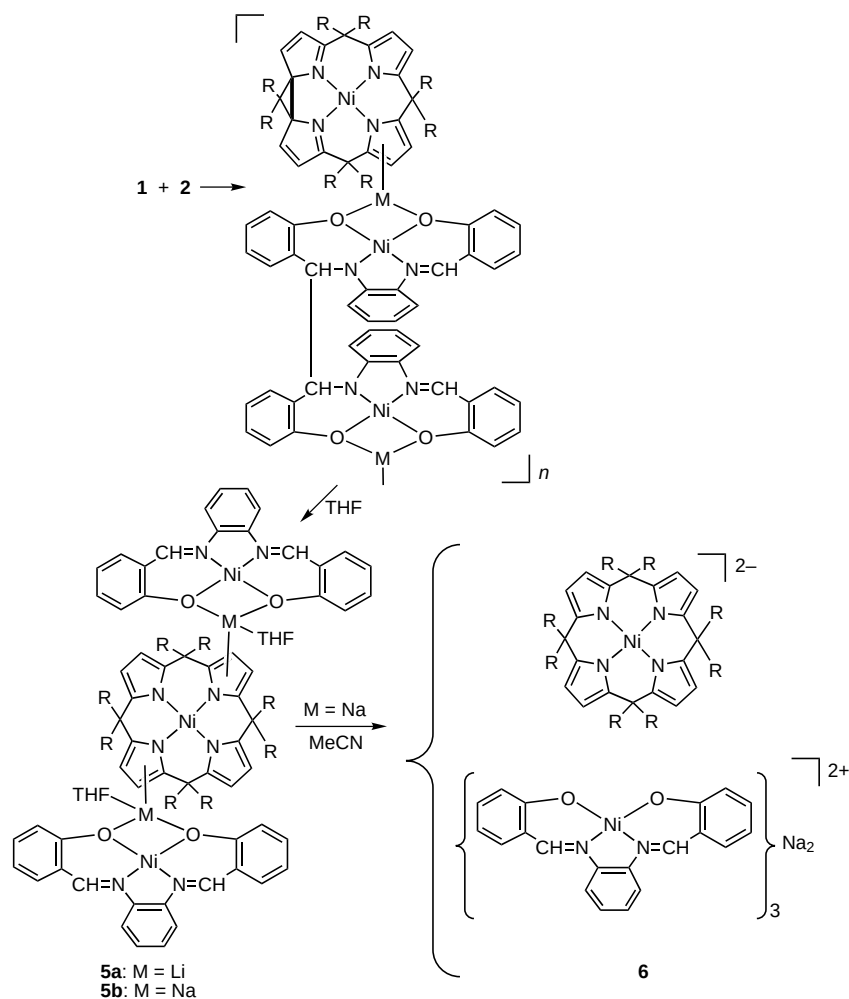
Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

used for storing and releasing pairs of electrons in a reversible manner.

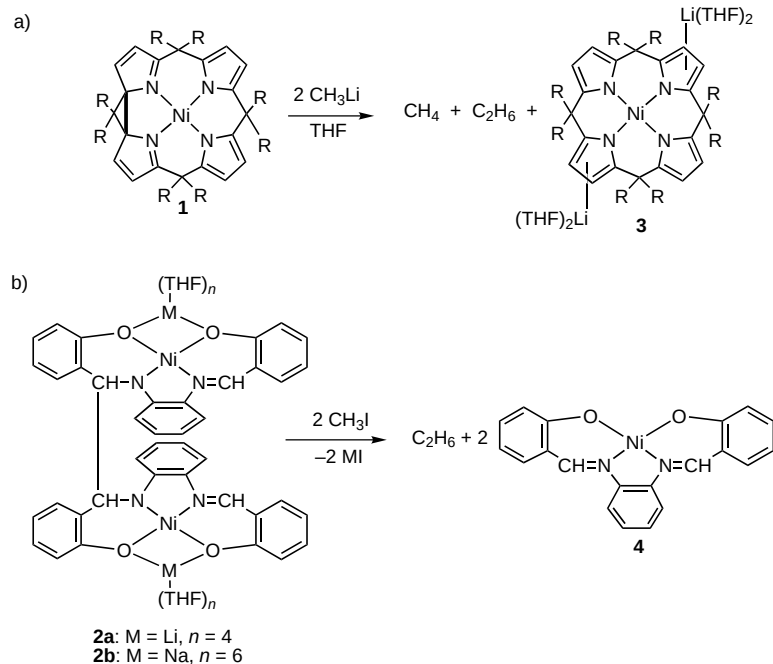
The novelty of the system reported here lies in the nature of the electron-storage and -release units, both of which are ubiquitous C–C single bonds, and on how the communication between them is mediated by metal ions. In addition, the two complementary C–C units operate without being involved, at any stage, in chemical reactions.

Redox chemistry involving exclusively C–C single bonds was investigated for complexes **1**, **2a**, and **2b**, and the complementary behavior of the two different C–C bonds was demonstrated. Although the two complementary systems are chemically quite different, they both bind alkali metal cations at the periphery.^[5, 6] They form tight ion-pair structures, in which the pyrrolyl anions or the Schiff base oxygen atoms, respectively, function as binding sites for the alkali metal cations. The oxidizing properties of **1** were demonstrated, among others, in its reaction with LiMe,^[7] which led to the expected evolution of a mixture of CH₄ and C₂H₆ and the cleavage of the cyclopropane unit (Scheme 2). The partner reaction of **2a** or **2b** with CH₃I^[7] also resulted in the formation of C₂H₆ and cleavage of the C–C bond across the two salophen units, whereby the C–C bond functioned as a two-electron donor.

The complementarity of the two processes was then proved by adding a solution of **2a** or **2b** in THF to a solution of **1** in THF, which led to immediate precipitation of **5a** or **5b**, respectively (Scheme 3). The latter was recov-



Scheme 3. Electron transfer system between electron-rich and electron-poor C–C bonds assisted by alkali metal ions.



Scheme 2. A C–C bond functioning as a two-electron oxidizing (a) and reducing agent (b).

ered as the ion-separated compound **6**^[8] under the crystallization conditions, rather than in the ion-pair form. The crystal structure of **6** is shown in Figure 1^[9].

The occurrence of intermolecular electron transfer and the nature of the final compound emphasizes the assistance of both the central transition metal ion and the alkali metal ion in the redox process. The chemical transformation displayed in Scheme 3 could be exploited for energy storage (e.g., storage cells) or transfer. Although for both model compounds, **2** and **1**, the C–C bond is the site of storage or deficiency, respectively, of a pair of electrons, these functional groups are not involved in any chemical reactions; the metal atom assists electron transfer from the C–C bond to the substrate.^[4e, f] This chemical behavior ensures complete chemical and energetic reversibility of the system. Apart from the practical applicability of this system, the novel concept of exploiting ubiquitous C–C bonds for energy-storing and electron-transfer processes is noteworthy.

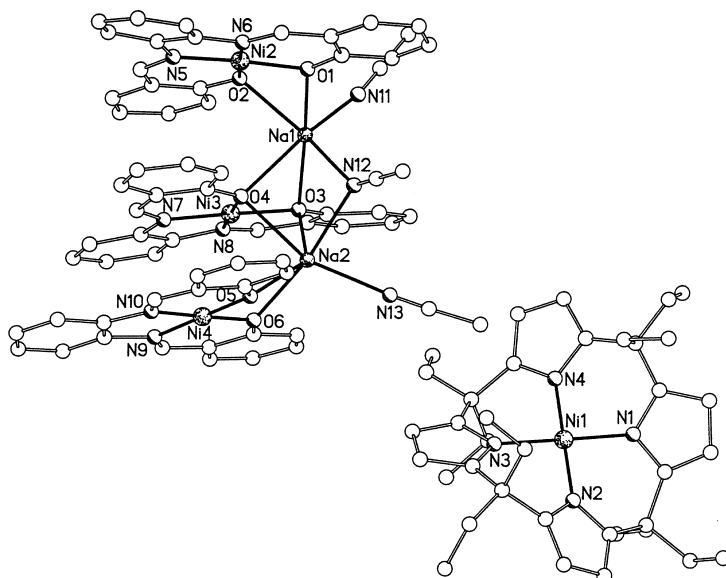


Figure 1. Crystal structure of **6** (hydrogen atoms and interstitial CH₃CN solvent molecules omitted for clarity).

Experimental Section

1: A solution of iodine (3.21 g, 12.7 mmol) in THF (100 mL) was added dropwise to a solution of [NiEt₈Py₄Na₂]·2Et₂O^[7] (10 g, 12.7 mmol; Py = pyrrolyl) in THF (100 mL). The resulting red suspension was stirred for 12 h and then concentrated to dryness. The residue was extracted with CH₂Cl₂ (60 mL) to give a suspension from which a red microcrystalline solid was collected and dried in vacuo (5.97 g, 79%). Elemental analysis calcd for C₃₆H₄₈N₄Ni: C 72.61, H 8.12, N 9.41; found: C 72.58, H 8.05, N 9.23; ¹H NMR (400 MHz, [D₆]benzene, 298 K): δ = 6.67 (d, *J* = 5.1 Hz, 2H, CH), 6.53 (d, *J* = 2.7 Hz, 2H, CH), 6.32 (d, *J* = 2.7 Hz, 2H, CH), 6.11 (d, *J* = 5.1 Hz, 2H, CH), 3.57 (q, *J* = 7.0 Hz, 2H, CH₂), 2.87 (q, *J* = 7.4 Hz, 2H, CH₂), 2.50 (q, *J* = 7.2 Hz, 2H, CH₂), 2.28 (m, 2H, CH₂), 1.84 (m, 4H, CH₂), 1.69 (q, *J* = 6.8 Hz, 2H, CH₂), 1.31–1.18 (m, 8H, CH₂, CH₃), 1.02 (t, *J* = 7.0 Hz, 3H, CH₃), 0.88 (m, 6H, CH₃), 0.70 (m, 6H, CH₃), 0.48 (t, *J* = 6.85 Hz, 3H, CH₃); ¹³C NMR (100.6 MHz, [D₆]benzene, 298 K): δ = 147.6, 139.3, 130.7, 130.0, 104.5, 104.0, 85.8, 67.1, 57.7, 51.8, 47.5, 44.8, 39.3, 33.3, 30.0, 27.9, 25.1, 11.2, 11.1, 11.0, 10.7, 10.3, 10.1.

5a: A red solution of **1** (0.75 g, 1.26 mmol) in THF (50 mL) was added to a dark green suspension of **2a**^[4a] (1.32 g, 1.26 mmol) in THF (50 mL). A brown-red precipitate separated immediately from the resulting brown solution. The suspension was stirred for 12 h then the solid was collected and dried in vacuo (1.41 g, 75%). Elemental analysis calcd for **5a**, C₈₄H₉₂Li₂N₈Ni₃O₆: C 65.87, H 6.05, N 7.31; found: C 65.38, H 5.75, N 7.30. IR (Nujol): $\tilde{\nu}$ = 1606 (s), 1578 (s), 1534 (s), 1488 (m), 1444 (s), 1326 (s), 1262 (w), 1196 (s), 1152 (m), 1129 (m), 1068 (w), 1042 (m), 950 (w), 929 (m), 880 (w), 840 (w), 813 (m), 747 (s), 735 (s), 721 (m), 700 (m), 622 (w), 570 (w), 547 (m), 507 (w), 450 (w), 408 cm⁻¹ (w).

5b and **6:** A red solution of **1** (0.87 g, 1.46 mmol) in THF (100 mL) was added to a dark green solution of **2b**^[4a] (1.79 g, 1.46 mmol) in THF (100 mL). A red precipitate separated immediately from the resulting dark orange-red solution. The suspension was stirred overnight then the solid was collected and dried in vacuo (1.81 g, 81%). Elemental analysis calcd for **5b**, C₈₄H₉₂N₈Na₂Ni₃O₆: C 65.87, H 6.05, N 7.31; found: C 65.38, H 5.75, N 7.30. IR (Nujol): $\tilde{\nu}$ = 1608 (s), 1578 (s), 1527 (s), 1483 (s), 1356 (m), 1330 (s), 1317 (s), 1286 (s), 1258 (m), 1235 (w), 1193 (s), 1151 (s), 1129 (m), 1053 (w), 1025 (w), 929 (m), 901 (w), 871 (w), 848 (w), 808 (w), 755 (s), 744 (s), 713 (s), 649 (w), 612 (w), 584 (w), 565 (s), 545 (s), 483 (w), 452 (m), 410 cm⁻¹ (m). The product was recrystallized from acetonitrile to give deep red crystals of **6** that were suitable for X-ray analysis. The crystals were collected, dried in vacuo, and analyzed. Elemental analysis calcd for **6**·CH₃CN, C₉₈H₉₃N₁₁Na₂Ni₄O₆: C 65.33, H 5.20, N 8.55; found: C 65.23, H 4.65, N 8.38.

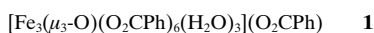
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- [7] For experimental details see Supporting Information.
- [8] In such complexes, the ligand distribution often gives rise to the least soluble complex in the solid state; hence, the [Ni(salophen)]/Na ratio is 3:2 rather than 1:1.^[4,6]
- [9] Crystal structure analysis of **6**: [C₆₆H₅₁N₉Na₂Ni₅O₆][C₃₆H₄₈N₄Ni]·3C₂H₃N, *M*_r = 2006.92, orthorhombic, space group *Pna*2₁, *a* = 20.868(3), *b* = 21.738(3), *c* = 20.9686(14) Å, *V* = 9512.0(19) Å³, *Z* = 4, ρ_{calcd} = 1.401 g cm⁻³, *F*(000) = 4200, MoK_α radiation (λ = 0.71073 Å), μ(MoK_α) = 0.855 mm⁻¹; crystal dimensions 0.20 × 0.14 × 0.10. For 13108 observed reflections (*I* > 2σ(*I*)) and 1227 parameters, the conventional *R* is 0.0926 (*wR*2 = 0.1572 for 15798 independent reflections). 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-137426. 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).

An Octanuclear Fe^{III} Compound Featuring a New Type of Double Butterfly Iron–Oxo Core**

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Christopher M. Kepert, Boujemaa Moubaraki,
Keith S. Murray, Leone Spiccia, and Bruce O. West*

Iron–oxo clusters are of interest both as models for the biomineralization of iron^[1, 2] and as magnetic materials with high-spin ground states.^[3] “Basic” iron carboxylates, such as **1**,

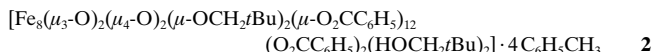


have been utilized as starting reagents to prepare a number of such species, for example Fe₁₀^[4, 5] and Fe₁₁ compounds,^[6] although the mechanism involved is still unclear.

In the course of studies concerned with the preparation of mixed Fe-metal-carboxylate-alkoxy derivatives for possible sol–gel processing to mixed metal oxides, we have been investigating the interaction between the benzoate **1** and various metal alkoxides. Reaction of **1** with Ti(OnPr)₄ in boiling *n*-propanol gave a sparingly soluble precipitate containing the bulk of the Fe. This precipitate was recrystallized from THF to give crystals identified by an X-ray diffraction study as the THF solvate of the known polynuclear Fe₁₁ compound [Fe₁₁(μ₃-O)₆(μ₃-OH)₆(O₂CPh)₁₅].^[6] The decanuclear “ferric wheel” compounds [Fe(OR)₂(O₂CR′)]₁₀^[4, 5] resulted from comparable reactions of basic iron carboxylates (**1**^[4] and [Fe₃(μ₃-O)(O₂CCH₃)₆(H₂O)₃](Cl)^[5] with specific alcohols in the presence of additional Fe³⁺ ions^[4] or pyridone.^[5] Therefore, it was thought highly likely in the present reaction that an initial complex, containing both alkoxide and carboxylate residues, may have formed by direct reaction between **1** and propanol, possibly also involving some group exchange between the Fe and Ti precursors. Hydrolysis by adventitious water during recrystallization could then have produced the Fe₁₁ compound. A related reaction between [Fe₃(μ₃-O)(O₂CPh)₆(H₂O)(py)₂](O₂CPh) (py = pyridyl) and Ti(OnPr)₄ in toluene in the presence of the bulky alcohol neopentanol gave [Ti₆(μ₃-O)₆(O₂CPh)₆[(OCH₂C(C(CH₃)₃))₆], a product with a [Ti₆O₆]¹²⁺ core similar to that recently found in [Ti₆(μ₃-O)₆(O₂CC₆H₄O-Ph)₆(OEt)₆],^[7] together with an Fe-only alkoxy–carboxylate

complex which unfortunately could not be obtained in a crystalline form suitable for X-ray structural analysis.

However, direct reaction between **1** and neopentanol in toluene did produce a suitably crystalline product that was found by X-ray crystallography^[8] to be the Fe₈ derivative **2**,



isolated as the tetratoluene adduct (Figure 1). Compound **2** contains discrete molecules of the centrosymmetric octanuclear complex with the eight Fe^{III} atoms linked in a chainlike fashion by 12 carboxylato, two alkoxo, two μ₃-oxo, and two μ₄-oxo bridging groups. Monodentate carboxylate and alkoxide groups are attached to the end Fe atoms (Fe1, Fe1*). Overall two Fe atoms are five-coordinate and the remainder six-coordinate. The two bridging alkoxo groups link pairs of Fe atoms (Fe3, Fe4*) associated with the two central Fe₄(μ₄-O) units.

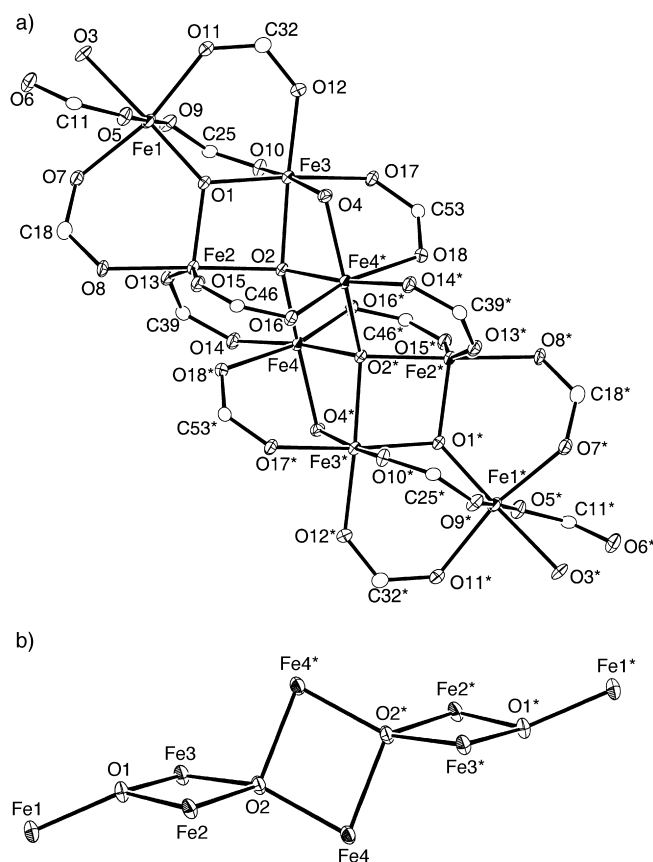


Figure 1. a) ORTEP plot of the molecular structure of **2** (30% probability ellipsoids). Phenyl groups have been omitted for clarity. b) View of the double-butterfly [Fe₈(μ₃-O)₂(μ₄-O)₂]¹⁶⁺ core of **2**. Selected bond distances [Å] and angles [°]: μ₃-O1–Fe1 1.871(2), μ₃-O1–Fe2 1.871(2), μ₃-O1–Fe3 1.938(2), μ₄-O2–Fe2 2.018(2), μ₄-O2–Fe3 2.024(2), μ₄-O2–Fe4 1.978(2), μ₄-O2–Fe4* 2.029(2), Fe1–O₅_{carbox} 1.979(3), Fe1–O₇_{carbox} 2.048(2), Fe1–O₉_{carbox} 2.023(3), Fe1–O₃_{alkox} 2.082(2), Fe2–O₁₃_{carbox} 2.002(3), Fe3–O₁₇_{carbox} 2.015(2), Fe3–O₄_{alkox} 2.028(2); Fe3–O₄_{alkox}–Fe4* 98.60(9), O3–Fe1–O5 85.7(1), O3–Fe1–O7 83.65(9), O1–Fe1–O3 176.7(1), O1–Fe1–O5 91.4(1), O1–Fe1–O9 92.0(1), O1–Fe2–O13 99.6(1), O1–Fe2–O15 98.71(10), O1–Fe3–O4 96.40(10), O1–Fe3–O10 89.06(10), O1–Fe3–O12 98.09(9), O2–Fe2–O8 173.78(10), O13–Fe2–O15 158.92(9), Fe1–O1–Fe2 129.0(1), Fe1–O1–Fe3 121.5(1), Fe2–O1–Fe3 100.6(1), Fe2–O2–Fe3 92.94(9), Fe2–O2–Fe4 108.00(9), Fe2–O2–Fe4* 120.3(1), Fe3–O2–Fe4 143.4(1), Fe3–O2–Fe4* 96.25(8), Fe4–O2–Fe4* 98.32(9).

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The Fe_8O_4 core may be viewed as a “double-butterfly” arrangement (Figure 1b). Within each Fe_4O_2 unit the O–Fe–O and Fe–O–Fe angles are close to corresponding angles in reported butterfly Fe_4O_2 cores.^[9] The dihedral angle between the planes defined by Fe1/Fe2/Fe3 and Fe2/Fe3/Fe4 is 152.8° . Within each Fe_4O_2 unit the associated μ -O atoms lie out of the planes of the Fe_3 sets. Thus, O1 (a μ_3 -O atom) lies $0.32 \text{ \AA}$ above the Fe1/Fe2/Fe3 plane, while O2 (a μ_4 -O atom) is $0.42 \text{ \AA}$ above the Fe2/Fe3/Fe4 plane. The centrosymmetric geometry of the Fe_8 molecule requires that the corresponding oxo groups in the other Fe_4O_2 unit lie below the appropriate Fe_3 planes. This displacement of a μ_3 -O atom from the Fe_3 plane is similar to that in other $[\text{Fe}_4\text{O}_2]$ cores.^[10]

The short O–O distance between the noncoordinated oxygen atom of a terminal carboxylate and the neighboring alkoxo oxygen atom (O6–O3 $2.58 \text{ \AA}$) indicates the existence of a hydrogen bond between them. In keeping with this, the C–O distance of the monodentate carboxylate group bound to Fe1 (C11–O5 $1.285 \text{ \AA}$) is longer than that involving the noncoordinated oxygen atom (C11–O6 $1.249 \text{ \AA}$), and therefore possesses greater single-bond character than the latter. The average C–O distance for bridging carboxylates in the rest of the molecule is $1.265 \pm 0.007 \text{ \AA}$. The distance from an iron center to the O_{alkoxo} atom (Fe1–O3 $2.082 \text{ \AA}$) is longer than to a bridging O_{alkoxo} atom (Fe3–O4 and Fe4–O4 av $1.991 \text{ \AA}$), and comparable to that for MeOH bound to Fe^{III} in a basic carboxylate.^[11] It is therefore concluded that an alcohol molecule is coordinated to Fe1 and hydrogen bonded to a monodentate carboxylate.

The Fe–O distances to the carboxylate, alkoxo, and oxo groups are comparable to those found in other basic Fe_3 carboxylates and polynuclear Fe-alkoxo-carboxylate complexes. The bond angles in the Fe_3 and Fe_4 arrays, however, diverge considerably from the ideal values (see the legend to Figure 1).

The solid-state Mössbauer spectrum of **2** measured at 81 K exhibits two broad lines, the sum of several unresolved quadrupole split doublets which were fitted with Lorentzian lines as the sum of four doublets. The doublets are centered at an isomer shift of $\delta = 0.51(1) \text{ mm s}^{-1}$ with quadrupole splitting parameters ΔE_Q of $0.31(6)$, $0.51(5)$, $0.70(8)$, and $0.86(6) \text{ mm s}^{-1}$ and corresponding relative areas of $27(2)$, $28(2)$, $23(2)$, and $22(2)\%$. The four site occupancies of about 25% are in agreement with expectations from crystallography. The smaller area observed for the more distorted sites could reflect the fact that no correction has been made for possible small differences in the Lamb–Mössbauer factor for the four sites. The quadrupole splittings are comparable to those of other high-spin Fe^{III} complexes with Fe_4O_2 butterfly cores;^[9, 10] these values are known to vary with the nature of the terminal ligands (ΔE_Q values as low as 0.3 mm s^{-1} have been noted in oxo-bridged systems of various nuclearities).

The magnetic moment behavior of **2** as a function of temperature, in a field of 1 T , is indicative of antiferromagnetic coupling. The effective magnetic moment μ_{eff} (per Fe_8 unit) of $7.9 \mu_B$ at 300 K decreases gradually at first, reaching approximately $2.5 \mu_B$ at 50 K , then more rapidly to approach a plateau just above zero (ca. $0.8 \mu_B$) at 4 K . This behavior indicates an $S = 0$ coupled ground state. A good fit of the μ_{eff}

data was obtained using Hendrickson’s tetranuclear model^[9] when the assumption was made that **2** consists of two independent tetranuclear butterfly clusters. A plot of the magnetic moment data per Fe_4 group is shown in Figure 2, together with the best-fit curve obtained using $g = 2.00$ and

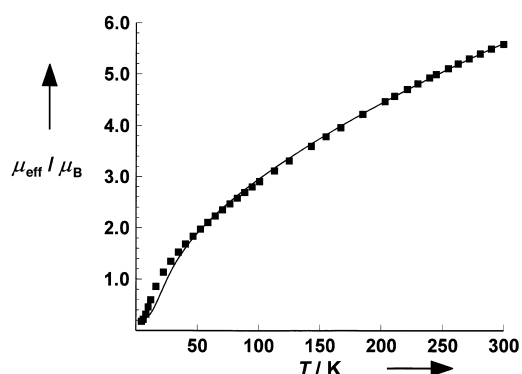


Figure 2. The magnetic moment μ_{eff} of **2** (♦), expressed per Fe_4 unit, as a function of temperature T . The solid line represents the relationship calculated assuming two independent butterfly Fe_4 species^[9] with $g = 2.0$ and $2J_{12} (=2J_{\text{wb}}) = -55 \text{ cm}^{-1}$; $2J_{23} (=2J_{\text{bb}})$ was indeterminate, and $2J_{44}$ assumed to be zero. Inclusion of a temperature independent paramagnetic susceptibility (TIP) $= 900 \times 10^{-6} \text{ cm}^3 \text{ mol}^{-1}$ per Fe_4 , as in ref. [9], improves the fit at low temperatures using $2J_{12} = -59 \text{ cm}^{-1}$.

$2J_{12} (=2J_{\text{wb}}) = -55 \text{ cm}^{-1}$; $2J_{23} (=2J_{\text{bb}})$ was indeterminate because of spin frustration. The $2J_{12}$ value is less than that in $[\text{Fe}_4(\mu_3\text{-O})_2(\text{O}_2\text{CCH}_3)_7(\text{bpy})_2](\text{ClO}_4)^{[9]}$ ($2J_{12} = -90 \text{ cm}^{-1}$; $\text{bpy} = 2,2'$ -bipyridyl), which also has an $S = 0$ ground state. This value is also lower than that estimated^[3] for the central Fe_4O_2 butterfly core (-120 cm^{-1}) in the octanuclear complex $[\text{Fe}_8(\text{tacn})_6(\mu_3\text{-O})_2(\mu_2\text{-OH})_{12}]^{8+}$ (tacn = 1,4,7-triazacyclononane), which possesses an $S = 10$ ground state because of the parallel alignment of the spins of the four outer Fe^{III} ions.^[12, 13] This nanomagnetic compound displays quantum-tunneling phenomena.^[14] These differences in $2J_{12}$ values for **2** probably relate to the nonplanarity of the two Fe_4O_2 groups, particularly around O2, compared to the other examples cited.

The chainlike, double-butterfly arrangement of the Fe_8O_4 core of **2** is unique amongst the family of known iron–oxo clusters. Of the four structurally characterized Fe_8 complexes, each of which also contains chelating ligands, three— $[\text{Fe}_8(\text{tacn})_6(\mu_3\text{-O})_2(\mu_2\text{-OH})_{12}]^{8+}$,^[12] $[\text{Fe}_8(\mu_4\text{-O})(\mu_3\text{-O})_4(\text{OAc})_8(\text{tren})_4]^{6+}$ (tren = tris(2-aminoethyl)amine),^[15] and $[\text{Fe}_8(\mu_4\text{-O})_4(\mu\text{-pz})_{12}\text{-Cl}_4]$ (pz = pyrazine)^[16]—have condensed three-dimensional structures while one— $[\text{Fe}_8(\mu\text{-O})_4(\mu\text{-BMDP})_4(\text{OH})_4(\mu\text{-OAc})_4]^{4+}$ (BMDP = *N,N,N'*-Tris((*N*-methyl)-2-benzimidazolylmethyl)-*N'*-methyl-1,3-diamino-2-propanol)^[17]—contains a square array of Fe atoms. Winpenny and co-workers^[18] have recently reported a Cr^{III} complex, $[\text{Cr}_8(\mu_4\text{-O})_4(\text{O}_2\text{CPh})_{16}]$, which also exhibits a double-butterfly M_8O_4 core. However, the perpendicular orientation of the two M_4O_2 units, rather than parallel as in **2**, gives rise to a distorted Cr_4O_4 cubane. Iron clusters with a nuclearity of eight reported thus far either have more condensed three-dimensional arrangements of the Fe atoms linked by oxo (and often hydroxo) bridges or are cyclic arrays of Fe atoms linked by carboxylates and alkoxides. Indeed, chainlike structures of equal or greater nuclearity than **2** have not yet been identified.

Experimental Section

2: Compound **1** (0.20 g 0.18 mmol) was suspended in dry toluene (4 mL) containing neopentanol (2.0 g 22.7 mmol). The minimum volume of toluene necessary to dissolve all the alcohol at room temperature was used. Stirring the solution for 24 h at room temperature allowed complete dissolution of the basic Fe carboxylate **1**, giving a red solution. Dark red single crystals of **2** suitable for X-ray study were deposited during the next 7 d (yield ca. 50%). No other product was deposited from the solution. Crystals of **2** lose solvent on drying under a stream of nitrogen and analyze as the ditoluene solvate: found: C 57.9, H 5.0%; calcd for $C_{132}H_{132}O_{36}Fe_8$: C 57.8, H 4.8%.

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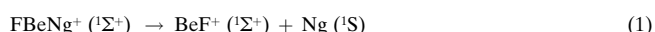
FBeNg⁺ (Ng = He, Ne, Ar): Suitable Cations for Salts of the Lightest Noble Gases?*

Massimiliano Aschi* and Felice Grandinetti*

Since the isolation by Bartlett of the first stable compound containing xenon,^[1] numerous ionic and covalent species of this element and certain analogues of krypton have been synthesized and characterized.^[2, 3] It is also well known that helium, neon, and argon form quite stable species in the gas phase,^[4] but no “true” chemical compounds of these elements have ever been prepared. Therefore, overcoming the chemical inertness of the lightest noble gases still remains a fascinating challenge of great experimental and theoretical interest.

The ArF⁺ cation has been suggested^[5] as being suitable for the preparation of salts like ArF⁺AuF₆⁻ and ArF⁺SbF₆⁻. We report here computational results on the structure, stability, and thermochemistry of the FBeNg⁺ cations (Ng = He, Ne, Ar), which open the challenging but not unrealistic perspective that not only FBeAr⁺ but also FBeNe⁺ and even FBeHe⁺ could form stable salts. Our calculations have been inspired by results reported on the neutral complexes between the BeO molecule and the noble gases.^[6, 7] All the OBeNg complexes, including OBeHe, were predicted^[6] to be stable with respect to dissociation into ground-state BeO (¹Σ⁺) and Ng (¹S). The heaviest members in this series—OBeAr, OBeKr, and OBeXe—have actually been observed in low-temperature matrix-isolation experiments.^[7] The OBe–Ng bond energies were calculated to range from about 3 kcal mol⁻¹ for Ng = He to about 13 kcal mol⁻¹ for Ng = Xe.^[6] It is plausible that, in its singlet ground state ¹Σ⁺,^[8, 9] the positively charged BeF⁺ could fix noble gases even more efficiently than the neutral, isoelectronic BeO.

The results of our calculations (Table 1) fully meet, and perhaps exceed, this qualitative expectation. In fact, all the FBeNg⁺ species proved to be stable with respect to dissociation into BeF⁺ (¹Σ⁺) and Ng (¹S). The enthalpy changes (at 298.15 K) of reaction (1) were computed, at the Gaussian 3



(G3)^[10] level of theory, to be 10.6 (Ng = He), 16.0 (Ng = Ne), and 34.5 kcal mol⁻¹ (Ng = Ar). These values are indeed

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Table 1. Optimized geometries, vibrational frequencies, and G3 total energies of FBeNg⁺, BeF⁺, and Ng.

Species	Symmetry	Be–Ng [Å] ^[a]	Be–F [Å] ^[a]	ν_1 (σ) [cm ^{−1}] ^[b]	ν_2 (σ) [cm ^{−1}] ^[b]	ν_3 (π) [cm ^{−1}] ^[b]	E [Hartree] ^[c]
FBeHe ⁺	¹ Σ ⁺	1.481 1.493	1.339 1.334	1504.0 (273.8)	673.3 (1.8)	183.9 (130.5)	−117.13518
FBeNe ⁺	¹ Σ ⁺	1.668 1.706	1.340 1.334	1494.7 (279.2)	405.0 (10.8)	135.1 (182.8)	−243.11376
FBeAr ⁺	¹ Σ ⁺	1.930 1.946	1.344 1.341	1496.7 (354.3)	384.0 (19.5)	155.2 (142.1)	−641.63995
BeF ⁺	¹ Σ ⁺		1.337 1.333	1448.9 (223.2)			−114.21809
He	¹ S						−2.90093
Ne	¹ S						−128.87092
Ar	¹ S						−527.36780

[a] The upper values were calculated at the MP2(FULL)/6-31G(d) level of theory and the lower values at CCSD(T)/6-311+G(d). [b] Infrared intensities [kmol^{−1}] are given in parentheses. [c] At 298.15 K.

remarkable and allow the prediction that FBeNg⁺ complexes are stable species in the gas phase, even at relatively high temperatures.^[11]

The large energy difference between the ¹Σ⁺ ground state of BeF⁺ and its first excited state ³Π (5.5 eV)^[8,9] and the large difference between the ionization potential (IP) of BeF (ca. 9 eV)^[12] and that of He (24.587 eV), Ne (21.565 eV), and Ar (15.759 eV) suggest that the FBeNg⁺ ions should be well described by single-configuration approaches. We have, however, checked for conceivable artifacts in the MP2(FULL)/6-31G(d) structures used to perform the G3 calculations by repeating the geometry optimizations of the FBeNg⁺ ions at the coupled cluster level of theory. As shown in Table 1, we found only minor differences between the CCSD(T)/6-311+G(d) and MP2(FULL)/6-31G(d) geometries. The structure of FBeHe⁺ obtained at the multiconfigurational quasi-degenerate perturbation level of theory (MCQDPT/6-311+G(d)) also proved to be quite similar (Be–F 1.330, Be–He 1.510 Å). In addition, the MCQDPT results concerning FBeHe⁺ confirmed the validity of a single-configuration description for the FBeNg⁺ cations.

We combined the experimental enthalpy of formation of gaseous BeF⁺ (168 kcal mol^{−1})^[13] with the calculated (G3) enthalpy changes of reaction (1) to estimate the enthalpies of formation of FBeNg⁺: 157.4 (Ng = He), 152.0 (Ng = Ne), and 133.5 kcal mol^{−1} (Ng = Ar). In addition, the results of CCSD(T)/6-311+G(d) calculations revealed that none of the neutral FBeNg compounds are bound species with respect to ground-state BeF (²Σ⁺) and Ng. Therefore, the electron affinities (EAs) of FBeHe⁺, FBeNe⁺, and FBeAr⁺ are predicted to be 198.0 kcal mol^{−1} (8.6 eV), 192.6 kcal mol^{−1} (8.4 eV), and 174.1 kcal mol^{−1} (7.5 eV), respectively (the enthalpy of formation of BeF is −40.6 kcal mol^{−1}). These estimated EAs are of considerable interest since they allow the prediction that a number of anions, including those with a relatively low IP, could form salts FBeAr⁺X[−], FBeNe⁺X[−], and even FBeHe⁺X[−] that are stable with respect to electron transfer. For example, the IP of NO₂[−] is about 2.3 eV, and the stabilization of solid FBeNg⁺NO₂[−] requires lattice energies larger than around

145, 141, and 120 kcal mol^{−1} for Ng = He, Ne, and Ar, respectively.

With the equation of Kapustinskii^[14] and the thermochemical radius^[15] of NO₂[−] (1.55 Å), and under the assumption that the thermochemical radii of FBeNe⁺ and FBeAr⁺ are similar to those of the isoelectronic CNO[−] (1.59 Å) and CNS[−] (1.95 Å), the lattice energies of FBeNe⁺NO₂[−] and FBeAr⁺NO₂[−] are estimated to be about 163 and 148 kcal mol^{−1}, respectively. Therefore, even though the thermochemical radius of FBeHe⁺ is assumed to be identical to that of FBeNe⁺, the lattice energies of all the FBeNg⁺NO₂[−] salts, including FBeHe⁺NO₂[−], appear in principle to be large enough to ensure stabilization with respect to electron transfer between gaseous FBeNg⁺ and NO₂[−].

The IPs of anions X[−] such as NO₃[−], CNO[−], CN[−], and N₃[−] are larger than that of NO₂[−], and we have invariably calculated lattice energies of the corresponding salts FBeNg⁺X[−], including FBeHe⁺X[−], which far exceed the difference between the EA of FBeNg⁺ and the IP of X[−]. Salts like FBeNg⁺AlF₄[−] and FBeNg⁺AuF₆[−] are predicted to be stable with respect to electron transfer, even when unrealistically low lattice energies are assumed. In fact, the charge exchange between FBeNg⁺ and X[−] is practically thermoneutral for AlF₄[−] (whose IP was recently theoretically estimated to be about 8.0 eV^[16]) and even largely endothermic for AuF₆[−] (IP > 10.0 eV). Of course, the IP of the anion is not the only limiting factor to the stabilization of salts FBeNg⁺X[−], which could be severely affected by the various exothermic reactions that gaseous FBeNg⁺ ions are able to undergo with X[−]. In the absence of thermochemical data for the conceivably formed species, we cannot determine whether reactions of FBeNg⁺ with anions like NO₂[−], NO₃[−], CN[−], CNO[−], and N₃[−] could make the formation of corresponding FBeNg⁺X[−] salts prohibitive. We can, however, use the enthalpy of formation of gaseous BeF₂ (−190.2 kcal mol^{−1}) to estimate the conceivable influence of the transfer of fluoride on the stability of salts FBeNg⁺MF_{*n*}[−]. For example, the gas-phase transfer of fluoride from AlF₄[−] to FBeNg⁺ with formation of BeF₂ and Ng is exothermic by 161, 156, and 137 kcal mol^{−1} for Ng = He, Ne, and Ar, respectively. Whereas the lattice energies required to stabilize FBeHe⁺AlF₄[−] and FBeNe⁺AlF₄[−] are probably exceedingly large, that required to stabilize FBeAr⁺AlF₄[−] does not appear as prohibitive. Thus, with the equation of Kapustinskii and a thermochemical radius of AlF₄[−] similar to that of AsF₄[−] (2.1 Å), the lattice energy of FBeAr⁺AlF₄[−] is estimated to be about 130 kcal mol^{−1}.

In conclusion, our calculations suggest that a number of quite common anions X[−] could form salts FBeNg⁺X[−], including FBeHe⁺X[−], that are stable with respect to electron transfer. Exothermic reactions other than the charge exchange could, however, severely limit the formation of these ionic species and make their experimental preparation challenging. Nonetheless, any successful effort along this direction would result in the unprecedented preparation of stable compounds of the lightest noble gases.

Computational Details

We have used Unix versions of the Gaussian 94^[17] and Gamess USA^[18] programs installed on an Alphaserp 1200 Compaq machine. The geometry optimizations and frequency calculations performed at the second-order Møller–Plesset^[19] level of theory (including the inner shell electrons for the correlation) were based on analytical gradients and second derivatives, whereas the geometry optimizations performed at the coupled cluster^[20] level of theory (including the contribution of single and double excitations, and an estimate of connected triples) were based on the algorithm by Fletcher and Powell.^[21] The optimization of FBeHe⁺ performed at the MCQDPT level of theory^[22] was based on a numerical grid of 0.05 Å size. The reference wavefunction, expanded on RHF orbitals within the C_{2v} Abelian subgroup, was derived from an active space of 12 electrons in 10 orbitals. The MP2(FULL)/6-31G(d) geometries were used to calculate the G3 total energies following the procedure described in the literature.^[10] With respect to the previous G2 theory,^[23] G3 significantly improves the calculation of the thermochemical properties of molecules such as CF₄, SiF₄, and NF₃. Therefore, the G3 thermochemical properties of the FBeNg⁺ adducts should be accurate to within less than 2 kcal mol⁻¹.

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Self-Assembly of Rotaxane-Like Complexes with Macrocycles Containing Reversible Coordinate Bonds**

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Remarkable advances in noncovalent and covalent chemistry have led to the efficient synthesis of various interlocked and intertwined supramolecular species with new functions.^[1] Rotaxanes are supermolecules composed of two distinct molecular components—a beadlike molecule and a dumbbell-shaped molecule—which possess mutual recognition motifs that exert weak intermolecular forces when they are assembled in a threading mode. The beadlike components used for the synthesis of rotaxanes to date are all covalently bonded macrocycles such as cyclodextrins, crown ethers, cucurbituril, and cationic or neutral cyclophanes.^[1] Although a variety of transition metal bridged macrocycles were reported over the last decade,^[2] none has been employed yet for the construction of rotaxanes.^[3] This is possibly due to the lack of driving forces for the formation of rotaxane-like assemblies, or because of self-aggregation into other supramolecular species such as catenanes.^[4] When macrocycles that are bridged by coordinate bonds are employed as bead molecules instead of conventional covalent macrocycles, an additional feature of the resulting rotaxanes is that the formation and dissociation might be reversibly controlled under certain conditions. In addition, the kinetic stability of rotaxanes could also be controlled by modifying the coordination sites of the ligands or by selecting an appropriate combination of transition metal and ligand. Here we report for the first time the reversible formation of rotaxane-like complexes from macrocycles that contain weak coordinate bonds.

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The mononuclear macrocycle **1a** (Figure 1), the bead component of the rotaxane, was self-assembled from osmium tetroxide, 2,3-dimethyl-2-butene, and the precursor bis-pyridyl ligand.^[5,6] Upon mixing **1a** (2 mM) with approximately

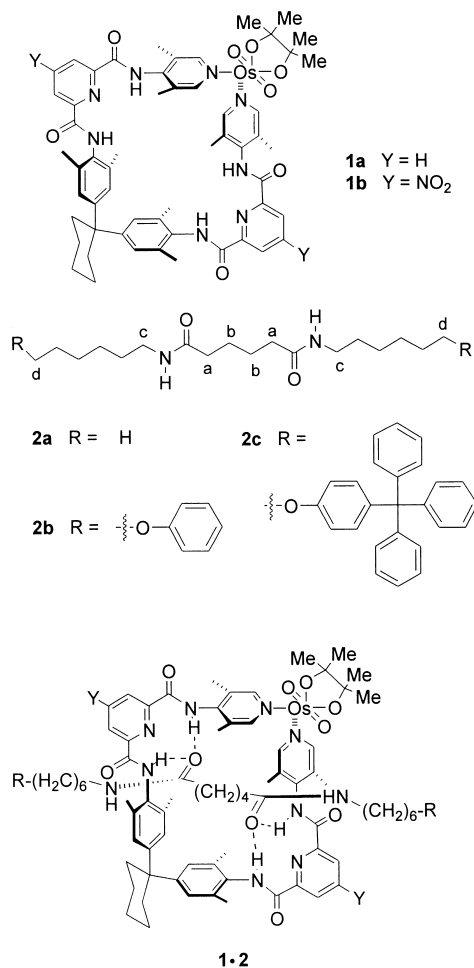


Figure 1. Macrocycles **1a–b**, threads **2a–c**, and schematic depiction of complexes **1·2**.

one equivalent of **2a** in CDCl₃ at 23 ± 1 °C, two NH signals of **1a** were shifted downfield ($\Delta\delta = 0.75$ and 0.88) as a result of hydrogen-bond formation. More importantly, the upfield shift of the H_a and H_b signals of **2a** ($\Delta\delta > 0.5$) strongly suggested that the adipic amide moiety of **2a** is inserted into the cavity of **1a**. These observations are consistent with the X-ray crystal structure (Figure 2),^[7] which clearly shows a pseudo-rotaxane complex, stabilized by four N–H...O=C hydrogen bonds in which the N–H protons of **1a** are located near the π electrons rather than near the lone-pair electrons of the carbonyl groups.^[8]

We then prepared two dumbbell-shaped threads **2b** and **2c**, which possess phenoxy and 4-tritylphenoxy stoppers at the ends, respectively. The former stopper is small enough to penetrate into the cavity of **1a**, but the latter is too bulky to pass through the cavity. The changes in the ¹H NMR spectrum of **2b** in CDCl₃ on addition of the macrocycle **1a** were similar to those observed for **2a**; time-averaged ¹H NMR signals for the free and complexed species were obtained (Figure 3b).

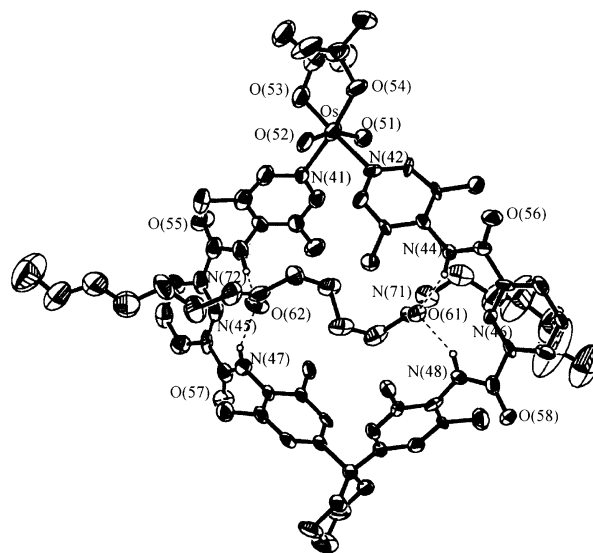


Figure 2. X-ray crystal structure of pseudo-rotaxane complex **1a·2a**. The dotted lines indicate hydrogen bonds, of which the N...O distances are 2.81–2.93 Å. All CH hydrogen atoms are omitted for clarity.

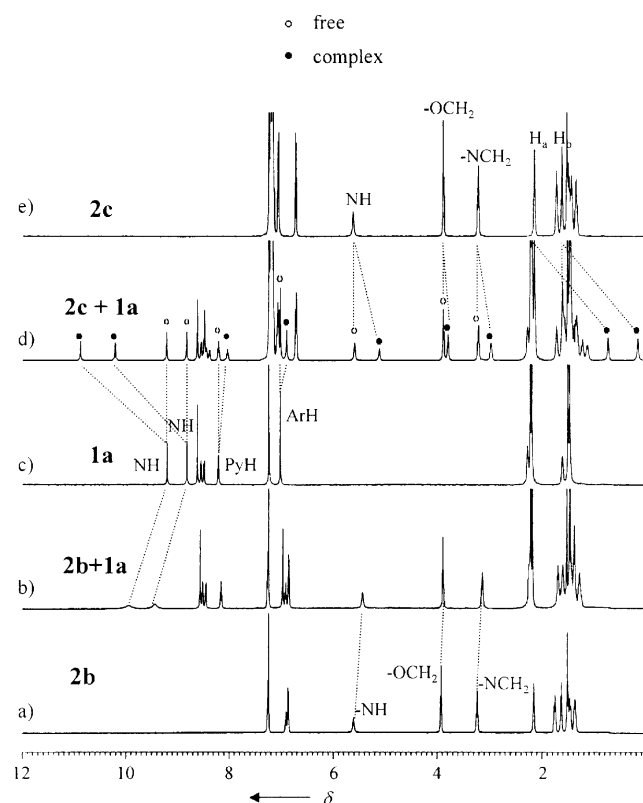


Figure 3. ¹H NMR spectra (500 MHz, CDCl₃, 23 °C) of a) **2b** (2 mM), b) **2b** (2 mM) + **1a** (2 mM), c) **1a** (2 mM), d) **1a** (2 mM) + **2c** (2 mM), and e) **2c** (2 mM).

The thread **2c**, with its much bulkier stopper, however, showed completely different behavior from **2a** and **2b** in the ¹H NMR spectrum (Figure 3d). The sharp and widely separated signals observed with thread **2c** indicate that the formation and dissociation of the complex **1a·2c** are slow on the NMR timescale. Two NH signals of complexed **1a** are shifted downfield relative to free **1** ($\Delta\delta = 1.40$ and 1.68) as a result of hydrogen-bond formation. Furthermore, the H_a and

H_b signals of complexed **2c** appear in the far upfield region ($\delta\delta = 0.77$ and 0.20 , respectively), and this indicates that these hydrogen atoms are located inside the cavity and surrounded by the aryl walls of **1a**, as a result of the formation of a rotaxane-like assembly. The binding constants between the macrocycle **1a** and the threads **2a–c**, measured in $CDCl_3$ at $23 \pm 1^\circ C$ by ^1H NMR titration (**2a** and **2b**)^[9] or ^1H NMR integration (**2c**)^[10] were $(1.3 \pm 0.1) \times 10^3 M^{-1}$ for **2a**, $(9.0 \pm 0.5) \times 10^2 M^{-1}$ for **2b**, and $(5.6 \pm 0.6) \times 10^2 M^{-1}$ for **2c**. The values depend only slightly on the size of the stoppers at the remote ends of the threads ($\Delta\Delta G^0 < 0.5$ kcal mol⁻¹).

Since the macrocycle **1a** contains weak, reversible Os^{VI}–N coordinate bonds, two pathways are possible for formation of complexes with threads (Figure 4). One is a slipping process in

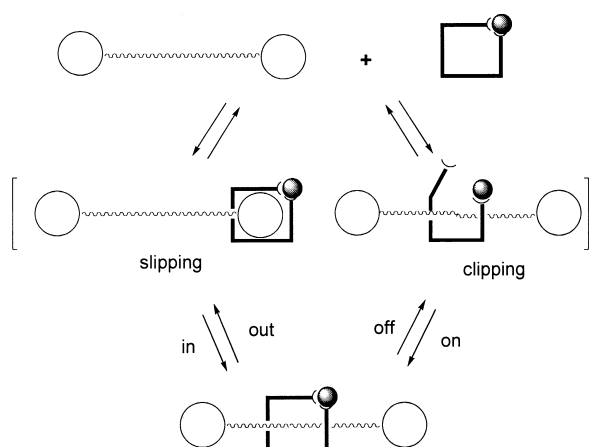


Figure 4. Schematic representation of two possible pathways for the formation and dissociation of complexes **1·2**.

which the threads are squeezed in and out the cavity of the macrocycle. The other is a clipping process that involves the dissociation of the Os^{VI}–N coordinate bond, followed by the formation of intermediate complexes, and finally the reconstruction of the coordinate bond. Both processes are possible for **2a** (no stopper) and **2b** (small stopper). However, only the clipping process is possible when the stopper is too bulky to pass through the cavity of **1a**, as in **2c**. The ^1H NMR spectra (Figure 3) clearly indicate that the rate of interconversion between the free species and the complex of **1a** and **2a** (or **2b**) is faster than that with **2c**, and this implies that the slipping process is faster than the clipping process. For quantitative comparison, an EXSY experiment^[11] was performed on the complex **1a·2c**, and the activation barrier $\Delta G^\ddagger$ for the exchange process between the free species and the complex was calculated to be 15.5 ± 0.1 kcal mol⁻¹ at 296 K, which corresponds to a rate constant k of 24 ± 4 s⁻¹. The energy barrier $\Delta G^\ddagger$ for the binding process of **1a** and **2b** was 12.3 ± 0.1 kcal mol⁻¹, based on the coalescence temperatures of the NH (261 K) and NCH₂ (253 K) signals of thread **2b**.^[12]

Due to the reversible nature of the Os^{VI}–N bonds, the relative population of the rotaxane-like complex **1a·2c** could be precisely controlled by varying the concentrations. The amount of the complex in $CDCl_3$ solution gradually increased with increasing concentrations of the individual components, from about 30% (1 mM) to about 65% (10 mM) of each

component). To enhance the intrinsic affinity of the bead molecule for the thread on formation of the rotaxane complex, macrocycle **1b** was prepared. The presence of nitro groups in the *para*-positions of the pyridine rings greatly increased the stability of the complex: the association constant K_a between **1b** and **2c** was $(1.0 \pm 0.2) \times 10^4 M^{-1}$ at $23^\circ C$ in $CDCl_3$, which is much greater than that between **1a** and **2c** ($\Delta\Delta G^0 = 1.7$ kcal mol⁻¹). When the macrocycle **1b** is employed as a bead component instead of **1a**, the equilibrium lies to side of the the rotaxane complex even at very low concentrations, for example, about 65% of the complex in a 0.5 mM solution.

Experimental Section

1a and **1b**: To a solution of the precursor bis-pyridyl ligands (ca. 0.1 g) in $CHCl_3$ (5–10 mL) were sequentially added 2,3-dimethyl-2-butene (ca. 1.1 equiv) and a 0.1 M solution of OsO₄ in toluene (ca. 1.1 equiv) in an ice–water bath. After the solution had been stirred for 10–30 min, the solvent was removed. The dark brown residue was repeatedly washed with diethyl ether and dried under vacuum to give the macrocycles **1a** or **1b** as dark brown solids in 81–86% yield.

1a: m.p. > 150 °C (decomp); ^1H NMR (500 MHz, $CDCl_3$): δ = 9.21 (s, 2H, NH), 8.83 (s, 2H, NH), 8.63 (s, 4H, lutidyl H), 8.56 (d, J = 7.8 Hz, 2H, pyridyl H), 8.50 (d, J = 7.8 Hz, 2H, pyridyl H), 8.22 (t, J = 7.8 Hz, 2H, pyridyl H), 7.04 (s, 4H, aniliny H), 2.31 (brs, 4H, cyclohexyl H), 2.25 (s, 12H, ArCH₃), 2.23 (s, 12H, ArCH₃), 1.64 (brs, 6H, cyclohexyl H), 1.50 (s, 12H, OC(CH₃)₂); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 160.4, 149.0, 148.9, 148.2, 147.6, 145.9, 140.4, 134.9, 131.2, 130.3, 126.9, 126.3, 125.9, 90.3, 45.2, 36.1, 26.4, 24.7, 22.9, 19.2, 16.4; IR (KBr): $\tilde{\nu}$ = 3449, 1684, 832 cm⁻¹; FAB-MS (*m*NBA matrix, based on ¹⁹²Os): m/z = 1169.4 (1.8%) [$M^+ - H$], 1152.4 (3.3%) [$M^+ - O$], 1052.4 (2.4%) [$M^+ - (O_2C_2(CH_3)_4)$]; elemental analysis calcd for C₅₆H₆₄N₈O₈Os: C 57.62, H 5.53, N 9.60; found: C 57.61, H 5.56, N 9.62.

1b: m.p. > 150 °C (decomp); ^1H NMR (500 MHz, $CDCl_3$): δ = 9.23 (d, J = 1.5 Hz, 2H, pyridyl H), 9.19 (d, J = 1.5 Hz, 2H, pyridyl H), 9.06 (s, 2H, NH), 8.73 (s, 2H, NH), 8.66 (s, 4H, lutidyl H), 7.04 (s, 4H, aniliny H), 2.31 (brs, 4H, cyclohexyl H), 2.25 (s, 12H, ArCH₃), 2.22 (s, 12H, ArCH₃), 1.65 (brs, 6H, cyclohexyl H), 1.50 (s, 12H, OC(CH₃)₂); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 158.6, 157.5, 152.5, 151.0, 149.3, 148.4, 145.2, 134.9, 131.3, 129.9, 127.1, 119.5, 119.1, 90.5, 45.4, 36.1, 26.4, 24.8, 23.0, 19.2, 16.4; IR (KBr): $\tilde{\nu}$ = 3314, 1688, 831 cm⁻¹; FAB-MS (*m*NBA matrix, based on ¹⁹²Os) m/z = 1259.4 (0.6%) [$M^+ - H$], 1242.4 (1.9%) [$M^+ - O$], 1142.4 (1.9%) [$M^+ - (O_2C_2(CH_3)_4)$]; elemental analysis calcd for C₅₆H₆₂N₁₀O₁₂Os: C 53.49, H 4.97, N 11.14; found: C 53.44, H 4.90, N 11.14.

The synthesis of threads **2a–c**, binding studies, and ^1H NMR experiments for determining activation barriers are described in the Supporting Information.

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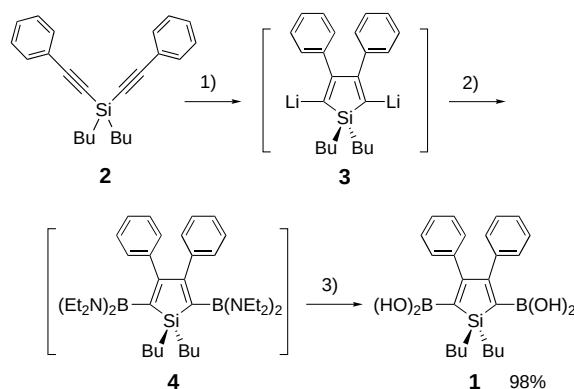
Silole–Thiophene Alternating Copolymers with Narrow Band Gaps**

Shigehiro Yamaguchi, Tomoyuki Goto, and Kohei Tamao*

In the chemistry of π -conjugated polymers, the control of the band gap, which is necessary to obtain specific electrical and photophysical properties, is a fundamental goal.^[1] Successful strategies for creating a narrow band gap involve the construction of donor–acceptor type polymers,^[2] planar ladder-type conjugated systems,^[3] polymers based on fused-ring systems,^[4] and copolymers with a specific combination of monomer units such as poly(thienylene–vinylene)s.^[5] A new alternative to these approaches would be the modification of carbon π -conjugated systems with main group elements such as boron, silicon, and phosphorus.^[6]

In this context, the silole–thiophene 1/1 alternating copolymer is an interesting target compound,^[7] in which the ring silicon atoms fix the labile *s*-cis butadiene skeleton of the poly(thienylene–butadienylene) chain. In addition, the silicon atoms in the ring are expected to affect the electronic structure through unique orbital interactions such as $\sigma^*-\pi^*$ conjugation.^[8] Although its narrow band gap has been predicted theoretically^[9, 10] and experimentally,^[7c] its synthesis has been hampered by the limited availability of suitable 2,5-difunctionalized silole precursors.^[11] These precursors should be isolable but sufficiently reactive towards coupling reactions for high molecular weight polymers to be obtained. We now report the preparation of silole–2,5-diboronic acid **1**, a suitable monomer,^[12] and its use in a Suzuki–Miyaura coupling^[13] for the first synthesis of silole–thiophene alternating copolymers.

The preparation of **1** is based on the intramolecular reductive cyclization of bis(phenylethynyl)silane **2**,^[14] (Scheme 1). Reaction of the diyne **2** with four equivalents of



Scheme 1. Synthesis of **1**: 1) LiNaph (4 equiv), THF, room temperature (RT); 2) $(\text{Et}_2\text{N})_2\text{BCl}$ (4 equiv), -78°C ~ RT; 3) 1N HCl.

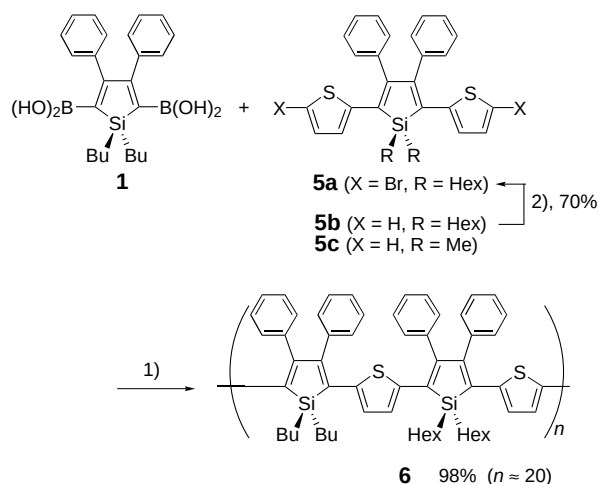
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- [6] The ^1H NMR spectra of macrocycles **1a** and **1b** remained constant over a wide range of concentrations (0.25–10 mM) in CDCl_3 , and this indicates that no aggregation or self-catenation occurs.
- [7] Single crystals of **1a**·**2a** were grown by slow evaporation over about one week of a CH_2Cl_2 /toluene/hexane solution containing an approximately 1:1 molar ratio of **1a** and **2a**. A dark brown crystal was selected under oil under ambient conditions, attached to the tip of a glass fiber, and transferred to a Bruker AXS SMART diffractometer/CCD area detector operating with ω scans. Crystal data: $\text{C}_{74}\text{H}_{100}\text{N}_{10}\text{O}_{10}\text{Os}$ ·hexane, crystal dimensions $0.36 \times 0.21 \times 0.14$ mm, monoclinic, $P2_1/n$, $a = 21.7391(4)$, $b = 16.9339(2)$, $c = 22.4259(2)$ Å, $\beta = 95.5360(10)^\circ$, $V = 8217.09(19)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.266$ g cm⁻³, $F(000) = 3280$, $\lambda(\text{MoK}\alpha) = 0.71073$ Å, $T = 193(2)$ K, $2\theta = 46.5$, reflections collected/unique 48602/11617 ($R(\text{int}) = 0.2205$). The structure was solved by direct methods (SHELXL-97) and refined by full-matrix least-squares methods on F^2 with 891 parameters. All non-hydrogen atoms except for those of the disordered solvent molecules (hexane) were refined anisotropically. Hydrogen atoms were assigned to idealized positions. $R_1 = 0.1089$ ($I > 2\sigma(I)$), $wR_2 = 0.2122$ (all data), GOF 1.015; max./min. residual density 0.805/–0.479 e Å⁻³. The high R value is partly due to the disorder of the solvent molecules, and poor quality of the crystal resulted from unavoidable loss of solvent during data acquisition. Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137734. 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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lithium naphthalenide yielded 2,5-dilithiosilole **3** quantitatively. Treatment of **3** with four equivalents of $(\text{Et}_2\text{N})_2\text{BCl}$ gave 2,5-diborylsilole **4** (not isolated), which was hydrolyzed to afford **1** in 98 % yield. The use of $(\text{Et}_2\text{N})_2\text{BCl}$ was essential because the typical procedure to obtain boronic acids, the direct reaction of the dilithiosilole with $\text{B}(\text{O}i\text{Pr})_3$ followed by hydrolysis,^[15] did not produce the desired product.

As the counterpart for the Suzuki–Miyaura coupling, we chose 2,5-bis(5-bromo-2-thienyl)silole **5a**, readily obtained by the bromination of 2,5-dithienylsilole **5b**^[16] (Scheme 2). The

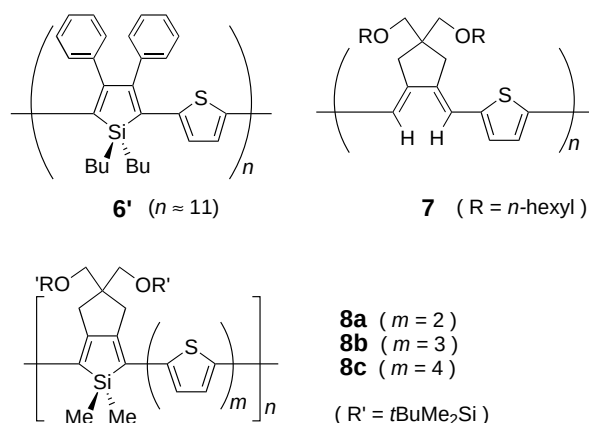


Scheme 2. Synthesis of **6**: 1) $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (0.025 equiv), PPh_3 (0.1 equiv), Na_2CO_3 (2 equiv), $\text{THF}/\text{H}_2\text{O} = 4/1$, reflux, 72 h. 2) *N*-bromosuccinimide (NBS) (2.1 equiv), DMF, RT. Hex = *n*-hexyl.

Suzuki–Miyaura coupling of the **1** with the dibromide **5a** was carried out under basic conditions with the catalyst system $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3/4\text{PPh}_3$ (Scheme 2) and afforded the alternating copolymer **6** in 98 % yield; molecular weights of **6** were determined by GPC analysis with polystyrene standards ($M_w = 48700$ and $M_n = 18400$ ($n \approx 20$ (≈ 80 five-membered rings in total))). The use of the tri-ring dibromide **5a** was important in obtaining high molecular weight polymer, for example, the coupling of **1** with 2,5-dibromothiophene yielded a lower molecular weight polymer **6'** ($M_w = 9000$, $M_n = 4600$, $n \approx 11$ (≈ 22 five-membered rings in total))) in 52 % yield. The structure of **6** was verified by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum shows only one singlet at $\delta = 6.19$, assignable to the thienylene protons, demonstrating the highly ordered structure of **6**. The polymer is remarkably stable and no decomposition was observed even after one year in air.

Polymer **6** is a bronze powder, but affords an ink-blue solution in THF or chloroform. The UV/Vis absorption spectrum of **6** in chloroform has λ_{max} at 648 nm, 230 nm longer than that of the methyl derivative 2,5-dithienylsilole **5c** (λ_{max} 418 nm)^[16a] and, moreover, 8 nm longer than that of **6'** ($\lambda_{\text{max}} = 640$ nm). This suggests that the π -conjugation is effectively extended over more than 22 rings, this being the average number of silole and thiophene rings in **6'**. The λ_{max} value of **6** is also 110 nm longer than that of the poly(thienylene–butadienylene) **7** ($\lambda_{\text{max}} = 538$ nm), recently prepared by Tilley and Lucht.^[17] The large difference between **6** and **7**

clearly demonstrates the significant structural and electronic effects the ring silicon atoms have on the electronic structure of the π -conjugated main chain.



The absorption spectrum of polymer **6** is highly temperature dependent (Figure 1). As the temperature decreases, the vibronic fine structure of the absorption band of **6**

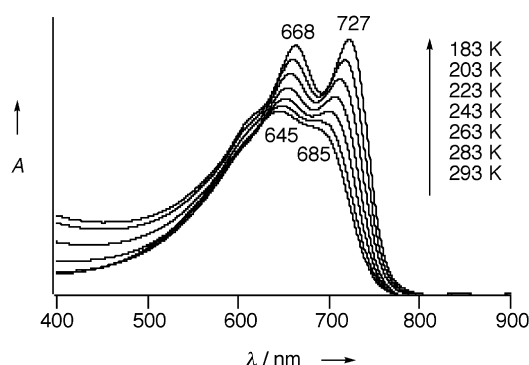


Figure 1. Variable temperature UV/Vis absorption spectra of **6** in 2-MeTHF in the range 293–183 K.

becomes obvious, and at 183 K, the λ_{0-0} band shifts to 727 nm. The band gap, determined from the λ_{0-0} band edge, is 1.55 eV, is small for linear π -conjugated polymers consisting of five-membered heteroaryls,^[1] but coincides well with the theoretical value predicted by Hong et al. ($E_{\text{g,calc}} = 1.55$ eV).^[9] A comparison of this value with those of the silole–thiophene copolymers **8a–c** previously prepared by us^[7c] shows a good linear correlation between the silole/thiophene ratio and the band gap ($E_{\text{g}} = 1.97 - 0.419(\text{silole/thiophene})$, $r = 0.995$), (Figure 2). The different substitution modes of the silole rings^[18] mean that some caution is required interpreting this comparison but the linear correlation suggests that narrower band gaps may be achieved by increasing the silole content.

The successful preparation of silole-2,5-diboronic acids has opened the door to a new chemistry of alternating silole–arene copolymers. This has been demonstrated by the present synthesis of silole–thiophene alternating copolymers and by the unique properties that these polymers display.

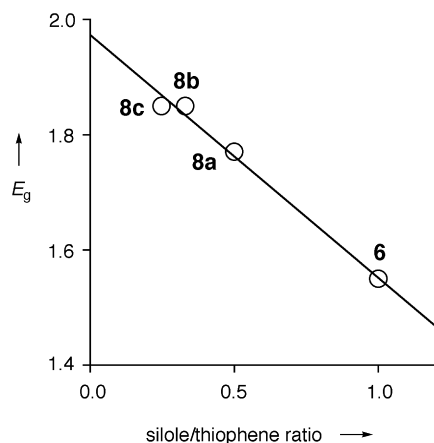


Figure 2. Plot of the band gaps (E_g) determined from absorption edge versus silole/thiophene ratios for a series of silole-thiophene copolymers.

Experimental Section

1: A mixture of granular lithium (139 mg, 20 mmol) and naphthalene (2.56 g, 20 mmol) in THF (12 mL) was stirred at room temperature under argon for 4 h before a solution of **2** (1.72 g, 5 mmol) in THF (11 mL) was added. The mixture was cooled to -78°C and a solution of $(\text{Et}_2\text{N})_2\text{BCl}$ (3.81 g, 20 mmol) in THF (10 mL) was added dropwise over 25 min. The resulting mixture was allowed to warm to room temperature over 6 h. After removal of solvents, Et_2O was added to the residue, and the insoluble materials were removed by filtration. 1N hydrochloric acid (60 mL) was added to the filtrate and the mixture was extracted several times with Et_2O . The combined organic layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was dissolved in a small amount of Et_2O and reprecipitated with hexane (ca. 200 mL) to give **1** (2.13 g, 4.9 mmol) in 98% yield as a white, spectroscopically pure solid: m.p. 82°C (decomp.); ^1H NMR (270 MHz, CDCl_3): δ = 0.99 (t, J = 7.0 Hz, 6H), 0.96–1.06 (m, 4H), 1.28–1.47 (m, 8H), 3.94 (s, 4H), 6.86–6.97 (m, 4H), 7.10–7.20 (m, 6H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 11.50, 13.80, 26.42, 26.45, 127.46, 127.98, 128.21, 140.95, 169.61. A satisfactory elemental analysis was not obtained probably due to contamination by a trace amount of water.

6: A mixture of **1** (868.5 mg, 2.0 mmol), **5a** (1.450 g, 2.0 mmol), $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (104 mg, 0.10 mmol), PPh_3 (105 mg, 0.40 mmol), and Na_2CO_3 (424 mg, 4.0 mmol) in a THF/ H_2O (4/1, 20 mL) mixture was refluxed for 72 h. The reaction mixture was poured into vigorously stirred hexane (400 mL) and the insoluble material collected by filtration. The residue was suspended in methanol/ H_2O (1/1; 120 mL) and sonicated for 10 min. The mixture was then filtered, and the insoluble part collected and washed with methanol (80 mL) then hexane (80 mL). Soxhlet extraction from the residue with THF gave the soluble polymer **6** (1.78 g) in 98% yield as a bronze solid: ^1H NMR (270 MHz, CDCl_3): δ = 0.70–0.90 (brm, 20H), 1.05–1.43 (brm, 24H), 6.19 (brs, 4H), 6.70–6.93 (brm, 8H), 6.98–7.19 (brm, 12H); ^{13}C NMR (67.8 MHz, CDCl_3): δ = 13.66, 14.11, 22.59, 23.34, 25.54, 25.93, 31.36, 32.44, 126.40, 126.81, 128.19, 129.33, 130.26, 139.80, 142.84, 153.55; UV/Vis (CHCl_3 , 293 K): λ_{max} (lg ϵ per recurring unit) = 648 (4.73), 685 (sh, 4.70); elemental analysis, calcd (%) for $(\text{C}_{60}\text{H}_{68}\text{S}_2\text{Si}_2)_n$: C 79.24, H 7.54; found: C 77.13, H 7.33.

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